Guide to the quality and safety of ORGANS FOR TRANSPLANTATION

European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO)

EDQM

7th Edition

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Guide to the quality and safety of organs for transplantation

7th Edition

European Directorate for the Quality of Medicines & HealthCare

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Foreword

Founded in 1949, the Council of Europe is the oldest and largest of all European institutions and now numbers 47 member states. One of its founding principles is that of increasing co-operation between member states to improve the quality of life of all European citizens. In this context of intergovernmental co-operation, the Council of Europe has consistently addressed ethical problems in the field of health. One of the most important ethical principles enshrined by the Council of Europe relates to the non-commercialisation of substances of human origin: blood, organs, tissues and cells.

Work on transplantation at the Council of Europe is co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM). This directorate is the key European organisation involved in the harmonisation, co-ordination, standardisation, regulation and quality control of medicines, blood transfusion, organ transplantation, pharmaceuticals, pharmaceutical care and consumer health, as well as cosmetics and food packaging.

Organ transplantation has progressed during recent decades in a way that nobody would have imagined in earlier years. Still the demand for transplantable organs far outweighs the available supply. This has important consequences for health because organ transplantation is the best, and frequently the only available treatment for end-stage organ failure. Kidney transplantation is also cost-effective compared with other renal replacement therapies, even in low-resource environments. However, as with all substances of human origin, transplantation of human organs entails risks of disease transmission that must be controlled by application of appropriate donor screening and selection criteria. Comprehensive quality systems in the transplantation setting must also be in place.

Since 2002, the European Committee (Partial Agreement) on Organ Transplantation of the Council of Europe (CD-P-TO) has been publishing guidance dealing with quality and safety aspects of the donation and transplantation of organs, tissues and cells. This is the 7th edition of the *Guide to the quality and safety of organs for transplantation*. The Guide collates updated information to provide professionals with the most recent advances in the field, as well as technical guidance to ensure the safety and quality of human organs intended for transplantation. It is essential that all concerned – the professionals involved in identifying possible organ donors, co-ordinators managing the process of donation after death and that of living donation, professionals responsible for the allocation and clinical use of human organs, quality managers of the donation and transplantation process and Health Authorities responsible for the oversight of donation and transplantation programmes – have easy access to this information. This Guide addresses this need by supporting professionals on a practical level to improve the rate of successful and safe organ transplantation.

Technical guidance on the donation and human application of tissues and cells of human origin has now been moved to a dedicated *Guide to the quality and safety of tissues and cells for human application*, currently in its 3rd edition. For blood and blood products, please refer to the Council of Europe *Guide to the preparation, use and quality assurance of blood components*, currently in its 19th edition.

This Guide contains the instructions considered to be the 'minimum standards' that align with the Council of Europe's fundamental principles and the relevant European Union (EU) Directives in the field. It provides assistance for those states outside the EU that consider adopting the EU requirements in their legislation. These standards state 'what must be done'. However, this Guide goes beyond these standards by providing additional advice, based on best practices consistent with current scientific knowledge and expert opinion. It describes background information that should be considered in policy decisions, as well as in educational initiatives, by explaining the 'why and how'. It also refers to developments that have yet to be incorporated into EU directives, thereby providing advance information and recommendations regarding developments in the field. Throughout this Guide, the use of the word 'must' indicates mandatory compliance, in alignment with Council of Europe treaties and EU directives, whereas the use of the word 'should' indicates recommended compliance in accordance with good practice.

In this 7th edition, all chapters have been thoroughly revised according to the state of the art, and new and important chapters have been added. Chapter 2, 'Identification and referral of possible deceased organ donors' has been updated, including a complete section devoted to the application of intensive care to incorporate the option of organ donation into the end-of-life care plans of patients. Chapter 3, 'Determination of death by neurologic criteria' and Chapter 4, 'Consent/authorisation for *post mortem* organ donation' are considered of great value to the Guide. Chapter 3 not only provides a detailed description of the physical exams and ancillary tests necessary for the diagnosis of brain death, but gives guidance on professional practice following the determination of death by neurologic criteria. Chapter 4 describes the current European legal frameworks regarding consent for organ donation, and has expanded on best practice in supporting relatives of deceased organ donors and communicating bad news, both in the process of donation after brain death and in that of donation after circulatory death.

Chapter 5, 'Management of the potential donor after brain death' has been updated, based on current knowledge in the field. Additionally, new sections have been included on nutritional support, management of brain dead multi-organ donors, optimisation of the timing in performing organ recovery and donor management during organ procurement.

Other enhancements to the Guide have been the complete revision of Chapter 6, 'General donor characterisation, assessment and selection criteria' to include summaries of all issues related to the donor without focus on any specific organ, covering the risk of disease transmission and which measures should be taken to avoid such unintended transmissions. Chapter 7, 'Specific organ characterisation, assessment and selection criteria' provides the information required for the evaluation of each organ individually considered.

Chapter 8, 'Risk of transmission of infectious diseases' has been fully revised to include up-to-date developments in the field of emerging pathogens. The screening algorithms for an extensive list of pathogens have been updated. The chapter has also taken into account the impact of new direct-acting antiviral agents in the treatment of hepatitis C virus infection to elaborate updated recommendations on the use of organs from donors infected by this virus. Chapter 9, 'Risk of transmission of neoplastic diseases' has been entirely reviewed to provide current evidence for assessment of the risk of transplanting organs from donors with a past or present history of malignancies. Grading of risk is provided for an extensive list of malignancies that may be identified in the donor history or be discovered at the time of organ procurement. Chapter 10, 'Risks related to the use of organs from donors with other conditions and diseases' has also been revised, to provide recommendations about the use of organs from donors with conditions other than poisoning and inherited diseases, e.g., allergies and auto-immune, neuro-degenerative and demyelinating diseases.

Chapter 11, 'Organ procurement, preservation and transportation' has been reviewed, providing up-to-date information on organ procurement and different perfusion solutions, with information about new trials in preservation (e.g. machine perfusion, cold storage, normo/hypothermic storage).

Chapter 12, 'Donation after circulatory death' and Chapter 13, 'Living donation' deal with topics that require special consideration of procedures, which differ greatly from those applied to the process of donation after death determined by neurologic criteria. As living donation and donation after circulatory death are expanding in the European landscape, these two chapters are considered of great added value and have been revised extensively. Chapter 12 now includes a detailed description of the use of *in situ* preservation techniques that may help to increase the quality of organs recovered from donors after circulatory death. It also includes, for the very first time, recommendations on the transplantation of hearts from this type of donor, based on the preliminary experience of Australian and British teams. In this new edition, Chapter 13 addresses aspects of

lung living donation, ABO- and HLA-incompatible living transplantation and kidney paired exchange programmes. The new Chapter 14, 'Donation of vascularised composite allografts' addresses this novel field of transplantation, which in many countries is still being performed under research protocols.

Chapter 15, 'Biovigilance and surveillance' has been expanded to provide guidance on how to identify, report, assess and manage severe adverse reactions and events, in alignment with the *Guide to the quality and safety of tissues and cells for human application*. Chapter 16, 'Achieving and measuring quality in organ donation and transplantation' has been updated to provide detailed principles of quality management for organ donation and procurement, as well as for transplantation activities. Finally, the new Chapter 17, 'Measuring outcomes in transplantation' reviews the factors to be considered when measuring outcomes in transplantation.

A dedicated working group including well-known experts nominated by national Health Authorities of Council of Europe member states was convened for the elaboration of this Guide. This group was chaired by Beatriz Domínguez-Gil (Organización Nacional de Trasplantes, Spain) and Carl-Ludwig Fischer-Fröhlich (Deutsche Stiftung Organtransplantation, Germany). This expert group made exceptional contributions by sharing their expertise, reviewing the literature in their respective specialist areas and extracting and distilling knowledge from numerous international guidelines, collaborative projects and diverse publications and websites, with the aim of ensuring that all this up-to-date information is made available and accessible to professionals and regulators. Members of the group co-ordinated the preparation of each chapter and ensured access to the best expertise in each field by engaging additional external experts, who co-authored and contributed to the discussions on various parts of this Guide. The names of all the experts that participated in the elaboration of this Guide can be found in Appendix 20.

The final draft was submitted to an open consultation where Health Authorities, relevant professional associations and additional experts nominated by them carefully revised the text and provided comments and suggestions. All the feedback was carefully analysed by the working group and, where appropriate, led to changes in the final text. In some instances, comments were deemed relevant but required extensive research and/or discussion so their inclusion was postponed to future editions. Our gratitude is extended to all these individuals who participated in the open consultation and provided extremely useful comments and suggestions.

Additionally, the European Society for Organ Transplantation (ESOT), and very particularly the European Donation and Transplant Coordination Organization (EDTCO-section of ESOT), along with The Transplantation Society (TTS), should also be thanked for sharing their expertise and knowledge.

The drafting and publication of the 7th edition of the Guide was co-ordinated by Marta López Fraga (Scientific Officer in charge of the Council of Europe European Committee on Organ Transplantation [CD-P-TO]) and Mar Lomero (Scientific Assistant), with the assistance of Ahlem Sanchez, David Crowe, Gerard M.-F. Hill and Isabelle Vernay. An extended thank you should also be given to Karl-Heinz Buchheit, Head of the Department of Biological Standardisation, OMCL Network & HealthCare (DBO), and Susanne Keitel, Director of the EDQM.

The entire project has been an exceptional combined effort, with extensive discussions dedicated to the common goal of increasing the safety, efficacy and quality of human organs for transplantation. The final result is this Guide, which constitutes a common European standard, based on the long-standing expertise and knowledge of the EDQM.

Chapter 1. Introduction

1.1. Scope and purpose of this Guide

Ever since the first successful kidney transplant in 1954, organ transplantation has saved and improved the quality of life of thousands of patients. Today it is the best life-saving treatment for end-stage organ failure and is performed in 111 countries all over the world. According to the database of the Global Observatory on Donation and Transplantation, 126 670 solid-organ transplants (kidney, liver, heart, lung, pancreas, small bowel) were performed in 2015, 84 347 of which were kidney transplants, followed by 27 759 liver transplants [1]. However, it is estimated that this represents less than 10 % of global needs. Long periods on the waiting list for organs may result in patients deteriorating or dying before transplantation. By the end of 2016, 90 930 patients were waiting for a transplant in member states of the Council of Europe, and 19 patients on the waiting list died every day because there was no organ available [2].

The field of organ donation and transplantation has been forced to evolve rapidly in order to cope with transplant needs, but this has come with inherent challenges. These include ensuring effective organisation, co-ordination and control of all crucial activities and services as well as the need for safeguards against exploitation and misuse [3]. In order to overcome such barriers and to facilitate access to safe and ethical transplantation therapy for all European citizens, the Council of Europe started work in this area back in 1987. In 1999, a working group was set up to prepare a guide on the quality and safety standards that should be achieved in services for the donation, procurement and transplantation of human organs, tissues and cells in member states. The 1st edition of that Guide was published in 2002, and it has evolved very much since then.

This is the 7th edition of the *Guide to the quality and safety of organs for transplantation* of the Council of Europe. This Guide has two main objectives. Firstly, it aims to provide sound information and guidance for all professionals involved in donation and transplantation of human organs, to optimise the quality and minimise the risks of these complex procedures. All material of human origin carries risks that must be controlled by application of scrupulous criteria for donor evaluation and selection, and by comprehensive systems to assess quality. The idea is to help professionals on a practical level by providing easy-to-use information at the bedside that will help improve the rate of success of organ transplantation. Secondly, this Guide reflects ethical principles and guidelines to be considered for the donation and transplantation of human organs.

The field of organ donation and transplantation is now highly regulated in many countries. In the EU, Directive 2010/53/EU of the European Parliament and the Council provides the mandatory standards for quality and safety of human organs intended for transplantation, and Commission Implementing Directive 2012/25/EU lays down the information procedures for the exchange, between EU member states, of human organs intended for transplantation. Both directives should already be transposed into the na-

tional legislations of the 28 EU member states. This Guide refers to those requirements where appropriate, providing technical examples of how they can be implemented, but goes beyond them to describe generally accepted good practice. Therefore, it will be useful as a source of practical information for those working within the EU legislative framework and those working within national legal frameworks in all Council of Europe member states and non-member countries. In summary, this Guide is not intended to provide a common legal framework but aims at presenting technical guidance according to the best practices accepted at European level.

In this Guide the term 'Health Authority' is used throughout to refer to the body to which has been delegated the responsibility on a national or regional basis (or even sometimes at supranational level) by the government to ensure that organ donation and transplantation are appropriately promoted, regulated and monitored in the interests of patient safety and public transparency. Other terms – such as 'regulatory authority' and 'regulatory agency' or, in the EU, 'competent authority' and 'delegated body' – can be considered as equivalent to it.

This Guide is the result of the collective effort and expertise gathered by the members and observers of the European Committee of Experts on Organ Transplantation (CD-P-TO) through an *ad hoc* Organ Expert Group (see Appendices 20 and 21). Unless otherwise indicated, 'member states' applies to member states of the Council of Europe.

Appendix 1 spells out the abbreviations and acronyms used throughout this Guide and Appendix 2 is a glossary of key terms.

For matters dealing with the use of tissues and cells, and of blood or blood products, see the Council of Europe *Guide to the quality and safety of tissues and cells for human application* and the *Guide to the preparation, use and quality assurance of blood components* [4], respectively.

1.2. European Committee on Organ Transplantation, the European Directorate for the Quality of Medicines & HealthCare and the Council of Europe

The Council of Europe, based in Strasbourg (France), is an international organisation that promotes co-operation between all European countries in the areas of human rights, democracy, rule of law, culture and public health. After the 3rd Conference of European Health Ministers on the Ethical, Organisational and Legislative Aspects of Organ Transplantation [5] held in Paris in 1987, the Council of Europe Committee of Experts on the Organisational Aspects of Co-operation in Organ Transplantation (SP-CTO) was created. This committee consisted of experts in different aspects of transplantation: immunologists, surgeons, physicians, donor co-ordinators and representatives from organ-sharing and organ-procurement organisations. In 2007, the secretariat responsible for activities related to organs, tissues and cells was transferred to the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe [6], and the newly appointed CD-P-TO took over as the steering committee [7]. This move to the EDQM facilitated closer collaboration and synergies with the EU and aimed, among other objectives, to avoid duplication of efforts.

It is under the mandate and aegis of the CD-P-TO committee that this Guide has been elaborated. Today, the CD-P-TO is composed of internationally recognised experts from Council of Europe member states, observer countries, the European Commission and the World Health Organization (WHO), with representatives from the Committee on Bioethics of the Council of Europe (DH-BIO) and several non-governmental organisations. The CD-P-TO actively promotes the non-commercialisation of human organs, the fight against organ trafficking, the development of ethical, quality and safety standards in the field of organs, tissues and cells, and the transfer of knowledge and expertise between member states and organisations.

1.3. General principles on donation and transplantation

Over the past 50 years, due to medical advances in the field and with the excellent results achieved in the transplantation of all types of human organs, organ transplantation has become a consolidated therapy. Kidney transplantation is the most costeffective treatment for end-stage renal diseases. Compared to renal-replacement therapies with dialysis, kidney transplantation allows for a longer life span (on average, kidney transplant patients typically live 10-15 years longer than those on dialysis alone), improved quality of life, fewer medical complications (e.g. anaemia, bone, heart and vascular disease related to dialysis therapy) and reduced costs for healthcare systems. For end-stage failure of organs such as liver,

lung and heart, transplantation is the only available treatment.

Most European countries have increased their number of deceased organ donors since the 1990s, and in four of those countries the number annually is over 1 000 (see Figures 1.1 and 1.2). For kidneys, the number of living donors is also generally on the rise. However, waiting lists persist and, due to the chronic shortage of organs, some transplant clinicians are extremely selective about the patients they place on waiting lists.

The scarcity of organs to cope with the needs of transplantation has many intertwined causes, including: the increase in the number of indications for transplants; the failure to identify possible donors in intensive care and other critical care units; consent declined to proceed with organ recovery; and, more generally, limited institutional support for deceased donation in some countries and the way health and transplantation systems are organised and managed. While the issues concerned may be complex, there is one clear fact: that organ shortage is an increasingly acute problem in the context of an ageing population and the increased incidence of hypertension, diabetes and obesity.

The need to tackle the problem of organ shortage within this particular context has led to consideration of different strategies to increase organ availability, including living donation, donation after death determined by circulatory criteria and the use of organs from expanded-criteria donors and from non-standard risk donors. All of these aspects are discussed at length in dedicated chapters of this Guide.

1.3.1. Risks and benefits of transplantation

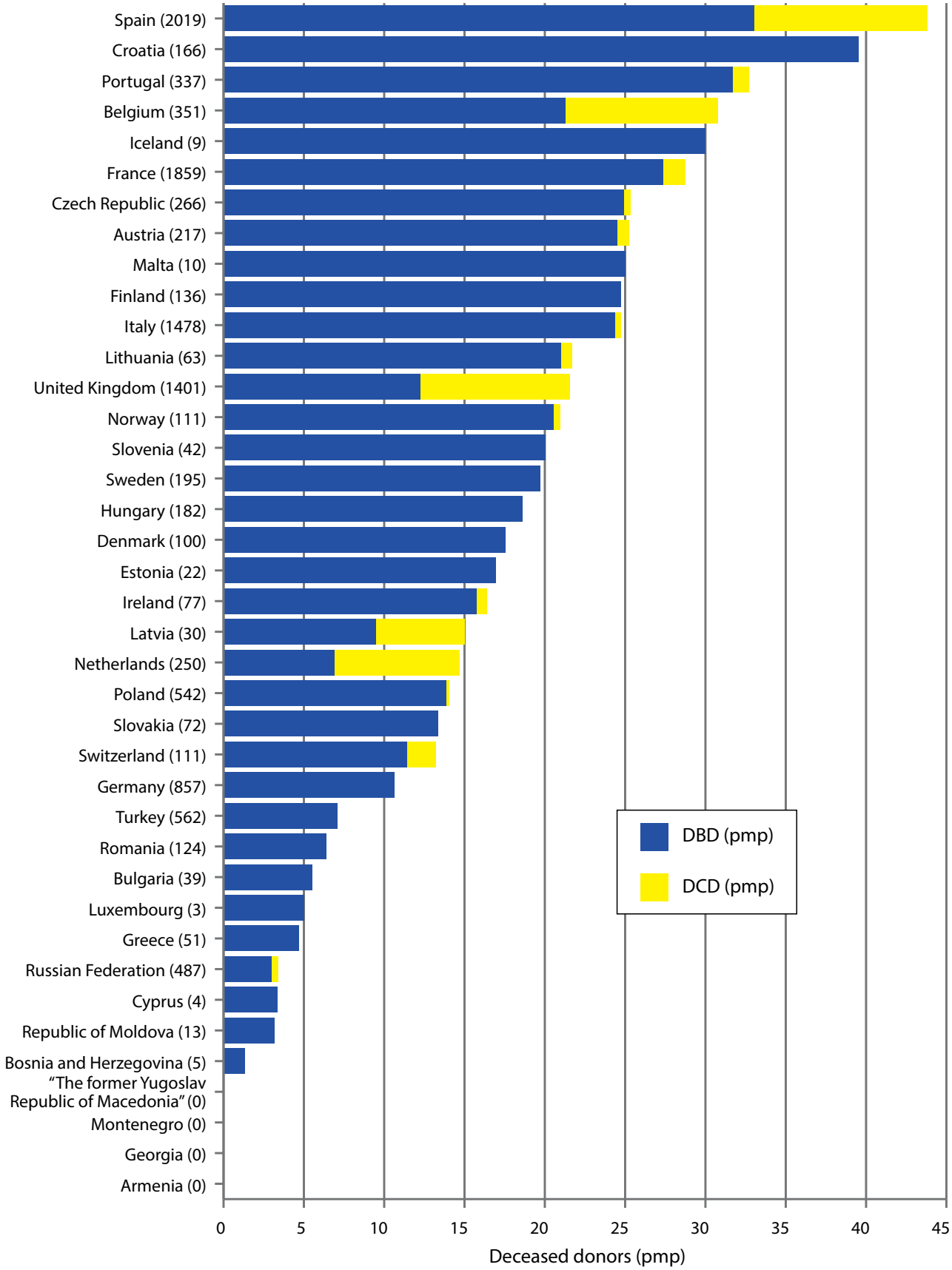
Transplantation is not without risks, and only organs procured under strict quality and safety parameters are likely to function properly and provide the best clinical outcomes for the recipients. Transplantation carries the risk of the operative procedure itself, of the lifelong immuno-suppression that will be necessary and of disease transmission. The factors influencing the clinical outcome of transplantation are complex: in particular, there is an interaction between two different biological systems, i.e. those of the donor and the recipient. Therefore, when assessing the risk of transplantation, both the donor and the recipient should be considered.

Risk evaluation of both donor and recipient factors has to be carried out on an individual, case-by-case basis. There may be factors that make a given organ from a donor absolutely unsuitable for a specific recipient, whereas the same organ could be effectively used, and indeed life-saving, for another recipient. It is the duty of the transplant team to carefully evaluate donor and recipient factors through an individual risk–benefit analysis. An individualised donor/organ profile should be produced for each patient enrolled on a transplant waiting list, weighing the risk of disease transmission or decreased quality of the transplanted organ against the risk of the recipient dying or deteriorating while on the waiting list. This approach facilitates the best use of all suitable organs. It is important to emphasise that the risks associated with transplantation can never be completely eliminated.

In the particular case of living donors, the short- and long-term outcomes should be assessed for the living donor, as well as for the recipient, to document benefit and harm. In both cases, the potential benefits of the transplant procedure should outweigh the risks. Donors must be carefully screened before donation; they must not be permitted to donate in clinically hopeless situations and must receive regular long-term follow-up care after donation. Transparent communication of these risks between all parties in the donation process is vitally important.

The transplantation of vascularised composite allografts (VCA) is a treatment for complex tissue injuries and defects and a growing field of activity in the past 15 years. To date, primary applications of this type of transplantation have been of the hand and face (partial and full), although there are also reported cases of several other VCA, including those of the larynx, knee, uterus or abdominal wall. VCA are differentiated parts of the human body, containing skin, muscles, bones, tendons and vessels that require surgical connection of blood vessels and nerves for allograft function. Once transplanted, they maintain their structure, vascularisation and capacity to develop physiological functions at a significantly autonomous level. They are also subject to the same time constraints as organs because of their vulnerability to ischaemia, the absence of storage options and the need for immuno-suppressive therapy. Therefore, VCA are considered as organs [8].

Figure 1.1. **Deceased donation rates per million in the Council of Europe member states**

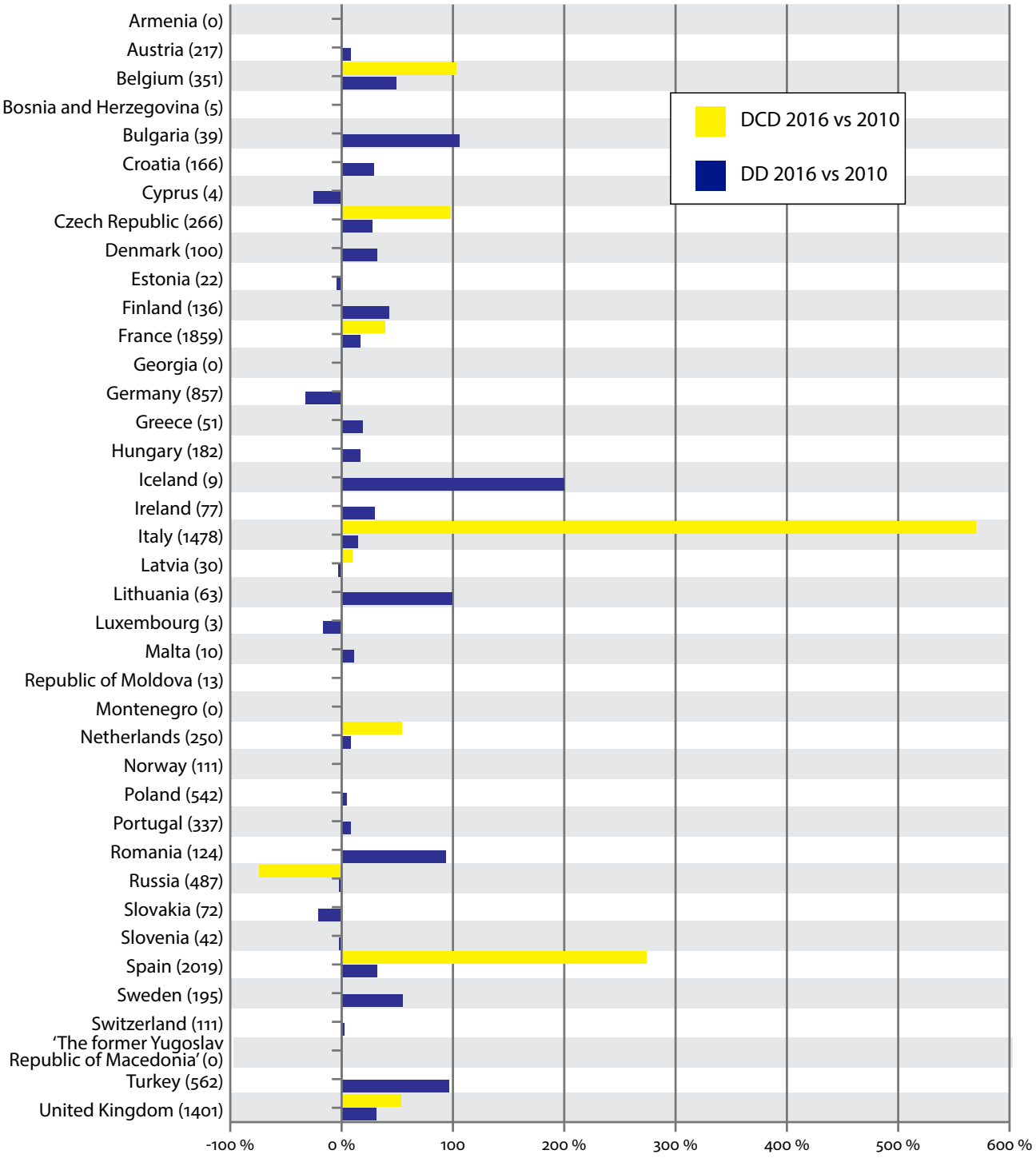


Source: *Newsletter Transplant*. Data from 2016.

DBD = donation after brain death; DCD = donation after circulatory death; pmp = per million population.

Data in parentheses: total number of deceased organ donors in 2016.

Figure 1.2. **Variation in deceased donation activities 2016 v. 2010 (%)**



Source: *Newsletter Transplant*.

In parentheses: total number of deceased donors in 2016.

DD: deceased donation (donation after brain death + donation after circulatory death); DCD: donation after circulatory death; pmp: per million population.

Unlike most solid-organ transplantations, the transplantation of VCA is not usually life-saving, and its primary aim is to improve a patient's quality of life. However, while the quality of form and function as restored with VCA have exceeded the results achieved with conventional surgical techniques, a lifelong regimen of immune-suppressive drugs remains indispensable, exposing the patient to risks that are not acceptable for purely functional or aesthetic purposes, except in very particular indications (e.g. closure of the abdominal wall, total dependence on third-party support in double hand amputees and inability to provide appropriate nutrition to patients with severe face wounds/defects). It is self-evident that recipients of VCA must actively participate in intensive physical therapy to obtain functionality, while there is a risk of

frustration and disappointment if functionality does not meet expectations. Moreover, there is the potential for allograft loss, which would lead to additional procedures in hand transplant patients, and there are limited reconstructive options for facial transplant patients. Therefore, there must be a critical balance in deciding whether functional ability, e.g. grasping and lifting objects, may be more easily and/or safely achieved by prosthetic devices than by VCA transplantation with its associated limitations. Because of the importance of selecting candidates who can withstand these physical and mental challenges, potential VCA transplant recipients should undergo extensive screening for both medical and psychosocial suitability.

Any medical treatment, including any surgical procedure, requires the informed consent of the patient. In transplant medicine, informed consent concerning the quality of an organ to be transplanted and the risk of the individual procedure cannot be easily described in all details because of the limitations and problems outlined in the following chapters of this Guide. In comparison with other medical procedures, there are no valid scientific data about individual donor–recipient risk correlations available based on donor–recipient populations of sufficiently large size.

Patients, when registered on transplant waiting lists, should be informed of general risks, i.e. about the surgical transplantation procedure, but also about the possibilities of disease transmission from donor to recipient. They should be advised that additional information or test results for a risk of disease transmission may become available only after transplantation. In this case, appropriate post-transplant testing, prevention and/or therapy should be offered to mitigate the risk or the severity of disease transmission. Additionally, there are risks associated with a new outbreak of latent infectious diseases under immuno-suppression, such as reactivation of *cytomegalovirus*. Presentation of complications due to immuno-suppressive therapy can increase, particularly if extended immuno-suppressive protocols (using mono- or polyclonal antibodies as induction therapy) are used.

It is advisable to explain the options and potential risks associated with accepting – or not accepting – an organ from a non-standard-risk donor at the time of enrolling for organ transplantation. This discussion should also clarify that risk factors may be present, but not recognised, at the time of an organ offer and that additional data related to risk may be discovered after the transplant procedure.

The patient should be reassured that the physicians and all personnel involved in the process of organ donation and transplantation are working on the basis of 'best knowledge' and will offer appropriate screening and treatment to mitigate any potential for disease transmission. Nevertheless, sometimes not all details of the medical history of a donor may be available because either the donor's family or the general practitioner in charge of a person does not know all the data, for various reasons.

When performing a transplant, the specific, informed consent and the will of the recipient should be taken into account in the allocation procedure. However, the criteria under which a given recipient would/could accept an organ may change over time as a result of a deterioration in their clinical situation. As a consequence, regular re-evaluations of recipient willingness to accept non-standard-risk organ donors should be made, particularly when there are changes in an individual's clinical status. For example, a highly urgent heart recipient in an intensive care unit with only a few days or weeks of life expectancy might be willing to accept a much higher risk from a donor organ compared to a recipient in a stable condition.

Knowledge in the field of transplantation medicine has increased to an extremely high level in the past 20 years. Given the number of transplants performed worldwide and the few reported adverse incidents, the risk of transplantation might not be seen as too high. However, some decisions in transplantation medicine are based on clinical experience, in addition to a high level of common sense. Clinical experience is basically the only source of data, since randomised clinical trials are not always feasible.

Decisions concerning the risk of disease transmission from a donor to one or more recipients should be based on the best scientific knowledge, and the expected results of such decisions should be verified through post-transplant follow-up.

All patients (or parents/legal guardians of under-age patients) who are candidates for transplant waiting lists, or those changing their status on waiting lists, should know about these risks.

1.3.2. Process of donation and transplantation of organs

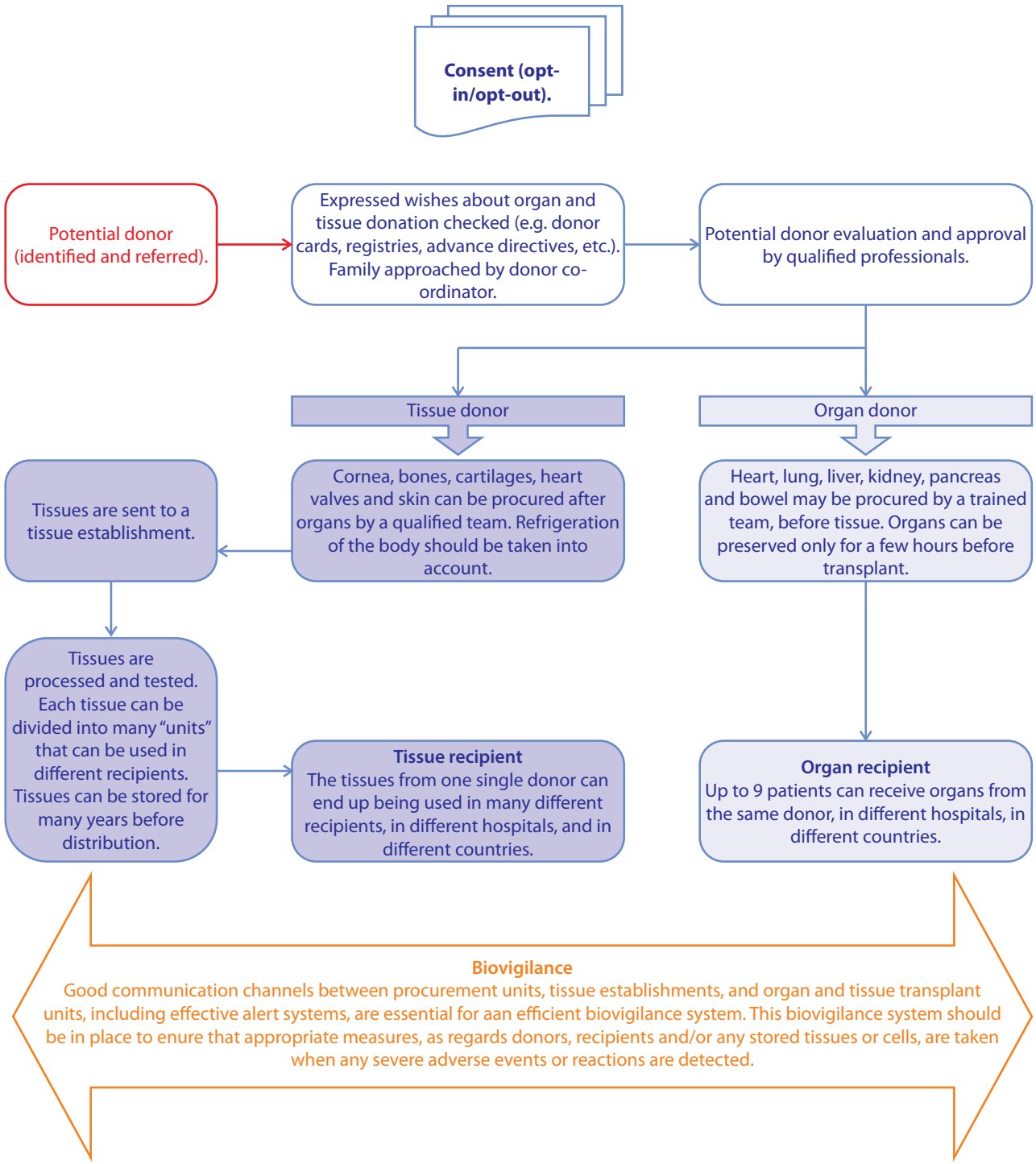
Organ donation and transplantation continue to be fast-moving fields, requiring control of all the crucial technical activities and services that enable organs to be removed from one person and transferred to another person, including: identification, referral and maintenance of donors; procurement,

transportation and preservation of organs; quality management; reimbursement of expenses and service charges; and safeguards against exploitation or misuse (e.g., formal requirements for consent from the potential donor before material may be taken).

The process of donation of organs from a deceased donor is, in many respects, quite different from the process in living donors. However, in all cases, a complex network of interactions underlies the many ways in which human organs, tissues and cells may be provided by one person for the benefit of others, and a complex chain of intermediaries (people and institutions) needs to be involved. Some of these complex links, using the example of a deceased organ- and tissue-donor, are summarised in Figure 1.3.

The entire process may be viewed in terms of organisation and work flows. In the case of donation after death, transplantation can take place only if trained professionals are available to approach the family of the potential donor, if there is the necessary infrastructure and human resources to procure

Figure 1.3. **Complex links between donors and recipients in the context of donation after death**



organs and tissues – including the steps of further processing –within a given timeframe, if appropriate services exist to transport organs and tissues in an adequate manner and if surgeons/physicians are available to participate in the transplantation procedure.

Similarly, for living donation to be made possible, professionals have to carefully select and evaluate potential donors, and ensure post-operative follow-up.

It is important to emphasise how consideration of policy surrounding donation must take into account the complex flows and multiple intermediaries involved in the process. Such awareness highlights the central part inevitably played in the donation and subsequent use of organs, tissues and cells by organisations and organisational structures. These include, for example, the creation of professional roles such as 'donor co-ordinator' and the extent to which they are expected to maximise opportunities for donation, how well one part of the system links with another and where responsibility is seen to rest, and the way professionals in different fields interact and co-operate with one another.

The increasing possibility of using organs and many forms of human tissues to benefit others in medical treatment has brought about increased pressure in member states to meet demand. There is a continual need to identify donors to maintain an adequate supply. Shortages of supply may affect particular subgroups of the population more than others because of the need to match grafts according to immunological criteria or age. 'Demand' for organs and tissues is inherently variable since scientific developments may modify treatment options: the demand for treatment of end-stage organ failure by transplantation may increase, while the development of alternatives, such as prevention strategies for end-stage organ damage (e.g. novel anti-viral drugs in hepatitis C) may reduce the demand. Public expectations of what medical science can achieve may serve to put further upward pressure on demand.

Talking in terms of 'supply' and 'demand' may resonate with the experience of many professionals and patients (potential recipients), who are only too aware of the impact of any shortage in supply. This feature is exacerbated in situations in which the requirement for a high degree of matching or phenotypical similarity between donor and recipient calls for recruitment from ethnic minorities and international collaboration. However, at the same time, it may imply a lack of consideration of the human nature of the source of the organs. It is important always to emphasise when using these impersonal terms that behind 'supply' and 'demand' are individual people and their lives.

1.3.3. Health authorities and/or national transplant organisations

Transplantation is a complex process requiring a large number of functions to be managed effectively by the health authorities. Optimising the outcome of organ transplantation entails a rules-based process that encompasses clinical interventions and *ex vivo* procedures from donor selection through to long-term follow-up of transplanted recipients. Ideally, these functions should all be the responsibility of a single public body, referred to as a national transplant organisation (NTO). However, a combination of local, regional, national and/or international bodies may work together to co-ordinate donation, allocation and/or transplantation, provided that the framework in place ensures accountability, co-operation and efficiency.

This Health Authority (or NTO) should be responsible for the authorisation (including accreditation, licensing and designation), organisation and monitoring of organ, tissue and cell donation and transplantation, and should have a statutory basis which clearly sets out its structure, powers and responsibilities.

According to Recommendation Rec (2006) 15 of the Committee of Ministers [9], health authorities should have competencies and mechanisms to organise and oversee the whole process of transplantation including: public education on transplantation; organ (and tissue) donation and procurement; national transplant recipient waiting lists; organ (and tissue) allocation; organ (and tissue) transportation, including international exchanges; authorisation of organ transplant teams or institutions; traceability of organs and tissues; and monitoring of the outcomes of transplantation and donations from living donors. Other competencies may include research into transplantation and responsibility for identifying and reporting to the relevant authorities any breaches of the national transplantation law.

The essential functions of an NTO (with its advisory committees) include:

a. running a central office which is operational 24 h a day, 7 days a week, with which all donors have to be registered and which manages national or international organ allocation;

b. ensuring that all relevant donor data, including screening results, are collected and communicated to the recipient's transplant team;

c. managing specific national waiting lists for organs, and, if applicable, for tissues, on the basis of agreed and transparent national admission criteria, containing sufficient up-to-date data on the recipient to ensure optimal matching;

d. ensuring that all donated organs are allocated to the most appropriate recipient in compliance with nationally agreed and transparent allocation rules, to ensure as far as possible equal access to transplantation for all patients who could benefit from a transplant;

e. ensuring that arrangements are in place for the safe and rapid transport of organs from the donor's hospital to the recipient's hospital;

f. ensuring the maintenance of a transplant database of all donors and recipients, including follow-up data on living donors and recipients, to ensure traceability and to audit the outcome of transplant programmes;

g. taking responsibility for running a transplant quality-assurance system consistent with internationally recognised standards;

h. providing accurate information to professionals on organ and tissue donation and the outcomes of transplantation as well as being responsible for professional education about transplantation and raising the awareness of the public about organ and tissue donation and transplantation;

i. ensuring complete transparency of national transplant procedures and processes in order to maintain or improve public and patient trust;

j. ensuring follow-up of each transplanted organ for proper biovigilance and analysis of quality of the donation–transplantation process, with adjustments to the state of the art if necessary;

k. taking up national/international responsibility for tissue donation and transplantation.

Additionally, the following functions should ideally be the responsibility of the NTO, or its advisory committees. Alternatively, they could be taken by other bodies in co-operation with the NTO:[1]

a. the recruitment, training and appointment of donor co-ordinators in all major hospitals with a potential for deceased organ donation;

b. the co-ordination and management of donors and/or other transplant co-ordinators;

c. conducting a regional/national potential donor audit to assess the potential donor 'pool' and identify reasons for non-donation;

d. managing national organ donor/non-donor registers (consent-to-donation registers), if applicable;

e. reviewing donor-screening methods and requirements to ensure compatibility with international standards and adapting them to any specific local requirements, if applicable;

f. determining specific information requirements for organ and tissue donors;

g. setting standards for donor management;

h. setting standards for organ-recovery procedures, in particular multi-organ procurement operations, in order to maximise organ quality and preservation;

i. organising and co-ordinating organ donation and procurement procedures;

j. setting standards for organ and tissue packaging, labelling and transportation;

k. organising the transport of organs and tissues from the donor's hospital to the recipient's hospital or tissue establishment;

l. setting criteria for the admission of patients to national organ- or tissue-specific waiting lists;

m. reviewing and analysing national transplant waiting lists, that is, waiting times according to demography, geography, clinical status etc., as a basis for recommending changes to allocation rules in order to ensure optimum allocation of organs;

n. managing and analysing transplant data through the donation process, including an analysis of allocation, to ensure that the rules are properly applied and to prevent organ trafficking;

o. offering organs to other NTOs if a compatible recipient is not available and/or on the basis of international co-operative agreements;

p. maintaining registers of all donors, including living donors, and all transplant recipients and/or designing and operating an integrated national transplant information system;

q. in cases where a disease is transmitted to a recipient, identifying all other recipients of organs or tissues from that same donor, and/or ensuring the disposal of any unused organs or tissues;

r. offering advice on the types of transplant that should be financially covered by national

1. Directive 2010/53/EU requires EU member states to designate one or more competent authorities (and delegated bodies) to implement a number of tasks that cover many of the functions described here, and defines broadly their tasks and responsibilities.

health systems and any that may be allowed in the private sector;

s. accrediting transplant teams and/or institutions allowed to perform organ transplants;

t. managing and overseeing haematopoietic progenitor cell transplants, including the importation of haematopoietic progenitor cells;

u. collecting data on outcomes and follow-up from transplant teams and units;

v. auditing transplant procedures and outcomes to allow constant improvements in the safety and quality of organ transplantation;

w. submitting outcome data to international transplant registers;

x. organising and managing public relations and communication strategies on national transplantation issues;

y. identifying and exposing possible cases of organ trafficking;

z. setting standards for the screening and selection of potential living donors;

aa. authorising living donor transplants.

In view of a potential conflict of interest, setting the criteria to determine death, either according to brain and brain stem failure or after circulatory death (if foreseen by national law), should not be the responsibility of the NTO but of a separate and independent body. It is mandatory that this independent body takes over the responsibility to ensure that death can be certified properly without delay when the relevant criteria are fulfilled.

Member states wishing to collaborate within the framework of a supranational organisation should consider that the NTO remains responsible for deciding on the functions to be allocated to an international body.

1.3.4. The central role of the donor co-ordinator

As mentioned earlier, organ donation and transplantation is a complex process that requires various services and therefore requires effective organisation and co-ordination of healthcare professionals. In many member states, the training and employment of donor co-ordinators has increased the rate of donation of organs and tissues for transplantation, enhanced the efficiency of their procurement and improved the functioning of local and national transplant systems. Donor co-ordinators may also be given other names, such as transplant co-ordinators or key donation persons. In Europe, different organisational structures and professional backgrounds for donor co-ordinators exist.

Council of Europe Recommendation Rec (2004) 19 of the Committee of Ministers defines the recommended role and training of these professionals. Donor co-ordinators responsible for the identification of potential deceased donors should be appointed in every hospital with an intensive care unit. They should have appropriate training and experience, be independent of any transplant teams and have clearly defined responsibilities for the establishment, management and audit of a hospital-based system for potential deceased donor identification and organ/tissue procurement. These professionals should be responsible not only for monitoring the donation and procurement process but also for identifying and implementing improvements.

These professionals should be properly accountable to senior management of the relevant health institution and to any regional transplant organisation or NTO. Donor co-ordinators may be supported by, or report to, other donor co-ordinators at regional or national level.

Donor co-ordinators should have a high standard of professional training consistent with internationally recognised standards, to ensure the highest possible professional and ethical practices in organ donation and procurement. Member states should establish formal national or international training and accreditation programmes for donor co-ordination activities/donor co-ordinators.

Their clinical responsibilities may include not only possible organ donors but also possible tissue donors. They should also manage, record and evaluate the living donor procedure with regard to transparency, free will and other legal and ethical considerations. Their professional activities should include:

a. detecting and identifying possible donors;

b. supporting other professionals involved in the donation process, when needed;

c. supervising donor maintenance and serological and functional testing in order to maintain good organ perfusion and to ensure the quality and safety of the organs and tissues for transplantation;

d. approaching the relatives of potential donors and obtaining consent to donation;

e. overseeing the entire administrative and legal process of donation, including obtaining court orders when required;

f. organising organ and/or tissue procurement and distribution, co-ordinating the necessary and available resources for their procurement

(operating rooms, anaesthesia, nursing, surgical teams etc.) and subsequent distribution and transport to their final destination;

g. referring any potential tissue donors to the tissue establishments in the area/region.

1.4. Ethical considerations

Human organs can be procured only from the body of a person – hence the ethical challenges associated with their use. This Guide describes the very different circumstances under which a person can donate. The donor may be living or deceased; in the latter situation, the determination of death may be done using neurologic or circulatory criteria. Whatever the case, handling and disposal of human organs must be carried out in a manner that shows respect for fundamental rights and for the human body.

Ethical standards of all aspects of organ, tissue and cell donation and transplantation have to conform to the Oviedo Convention on Human Rights and Biomedicine (1997) [10] and the Additional Protocol on transplantation of organs and tissues of human origin (2002) [11]. In addition, all EU member states must comply with the EU directives in the field (see §1.5.3). Other important guidelines to be respected from an ethical viewpoint are Resolution (1978) 29 of the Committee of Ministers on harmonisation of legislation of member states relating to removal, grafting and transplantation of human substances [12], the WHO guiding principles on human cell, tissue and organ transplantation [13] and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism [14].

1.4.1. Consent

The Oviedo Convention states that an intervention in the health field may be carried out only after the person concerned has given free and informed consent to it [10]. This person must make a free choice in the absence of any undue influence and must be given appropriate information beforehand as to the intended use and nature of the intervention as well as its consequences and risks. The person concerned may freely withdraw consent at any time. In the case of organ donation after death, consent can be given by relatives who know or can infer the willingness of the deceased person to donate. Where the willingness of the deceased person is not known, relatives may give consent based on their own judgement.

The Additional Protocol to the Convention on Human Rights and Biomedicine concerning transplantation of organs and tissues of human origin expands these provisions further for the specific case of donation and transplantation [11]. These provisions, along with other relevant information in the case of *post mortem* donation, are explained further in detail in Chapter 4. Specific cases related to consent in donation after circulatory death and living donation are outlined in Chapter 12 and Chapter 13, respectively.

The 'dead-donor rule' (which states that patients must be declared dead before procurement of any vital organs or tissues for transplantation) must be strictly respected [15]. Organs must not be removed from the body of a deceased person unless the death of this person has been certified in accordance with the national law and consent or authorisation has been obtained. The procurement must not be carried out if the deceased person had objected to it.

Finally, it is crucial to emphasise the importance of consent in creating and maintaining the trust of the general public in health professionals and the healthcare system as a whole. Medical mistrust, or distrust of the healthcare system, is one of the reasons why people are reluctant to donate organs. This may be associated with concerns about consent in that the terms of the consent may be abused (for example, by using the donated material in a manner which is not in accordance with consent) or that additional material may be taken without explicit consent. Honesty and trust are central in both professional and personal relationships when donation of organs or tissues or cells takes place. Therefore, it is of vital importance that the limits of the consent are clearly established, explicit and scrupulously respected.

The recipient and, as necessary, the person or official body providing authorisation for the transplant, must be given appropriate information beforehand as to the purpose and nature of the procedure, and its consequences and risks, as well as on the alternatives to the intervention.

In summary, all donation and transplantation programmes are dependent upon goodwill and voluntary donation. It is therefore important that public confidence is maintained by standards of good practice. By engaging donor trust and commitment through obtaining consent, the risk of nefarious trading and potential physical harm from the use of organs will be reduced.

1.4.2. Conflicts of interest

To avoid any potential conflict of interests, doctors certifying the death of a person must not be involved in the allocation procedure or be the same doctors who participate directly in the procurement

of organs or tissues from the deceased person, or in subsequent transplantation procedures, or have responsibilities for the care of the potential organ or tissue recipients.

Health authorities will set out the legal standards for determining that death has occurred and specify how the criteria and process for determining death will be formulated and applied.

1.4.3. Financial aspects of donation and transplantation

Discussions around how to increase the supply of human organs often focus on questions of donor motivation, i.e. how individuals may best be encouraged to donate. Nevertheless, it is essential to recall the Oviedo Convention which, in Article 21, clearly states that the human body and its parts must not, as such, give rise to financial gain [10]. This stipulation is reiterated in the Additional Protocol to that Convention, in its Article 21 [11].

The Council of Europe Convention against Trafficking in Human Organs [16] clearly identifies distinct activities that constitute 'trafficking in human organs', which ratifying states are obliged to criminalise. The central concept is 'the illicit removal of organs', which includes removal where a living donor (or a third party) has been offered or received a financial gain or comparable advantage, or removal from a deceased donor where a third party has been offered or received a financial gain or comparable advantage.

These provisions do not prevent payments that do not constitute a financial gain or a comparable advantage, in particular:

a. compensation of living donors for loss of earnings and any other justifiable expenses caused by the removal or by the related medical examinations;

b. payment of a justifiable fee for legitimate medical or related technical services rendered in connection with transplantation;

c. compensation in case of undue damage resulting from the removal of organs from living persons.

In the donation of any organ, removal of barriers to donate must not render a decision to donate non-altruistic. Initiatives that reduce the barriers to donation should only facilitate an action that the individual was already inclined to take by concern for the welfare of the recipient. In this sense, the Nuffield Council on Bioethics suggests distinguishing between two types of intervention, both of which aim at increasing donation by changing its costs and benefits [15]. The first type is 'altruist-focused interventions', which typically involve removal of various disincentives to act and, in doing so, remove countervailing concerns that may hinder potential donors from acting on their altruistic motivations. For the purpose of this Guide, we will call these interventions 'compensation'. The second type is 'non-altruist-focused interventions', which are targeted at persons who have no strong motivation to help others through donation of their bodily material, but who would be disposed to donate if provided with different reasons for action, perhaps in the form of a payment or incentive going well beyond the reimbursement of expenses. These incentives are particularly worrisome as they may change the donor's perception of the relative risks and benefits of a donation that is not free of potential health hazards and psychological consequences, and they will target the impoverished and vulnerable.

In summary, voluntary unpaid donation must continue to have a central role in the donation process of any organ. Compensation to donors should be strictly limited to making good the expenses and loss of income related to the donation and should not act as an incentive or inducement (either direct or indirect).

Physicians and other health professionals must not engage in transplantation procedures, and health insurers or other finance providers should not cover such procedures, if the organs concerned have been obtained through exploitation or coercion of, or payment to, the donor or the next of kin of a deceased donor.

Promotion of altruistic donation of human organs by means of advertisement or public appeal may be undertaken in accordance with domestic regulations. However, advertising the need for, or the availability of, organs with a view to offering or seeking financial gain or comparable advantage for the donor him/herself or a third party (e.g. the next of kin of the deceased organ donor) must be prohibited. Brokering that involves payment to such individuals or to third parties must also be prohibited.

1.4.4. Equal access to transplantation

Healthcare in general is a human right because it secures and protects access of people to the normal range of opportunities and because it allows people to thrive. Given the importance of health for general well-being, every person, regardless of his/her income or financial means, should have access to a decent minimum of healthcare.

The demand for human organs in many instances exceeds their availability. Significant practical and ethical questions regarding efficiency and fairness arise as to how to distribute these limited resources. Article 3 of the Additional Protocol to the Convention on Human Rights and Biomedicine concerning transplantation of organs and tissues of human origin states that transplantation systems must exist to provide equity in access to transplantation services for patients.

All patients suffering from end-stage organ disease should be evaluated to assess their suitability for inclusion in the transplantation waiting list. Organs donated for transplantation from a deceased donor enter a common pool to be used according to need and should not be directed to a particular individual or specific group if individuals. Except in the case of direct living donations, organs must be allocated to patients only in line with transparent, objective and duly justified rules according to medical criteria. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified, transparent and open to scrutiny. The persons or official bodies responsible for the allocation decision must be designated within this framework.

While kidney transplants are now common practice, not all countries have yet developed capacities to transplant and/or to procure all types of organs. To develop such programmes and to offer other options to their patients, as well as to avoid losing organs, many countries have engaged in international organ exchanges, via bilateral (between two countries or authorities) or multilateral agreements (e.g. in Europe: Eurotransplant, Scandiatransplant or the South Alliance for Transplantation). In the case of international organ exchange arrangements, procedures must also ensure justified and effective distribution across the participating countries in a manner that takes into account the solidarity principle within each country.

1.4.5. Equity in donation

Individual motivation and choice is only one part of the donation picture; the central role of organisations, organisational procedures and professionals in facilitating donation should not be underestimated, nor indeed the importance of trust in these systems. An example of such organisational aspects is that, whenever a person dies in circumstances where donation is a possibility, this possibility should be raised with their family.

The role of the state with respect to donation should be understood as one of stewardship: that is, actively promoting measures that will improve general health (thereby reducing the demand for some forms of bodily material) and facilitating donation [15]. Such a stewardship role should extend to taking action to remove inequalities that affect disadvantaged groups or individuals with respect to donation. Equity in donation refers to the absence of systematic disparities in the burden of donation between social groups who have different levels of underlying social advantage/disadvantage (i.e. different positions in a social hierarchy). Inequities in donation would, in a systematic manner, put groups of people who are already socially disadvantaged (e.g. by virtue of being poor, female and/or members of a disenfranchised racial, ethnic or religious group) at further disadvantage with respect to their health.

As discussed above, introduction of financial incentives for donation renders certain social groups particularly susceptible to disparities based on social and economic status.

Safeguards must be in place to guarantee that all living donors, regardless of their origin, receive similar care and follow-up. To prevent the abuse of donors coming from abroad, clear traceability arrangements must be in place to ensure that an initial evaluation of the donor has been undertaken by the referring hospital, that free and specific consent to the donation has been given and that long-term follow-up care can be provided.

1.4.6. Anonymity

The identity of the donor and recipient should (except in the case of living donation between persons having a close personal relationship) be maintained in strict confidentiality. Such precautions will prevent abuse and protect the families of donors and recipients from feelings of anxiety associated with emotional involvement, obligation to return favours or guilt.

1.4.7. Transparency and protection of personal rights

The organisation and execution of donation and transplantation activities, as well as their clinical results, must be transparent and open to scrutiny, while ensuring that the personal anonymity and privacy of donors and recipients is always protected (if relevant).

Transparency can be achieved by maintaining public access to regularly updated comprehensive

data on processes (in particular, allocation), transplant activities and outcomes for both recipients and living donors, as well as data on organisation, budgets and funding. Such transparency is not inconsistent with shielding (from public access) information that could identify individual donors or recipients, while still respecting the requirement of traceability. The objective of the system should be not only to maximise the availability of data for scholarly study and governmental oversight but also to identify risks (and facilitate their mitigation) to minimise harm to donors and recipients.

1.5. Recommendations and regulations in the field

1.5.1. Council of Europe

Within the framework principle of sharing knowledge through international co-operation, the Council of Europe has established widely recognised recommendations and resolutions in the field of transplantation covering the ethical, social, scientific and training aspects of the donation and transplantation of organs, tissues and cells [17]. Whereas agreements and conventions are binding on the states that ratify them, resolutions and recommendations are policy statements to governments that propose a common course of action to be followed.

The Council of Europe Convention for the Protection of Human Rights and Fundamental Freedoms (European Treaty Series, No. 5) [18] is an international treaty to protect human rights and fundamental freedoms in Europe. It was drafted in 1950 by the then newly formed Council of Europe and entered into force on 3 September 1953.

The European Agreement on the Exchange of Therapeutic Substances of Human Origin (European Treaty Series, No. 26) [19], signed in Paris on 15 December 1958, aims to provide mutual assistance with respect to the supply of therapeutic substances of human origin.

The European Agreement on the Exchange of Tissue-Typing Reagents (European Treaty Series, No. 84) [20], signed in Strasbourg on 17 September 1974, laid the groundwork for the development of mutual assistance in the supply of tissue-typing reagents and establishment of joint rules between signatory parties.[2] The Additional Protocol (European Treaty Series, No. 89) [21], opened for signature on 24 June 1976 and which entered into force on 23 April 1977, provides for the accession of the European Community (now the EU) to this agreement.

The Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (European Treaty Series, No. 164) [10] was opened for signature on 4 April 1997 and came into force on 1 December 1999. It is the first legally binding international text designed to preserve human dignity, fundamental rights and freedoms, through a series of principles guarding against the misuse of biological and medical applications. The Convention is inspired by the principle of the primacy of human beings over the sole interest of science or society. It lays down a series of principles applying to medical practice as well as biomedical research, organ transplantation and genetics. The Convention includes the principle of consent, non-discrimination on the basis of genetic characteristics, and protection of private life and access to information. The Convention specifically prohibits financial gain arising from the body and its parts, as such.

This latter Convention was extended further by an Additional Protocol to the Convention on Human Rights and Biomedicine concerning transplantation of organs and tissues of human origin (European Treaty Series, No. 186) [11], which was opened for signature on 24 January 2002 in Strasbourg and came into force on 1 May 2006. This Additional Protocol aims to protect the dignity and identity of everyone and to guarantee, without discrimination, respect for his/her integrity and other rights and fundamental freedoms with regard to transplantation of organs and tissues of human origin, thereby establishing principles for the protection of donors and recipients.

The Council of Europe Convention on Action against Trafficking in Human Beings, with its Explanatory Report (European Treaty Series, No. 197) [22], which was opened for signature in Warsaw on 16 May 2005 and came into force on 1 February 2008, addresses the trafficking of human beings for the purpose of organ removal.

The Joint Council of Europe/United Nations Study on trafficking in organs, tissues and cells and trafficking in human beings for the purpose of the removal of organs [3], presented at the United Nations headquarters in New York on 13 October 2009, focuses on trafficking in organs, tissues and

2. The CD-P-TO carefully examined at its 14th meeting (Rome, 9-10 October 2014) the European Agreement on the Exchange of Tissue-Typing Reagents and decided that, considering the state-of-the-art advances in the field of tissue-typing, this Treaty should be declared inactive without further need for promotion or monitoring by the CD-P-TO.

cells for the purpose of transplantation. The Joint Study made evident that existing criminal-law instruments dealing exclusively with trafficking in human beings (including for the purpose of organ removal) left loopholes that allowed several unethical transplantation-related activities to persist. This is why the Council of Europe decided to undertake the task of drafting a new international legally binding instrument against trafficking in human organs.

The Council of Europe Convention against Trafficking in Human Organs [16] and its Explanatory Report [23], which opened for signature in Santiago de Compostela on 25 March 2015, identifies distinct activities that constitute 'trafficking in human organs'. The central concept is 'the illicit removal of organs', which consists of removal without the free, informed, and specific consent of a living donor; removal from a deceased donor other than as authorised under domestic law; removal when, in exchange, a living donor (or a third party) has been offered or received a financial gain or comparable advantage; or removal from a deceased donor when a third party has been offered or received a financial gain or comparable advantage.

The document *Organ shortage: current status and strategies for the improvement of organ donation – a European consensus document* (2003) [24] aims to provide a step-by-step guide to the most effective ways of procuring the maximum number of high-quality organs for transplantation from deceased donors, based on an analysis of the scientific data available and relevant international experience.

Other major Council of Europe resolutions and recommendations [25] in the field of organ donation and transplantation include:

- Resolution CM/Res (78) 29 on harmonisation of legislations of member states relating to removal, grafting and transplantation of human substances [12], recommending the governments of member states to conform their laws to a set of rules annexed to this resolution or to adopt provisions conforming to these rules when introducing new legislation.
- Recommendation No. (97) 15 of the Committee of Ministers to member states on xenotransplantation [26], recommending governments of member states to establish a mechanism for the registration and regulation of xenotransplantation with a view to minimising the risk of transmission of known or unknown diseases and infections to either human or animal populations.
- Recommendation No. (97) 16 of the Committee of Ministers to member states on liver transplantation from living related donors [27], providing rules and guidelines for carrying out transplantations using livers derived from living donors related to the recipients of those organs.
- Recommendation Rec (2001) 5 of the Committee of Ministers to member states on the management of organ transplant waiting lists [28], providing rules and guidelines for the creation, management and enrolment of patients in organ transplant waiting lists.
- Recommendation Rec (2003) 10 of the Committee of Ministers to member states on xenotransplantation [29] and its Explanatory Memorandum [30], providing principles and guidelines for governments to set up their own legislation and practice in the field of xenotransplantation, with a view to minimising the risk of transmission of known or unknown diseases and infections to populations.
- Recommendation Rec (2003) 12 of the Committee of Ministers to member states on organ donor registers [31], providing rules and guidelines for the creation, purpose, management, characteristics and enrolment of persons in organ donor registers.
- Recommendation Rec (2004) 7 of the Committee of Ministers to member states on organ trafficking [32], providing a list of requirements to protect the dignity and identity of all persons and to guarantee without discrimination their fundamental rights and freedoms with regard to organ, tissue and cell donation (both living and deceased) and transplantation.
- Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities [33], providing guidelines to governments to ensure they provide high-quality transplant services for the benefit of their citizens.
- Recommendation Rec (2005) 11 of the Committee of Ministers to member states on the role and training of professionals responsible for organ donation (transplant donor co-ordinators) [34], providing guidelines and recommendations to governments of member states as regards the role, functions, responsibilities and training of the donor co-ordinators who should be appointed in every hospital with an intensive care unit.
- Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities

of an NTO [9], recommending governments of member states to set up comprehensive national transplantation systems with competencies and mechanisms to organise and oversee the entire process of transplantation, including: public education on transplantation; organ (and tissue/cell) donation and recovery; national transplant recipient waiting lists; organ (and tissue/cell) allocation; organ (and tissue/cell) transportation, including international exchanges; authorisation of organ transplant teams or institutions; the traceability of organs and tissues; and monitoring of the outcomes of transplantation and donations from living donors. Other NTO competencies may include research into transplantation and responsibility for identifying and reporting to the relevant authorities any breaches of national transplantation law.

- Recommendation Rec (2006) 16 of the Committee of Ministers to member states on quality improvement programmes for organ donation [35], recommending that the governments of member states take all necessary measures to ensure that quality improvement programmes for organ donation are put in place in every hospital where there is potential for organ donation, and providing guidelines for their creation, implementation and management.
- Resolution CM/Res (2008) 4 on adult-to-adult living donor liver transplantation [36], recommending that member states instruct the organisation responsible for accrediting transplantation programmes and regulating the allocation of organs to explicitly address the issue of adult-to-adult living donor liver transplantation and to establish accredited transplantation programmes for the performance of this type of transplantation, in compliance with strict quality, safety and ethical parameters.
- Resolution CM/Res (2008) 6 on transplantation of kidneys from living donors who are not genetically related to the recipient [37] provides general principles and measures to be taken into account when establishing regulations and procedures relating to the donation of a kidney for transplantation by a living donor not genetically linked to the recipient.
- Resolution CM/Res (2013) 55 on establishing procedures for the collection and dissemination of data on transplant activities outside a domestic transplantation system [38], recommends member states to adopt and implement appropriate tools for data collection on illicit transplantation activities.
- Resolution CM/Res (2013) 56 on the development and optimisation of live kidney donation programmes [39] and its Explanatory Memorandum [40] recommend member states to foster programmes for kidney donation from live donors based on recognised ethical and professional standards.
- Resolution CM/Res (2015) 10 on the role and training of critical care professionals in deceased donation [41] recommends member states to provide a clear legal and ethical framework that will: guide healthcare professionals caring for potential organ donors; help ensure that professionals working in intensive care units and emergency departments receive continuous training from the outset of their clinical practice; encourage hospitals to incorporate organ donation as a routine activity in intensive care units and emergency care departments by appointing designated professionals in these areas where there is a potential for organ donation; and support the development of scientific and health services research in the field of donation after death.
- Resolution CM/Res (2015) 11 on establishing harmonised national living donor registries with a view to facilitating international data sharing [42] sets out the general guidelines for the construction of such national/international registries. In addition, the Explanatory Memorandum [43] accompanying this resolution provides a detailed list of the parameters intended for inclusion in any national living donor registry, defining a mandatory data set and an expanded set of variables, as well as those to be included in a 'Registry of registries' aimed at international data sharing.
- Resolution CM/Res (2017) 1 on principles for the selection, evaluation, donation and follow-up of non-resident living organ donors [44], is a new resolution, elaborated by the European Committee on Organ Transplantation (CD-P-TO). It is aimed at protecting non-resident living donors who, for a number of reasons – economic, emotional, cultural or physical – may be particularly vulnerable, and whose post-donation care and follow-up may be difficult to guarantee.
- Resolution CM/Res (2017) 2, on establishing procedures for the management of patients having received an organ transplant abroad upon return to their home country to receive

follow-up care [45], is also a new resolution. It aims to protect all patients who have received an organ transplant, regardless of the circumstances in which it was obtained, and it also aims to safeguard public health by recommending that all patients undergoing organ transplantation are systematically registered in national transplant records.

Monitoring of practices in member states has become an evident need for the sake of transparency and international benchmarking. Keeping this goal in mind, since 1996 the EDQM/Council of Europe has published the *Newsletter Transplant* [2], which is co-ordinated by the Organización Nacional de Trasplantes (ONT) in Spain. This publication summarises comprehensive data provided by national focal points, designated by governments, on donation and transplantation activities, management of waiting lists, organ-donation refusals and authorised centres for transplantation activities. *Newsletter Transplant* provides information from ≈ 70 countries, including Council of Europe member states, observer countries and observer networks (e.g. the Iberoamerican Donation and Network Council on Organ Donation and Transplantation, the Mediterranean Network). The *Newsletter Transplant* database is connected with other international projects on data collection (e.g. the WHO Global Observatory on Organ Donation and Transplantation, the Eurocet database of the European Registry for Organs, Tissues and Cells) to avoid duplication of efforts. *Newsletter Transplant* has evolved into a unique official source of information that continues to inspire policies and strategic plans worldwide.

The Council of Europe also produces other guidelines, including this 7th edition of the *Guide to the quality and safety of organs for transplantation*, the 3rd edition of the *Guide to the quality and safety of tissues and cells for human application* and the 19th edition of the *Guide to the preparation, use and quality assurance of blood components* [4].

1.5.2. World Health Organization

In 1987, the 40th World Health Assembly, concerned about the trade for profit in human organs, initiated the preparation of the first WHO Guiding principles on transplantation, endorsed by the Assembly in 1991 through Resolution WHA44.25 [46]. These guiding principles have greatly influenced professional codes and practices, as well as legislation, around the world for almost two decades. After a consultation that took several years, on 21 May 2010 the 63rd World Health Assembly adopted Resolution WHA63.22 [47], which endorsed the updated WHO Guiding principles on human cell, tissue and organ transplantation [13] and called on WHO member states to implement these guiding principles, promote voluntary and unremunerated donation, oppose trafficking, and promote transparent and equitable allocation. It also urged its members to strengthen oversight, to collect and publish activity data, including adverse events and reactions, and to implement globally standardised coding. These guidelines are intended to provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes.

The World Health Assembly adopted Resolution WHA57.18 [48] in 2004, which urged WHO member states 'to take measures to protect the poorest and vulnerable groups from transplant tourism and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs'. Robust bi-directional donor–recipient traceability is a prerequisite to achieving effective vigilance and surveillance worldwide. For this reason, Resolution WHA63.22 [47] also urged WHO member states to collaborate in collecting data (including adverse events and reactions) in addition to implementation of globally consistent coding systems. The NOTIFY project was a specific follow-up action that was led by the WHO to promote the sharing of information on adverse incidents for improving safety and efficacy [49].

As a result of resolutions WHA57.18 and WHA63.22 (which requested that global data on the practice, safety, quality, efficacy and epidemiology of transplantations be collected in the WHO member states that have transplantation programmes), an international watchdog on transplantation was set up as a collaborative initiative between the Spanish ONT and WHO, and was termed the Global Observatory on Donation and Transplantation [1]. The universal availability of these data is recognised as a prerequisite for global improvements in demonstrating transparency, equity and compliance, and for monitoring national systems. In addition, the data provided also help to give an overview of the legal and organisational aspects in very different settings and countries, which enables the regulating bodies to monitor transplantation activities.

The WHO has also published two *aides-mémoire* specifically on the donation and transplantation of tissues and cells [50-51].

In recent years, the WHO has been promoting use of the term 'medical products of human origin'

(MPHO). This category includes blood, organs, tissues, bone marrow, cord blood, reproductive cells and milk derived from humans for therapeutic use. Use of these MPHO, obtained from living and deceased donors, entails practical, scientific and ethical considerations.

1.5.3. European Union

The EU is an economic and political union of 28 member states that are located in Europe, together with candidate countries and associated countries. The EU operates through a system of European institutions (including the European Commission, the Council of the European Union and the European Parliament) and intergovernmental decisions negotiated by the member states. In the field of organs, but also tissues and cells and blood, the Council of Europe (EDQM) and the European Commission [52] have a standing collaboration aimed, among other objectives, at avoiding duplication of efforts and at increasing the dissemination and exchange of knowledge and expertise.

Acknowledging that organ transplantation is an expanding medical field that offers important opportunities for the treatment of organ failure, the EU aims for a common approach to regulation across Europe.

Article 168 of the Treaty on the Functioning of the European Union [53] (previously Article 152 of the Treaty of Amsterdam) gives the EU a mandate to establish high quality and safety standards for substances of human origin, such as blood, organs, tissues and cells.

Directive 2010/53/EU of the European Parliament on standards of quality and safety of human organs intended for transplantation [54] was adopted on 7 July 2010 (see Corrigendum [55] to the Directive). This directive clearly states that 'Member States shall ensure that donations of organs from deceased and living donors are voluntary and unpaid'. It provides for the appointment of Competent Authorities in all member states, for the authorisation of procurement and transplantation centres and activities, for the establishment of traceability systems, and for the reporting of serious adverse events and reactions. Moreover, the directive sets requirements for the safe transportation of organs and for the characterisation of every donor and organ. More specifically, for human organs exchanged between EU member states for transplantation purposes, Commission Implementing Directive 2012/25/EU was adopted on 9 October 2012 to lay down information procedures [56]. This directive refers only to organs exchanged across borders and does not cover patients travelling to another country for transplantation purposes, which should only be done in the strict framework of bilateral or multilateral co-operation agreements between member states and/or organ exchange organisations.

The EU [57] has addressed three different challenges in the field of organ donation and transplantation in the European setting: increasing organ availability, enhancing quality and safety, and making transplantation systems more accessible. It has done this by supporting its member states in their efforts to implement Directive 2010/53/EU and the Commission's Action Plan on Organ Donation and Transplantation (2009-2015): Strengthened Cooperation between Member States [58]. To mark the mid-term period of the action plan, EU member states adopted in December 2012 the conclusions of the Council of the European Union on organ donation and transplantation [59], recalling the main principles and objectives. In addition, based on the Actor Study [60], the Commission issued a document where efforts at national and European levels were mapped [61].

Aimed at improving co-operation between EU member states in this field, several projects have been funded by the European Commission under the Research Programme – 6th and 7th Framework Programmes, Horizon 2020 – and under the (Public) Health Programmes run by the Consumers, Health, Agriculture and Food Executive. Some of these projects [62] are:

- Alliance-O [63] (European Group for Co-ordination of National Research Programmes on Organ Donation and Transplantation, 2004-2007, FP6): the objective of this project was to ensure co-ordination of national research programmes in the field of organ transplantation for the seven countries involved.
- Dopki [64] (Improving Knowledge and Practices in Organ Donation, 2006-2008, FP6): this project sought to improve organ donation rates. Researchers developed a methodology to determine the potential for donation and its likely outcome. The project produced indicators to be used to benchmark organ donation potential; it also defined risk levels in the donor evaluation process, produced actions to improve organ donation rates (and, thus, increase organ transplant activity) and developed recommendations about organ donation to be used by European healthcare policy-makers.
- Eulod [65] (EUropean Living Organ Donation, 2010-2012, FP7): this project focused on living organ donation as a complementary

approach to bridge the gap between demand for and supply of organs. Living organ donation presents opportunities, but it also involves ethical, legal and psychosocial implications. As a response to these challenges, this project was set up to increase collaboration between EU member states in order to improve the exchange of best practice on living organ donation programmes.

- Project EDD [66] (European Donation Day, 2009-2011) aimed to develop guidelines for organising European organ donation days. The EDD celebration is envisaged as becoming the primary awareness-raising 'voice' for events promoting organ and tissue donation and transplantation in Europe. The main goal of this project was to propose tools and examples to help in the organisation of such events.
- Efretos [67] (European FRamework for the Evaluation of Organ TransplantS, 2009-2011): the general objective of this project was to provide a common definition of terms and a methodology to evaluate the results of transplantation by promoting a compendium of follow-up registries. In the long term, a Europe-wide registry could enable the monitoring of patients and the evaluation of transplant results, and lead to a more efficient and safer organ allocation system.
- The Elpat Conferences [68] (Ethical, Legal and Psychosocial Aspects of Transplantation), organised by this section of the European Society for Organ Transplantation, were also supported by the European Commission in 2003, 2007 and 2010.
- Eulid [69] (EUropean LIving Donation and Public Health, 2008-2010) and Elipsy [70] (European LIving Donor – PSYchosocial Follow-up, 2010-2012) were projects led by the same consortium as the Lidobs Conference [71] (LIving Donor OBServatory, 2014): the main objective of these two projects and the conference was to make recommendations about adequate legal and ethical frameworks, living donor protection practices and long-term psychosocial and quality-of-life follow-up of living donors. It also aimed at creating tools and standardising protocols for the follow-up of living donors throughout Europe, to guarantee their health and safety.
- Etpod [72-73] (European Training Program on Organ Donation, 2009): this project designed a professional European training programme on organ donation at different levels of involvement, in order to increase knowledge about organ donation, to maximise the rate of organ donation and to disseminate reliable information to the EU community.
- Transplant Co-ordinators 'Train the Trainers' course (2010-2011): the European Commission encourages its member states to appoint and train donor co-ordinators in all hospitals where there is potential for organ donation. To help achieve this objective, the Commission contracted a consortium formed by Iavante and the Spanish ONT to train 80 donor co-ordinators from all of its member states, and to provide them with the necessary knowledge to replicate this training at a national level.
- Odequs [74] (Organ Donation European QUality System, 2011-2013) created useful evaluation tools to increase the efficiency of organ donation in all European countries. Differences among countries in national donation rates and in the effectiveness of donation programmes can be partly explained by the type of donation programmes implemented, but other issues – such as the structure of their donation services, their efficiency and social factors – have a big impact. The main objective of the project was to define a methodology to assess the performance of organ procurement at hospital level, including an audit system.
- Coorenor [75] (COORdinating a European initiative among National ORganisations for organ transplantation, 2010-2012) established a co-ordinated network between existing national programmes in the field of organ transplantation, taking into account some major issues such as deceased donation, living donation and organ exchange.
- The joint action Mode [76] (Mutual Organ Donation and Transplantation Exchanges, 2010-2011) aimed at improving and developing deceased organ donation and transplantation programmes. The project targeted the transfer of best practice and the creation of positive synergies among participating EU member states to support authorities in decision-making and policy contexts. The main issues tackled were donation/transplantation laws, transplant activities, brain death diagnosis and quality programmes for donation/transplantation, traceability, structures and organisational networks.
- The joint action Accord [77] (Achieving Comprehensive Coordination in ORgan Donation throughout the European Union, 2012-2015)

aimed at improving co-operation between intensive care units and donor co-ordinators to facilitate deceased donation, proposing guidance and tools for the development of national and supranational living donor registries, and exchanging best practice through twinning activities.
- The joint action Foedus [78] (Facilitating Exchange of Organs Donated in EU Member States 2013-2016) focused on facilitating collaboration on organ donation between national authorities in the EU. An IT tool was developed to enable quick organ offers or urgent requests between countries.
- Edith [79] (2017-2019) is a project co-financed by the European Commission that aims to assess the different treatments for end-stage kidney disease currently used across the EU and to examine the factors that influence the different treatment choices. Edith supports the establishment of follow-up registries in order to collect crucial information that can help to improve the quality and safety of living donors and all transplant recipients.

Some projects funded by the EU in the field of tissues and cells, addressing inspection standards or vigilance and safety, were also relevant to the field of organ transplantation, such as:
- Eustite [80] (EUropean Standards and Training in the Inspection of Tissue Establishments) and
- SoHO V&S [81] (Vigilance and Surveillance of Substances of Human Origin).

Finally, organ transplantation research has also been supported in successive EU framework programmes for research and innovation, including the projects BIO-DrIM (BIOmarker-Driven personalised immuno-suppression) [82], Cope (Consortium on Organ Preservation in Europe) [83] and HepaMAb (Human monoclonal antibody therapy to prevent hepatitis C virus reinfection of liver transplants) [84], and the ONE Study (A unified approach to evaluating cellular immunotherapy in solid-organ transplantation) [85]. All these projects have strengthened collaboration among national health authorities and between these latter and the professional associations in the area of organ donation and transplantation, allowing continuous input from the field into the regulatory framework and vice versa.

Additionally, to support initiatives outside the EU, some support is also provided in the field via Technical Assistance and Information EXchange (TAIEX) grants [86], managed by the Directorate-General of Enlargement of the European Commission and EU delegations in the different countries. TAIEX supports partner countries with regard to the interpretation, application and enforcement of EU legislation.

1.5.4. Other organisations and associations

Kidney transplant physicians and surgeons met in Amsterdam, the Netherlands, in April 2004 for the International Forum on the Care of the Live Kidney Donor. The objective of the Amsterdam Forum was to develop an international standard of care with a position statement from The Transplantation Society (TTS) on the responsibility of the community towards living kidney donors [87-88]. A subsequent international conference of transplant physicians, surgeons and allied health professionals was held in Vancouver, Canada. The Vancouver Forum was convened under the auspices of TTS and its objective was to develop an international standard of care for live lung, liver, pancreas and intestinal organ donors [89].

The Declaration of Istanbul on Organ Trafficking and Transplant Tourism [14] was adopted in 2008 as an initiative of TTS and the International Society of Nephrology. This declaration emphasises that organ trafficking and transplant tourism should be prohibited because they violate the principles of equity, justice and respect for human dignity. The declaration asserts that transplant commercialism should also be prohibited, because it targets impoverished and otherwise vulnerable donors and leads inexorably to inequity and injustice. Organ trafficking, transplant tourism and transplant commercialism were defined by the declaration, which also provided principles of practice based on those definitions. The Declaration of Istanbul distinguishes transplant tourism from proper travel for transplantation. Travel for transplantation is the movement of organs, donors, recipients or transplant professionals across jurisdictional borders for transplantation purposes. Travel for transplantation becomes transplant tourism if either (a) it involves organ trafficking and/or transplant commercialism, or (b) the resources (organs, professionals and transplant centres) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population.

The European Donation and Transplant Coordination Organisation (EDTCO) is a visible and active section within the European Society for Organ Transplantation (ESOT), intended to deal with all aspects of deceased and living donation, clinical co-ordination and procurement. EDTCO provides

continuous training and education of donor co-ordinators and all other professionals with an interest in the area of donation and procurement. EDTCO promoted the development of the Certification of European Transplant Co-ordinators (CETC) project placed under the auspices of the European Union of Medical Specialists (UEMS) to ensure co-ordinators are offered the possibility of standardised recognition of their knowledge and expertise.

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Chapter 2. Identification and referral of possible deceased organ donors

2.1. Introduction

Through the Madrid Resolution, participants at the 3rd World Health Organization (WHO) Global Consultation on Organ Donation and Transplantation, held in Madrid (Spain) in 2010, called on governments and healthcare professionals to pursue self-sufficiency in transplantation, that is, to comprehensively satisfy the transplantation needs of their patients by using resources from within their own population [1]. Addressing self-sufficiency entails a combination of strategies targeted at decreasing the burden of diseases treatable through transplantation and also targeted at maximising the availability of organs for transplantation, with priority given to donation from deceased donors. Deceased organ donation is an essential component of self-sufficiency. Countries that have achieved the highest transplantation rates – and best access of their patients to transplant therapy – are those with well-established deceased donation programmes [2].

Donation after brain death (DBD) represents the main source of solid organs from deceased donors. However, the persisting shortfall in the availability of organs that are needed to satisfy the transplantation needs of patients has prompted many countries to re-introduce programmes of donation after circulatory death (DCD). DCD donors already represent 16% of all deceased organ donors reported to the Global Observatory on Donation and Transplantation (2015 data), even though this activity is developed only in a limited number of countries because of legal, organisational and technical constraints specific to this type of donation [3].

Donation from DBD and DCD donors is a complex process, a sequence of procedural steps which must be properly realised to achieve successful organ transplantation, although the process may be structured in various ways. The Madrid Resolution yielded a list of practical recommendations for self-sufficiency in transplantation and the publication of the WHO Critical Pathway for Deceased Donation, classifying organ donors on the basis of the subsequent phases of the deceased donation process [4]. The Madrid Resolution further stated that, in pursuing self-sufficiency in transplantation, donation should be included as a consideration in every end-of-life care pathway. This recommendation is consistent with the generally accepted principle that the treating physician or team should respect the overall best interests of the dying patient in the decision-making process at the end of life [5]. This assessment of best interest is not based simply on the patient's medical or clinical interests, but should include a more holistic approach, where the patient's other values, beliefs and preferences are also taken into account, including their wishes to donate (or not donate) their organs after their death [6-8].

Although some aspects of deceased donation are similar in both DBD and DCD, there are also important differences between the two, and DCD poses some very specific challenges. The identification and subsequent referral of organ donors by treating phy-

sicians, usually from intensive care units (ICUs) or emergency departments, to the donor co-ordinator or the staff of the corresponding organ procurement organisation (OPO) is the first and most crucial step of the deceased donation process. In both DBD and DCD pathways, organ donation cannot take place unless possible donors are identified and referred in a timely fashion, marking the beginning of both organ donation pathways. Failure to identify and refer organ donors is in fact one of the main reasons for substantial differences in deceased donation rates between countries, regions and hospitals [9].

This chapter describes and structures the process of donation after death, both DBD and DCD, from the perspective of the WHO Critical Pathway for Deceased Donation [4]. It addresses changes in end-of-life care practices that can affect the pool of potential organ donors, and it then focuses on the steps of donor identification and referral. Recommendations for ways to succeed in the subsequent phases of the deceased donation process are provided in other chapters of this guide.

It should be noted that every organ donor can also be a tissue donor. For specific recommendations about tissue donation, refer to the *Guide to the quality and safety of tissues and cells for human application*.

2.2. Types of deceased donor based on the criteria used to determine death

There are two deceased organ donation pathways, depending on the criteria used to determine death before the recovery of organs: DBD and DCD.

DBD refers to donation from persons who have been declared dead based on the irreversible loss of neurological functions. Confirmation of death must comply with national legal requirements. Legislation related to the determination of death by neurological criteria varies from country to country, and determination of death must be undertaken in strict compliance with national protocols and guidelines.

DCD refers to donation from persons who have been declared dead using circulatory criteria. Depending on the clinical scenario in which cardiac arrest occurs, there are four different categories of DCD donors, first described in Maastricht (Netherlands) in 1995 and updated in Paris (France) in 2013 (see Table 2.1) [10-11]. Categories I and II describe donors whose death has occurred following an unexpected cardio-respiratory arrest – uncontrolled DCD (uDCD) donors – while category III describes donation from persons whose death has resulted from the planned withdrawal of life-sustaining therapy (WLST) – controlled DCD (cDCD) donors. Category IV may be controlled or uncontrolled, depending on whether the circulatory arrest in a person with a suspected or confirmed brain death (BD) condition was sudden or planned (after BD diagnosis, but before organ recovery).

DCD is practised in a limited number of countries. Some countries perform donation only from selected categories of DCD donors. The determination of death based on circulatory criteria also varies across countries, e.g. with regard to the period of observation required following the cardio-respiratory arrest. Detailed information on DCD practices is provided in Chapter 12.

Table 2.1. **Donation after circulatory death: categories of donor**

Maastricht category and type of donation after circulatory death (DCD)	**Observations**
I: Found dead (uncontrolled) I.a: out of hospital I.b: in hospital	Sudden unexpected cardiac arrest, with no attempt at resuscitation by a medical team
II: Witnessed cardiac arrest (uncontrolled) II.a: out of hospital II.b: in hospital	Sudden unexpected irreversible cardiac arrest, with unsuccessful resuscitation by a medical team
III: Withdrawal of life-sustaining therapy (controlled DCD)*	Planned, expected cardiac arrest, following the withdrawal of life-sustaining therapy
IV: Cardiac arrest while brain dead (uncontrolled or controlled)	Sudden or planned cardiac arrest after diagnosis of brain death, but before organ recovery

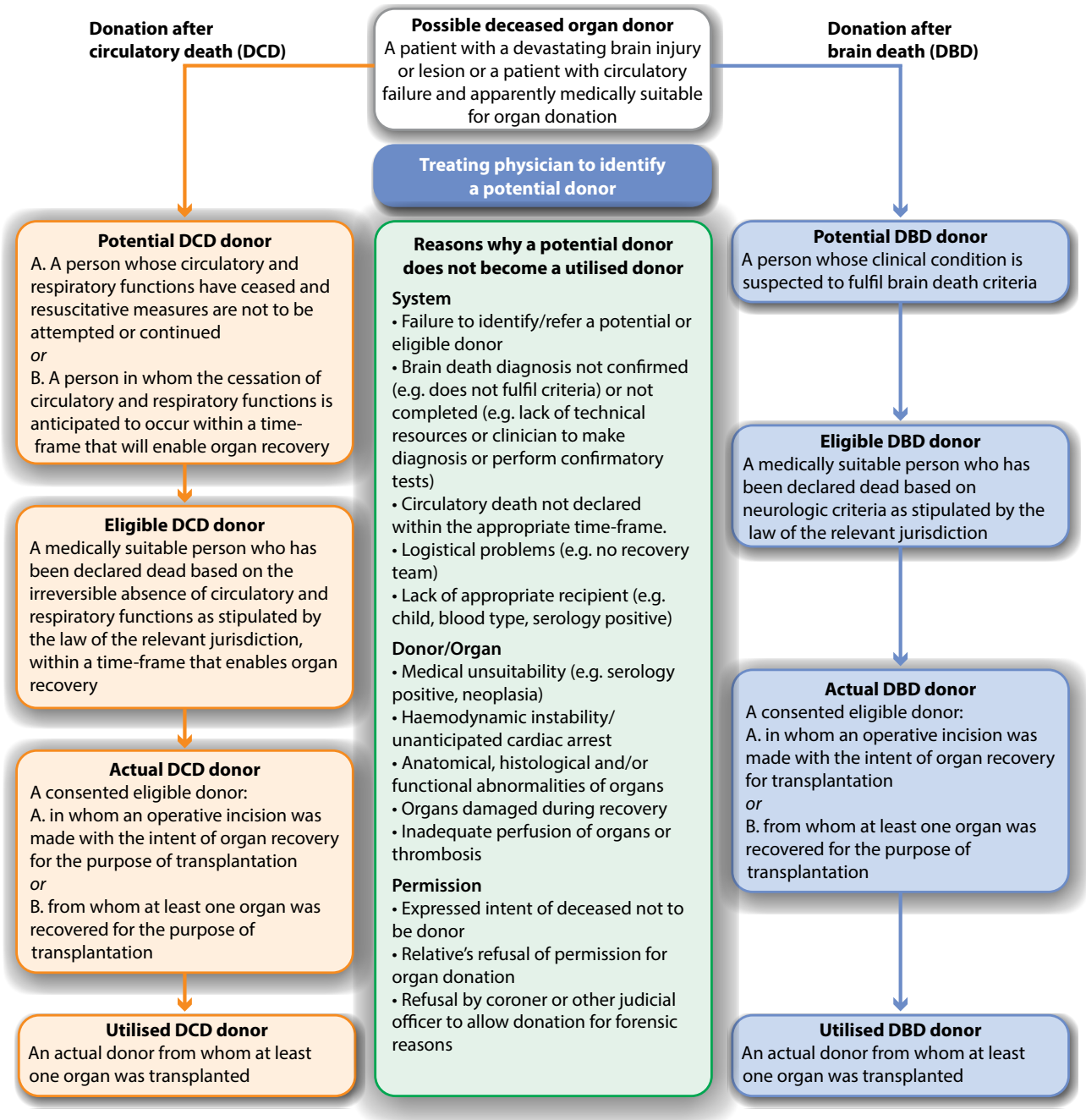
Modified Maastricht classification, Paris 2013 [11].

* This category III mainly refers to the decision to withdraw life-sustaining therapies. Legislation in some countries allows euthanasia (medically-assisted cardiac arrest), and subsequent organ donation is described as an additional category.

2.3. The process of deceased donation: the WHO Critical Pathway

The WHO Critical Pathway for Deceased Donation [4] was conceived as a useful clinical tool applicable to every country (region or hospital) for assessing the potential of deceased organ donation, evaluating performance in the deceased donation process and identifying areas for improvement. The particular value of this tool is that it creates uniformity in the description and assessment of the deceased donation process. The Critical Pathway for Deceased Donation addresses both DBD and DCD, and defines types of donors based on the different phases of the donation process: possible, potential, eligible, actual and utilised organ donors (see Figure 2.1).

Figure 2.1. **The World Health Organization critical pathways for deceased donation**



The 'dead donor rule' must be respected. That is, patients may become donors only after death, and the recovery of organs must not cause a donor's death.

Adapted with permission from *Transpl Int* 2011;24(4):373-8 [4].

2.3.1. Possible deceased organ donors

A possible deceased organ donor is a patient with a devastating brain injury (DBI) or lesion, or a patient with a circulatory failure, who is apparently medically suitable for organ donation. The patient with a DBI is a patient with an imminent risk of death of a neurological origin whose treatment team gives consideration to not initiating or not continuing life-sustaining therapies on the grounds of futility in favour of palliative and end-of-life care. This is frequently a patient already admitted to an ICU and receiving mechanical ventilation, but it can also be a patient in whom the decision has been made not to initiate or continue mechanical ventilation and/or not to admit to the ICU with a therapeutic purpose. Organ donation is possible in this particular scenario if intensive care is initiated or continued despite futility, that is, if intensive care to facilitate organ donation (ICOD) is applied as described in section 2.4.

A patient with circulatory failure is also a possible organ donor. If advanced cardio-pulmonary resuscitation (CPR) in a patient with a sudden cardiac arrest is considered to be unsuccessful, this would represent the starting point of the uDCD process.

The possible deceased organ donor with a DBI as defined above represents the common starting point of the two different pathways for deceased organ donation, DBD and/or DCD, pathways that will be activated depending upon the outcome of the patient's condition, the end-of-life care practices and national legal frameworks.

The WHO Critical Pathway for Deceased Donation identifies the possible organ donor as the ideal starting point for identification and referral of the potential donor by the treating physician to the donor co-ordinator or staff of the corresponding OPO. However, early referral is not considered appropriate or is not legally possible in all jurisdictions, which leads to the need for delay in referral, particularly in DBD, to the point where the person already exhibits clinical signs consistent with BD or to the point where BD has already been declared as per the national standards [1].

2.3.2. Potential deceased organ donors

A potential DBD donor is a person whose clinical condition is consistent with BD. A potential DCD donor is either a person whose circulatory and respiratory functions have ceased and in whom CPR was attempted but was (or is now) considered unsuccessful and not to be continued (potential uDCD donor), or a person in whom CPR will not be attempted and the cessation of circulatory and respiratory functions is expected to occur within a time frame that will enable organ recovery (potential cDCD donor). This last scenario refers to persons with a DBI in whom further treatment has been deemed futile and for whom a decision has been made in favour of WLST [11]. Potential cDCD donors also include patients with end-stage neurodegenerative or cardiac/respiratory diseases for whom a decision of WLST has been made because sustaining life is no longer in the best clinical interests of the patient. Although the majority of actual cDCD donors die from acute brain injury, data from the Netherlands, Spain and the United Kingdom suggest that up to 15% of cDCD donors die from other conditions.

The transition from possible to potential deceased organ donor depends on a variety of factors, particularly the end-of-life care practices in place. The Ethicus study, undertaken by the European Society of Intensive Care Medicine, described the circumstances of death of patients dying in European ICUs [12]. The study revealed that the incidence of BD was significantly higher in southern Europe compared to northern European countries (12.4 v. 3.2%). On the other hand, the percentage of patients who died following WLST was significantly higher in northern Europe, compared with the south (47.4 v. 17.9%). These findings highlight how the practice of WLST when further treatment is considered futile is frequent in northern Europe, but relatively rare in southern Europe. These different approaches to end-of-life care – in the particular context of a patient's death as a result of a DBI (possible organ donors) – were also evident in the ACCORD Joint Action project, which revealed that only a few European countries consider the admission of patients with a DBI into the ICU with the aim of incorporating the option of organ donation into end-of-life care [13].

However, multiple recent studies from different countries have demonstrated that the pool of potential donors is very often incompletely exploited and that the number of actual donors represents a small proportion of the pool of potential donors [14-15]. According to a Spanish study, 2.3% of hospital deaths and 12.4% of deaths in an ICU could yield potential donors, and the number of actual donors could be 21% higher if all potential donors were to be identified and followed up, even in the country with the most effective donation model in the world [16]. In a report from Belgium, the authors found that 57% of deceased potential donors were missed in the donation process due to non-identification, missed referral or lack of consent [9]. Therefore, the major target in efforts to increase the number of organs available for trans-

plantation has to be expansion of the pool of actual donors to include all potential donors in hospitals.

The countries which have comprehensively and successfully overcome each critical step in the process of deceased donation, moving from potential to actual donors, have reached the highest rate of organ donation in the world and made organ transplantation more accessible to their residents [17].

2.3.3. Eligible deceased organ donors

The eligible DBD donor is a medically suitable patient who has been declared dead based on neurological criteria as stipulated by the law of the relevant jurisdiction. An eligible DCD donor is defined as a patient who is medically suitable for organ donation and in whom death has been declared on the basis of circulatory criteria according to national standards. Death should also have occurred within a time frame that enables organ recovery (see Chapter 12).

A potential DBD donor might not become eligible for organ donation because the diagnosis of death by neurological criteria has not been confirmed – e.g. because of a lack of the technical and human resources needed for confirmation. It is worth noting that in some European countries and the USA up to 30 % of patients who exhibit a clinical condition consistent with BD are not tested to confirm the diagnosis, a practice that completely removes the possibility of DBD [12, 18]. In circumstances where BD is not confirmed, cDCD might be activated, but opting for cDCD in place of DBD should be avoided whenever possible.

A potential cDCD donor might not be eligible for organ donation because death by circulatory criteria has not been determined within a time frame that allows organ recovery. cDCD will occur only if the cardio-respiratory arrest follows soon after WLST. This time limit has been most commonly established at 2 hours, but it is being extended in some countries (for example, to 3-4 hours in the United Kingdom), although death following WLST not infrequently occurs beyond this time limit [19].

In the uDCD setting, non-eligibility is frequently determined because of an excessive time to develop the process, which renders organs unsuitable for transplantation due to the deleterious effects of warm ischaemia on organ viability.

Potential donors (DBD or DCD) might also be ineligible because they are considered medically unsuitable. Although there are very few absolute contraindications to organ donation, a perception of medical unsuitability is a frequent reason for not referring potential donors to the donor co-ordinator or staff of the OPO. Moreover, external audits in some countries have revealed that 11 % of the decisions not to refer a potential DBD donor on medical grounds were incorrect [16]. A patient's suitability to donate organs is dependent on recipient factors as well as donor factors, and some organs may be acceptable whereas others may not. The primary role of the team treating the potential donor patient is to identify and refer potential donors, and leave decisions regarding medical suitability for donation to the donor co-ordinator and the relevant transplant teams.

2.3.4. Actual deceased organ donors

An actual DBD and an actual DCD donor are defined in the same manner – as a consenting, eligible organ donor in whom an operative incision has been made with the intention of organ recovery for the purpose of transplantation. An actual deceased organ donor is also defined as a person from whom at least one organ has been recovered for transplantation purposes.

The main reason why organ recovery does not proceed in an eligible organ donor is that consent/authorisation was declined, either by the individual during their lifetime or by their relatives. Consent rates to organ donation are influenced by a variety of factors – both modifiable and non-modifiable. In the Accord Joint Action [13], within a dedicated study undertaken at 67 hospitals from 15 EU member states, 24 % and 33 % of families approached to discuss organ donation declined authorisation for organ recovery, in the DBD and DCD processes respectively. The rate of declined consent for organ recovery in the DBD process was, however, underestimated since the rate referred only to those families approached to discuss organ donation from persons whose death was already confirmed by neurological criteria. The moment when the family is first approached to discuss organ donation has indeed an impact on consent rates [20]. In a Spanish study, consent was more frequent if the family was approached once the patient already fulfilled BD criteria or if the BD diagnosis had been completed, compared with situations when BD was likely but had not occurred yet [21]. These data reveal the more complex communication with the family in the context of ICOD.

2.3.5. Utilised deceased organ donors

Utilised DBD and DCD donors are defined as those actual DBD or DCD donors from whom at least one solid organ has been transplanted.

Once recovered, organs might not be transplanted because of anatomical or histological findings in the donor or in the organs themselves, poor perfusion, organ damage during recovery or lack of suitable recipients, among others. Non-utilisation of actual donors is more frequent in the case of expanded-criteria donors (see Chapter 7) and in DCD in comparison to the DBD process (see Chapter 12). Non-utilisation rates are also higher in uDCD than in the cDCD setting [3].

2.4. Intensive care to enable organ donation

A possible organ donor may be a person with a DBI in whom further therapy is deemed futile, either in the emergency department or in the hospital ward, and for whom admission to an ICU, and even the initiation of mechanical ventilation, is not deemed therapeutically indicated because neither procedure is considered to be in the patient's best clinical interest. In this context, intubation and initiation of mechanical ventilation – that is, elective non-therapeutic ventilation (ENTV) – and admission to an ICU could be considered with the purpose of incorporating the option of organ donation into the end-of-life care of the patient [22].

The potential for organ donation could be therefore considered in patients with a DBI, that is, patients with acute, severe neurological damage and an apparently hopeless prognosis, where the treating team is considering a shift from active treatment to palliative and end-of-life care. In this situation, a patient with DBI and impending death could be considered for ICOD, which may include ENTV and protective organ treatment. In practice, this means admission to the ICU [23]. Candidates for ICOD are mainly identified in the emergency department, but also on hospital wards (neurology, neurosurgery and others). Close collaboration between donor co-ordinators or OPO staff, ICU personnel and professionals from the above-mentioned departments is necessary and thus represents a crucial starting point for the successful realisation of this particular donation practice.

Today, ICOD, inclusive of ENTV or not, is a common clinical practice in most but not all countries [12] since it still raises some ethical, legal, community and professional concerns in some settings [24-26]. What is clear is that ICOD and ENTV result in an increase in the total number of organs available for transplantation, and the combination is of particular interest given the markedly reducing pool of 'standard' DBD donors throughout the world because of the decreased incidence of death from brain trauma and stroke [27-28].

Since ICOD and ENTV are relatively new as successful organ-donation practices, a few details are discussed below.

In patients with a severe neurological injury, a consensus concerning the patient's prognosis and non-treatable condition should be established by an expert multidisciplinary team before ICOD is considered. The decision not to pursue active treatment should be based as much as possible on scientific evidence, expert opinion, clinical experience and the patient's age and co-morbidity; moreover, it should be made on an individual, case-by-case basis [29].

Patients identified as potential candidates for ICOD and ENTV should be immediately referred to the donor co-ordinator or the staff of the corresponding OPO. Early referral allows enough time for the assessment of suitability for donation, reduces the delay for ICU admission and enables a planned approach to the patient's family. Clinical and radiological triggers facilitate possible donor identification and should be developed and recommended by a multidisciplinary expert team for adoption in every hospital with a potential for organ donation. Once referred, patients with a DBI should not be considered candidates for ICOD unless it is likely that BD will occur within a short period of time and the patient has no apparent medical contraindications to organ donation.

Although informed consent for ICOD and ENTV cannot be obtained from a patient with a DBI, these procedures can be considered to be in the patient's best interests if they are consistent with the patient's known moral values and beliefs, including any expressed wish to donate organs after death. Family consent must be obtained before using interventions that are intended to incorporate organ donation into end-of-life care. The patient's relatives must be given clear and understandable information that the prognosis is hopeless either for survival or an acceptable functional outcome, and that ICOD and ENTV are only to be introduced once they have accepted the decision that active treatment will not be pursued. The family should be informed that interventions will be initiated or continued to allow organ donation when the patient deteriorates to BD and that measures will be undertaken to avoid any potential distress, pain and discomfort. The family should be able to revoke their decision at any time. Due to the family's likely initial shock and inability to make decisions, information should be provided in a gradual and progressive manner adapted to the emotional and other needs of the family. These complex communications

with a patient's relatives need to be conducted by highly skilled staff with knowledge and experience in organ donation and in this particular type of interview (see Chapter 4). A large number of patients with DBI will have been intubated in a prehospital setting, facilitating a decision for ICOD while waiting until the patient's and their family's wishes regarding organ donation have been established.

ICOD is not applicable only to patients with a DBI who are outside the ICU but also to dying patients with a hopeless neurological prognosis in the ICU who are not yet brain dead, and in whom the multidisciplinary ICU team has concluded that further invasive therapy no longer has a beneficial therapeutic effect. Although cDCD may be considered in this setting if it is allowed by national legislation, if BD is likely to occur within a short period of time, delaying WLST may be a preferred option to allow the confirmation of death using neurological criteria.

Once consent for ICOD – and ENTV – has been obtained, patients will be subject to mechanical ventilation and somatic organ-protective measures until BD is established and then until the recovery of transplantable organs. Sedation with or without analgesia should be provided to ensure the patient's comfort with drugs and doses that do not interfere with the subsequent BD diagnosis. The majority of possible deceased organ donors subject to ICOD develop BD and fulfil the criteria of potential DBD donors during the first 72 hours following the brain injury [27]. In patients who have not deteriorated to BD about 72 hours following admission to ICU, cDCD may be considered and discussed with the relatives.

The use of ICOD in nearly dead patients solely to preserve their organs for transplantation and to optimise the chance for deceased donation may raise some legal and ethical concerns. In general, however, specific legislation for this practice is absent. The practice of ICOD is currently justified by the legal and ethical considerations of fulfilling the patient's overall best interests including the patient's living will and beliefs, not solely their clinical benefit. The main threat to decisions regarding the use of the medical treatment for organ donation in end-of-life situations must be respect for the patient's individual dignity and autonomy carrying out as far as possible what would have been their wishes if they could express them. The decision-making process regarding medical treatment and the use of some invasive clinical procedures in these circumstances both have to meet the requirements of internationally acknowledged ethical principles, namely autonomy, beneficence, non-maleficence and justice [5]. Moreover, admission of a critically ill patient with DBI to the ICU provides the best opportunity for end-of-life and palliative care, it allows time to establish a safer prognosis and it gives the family the time to adapt to a tragic and unexpected event [30].

From the perspective of using ICU resources for non-curative purposes, the fast deterioration to BD in the majority of patients with DBI means that ICOD does not place unacceptable pressures on ICU capacity. The admission of a dying patient with DBI to the ICU, when end-of-life care and organ donation are being considered, is acceptable due to appreciable community benefit, yielding an average of over seven times in the quality-adjusted life-years (7.3 QALYs) per ICU bed-day compared with the average benefit for ICU patients expected to survive [31]. The family distress caused by the high risk of impending death of their loved one and the application of invasive non-therapeutic interventions can be mitigated by the awareness that this procedure is necessary to meet the desire of their family member and that it might save other lives owing to the organ donation.

Another approach is to avoid early decisions on WLST in the emergency department and to admit all intubated patients with a DBI to the ICU with the primary intention of ensuring the safety of the prognostication, which is virtually always in a patient's best interest [29-30]. These pathways aspire to improve end-of-life care for patients and their families, and also ensure that organ donation is always considered as part of the patient's end-of-life care (see Figure 2.2, Figure 2.3). This approach is similar to, and broadly based upon, that developed for the management of patients with hypoxic brain injury who remain comatose after resuscitation from an out-of-hospital cardiac arrest [32].

2.5. Identification and referral of possible organ donors

Failure to identify and refer organ donors is one of the most important reasons for failure to realise the deceased donation process as described in Figure 2.1 [9]. In the ACCORD project, 35 % of patients who died as a result of a DBI were never referred to the donor co-ordinator or the staff of the OPO, thus immediately ruling out the possibility of organ donation [13].

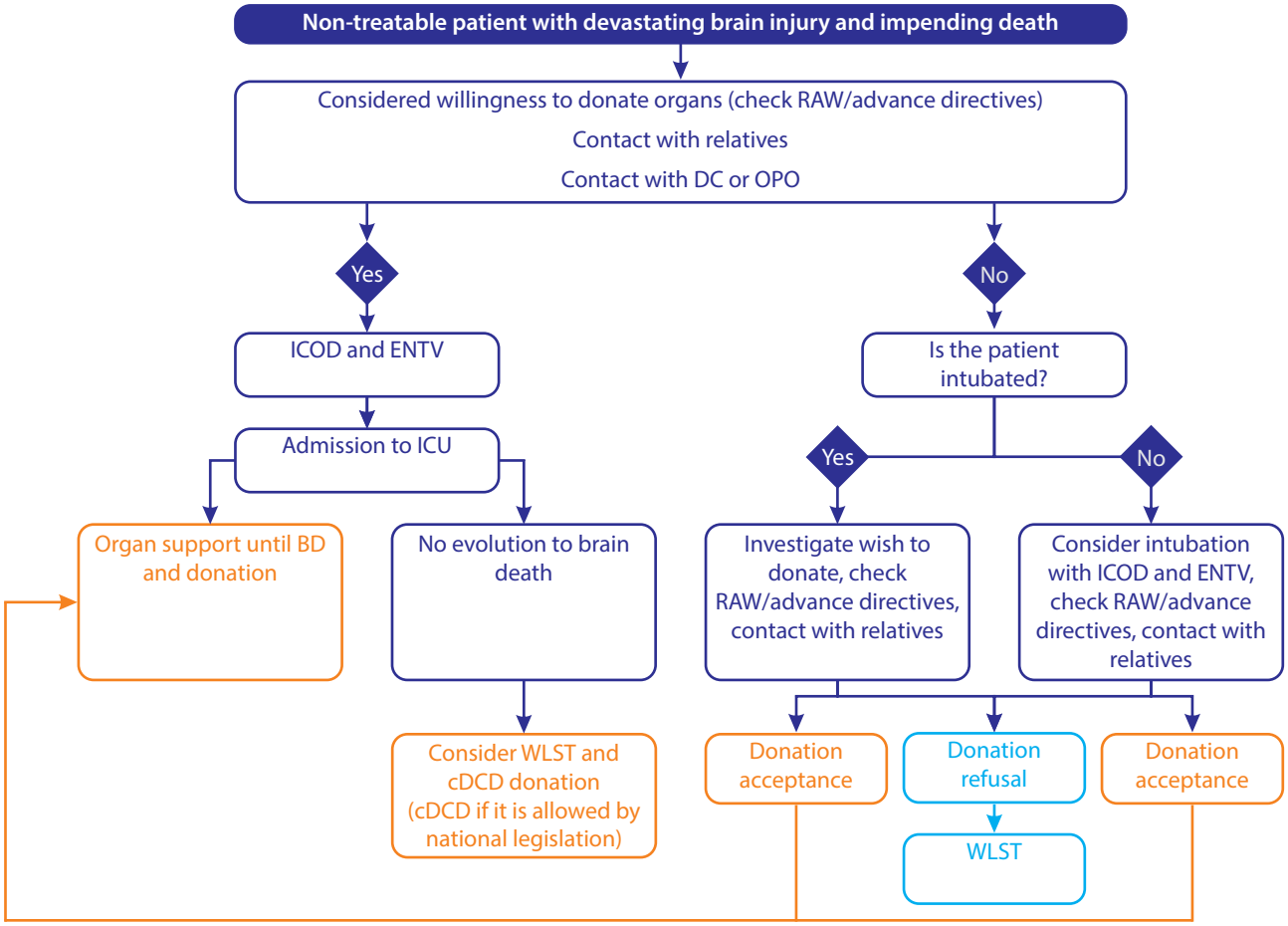
Identification by the treating physicians of opportunities for deceased organ donation, and referral of cases to the donor co-ordinator, can occur at different stages of the (previously defined) WHO Critical Pathway for Deceased Donation. In most European countries there is no consensus on the timing of re-

ferral, and nor are there uniform criteria for donor referral. The stage for referral has been defined only in some national guidelines, with significant variation between countries.

However, if legally possible, referral should ideally occur at an early stage, as soon as the possible organ donor is identified. In general terms this is the point at which a patient's death is considered to be inevitable and imminent, and when the objectives of treatment transition from active therapy to palliative and end-of-life care [6]. Referral can also occur based systematically on a poor prognosis of the patient, even if active medical treatment is to be continued. Referral at this point is considered as a notification rather than a formal referral, and allows donor co-ordinators to be aware of cases for planning purposes, but with no immediate action to be necessarily taken by them. Early referral has many advantages. Assessment of medical suitability for organ donation can begin earlier, which may reduce delays for both the ICU and the donor's family. If needed, expert assistance for BD testing or physiological optimisation of the donor can be provided. Early referral also allows better planning of the family approach and prompt identification and resolution of potential coroner/judicial issues.

Whatever the point at which the decision is taken to communicate a case to the donor co-ordinator, referral should be a routine practice. Donor identification and referral should be underpinned by dedicated protocols, developed at national or local level, that specify clinical triggers for referral, education and training of critical-care professionals and quality-control assessment.

Figure 2.2. **Proposed pathway for clinical decisions regarding initiation of intensive care to facilitate organ donation and elective non-therapeutic ventilation**

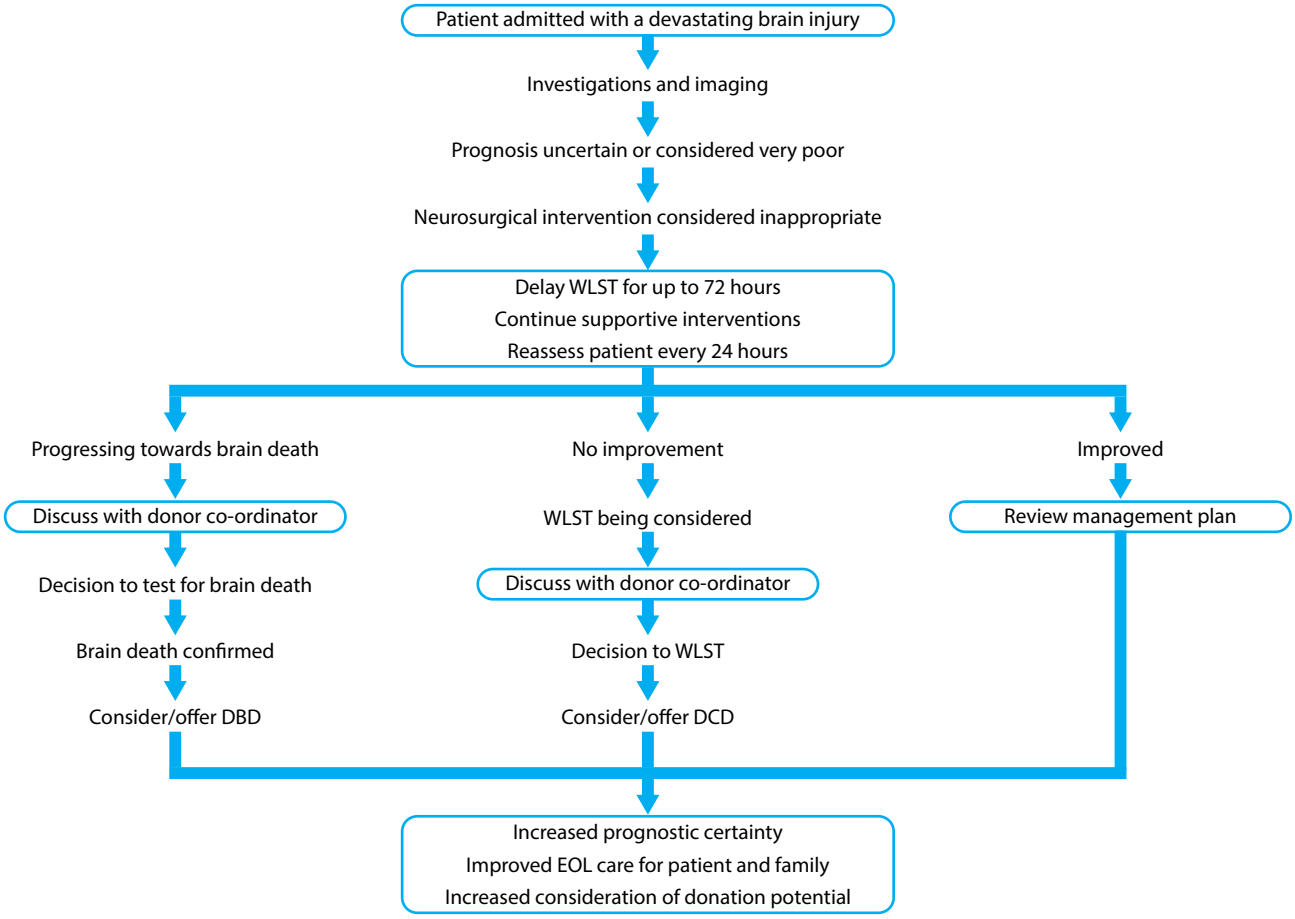


* cDCD: controlled donation after circulatory death, only if it is allowed by national legislation.

BD: brain death; DC: donor co-ordinator; DCD: donation after circulatory death; ENTV: elective non-therapeutic ventilation; ICOD: intensive care to facilitate organ donation; ICU: intensive care unit; OPO: organ procurement organisation; RAW: registry of anticipated willingness; WLST: withdrawal of life-sustaining treatments.

Figure 2.3. **Proposed pathway for the management of patients with devastating brain injuries**

This pathway, with the primary objective of ensuring safe prognostication, also aims to improve end-of-life care and make consideration of organ donation an essential component of the pathway [30].



DBD: donation after brain death; DCD: donation after circulatory death; EOL: end-of-life; WLST: withdrawal of life-sustaining treatments.

2.5.1. Clinical triggers for the identification and referral of deceased organ donors

The specification of clinical triggers in local or national protocols facilitates compliance with the routine referral policy. Clinical triggers take the form of specific clinical criteria which, when met, should result in referral by the treating team. They should be agreed by consensus and developed by an interdisciplinary panel of experts that includes all professionals who care for patients with a DBI (e.g. personnel from ICUs, emergency care departments, neurology and neurosurgery). Clinical triggers should be simple, clearly defined and easy to audit. They should focus on prognostic factors and should lead to referral regardless of a patient's age or co-morbidity, since limiting referral based on age or apparent medical contraindications to donate may lead to a significant number of lost opportunities for organ donation. Clinical triggers should be easily available to critical-care professionals, for example, on simple posters containing the relevant information and located at visible places in critical-care units (see Figure 2.4).

Sections 2.5.1.1 and 2.5.1.2 provide examples of clinical triggers for the referral of DBD and DCD donors. It should be noted that the triggers specified for DBD donors can be also applicable to cDCD donors in cases where the patient with a DBI does not deteriorate to BD and the decision to move to WLST is made.

2.5.1.1. *Clinical triggers for the identification and referral of donors for donation after brain death*

The Glasgow Coma Scale (GCS) is most commonly used to define clinical triggers for referring DBD donors (e.g. GCS < 8). In Croatia, certain scores of different neurological scales, depending on the aetiology of brain injury, are recommended to trigger notification to the donor co-ordinator:

a. For patients with ischaemic brain injury, a National Institute for Health (UK) stroke severity scale ≥ 27 [33];
b. For patients with cerebral haemorrhage, an intracerebral haemorrhage scale [34] or a Hunt–Hess scale [35] ≥ 4;
c. For patients with secondary cerebral anoxia, central nervous system tumours or infections, or severe cerebral trauma, a GCS ≤ 6.

Patients at this stage may still be receiving active treatment. However, according to Croatian guidelines, those patients should be reported as possible donors to the donor co-ordinator [36] (see Table 2.2). It is of the utmost importance to ensure monitoring of brain damage, preferably every hour, and documentation of GCS, size of pupils and reaction to light, brainstem reflexes and spontaneous respiration in the ICU chart – an examination that is in any case a basic standard in ICUs. Patients evolving to a situation consistent with imminent death as defined by de Groot *et al.* must be reported to the donor co-ordinator [37]. Imminent death is defined by a GCS of 3 and the progressive absence of at least three out of six brainstem reflexes or a FOUR score of EoMoBoRo [37-38].

The National Institute for Health and Care Excellence recommendations for the identification and referral of possible organ donors in the United Kingdom are based on the principle that organ donation should be a component of end-of-life care planning, and are incorporated into an NHS Blood and Transplant strategy for implementation of these recommendations [39]. In patients with a catastrophic brain injury, referral is recommended in the absence of one or more brainstem reflexes and a GCS ≤ 4, unless there is a clear reason why the above clinical triggers are not met (for example, because of sedation) and/or a decision has been made to perform BD testing, whichever is the earlier.

In the United States, all hospitals are legally required to refer all imminent deaths to the local OPO. 'Required referral' or 'routine notification' represents a unique practice internationally in terms of being mandatory [40]. A patient with imminent BD is defined as a mechanically ventilated, deeply comatose patient, admitted to an ICU, with irreversible catastrophic brain damage of known origin (e.g. traumatic brain injury, subarachnoid or intracranial haemorrhage). Electronic clinical decision systems can be helpful in this setting [41].

There is an ongoing area of research on clinical and radiological factors to predict progression to BD in patients with a DBI in whom the decision has been made not to treat on the ground of futility. Derived new prognostic scores may become clinical triggers for the referral of possible DBD donors and may support physicians in making difficult decisions on ICOD. In a retrospective analysis of patients with acute stroke and high probability of developing BD in five centres in Lorraine (France), the authors identified six clinical and radiological factors which could form a predictive score of BD in acute phase of severe stroke with high predictive values (score 1 v. score 2: 72 v. 77%). The GCS score ≤ 6 before sedation, stroke volume > 65 mL, presence of herniation and/or hydrocephalus on brain imaging, initial systolic blood pressure > 150 mmHg and history of alcohol abuse represent six different predictive factors of poor prognosis and high probability of progression to BD within 24 h following stroke onset. Taken together, these factors can make a simple score system that can help clinicians at emergency departments, neurological wards or stroke units to more accurately assess patients with severe stroke as possible organ donors and to facilitate discussions with family members about treatment futility and ICOD [42]. Non-contrast computed tomography (CT) appearance of acute extravasation of blood into a cerebral haematoma (swirl sign) and CT angiographic spot sign visible as unifocal or multifocal contrast enhancement within an acute, primary intracerebral haemorrhage both represent sites of active haemorrhage and are independent predictors of early haematoma expansion and poor outcome in patients with intracerebral haemorrhages [43].

Table 2.2. **Clinical triggers for identification and referral of donors for donation after brain death in Croatia**

Clinical triggers	Ischaemic brain injury	Intracerebral haemorrhage	Secondary cerebral anoxia	CNS tumour	CNS infection	Cerebral trauma
Recommended referral	NIHSS ≥ 27	ICHS or Hunt–Hess ≥ 4	GCS ≤ 6			
Required referral	GCS 3 and progressive absence of at least three out of six brain stem reflexes or FOUR score of EoMoBoRo					

Note: CNS: central nervous system; GCS: Glasgow coma scale; ICHS: intra-cerebral haemorrhage scale; NIHSS: National Institute for Health stroke severity scale
Source: Župan Ž. Proposal of the National Strategy for Optimisation of Organ Donation Pathway 2011-2016, Medix 2011 [36].

Some ICD-10 codes are related to potentially devastating cerebral lesions that can lead to BD (see Table 2.3) [13, 44]. Review of this codified data collection (or of the non-codified list of diagnoses of patients at hospital admission or when complications occur) can be used by donor co-ordinators to proactively identify patients at risk of dying as a result of a DBI. Patients with such ICD-10 codes should be monitored. This tool can also be used to evaluate compliance with donor referral, which should be standard practice. In case of non-compliance, the underlying root cause should be identified and efforts be made to educate treating physicians in the routine referral policy.

2.5.1.2. *Clinical triggers for the identification and referral of donors for donation after circulatory death*

cDCD and uDCD donors proceed from very different clinical scenarios that require separate and distinct clinical triggers for identification and referral.

The potential for cDCD should be considered in any critically ill patient in whom a decision of WLST is being considered or has been made because treatment is no longer in the best interests of the patient. Most cDCD donors have suffered a DBI similar to DBD donors, but have not deteriorated to BD. It is always important that the treating physician considers if death by neurological criteria might be determined if supportive treatment is maintained and WLST is delayed. It has been estimated that about 30 % of actual cDCD donors in the United Kingdom had the potential to progress to BD and DBD if the WLST had been delayed by 36 hours [45]. DBD should always be considered preferable to cDCD, since DBD yields a higher number and better quality of organs than DCD. There is a percentage of potential cDCD donors in whom the decision to withdraw treatment is made in the context of end-stage respiratory or neuromuscular disease. An undesired replacement of DBD by cDCD is not a possibility in this particular context.

The possibility of cDCD must always be considered separately from any decision on WLST. Following a decision to withdraw treatment, the patient should be referred to the donor co-ordinator or the OPO to assess suitability for organ donation. This timely referral will avoid unnecessary delays in WLST that may cause distress to relatives of the potential cDCD donor [3]. After the referral, the donor co-ordinator or the OPO should assess any obvious contraindication to DCD. Discussions with the relatives of potential cDCD donors should be initiated by the donor co-ordinator in close co-operation with the treating physician, in a conversation that should be decoupled from that about the decision on WLST (see Chapter 4). Despite different approaches to this topic in various European countries and worldwide, a joint approach to the family by the in-house co-ordinator and the treating physician is ideal and has recently been recommended as the best practice [17, 21].

Figure 2.4. **Poster containing information for the referral of possible donors from the emergency department to the donor co-ordination team**

Developed by E.A. Feller, San Camillo Hospital (Rome, Italy), as part of a cycle for improvement in organ donation during the European Union co-funded project Accord.

The identification of uDCD donors poses a different set of challenges because of the organisational and logistical differences, since this type of donation is activated by identification of an unexpected cardiac arrest unresponsive to advanced CPR that may have occurred either in hospital or outside [49]. Activation of the uDCD process requires carefully planned co-operation between teams in charge of CPR (emergency and ICU) and the donor co-ordination team. Dedicated protocols also specify different selection criteria. Potential uDCD donors should be medically suitable based on similar criteria to those applied in the DBD setting. In addition, some other specific selection criteria must be met and there are limits to the time extending from the cardiac arrest to the initiation of preservation measures (warm ischaemia time).

Recommendations for the identification and referral of potential DCD donors have been devel-

oped in most countries where DCD is standard practice [48-51]. More detailed information is provided in Chapter 12.

Table 2.3. **ICD-10 codes of diseases associated with potentially devastating cerebral lesions related to brain death**

Group of cerebral lesions	ICD-10 code*
Trauma	S02 Fracture of skull and facial bones
	S06.1 Traumatic cerebral oedema
	S06.2 Diffuse brain injury
	S06.3 Focal brain injury
	S06.4 Extradural haemorrhage
	S06.7 Intracranial haemorrhage with prolonged coma
	S06.8 Other intracranial injuries
	S06.9 Intracranial injury unspecified
Cerebrovascular accidents	I60 Subarachnoid haemorrhage
	I61 Intracranial haemorrhage
	I62 Other non-traumatic intracranial haemorrhage
	I63 Cerebral infarction
	I64 Stroke not specified as stroke or infarction
	I65 Occlusion and stenosis of precerebral arteries
	I66 Occlusion and stenosis of cerebral arteries
Cerebral damage	G93.1 Anoxic brain damage
	G93.5 Compression of brain
	G93.6 Cerebral oedema
Cerebral neoplasm	C71 Malignant neoplasm of the brain
	D33 Benign neoplasm of the brain
CNS infections	G00, G01, G02, G03 Meningitis

* In the case of an ICD code with three digits – e.g. G93.1 – all subclassifications should be included.

Sources: Achieving Comprehensive Coordination in Organ Donation through the European Union–Accord Joint Action [13]; Humbertjean L, Mione G, Fay R et al. Predictive factors of brain death in severe stroke patients identified by organ procurement and transplant coordination in Lorraine, France [42].

2.5.2. Training and education

An effective system for the routine identification and referral of organ donors requires close cooperation between healthcare professionals caring for critically ill patients (personnel from ICUs, the emergency department, neurology and neurosurgery community) and the donor co-ordination team or OPO staff. Continuous education and training of these professional groups on the identification of possible organ donors and their timely referral is of utmost importance and supports the dissemination of basic concepts about organ donation. Donor co-ordinators must actively ensure and help to deliver this continuous education and training through various means that must include dedicated courses on a regular basis. The target of these courses should be all medical and non-medical staff from intensive and emergency care units and from other units caring for patients with DBI. The type and duration of these training courses, as well as the frequency of attendance, are to be agreed upon at hospital/regional/national level. Training courses can be organised at national level through national programmes or at international level through international educational programmes, courses, exams and certification initiatives, such as the Transplant Procurement Management courses or the European Donation and Transplant Coordination Organisation of the UEMS and its Certification for European Transplant Co-ordinators. It is recognised that the training of healthcare professionals involved in deceased organ donation has a positive impact on the effectiveness of the deceased donation process, improving the functioning of local and national transplant systems [52].

2.5.3. Quality system

As part of the quality-control system (see Chapter 16), a proactive donor-referral programme must be developed at national, regional or local level and implemented at each hospital where there is a potential for organ donation. This quality-control system requires the development of dedicated protocols on donor referral targeted at all those professionals attending to critically ill patients.

The EU-funded project Odequs (Organ Donation European Quality System) was designed as a tool for quality systems in the donation process. The project counted on the participation of health authorities and hospitals from 16 European countries. It described detailed quality criteria and quality indicators for both types of deceased organ donor, DBD and DCD [53]. These quality criteria and indicators were proposed with the aim of evaluating performance of procurement hospitals in all steps of the deceased donation process. Indicators were developed to allow comparison of performance between different hospitals. Several of these quality criteria and indicators were particularly focused on the critical step of donor identification and referral. Quality criteria for donor identification and referral developed in the Odequs project are depicted in Table 2.4. Both DBD and DCD pathways can be addressed through these indicators to identify specific areas in the deceased donation process that can be improved at hospital level.

A quality system for donation processes should be developed at all procurement hospitals as well as

at national level. Regular audits should be conducted at each donor hospital. Accurate audit of practices is a prerequisite of any attempt to improve organ donation. It allows assessment of the potential for organ donation, evaluation of performance in the deceased donation process and identification of areas for improvement. Ongoing data collection at local, regional and national levels is a prominent feature of successful donation programmes.

Regular audits should include internal audits (performed by in-house staff) and external audits (performed by external experts) [16, 54]. Results of these audits should be analysed regularly and at least annually. The quality system at national level should include an analysis of performance of all hospitals with the potential for organ donation. This should contribute to identifying the weakest points in the organ donation process and to applying appropriate measures for improving performance.

The starting point in auditing deceased donation is variable. Existing national data collections consist of a clinical chart review of deaths occurring

Table 2.4. **ODEQUS quality criteria on donor identification and referral [54]**

Donation after brain death	Donation after circulatory death
Each hospital should implement a systematic approach to evaluate the possibility for organ donation in every end-of-life care pathway.	Each hospital should implement a systematic approach to evaluate the possibility for organ donation in every end-of-life care pathway.
Written definition of 'possible donor' is available and known by personnel of the units of the hospitals where possible donors may be found.	Written definition of 'possible donor' is available and known by personnel of the units of the hospitals where possible donors may be found.
A possible donor is always referred to the donation team irrespective of the patient's medical condition (age, past medical history etc.).	A possible donor is always referred to the donation team irrespective of the patient's medical condition (age, past medical history etc.).
	In all potential donors, the timing of treatment withdrawal should be delayed until the different donation opportunities have been considered by the donation team.
The clinical responsibilities and specific targets of the physicians of each ICU and ED should include possible donor identification.	The clinical responsibilities and specific targets of the physicians of each ICU and ED should include possible donor identification.
	Each hospital that has an out-of-hospital uDCD programme should have an updated collaborative protocol with emergency services outside the hospital in order to establish criteria for the identification of potential DCD donors.
All patients identified as possible donors should be referred to the donation team and homeostasis maintained, facilitating early brain death diagnosis as soon as the clinical criteria to test are met.	
Donation team monitors the progression of each possible donor admitted in the ICU on a daily basis.	
	In all potential uDCD donors, the asystolic time before CPR is initiated by the Emergency Service should be lower than the predetermined time (specified in the protocol) after cardiac arrest has occurred.
	All patients with irreversible cardiocirculatory arrest, no medical contraindication for organ donation and a warm ischaemia time that is low enough to allow for the extraction of organs suitable for transplant should be considered potential uDCD donors.
	Each hospital that has an in-house uDCD programme should have an updated protocol, which should be known by all healthcare professionals working in the hospital, in order to establish criteria for the identification of potential DCD donors.
	Each hospital that has a cDCD programme should have an updated protocol, which should be known by all healthcare professionals working in critical care settings and transplant team members, in order to establish criteria for identification of patients who can potentially be eligible for DCD.
	All potential DCD donors should be reported to the donation team as soon as the decision to withdraw treatment is made.

Note: cDCD: controlled donation after circulatory death; DBD: donation after brain death; ED: emergency department; ICU: intensive care unit; uDCD: uncontrolled donation after circulatory death.

at the ICU or emergency department of procurement hospitals to then identify potential DBD and, if appropriate, potential cDCD donors [16, 54-57]. But the clinical chart review can be extended to deaths occurring at any hospital unit beyond the ICU. This activity can be facilitated by focusing on deaths likely to have been caused by a DBI, particularly those conditions that are known to be common causes of BD. For administrative purposes, nearly all hospitals use ICD-10 coding linked to other patients' data during hospital stays. It is helpful to use such pre-existing administrative data collections provided by the IT system via the admission department for simplified and targeted clinical chart reviews and/or quality analysis. Table 2.3 includes a list of ICD-10 codes potentially associated with devastating cerebral lesions.

Identifying potential DBD donors based on data available in a clinical chart must be performed in a uniform and consistent manner – the corresponding criteria used in the Spanish Quality Assurance Programme are described in Appendix 3 [16]. Once potential donors are identified through the clinical chart review, information should be collected and documented on the reason for non-referral, if appropriate. In every case, additional reasons why potential donors were not converted into actual donors should also be addressed.

2.6. Conclusion

Unless an active donor identification and referral programme is established at each procurement hospital, opportunities for deceased organ donation will continue to be lost. Failure to identify possible organ donors is the most important reason explaining differences in deceased donation rates across jurisdictions. Dedicated protocols with specified clinical triggers to facilitate donor identification and referral must be established at each hospital. Donor coordinators will play a key role in ensuring the quality of these protocols. Efforts should be made to ensure education and training of all healthcare professionals who care for patients with a DBI, especially in ICUs, emergency departments and neurology/neurosurgery departments.

The principle that organ donation must be a component of end-of-life care should underpin the practice of routine referral by critical-care physicians. Their primary duty when caring for patients with a DBI is to preserve life. However, when the patient has deteriorated to a BD condition or the futility of further treatment has been recognised, the duties of critical-care physicians shift from active treatment to palliative and end-of-life care. Approaches that regard organ donation as a component of end-of-life care allow physicians to make this transition without fear of being conflicted. The emergence of such philosophies will continue to require the adaptation of existing legal frameworks and professional and public debate in most countries.

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Related material

- Appendix 3. Criteria for the identification of potential donors after brain death in a retrospective clinical chart review (Spain)

Chapter 3. Determination of death by neurologic criteria

3.1. Introduction

Since August 1968, when they were published, the Harvard Committee report and the Sydney declaration of the 22nd World Medical Assembly have led to a new model for diagnosing human death, based on neurologic criteria [1-2]. A decade previously, in 1957, the allocution of Pope Pius XII, *The prolongation of life*, pointed out the possibility – with the help of new artificial processes, such as mechanical ventilation – of artificially keeping a person 'alive' after the brain has ceased to function.

The focus of attention shifted from the condition of the heart to the state of the brain as a consequence of the introduction of artificial ventilation in the polio epidemics of the early 1950s in Europe [3]. Consequently many European investigators observed, and later on concluded, that irreversible failure of brain functions is equivalent to death after proper confirmation and they considered discontinuing further therapy [2, 4]. Two landmark accounts appeared in 1959 when, studying comatose and apnoeic patients, Wertheimer and Jouvet described the 'death of the nervous system' [5] and Mollaret and Goulon coined the term *coma dépassé,* translated as 'beyond coma' or 'ultra coma' and subsequently by others as 'irreversible coma' [6]. These patients had lost consciousness, brainstem reflexes and respiration, and their electro-encephalograms were permanently flat. The investigators' conclusion was that the brains of these patients were irreversibly dysfunctional and that it was justifiable to disconnect the patient from the respirator.

The subsequent development of organ and tissue transplantation activities, initially in the field of kidney–heart–cornea transplantations, provoked discussion on the neurologic determination of human death. At present, the complete and irreversible failure of central nervous system (CNS) functions constitutes the authentic frontier between life and death of human beings. However, not all medical schools accept the same concept of brain death. Consequently the criteria for diagnosis are different according the concept of brain death used. The 'whole brain death concept' is the most widespread concept, and it is characterised by the irreversible cessation of hemispheric and brainstem neurological functions [1]. In 1976, the Conference of Medical Royal Colleges and their Faculties in the United Kingdom published a statement on the diagnosis of brain death defined as the 'complete, irreversible loss of brainstem function', which pointed to the brainstem as the centre of brain function (brainstem death) [7].

This 'brainstem death' concept, in place of the concept of 'whole-brain death', explains why, in some countries, complementary tests are not legally required for the confirmation of clinical brain-death diagnosis, based upon cessation of brainstem function. However, they can be performed as an ancillary study to assist the clinician in specific situations (neurodepressive agents, metabolic disorder, facial or brainstem damage, infants and children).

Brain death takes place in intensive care units (ICUs) ensuring the presence of suitably qualified, trained and competent personnel and appropriate facilities and equipment. To ensure that a brain death

declaration is beyond reproach, it needs a complete and comprehensive clinical evaluation performed by trained physicians. This should be based on scientific, nationally agreed criteria, with rigorous protocols for the complementary tests used, and should acknowledge that the determination of death and the time of declaration of death stay under the legal responsibility of the physician in charge of the dead patient.

Nowadays in Europe, donation after brain death (DBD) donors represent the principal source of transplantable organs and tissues, ahead of donation after circulatory death (DCD) donors or living donors.

The purpose of this chapter is to provide some guidance on brain-death diagnosis according to the best practices usually applied at European level, knowing that important differences still exist between countries concerning legal frameworks or national recommendations on criteria for brain-death diagnosis. For this reason, each donor co-ordinator, as well as any physician qualified to perform brain-death diagnosis, must be familiar with the national formal rules in his/her home country, ensuring strict adherence to these rules on the basis of legal texts or official guidelines.

3.2. Epidemiology and aetiology of brain death

Up to 15 % of patients dying in European ICUs can be expected to present with a clinical condition consistent with brain death [8]. Other data collected in European countries (in particular, Germany) suggest that 50-65 % of all deaths with an acute primary or secondary cerebral lesion (ACLD) in an ICU (traumatic brain injury, haemorrhagic and ischaemic stroke, subarachnoid haemorrhage, meningitis, encephalitis, CNS neoplasia, anoxia, toxic and poisoning cerebral lesions) may fulfil brain death criteria [9].

As only mechanically ventilated patients with acute cerebral lesions may eventually deteriorate and be evaluated for brain death, the number of ACLDs in ICUs represents the maximum of brain-dead persons and hence of potential DBD donors. Consequently, the number of ACLDs in ICUs per million population is a useful parameter for evaluating and comparing brain death potentiality. Subsequently, ACLDs can be split by aetiology to monitor in detail the clinical epidemiology of possible organ donors in different countries, regions and centres.

The aetiology of the devastating lesion leading to death may *per se* affect the probability of developing brain death. In particular, traumatic brain injury and intracranial bleeding are the two acute cerebral lesions most frequently linked with brain death declaration. A smaller proportion of patients with another aetiology of primitive or secondary acute cerebral damage, e.g. anoxia, infection and neoplasia, may deteriorate to brain death. Case reports of brain death declaration followed by successful donation after brain death have been published, in which cerebral catastrophic events were due to poisoning by methanol, tricyclic anti-depressants, insulin, carbon monoxide, ecstasy and other toxins [10].

It is feasible that death from traumatic non-controlled intracranial pressure may be less frequent in young patients than in the past [11]. Moreover, in recent decades the number of severe head injuries related to high-speed road traffic accidents has dramatically decreased in European countries, where strict preventive rules have been implemented. Globally, fatalities from road traffic accidents decreased by 50 % in a decade in Europe (from 54 950 in 2001 to 28 000 in 2012), but eastern European countries still exhibit high traumatic mortality rates – around 80-100 per million population v. 30-60 per million in France, Germany, Italy or the United Kingdom. Around 25 % of traumatic deaths occur in patients over 65 years of age. Thus, traumatic donation after brain death is no longer the gold standard for organ donation in most European countries, where stroke is the leading cause of brain death and donation after brain death. In addition, stroke mortality is decreasing, whereas the ageing European population will continue to increase the absolute number of cases. European mortality rates are also higher in eastern countries compared to northern and western countries, with substantially more deaths in both sexes and among younger individuals [12]. Moreover, lower-income countries with weak healthcare systems could exhibit a persistent increase in mortality over time, particularly if control of some risk factors – mainly arterial hypertension or diabetes mellitus – is not achieved.

In practice, the increasing age of utilised DBD donors who died by stroke strongly suggests that potential donors with these clinical findings should be considered as medically suitable for donation.

On the other hand, deaths caused by stroke (ischaemic or haemorrhagic) in elderly persons mainly occur outside the ICU. The possibility of admission to an ICU when treatment is deemed futile may serve to allow ventilation during progression towards brain death (so-called 'elective non-therapeutic ventilation'). This option may constitute a challenge for ICUs with limited resources for acute treatable patients. At the same time, the patient's overall best

interests in end-of-life choices and the social value of donation have to be weighed up. Elective non-therapeutic ventilation for stroke patients who could progress to brain death could reasonably be an important area for increasing organ donation over the next few years and thus could be recognised as an indication for ICU admission (see Chapter 2).

The progression towards brain death requires the active support of ventilation and circulatory function in the dying patient in the ICU for hours or days. In practice, the ratio between DBD and DCD donors as a result of withdrawal of life support (WLST) is very different in northern and southern Europe: evolution to brain death was more frequent in southern European countries – 12.4 % v. 3.2 %; WLST was used more in northern European countries – 47 % v. 17.9 % [13]. Given that DCD is increasingly frequent, the shift from DBD to DCD should be avoided. In view of the different existing models of end-of-life care across Europe, there may be the potential to adapt such models in a way that is consistent with optimum care of the patient while preserving the possibility of organ donation [14].

Actually, donation after brain death potentiality depends on the epidemiology of acute cerebral lesions in ICUs and end-of-life care of patients with devastating brain lesions. Both may vary greatly across European countries as well as across regions and centres within the same country. Nowadays, the epidemiology of brain death strongly depends on the absolute number and the ratio between severe brain injuries and strokes (ischaemic or haemorrhagic) admitted to the ICU, with logistic limitations due to critical-care facilities and emergency systems. Critical-care bed numbers vary considerably between European countries: while the total of ICU beds is 73 500 (11.5 per 100 000 of population), a wide range exists, with more than 29 per 100 000 in Germany and fewer than 5 per 100 000 in Portugal [15]. Thus, it is likely that healthcare systems have a major impact on the utilisation of these resources and possibly on admission and discharge criteria of patients with devastating cerebral lesions to the ICU. Nevertheless, organ donation is not strictly related to the absolute number of ICU beds, as proved by Portugal with one of the best donation rates in Europe. Consequently, considering the wide differences across countries in the number of severe head injuries, life expectancy, ICU bed resources, ethical principles for end-of-life management and admission policy to ICU for elderly patients with stroke, brain death potentiality in Europe cannot be considered homogeneous and should be monitored in each country and compared with the absolute number, aetiology and age of ACLDs in each ICU.

Globally, the levels of actual organ donation achieved in ICUs nowadays still fail to match the potentiality, essentially because of a failure to identify all patients who may fulfil brain death criteria at any time. The analysis of this step is the main target of quality programmes adopted in many countries; in particular, the Dopki project compared the monitoring systems in European countries with a view to defining efficiency indicators in the donation after brain death process [8]. A simple and effective method for obtaining retrospective but objective data is the standard use of ICD-10 codes (see Chapter 2) identifying acute cerebral pathologies; the same ICD codes can be used for detecting and monitoring all deaths with acute cerebral lesions outside the ICU, which may represent a good proxy for hospital-possible DBD donors [16]. Prospective national registries including all deaths with acute cerebral lesions, inside and outside the ICU, could be useful for calculating the potentiality of brain death detection as well as for monitoring aetiologies and age of potential DBD donors (see Chapter 2).

In the dying patient, the precise definition of an established aetiology capable of causing brain death is a prerequisite for using neurologic criteria in determining the irreversibility of the cerebral damage and excluding any possible pitfalls and reversible confounding factor in brain-death diagnosis. Consequently an investigation and imaging aimed at a precise definition of the aetiology should always be performed. In particular, knowledge of the cause of brain damage and evaluation of its severity and consistency with the development of brain death should be clearly requested by any national guidelines about the determination of brain death.

3.3. Clinical diagnosis of brain death

Brain-death diagnosis first relies on a clinical examination and the study of brainstem function. It is the most immediate, reliable and easy way to determine brain death in non-reactive comatose patients with devastating brain injuries, where no brain function is and will be possible, invariably ending in somatic death. Key aspects of the clinical diagnosis of brain death are summarised in Table 3.1.

Table 3.1. **Key points for the clinical diagnosis of brain death**

Prerequisites for clinical determination of brain death

- Clinical history, known aetiology and irreversible condition compatible with brain death (BD) diagnosis
- Exclusion of medical conditions which could influence clinical examination (severe disturbances in electrolytes, acid-base or endocrine metabolism)
- Exclusion of central nervous system-depressant drugs: administration/intoxication
- Exclusion of neuromuscular blocking agents
- Body temperature >35 °C (see §3.3.1.2.a)

Three mandatory clinical signs

- Glasgow Coma score 3
- Absence of brainstem reflexes
- Absence of spontaneous breathing – apnoea test

Glasgow Coma score 3

- Hypotonic and nonreactive coma: absence of cerebral motor response to pain stimuli in body parts innervated by cranial nerves (e.g. sustained pressure on temporomandibular joint or supraorbital region), although spontaneous medullar reflexes might still be present.

Absence of brainstem reflexes

- During progression to BD, the loss of brainstem reflexes follows a rostro-caudal direction, from the midbrain (mesencephalon) to the pons and at the end, the medulla (oblongata).
- No pupil reactivity: lack of photo-reactivity, with no response to bright light of the fixed pupils (pupil diameter 4 to 9 mm).
- No eye movement, no movement of eyeballs, lack of oculocephalic/oculovestibular reflex after stimulation by:
  - Rapid movement of the head (oculocephalic), tested in the absence of spinal injury.
  - Cold caloric manoeuvre (oculovestibular – if tympanum integrity): irrigation of each tympanum with 50 mL of cold water (1 min delay after injection and 5 min interval between the irrigation of both ears).
- Corneal reflex loss (avoid cornea damage): no palpebral movement after a drop of saline or no palpebral movement when touching cornea edge using a sterile compress carefully.
- No cardiac response after oculo-cardiac reflex (mandatory only in some countries).
- No cough at bronchial suctioning, lack of pharyngeal and tracheal reflexes (mandatory only in some countries).
- Lack of heart rate response after 0.04 mg/kg IV infusion of atropine (mandatory only in some countries).

Apnoea test

- Lack of spontaneous breathing due to the loss of respiratory centre function (medulla oblongata), i.e:
  - Pre-oxygenation requirement under FiO_2 100 % – minimal PEEP 5 cmH_2O – adequate tidal volume and respiratory frequency to obtain: PaO_2/FiO_2 > 200 mmHg (>26.7 kPa), $PaCO_2$ 35-45 mmHg (4.7-5.9 kPa).
  - In case of PaO_2/FiO_2 ratio < 200 mmHg (< 26.7 kPa), the procedure is at risk of cardiac arrhythmias/bradycardia/cardiac arrest and should be considered with caution, performed with alternative method, or abandoned (reasons recorded in the BD sheet).
  - Disconnect the patient from the ventilator for a period of usually 3-5 minutes (maximum 10 minutes) – SaO_2 monitoring is mandatory to detect any drop, while administering O_2 through the endotracheal tube with a flow of 6-8 L/min.
  - Attention to the diameter of the suction catheter and the risk of airway obstruction.
  - Recruitment manoeuvre to be applied after reconnection in order to limit lung atelectasis.

Possible alternative procedures

- After pre-oxygenation:
  - Disconnect patient from the ventilator and connect to self inflating bag with CPAP valve, supplied with an O_2 flow of 6 L/min connected to endotracheal tube,
  - Ventilator set up on CPAP mode without disconnection,
  - Hypoventilation with FiO_2 of 1.0 to obtain required $PaCO_2$ level, then CPAP for 1 minute with or without ventilator disconnection.

Collect sample of arterial blood after an interval of about 5 minutes and reconnect the ventilator, if required $PaCO_2$ is achieved; if not, continue the test.
The test is positive if the $PaCO_2$ level increases by more than 20 mmHg (2.7 kPa) compared to the reference baseline value.
Some countries require a $PaCO_2$ level ≥ 60 mmHg (≥ 8.0 kPa).

Note: CPAP: continuous positive airway pressure; PEEP: positive end-expiratory pressure. Sources: [20, 22-27].

3.3.1. Preconditions for clinical examination

3.3.1.1. *Brain-death diagnosis: two mandatory criteria*

Brain-death diagnosis should follow a strict step-by-step pathway, beginning with two absolutely mandatory criteria [17-19]:

a. A structural cause and pathogenesis of brain death must be identified.

Comas of unknown origin are not suitable for brain-death diagnosis. Catastrophic brain damage, when demonstrated, supports the conclusion of irreversibility of such condition (e.g. massive brainstem haemorrhage). The cause of coma is usually demonstrated by neuro-imaging but, in some cases, ancillary tests – such as laboratory tests or clinical findings (e.g. meningitis, encephalitis, poisoning,

and early period after cardiorespiratory arrest) – may be necessary.

Brain death may be partially simulated by neurologic clinical situations, such as locked-in syndrome, post-anoxic encephalopathy, minimally conscious states or persistent vegetative states. In such cases, any sign of consciousness or spontaneous brain-related movements including convulsions, any brainstem reactivity to stimuli or the presence of spontaneous breathing are key indicators for excluding brain death. Rare cases of Guillain–Barré syndrome involving all peripheral and cranial nerves, endocrine crisis, snake bite or baclofen overdose (potentially reversible situations) can all mimic brain death, leading to a potentially dangerous diagnostic error if the clinical evolution is not deeply investigated or proper ancillary tests are not performed.

b. Any factor that can interfere with the clinical diagnosis and make it unreliable must be excluded.

The absence of any confounding factors that can lead to a misdiagnosis is essential to the conclusion that the absence of brain function detected in the clinical examination is completely related to the structural cause identified above and irreversible.

3.3.1.2. *Brain-death diagnosis: factors to exclude*

Severe physiological derangements must be excluded before performing the clinical examination to ensure the reliability of brain-death diagnosis, which is the irreversible loss of cerebral functions [20]:

a. Core temperature should be > 35 °C: brainstem reflexes may disappear when core temperature drops below 28 °C. Moreover, the response to light is lost at core temperatures between 28 °C and 32 °C. Long-term hypothermia, particularly in anoxic brain injury and therapeutic hypothermia (32 °C to 34 °C) need a complete timely reverse to detect any cerebral function;

b. Haemodynamic stability, adequate oxygenation and euvolaemia must be ensured: mean arterial blood pressure > 65 mmHg (> 8.7 kPa);

c. Exclusion of metabolic conditions that may confound the clinical assessment (severe electrolyte, acid-base or endocrine disturbance);

d. Any possible effect of CNS-depressant drugs and neuromuscular blocking agents should be strictly evaluated and excluded (barbiturates, benzodiazepines, tricyclic anti-depressants etc.) Screening tests may be helpful, but some toxics may not be detectable by routine assessments (e.g. cyanide, lithium and fentanyl). A reasonable approach for unknown or suspected drugs or toxics is to prolong the observation period for 48 h to determine whether a change in brainstem reflexes occurs; if no change is observed, a confirmatory test must be performed [17]. If the substance known to be present cannot be quantified, the observation period should be at least four times the clearance half-life of the substance (excluding interferences by other drugs or organ dysfunction). Clinical diagnosis is allowed if serum drug levels are below the therapeutic range and/or clinical evidence shows that the neurologic deficit is not explained by the existence of the drug;

e. Extreme caution should be used whenever patients are subject to therapeutic hypothermia or non-pulsatile continuous-flow mechanical circulatory support devices, since these situations modify drug clearance, e.g. of propofol and baclofen. An appropriate time for neurologic recovery should be allowed or confirmatory tests should be used to achieve certainty about the irreversibility of neurologic findings [21];

f. The clinical examination including apnoea test must be complete, rigorous and reliable: possible pitfalls may depend on facial, ocular or high cervical trauma and pre-existing pupillary abnormalities. These factors may impede the examination of all the brainstem reflexes. Sleep apnoea or severe pulmonary disease resulting in chronic retention of CO_2 should lead to a tailored apnoea test. In all these circumstances confirmatory tests are recommended [20].

3.3.1.3. *Brain-death diagnosis: irreversibility*

Irreversibility of brain function loss due to a known devastating cerebral lesion is the key factor for brain-death diagnosis. Irreversibility has three factors requiring clinical judgment:

a. The cerebral lesion must be sufficient and congruent to be directly linked to the total brain destruction;

b. Treatable and reversible medical conditions known to depress brain function should be excluded. If any potential confounding factor cannot be reversed or excluded, brain-death diagnosis must be completed with proper confirmatory ancillary tests;

c. The absence of brain function should be confirmed during an observation period clinically tailored to type of lesion, age or other relevant

factors but, in most countries, guided by national guidelines or legal procedures.

Confirmatory ancillary tests, mainly those demonstrating the absence of cerebral blood flow (CBF), should be applied whenever there is a reasonable doubt. These confirmatory tests, once performed, may shorten the observation period.

As the interpretation of a clinical examination is dependent on these two items – irreversibility of brain function and confirmatory ancillary tests – and evidence of irreversibility is required for the final conclusion of brain-death diagnosis, it is recommended that physicians experienced in neurologic-critical situations perform this diagnosis.

3.3.2. Clinical examination

The confirmation of brain death through clinical examination is established by neurologic testing of comatose patients that fulfils the above-mentioned preconditions (see §3.3.1) and in whom there are no spontaneous breathing movements and no brainstem reflexes.

Neurologic tests should be performed when physiological conditions (haemodynamic, metabolic, respiratory and non-hypothermic) are stabilised, making possible a response from any living neurons. Before carrying out diagnostic tests that may have a negative effect on the brain, it is advisable to run tests that do not have such an effect, thus preventing further damage if death is not confirmed. The apnoea test should be the last to be performed, when the necessary rise in partial carbon dioxide pressure ($PaCO_2$) increases intracranial pressure with the risk of brain damage [17, 19]. If any brainstem function reflex is positive, or if in any way there are reasonable doubts about the brain-death diagnosis, the apnoea test should not be performed. If breathing movements are detected, the apnoea test should be aborted, and controlled ventilation restarted.

It is recommended to ventilate the patient with FiO_2 1 and adjust the ventilator to obtain normocapnia for 15-30 minutes before beginning the clinical examination.

The head of the bed should be elevated at 30 °. Previous inspection of tympanic membranes is recommended in all cases to exclude lesions or cerumen that could diminish sensitivity of the oculovestibular reflex. In case of a traumatic aetiology, the presence of blood clots has a similar effect and is frequently related with possible temporal bone fractures (which can be associated with absence of facial anatomic integrity and/or that of auditory/vestibular nerve responses) [17]. In these cases, caution should be taken when drawing conclusions about the results of absence of facial motility and/or absence of vestibular reflexes, as they may not be related to the absence of brainstem function. This kind of pitfall also applies to other cranial or somatic deranged structures (nerves), and caution in final interpretation should be taken.

All brainstem reflex tests (before the apnoea test) should be performed under controlled ventilation. An arterial blood gas sample obtained just before the beginning of the physical exam is recommended, to confirm respiratory status and orientate the duration of the apnoea test.

3.3.2.1. *Brainstem reflexes*

Deep coma (Glasgow Coma Score of 3) must be confirmed at the beginning. The patient is unresponsive to verbal stimuli, and decerebrate and decorticate posturing or seizures at inspection are excluded, since these are signs of encephalic activity excluding brain death. However, movements related to medullar reflexes may still be present. The physical examination of brainstem reflexes is summarised in Table 3.1.

3.3.2.1.1. Photomotor reflex (afferent II cranial nerve, efferent III cranial nerve)

In the Collaborative Study Criteria (published by the US National Institutes of Health in 1980), dilated and fixed pupils were considered mandatory, because mid-position fixed pupils can be seen in cases of drug intoxication [20]. Nowadays, careful history and drug screening obtained before any brain-death diagnosis allows mid-position fixed pupils to be judged consistent with brain death in the presence of negative toxicology screening. Usually, pupils are 4-6 mm in diameter but may vary to unilateral or bilateral dilation size (9 mm). They are always fixed on light stimulation. Also no blinking reflex is noted upon stimulation [19].

3.3.2.1.2. Corneal reflexes (afferent V cranial nerve, efferent VII cranial nerve)

In brain death, no blinking, tearing or reddening can be obtained upon corneal stimulation. The stimulus is obtained with physical contact of the edge of a swab over the limbal margins of the corneas; middle (central) corneal area stimulations should be avoided, as they are related to central vision where potential harm may occur with no evidence of superior threshold stimulus at that zone. To avoid this

potential problem, stimulation with a drop of saline serum is recommended.

3.3.2.1.3. Oculovestibular and oculocephalic reflexes (afferent VIII cranial nerve, efferent III and VI cranial nerves)

In oculovestibular reflexes testing, the stimulus is an irrigation with 50 cc icy saline slowly into one external auditory canal with both eyes open; after instillation, waiting for at least 1 minute; any deviation of eye's axis or eye's movement and autonomic response must be excluded to fulfil brain-death criteria. Stimulation of the opposite auditory canal should be performed with a 5-minute delay.

Alternatively, the oculocephalic reflexes may be tested: eyelids are kept open while the head is turned abruptly from side to side; observation of the eyes' position in the immediate seconds will reveal no change in the axis in brain-dead patients; in normal responses, the eye's axis follows the head movement with some delay.

Assessment of one or both reflexes depends on the physician's judgment, but oculovestibular tests are more popular, mainly in trauma cases, where sharp cervical movements may be dangerous.

3.3.2.1.4. Pharyngeal (nausea or gag) and cough reflexes (afferent IX cranial nerve, efferent X cranial nerve)

No response to posterior pharynx stimulation with a tongue blade and no response to tracheobronchial suctioning (carenal stimulation) must be observed, and no respiratory movements should occur at all.

3.3.2.1.5. Facial movement in response to noxious stimuli

No response to painful trigeminal (facial) area stimulation (i.e. temporo-mandibular joint zones or supraorbital nerves at the supraorbital ridges) must be observed. No reaction or grimacing must be observed after applying painful stimulus on body somatic areas (neck, thorax, limbs or abdomen) such as pressure on a nail bed.

It is always important to remember that any demonstration of arousal or awareness is not compatible with brain death.

3.3.2.1.6. Atropine test (efferent X cranial nerve)

The atropine test consists of the intravenous administration of 0.04 mg/kg atropine, which will increase cardiac frequency by more than 10 % of the baseline pulse in non-brain-dead patients. Heart rate increase is obtained by stimulus at the nucleus of the vagus nerve, in the lower medulla. In brain-dead patients there is a lack of heart rate response. This test is easy to perform and important to confirm the neurological diagnosis of brain death, stimulating by a pharmacological stimulus the same critical deep area of the brainstem investigated by the apnoea test. In most countries this test is not required by national guidelines. When indicated, it may be used as a complementary test before the apnoea test is performed.

3.3.2.1.7. Apnoea testing

The apnoea test aims at demonstrating loss of respiratory brainstem function. However, this test is at high risk of causing hypotension, hypoxia and cardiac arrhythmias if adequate oxygenation and volaemia are not achieved before testing. Sometimes, these complications create barriers for completing the test, leading to the need for additional confirmatory studies.

Prior to this test, the patient is pre-oxygenated with FiO_2 of 1.0 for at least 5 minutes and a baseline arterial blood gas sample is obtained (objective pH 7.38-7.40; $PaCO_2$ 35-45 mmHg, i.e. 4.67-5.9 kPa). The patient is disconnected from the ventilator (while oxygenation is ensured by apnoeic oxygenation-diffusion with 6-8 L/min of O_2 through the tracheal tube), or maintained under continuous positive airway pressure mode (CPAP) and 100 % oxygen without any artificial drive support, to maximally stimulate the brainstem respiratory neurons (around 5-10 minutes). An insufflation catheter with an outer diameter < 70 % of the endotracheal tube inner diameter may prevent inappropriate lung pressure and volume during the apnoea test [22]. Any ventilator movement or any ventilator drive are excluded by careful observation of the chest and/or meticulous capnographic monitoring. At the end of the test, a second arterial blood gas sample is obtained: if there is an increase of the $PaCO_2$ of more than 20 mmHg (2.7 kPa) compared to the reference sample, the test is indicative of cessation of respiration in absence of any ventilatory activity observed. In most countries, it is recommended that terminal $PaCO_2$ should be higher than 60 mmHg (≥ 8.0 kPa). Some countries also require a pH less than 7.40.

Once an apnoea test is performed in a potential lung donor, lung collapse, atelectasis and oedema should be avoided. Recruitment manoeuvres performed after the apnoea test may improve the PaO_2/FiO_2 ratio and prevent acute lung complications [23].

In the case of serious lung damage with PaO_2/FiO_2 ratio < 200, very fast desaturation followed

by circulatory disturbances may be observed after ventilator disconnection. To avoid this, alternative methods of apnoea test based on the use of CPAP systems with oxygen supplementation may be recommended. First, as mentioned above, without ventilator disconnection under CPAP mode and trigger exclusion (ventilator self-cycling can be confused with brainstem-mediated respiratory effort as a phenomenon of auto-triggering) [24]. This option is rarely possible nowadays, because for safety reasons the majority of modern ventilations have non-suspendable automatic apnoea backup ventilation. Alternatively, CPAP may be applied with self-inflating bag with CPAP valve supplied with an O_2 flow of 6 L/min connected to endotracheal tube [25] or with circle system of anaesthesia machine [26]. Another option for apnoea test in extremely hypoxaemic patients is hypoventilation, with minute ventilation reduced approximately by 50 % (following pre-oxygenation), to obtain required $PaCO_2$ level. Afterwards, ventilation mode is switched to CPAP mode for 1 minute with or without ventilator disconnection. Periodic arterial blood gas analysis should be taken until $PaCO_2$ achieves the required level [27].

3.3.2.2. Spinal reflexes

Since brain death means loss of the encephalic function, neurologic activity depending on spinal cord may persist and be detectable, either clinically or in ancillary tests. In brain death, complex withdrawal movements originated in the spine are possible, and must be differentiated from seizures, decortication and decerebration posturing movements, which indicate brainstem activity (and cortical activity in the case of seizures).

Several studies confirm this phenomenon with a prevalence of about 50 % in cases of confirmed brain death, and its presence does not alter but indeed confirm the reliability of brain-death diagnosis. In fact, recovery of spinal activity of the well-perfused and oxygenated spinal neurons occurs in hours or days after the immediate spinal shock, due to the ultimate brain dying process leading to brain death. Without any superior (encephalic) control, the spinal neurons easily react to even minimal stimuli (i.e. body touching, respiratory acidosis during the apnoea test, any painful stimulation and surgical stimuli during organ recovery) creating gross and never finalised body movements and huge vegetative response.

In one prospective study of cases with the diagnosis of brain death confirmed by angiography, deep tendon and stretch reflexes were shown to be frequently absent in the first day of injury and to return after 24 h [28]. It was also noticed that brain-dead patients without spinal reflexes were also continuously haemodynamically unstable. Ipsilateral extension–pronation responses on upper chest pain stimulation were present in 33 % of cases and ipsilateral flexion withdrawal responses on L3/4 dermatome stimulation in 79 %. Wijdicks found during the apnoea test, on transportation of the patient, in synchrony with the ventilator's activity or at the time of abdominal incision, occasions where spinal movements appear: 'slow body movements may even include a brief attempt of the body to flex at the waist, making it seem to rise. The arms may be raised independently or together … legs seldom move spontaneously. … Other manifestations include slow turning of the head to one side and facial twitching' [17]. Consistent clinical documentation of brain death and confirmation by an ancillary test will give the final evidence for brain death.

3.3.2.3. *Clinical observations compatible with the diagnosis of brain death*

Several manifestations occasionally seen in brain death patients should not be misinterpreted as evidence for brainstem function [20]. These manifestations (see Table 3.2) include not only spinal reflexes (spontaneous movements of limbs other than pathologic flexion or extension response, respiratory-like movements, deep tendon reflexes etc.) but also other reflexes as a consequence of the persistence of certain hormonal activity dependent on the hypothalamic-pituitary axis (sweating, blushing and tachycardia; hyperthermia, normal blood pressure without pharmacologic support, absence of diabetes insipidus etc.) [29].

Table 3.2. **Clinical observations compatible with a diagnosis of brain death [20]**

American Academy of Neurology protocol list of occasional phenomena that should not be misinterpreted as evidence for brainstem function
• spontaneous movements of limbs other than pathologic flexion or extension response;
• respiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes);
• sweating, blushing and tachycardia;
• hyperthermia;
• normal blood pressure without pharmacologic support, or sudden increases in blood pressure;
• absence of diabetes insipidus;
• deep tendon reflexes, superficial abdominal reflexes or triple flexion response;
• Babinski reflex.

Despite the lack of cerebral blood-flow in brain death, perfusion responsible for maintenance of the hormonal secretion by the hypothalamic-

hypophyseal axis could exist. In brain-death patients, the absence of antidiuretic hormone secretion limited neurogenic diabetes insipidus to 46 % to 78 % of cases [30], while several studies have shown that some patients maintain adequate levels of hypothalamic hormones [29]. These findings, together with the complex and variable hypothalamic vascularisation, could explain also the function of the thermoregulatory centre and thus hyperthermia in patients showing infection and brain death [31].

3.3.3. Observation period

Since the initial Harvard Committee report of 1968, all protocols mention the need for an observation period and repeated clinical examinations to confirm the initial diagnosis of brain death. There is controversy about the irreversibility of the clinically observed status. However, particularly when an ancillary confirmatory test is used and the clinical evolution and the aetiology are well known, it may be clinically reasonable to confirm brain death even when there is a short interval between two clinical examinations that include the apnoea test. In most countries, this clinical option is overcome by guidelines or rules that make it mandatory to legally declare death by neurological criteria.

Nevertheless, from the medical point of view, it may be better to confirm brain-death diagnosis over a period of time, mainly if the irreversibility of the damage responsible for brainstem function loss is not obvious, particularly in post-anoxic patients. As a diffusely accepted clinical rule due to the peculiar pathogenesis of a cerebral ischaemic-anoxic lesion, at least 24 hours should be the interval between the cerebral anoxic insult and a reliable clinical diagnosis of brain death. In comatose survivor patients after cardiac arrest treated with therapeutic hypothermia, this interval should be extended up to 72 hours [32].

3.3.4. Brain-death declaration

Brain death is based on clinical criteria fulfilled by neurological examination, in some cases confirmed by ancillary test proving absence of metabolic/electrical cortical/encephalic activity or absence of CBF. Nevertheless, in most countries definite procedures are mandatory to give legal and social validity to the clinical diagnosis. It is important to emphasise the need for all countries to have a protocol at national level for brain-death diagnosis. Having a national protocol has many benefits, including promoting safe practices and assuring that there are no diagnostic errors in the determination of death, protecting patients and healthcare professionals, improving public and professional confidence in the deceased donation process, and increasing the availability of organs obtained by ethically legitimate donation and procurement practices.

Practice varies widely, even in European countries, particularly in the number and professional background of physicians needed to perform from one to four clinical examinations, the observational period that may last up to 72 hours, particularly in children, and may be reduced if ancillary tests are performed, and the mandatory or optional use of different ancillary tests [33-34]. However, at least a preliminary ancillary test is recommended in all protocols either to overcome any residual doubt about the reliability of clinical observations, due to possible confounding factors, or to reduce the observation period.

Ultimately, harmonisation of European procedures remains one of the most important issues to improve the medical and social acceptance of the declaration of brain death.

3.4. Ancillary tests for the diagnosis of brain death

Whatever the adopted concept is, 'brainstem death' or 'whole-brain death', the first step remains the clinical assessment of permanent brain death. Neurologic examination should be clearly consistent with a clinical brain-death state on the basis of a strict validation of all the required criteria (see §3.3.1 and §3.3.2) before performing any complementary test. The choice of ancillary study is a function of factors such as local facilities, equipment availability or special circumstances, e.g. children, non-airtight-cranium patients, residual circulation of sedative agents. Nonetheless, some national guidelines correctly state that ancillary tests that confirm irreversible cerebral circulatory arrest can be used as an appropriate tool for the decision on when neurologic examination can be done for the clinical assessment of permanent brain death (independently of leftover interaction caused by sedative drugs etc.). In this special case, the results of the particular ancillary test may be used too.

3.4.1. Brain blood-flow tests

3.4.1.1. *Conventional angiography*

The classic four-vessel arteriogram has been for a long time the gold standard of CBF investiga-

tion in brain-dead patients since it is not interfered by hypothermia nor depressants of CNS. Although an invasive method, angiography remains one of the recommended tests to be performed in Canada and the United States for the diagnosis of cerebral circulatory arrest [20, 35]. The cessation of circulation is not instantaneous, but progressive. Various gradual patterns, from partial or delayed intracranial arterial filling to no filling, all consistent with brain death, can be observed:

a. Extreme slowing of arterio-venous circulation time (lengthening greater than 15 seconds is not compatible with cerebral function);

b. Halt of cerebral arterial circulation at Circle of Willis;

c. Total arrest of arterial contrast and lack of vein filling; the contrast material disappears retrogradely.

However, angiography has some disadvantages, such as a need to move the patient outside the ICU, the use of potentially nephrotoxic contrast agents and arterial puncture.

Intravenous digital subtraction angiography is successfully used to verify cerebral circulatory arrest and based on the same principles as conventional arteriography.

3.4.1.2. *Angio-scintigraphy*

Following the development of lipophilic radio-substances, radionuclide CBF testing has interesting possibilities in brain-death diagnosis. Since the first era of ^{99m}Tc pertechnetate scintigraphy, angio-scintigraphy using ^{99m}Tc-labelled hexamethylpropyleneaminoxime (HMPAO) as a diffusible radiotracer has become a common test, performed in a large number of countries.

Angio-scintigraphy with ^{99m}TcHMPAO consists of two phases: the first, to evaluate the CBF, and the second, 5-10 minutes after injection, in which static images in anterior, lateral right and lateral left projections are obtained, to evaluate the parenchymal capture. The lack of isotope uptake in brain parenchyma ('hollow skull phenomenon') confirms CBF cessation. Angio-scintigraphy with ^{99m}TcHMPAO is easy to carry out, highly sensitive and specific, with no interference from the patient's clinical conditions or the administration of CNS-depressant drugs. Like other CBF tests, scintigraphy does not show 100 % accuracy for brain-death diagnosis.

With or without radionuclide angiography, planar imaging continues to be the pillar for the scintigraphic confirmation of brain death. Static planar imaging, with the use of ^{99m}TcHMPAO and multi-projection, can be used to evaluate the flow of supratentorial (cerebral hemispheres, basal ganglia, thalamus) and infratentorial structures (cerebellum, brainstem). Single-photon emission computed tomography gives cross-sectional information, but the reliability of the test to exclude flow and metabolism remains to be validated. Bi-planar imaging should be performed as a minimum.

Some authors show a sensitivity of 98.5 % for brain-death confirmation when using planar imaging without the use of specific brain tracers [36]. Other studies support the idea that the sensitivity of ^{99m}TcHMPAO planar imaging is very high while the specificity (absence of cerebral perfusion with clinical brain-death confirmation) is near 100 % [37].

This test does not require the use of iodinated contrast, is easy to interpret and exhibits high concordance with cerebral angiography. As a significant advantage, this CBF test is not influenced by CNS depressants, hypothermia or metabolic disorders. Its main limitation is that it might demonstrate CBF in patients with some degree of skull opening, such as children under 1 year of age, individuals with open head injuries or after extensive craniotomy [37].

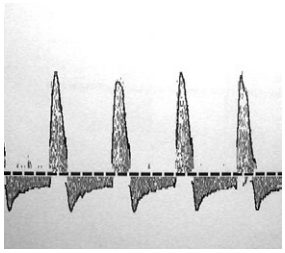
3.4.1.3. *Transcranial Doppler*

Transcranial Doppler (TCD) is a technique based on the ultrasonographic measuring of the blood velocity in arteries at the base of the skull. Besides its routine use for the management of patients with cerebrovascular and traumatic brain injuries, TCD is very useful in the diagnosis of the progressive circulatory cessation at the large intracranial arteries found in brain death.

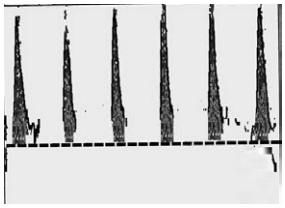
Brain circulatory cessation is, in most cases, due to an increase of intracranial pressure: when the level of intracranial pressure reaches the same value as the mean arterial pressure, the cerebral perfusion pressure approaches zero (cerebral perfusion pressure = mean arterial pressure – intracranial pressure). TCD can verify the kinetics of the cerebral circulation loss as a process that begins (especially in supratentorial pathology with intracranial hypertension) with a progressive decrease of the diastolic velocity, continuing with a separation of the diastolic and systolic wave, an inversion of the diastolic flow wave (reverberant flow), a disappearance of the diastolic wave and finally, especially in patients with a greater than 24-hour cerebral circulatory arrest, the impossibility of obtaining any sign of cerebral flow. In 1998, the Task Force Group on Brain Death of the Neurosonology Research Group of the World Federation of Neurology produced a consensus document in which two different sonographic patterns compat-

ible with a diagnosis of brain death were considered: 1. a reverberant flow pattern; 2. a pattern of systolic spikes (see Figure 3.1) [38-39].

Figure 3.1. **Transcranial Doppler wave forms of the middle cerebral artery compatible with brain death**



1a. Reverberating flow



1b. Systolic spikes

The existence of inter-hemispheric or inter-compartmental (supratentorial/infratentorial) asynchronies on CBF can be also detected by TCD before completing the cerebral circulatory arrest.

In order to make a diagnosis of brain death by TCD, the cerebral circulatory arrest must be documented by bilateral registration of reverberant diastolic flow and systolic spikes, in the anterior and posterior circulation, and in two different explorations separated by 30 minutes. These findings must be demonstrated by insonation of both middle cerebral arteries (anterior circulation) and basilar arteries (posterior circulation) [39]. Additionally, some authors recommend also examination of internal carotid and vertebral arteries [39].

The accuracy of TCD for the diagnosis of brain death varies in the literature. In a recent systematic review of the literature and meta-analysis, including 22 studies comprising 1 671 total patients, TCD sensitivity was 90 % (95 % CI, 0.87-0.92) and specificity 98 % (95 % CI, 0.96-0.99), suggesting that transcranial Doppler is a highly accurate ancillary test for brain death confirmation [40]. In some studies, the non-exclusion of patients without airtight cranium (external ventricular derivation, large craniotomies) probably contributes to a lower TCD accuracy: these patients are not suitable for TCD investigation [41]. TCD can also be difficult in the absence of insonation for middle cerebral arteries using a transtemporal window; one solution could be the use of the orbital window for the insonation of the carotid siphon [42].

TCD is a non-invasive and easy-access technique at the bedside, and it can be repeated. It has also the advantage of not being influenced by the effects of CNS-depressant agents and does not require the use of contrast medium. Although it has a high positive predictive value, not all countries recognise it as a legal test. This test needs a good level of expertise, and is operator-dependent. On the other hand, this is the perfect tool to detect the optimal time to perform a CBF study or EEG. A reproducible measurement of results by TCD, compatible with cerebral circulatory arrest in a time period of more than 30 minutes, can be used as a confirmatory test. It is self-evident that, at a low blood pressure (MAP < 60 mmHg), the probability of obtaining signals as reverberating flow or systolic spikes decreases.

3.4.1.4. *Computed tomographic angiography*

In 1998, Dupas *et al.* described how computed tomographic angiography (CTA) could be useful in demonstrating a lack of intracerebral blood flow and reported the first application of CTA to the diagnosis of brain death [43]. The authors proposed a 7-point CTA score for the confirmation of brain death, according to opacification or non-opacification of the pericallosal arteries, cortical segments of the middle cerebral arteries, the internal cerebral veins and the great cerebral vein (see Figure 3.2.a). In 2009, Frampas *et al.* introduced an alternative 4-point score based on the lack of opacification of cortical segments of the middle cerebral arteries and the internal cerebral veins (see Figure 3.2.b) [44]. Since then, several major studies of this application have been published, and national guidelines have been introduced in several European countries (e.g., France and Germany) [45]. Unfortunately, these guidelines are not standardised between countries and there are significant protocol differences in evaluation scale and scanning time. These variations may lead to discrepant diagnoses of cerebral circulatory arrest, especially in cases with borderline progression of cerebral oedema. Therefore, European harmonisation of CTA protocols in brain-death diagnosis is warranted.

A first meta-analysis, including 10 studies published between 1992 and 2012, that compared the results of CTA in patients with brain-death diagnosis, reported its relatively low overall sensitivity of 85 % [46]. However, this meta-analysis included older studies, whereas recent large multicentre trial with 82 brain-dead patients shows sensitivity > 96 % according to a 4-point score [47]. This difference could be explained by continuing technical progress in CT scanners, which allows assessment of faint opacification of cerebral vessels more precisely, together with the increasing experience of radiologists performing the test. Therefore CTA should be considered as a valuable ancillary test in brain-death diagnosis.

False negative CTA results (opacification still present in clinically confirmed brain death) may be seen in rare situations like decompressive craniectomies, skull fractures, ventricular shunts or

infants with pliable skulls. In such cases, other tests than CBF studies should be used to confirm brain death. It should be mentioned that increase of intracranial pressure leading to brain death is a continuous process and secondary to it, and cessation of cerebral circulation is continuous too. Therefore at early stages after the onset of brain stem areflexia, brain oedema may not increase intracranial pressure above the blood pressure. In such situations an opacification of peripheral segments of cerebral arteries may still persist. Therefore, there should be a recommendation to perform CTA with a delay of at least 6 hours after the appearance of clinical signs of brain death. If the first CTA test is negative, the test should be repeated after 12-24 hours.

Computed tomographic angiography has the advantages of being widely available, less invasive and less technically complicated than the reference digital subtraction angiography (DSA), less time-consuming than cerebral scintigraphy and less operator-dependent than transcranial Doppler. When using a CTA test, physicians should also consider the possibility, at the same time, of completing the evaluation by a whole-body CTA (chest, abdomen and pelvis) giving a precise view of the entire vascularisation and organ morphology; it can also detect anatomical variants and contraindications to donation.

3.4.1.5. *Magnetic resonance angiography*

Magnetic resonance angiography could potentially be an alternative to CTA. But technical constraints, in particular the need to use MR-compatible devices (like ventilator and infusion pumps), along with limited experience and lack of proven superiority, often limit its use for the purpose of brain-death diagnosis.

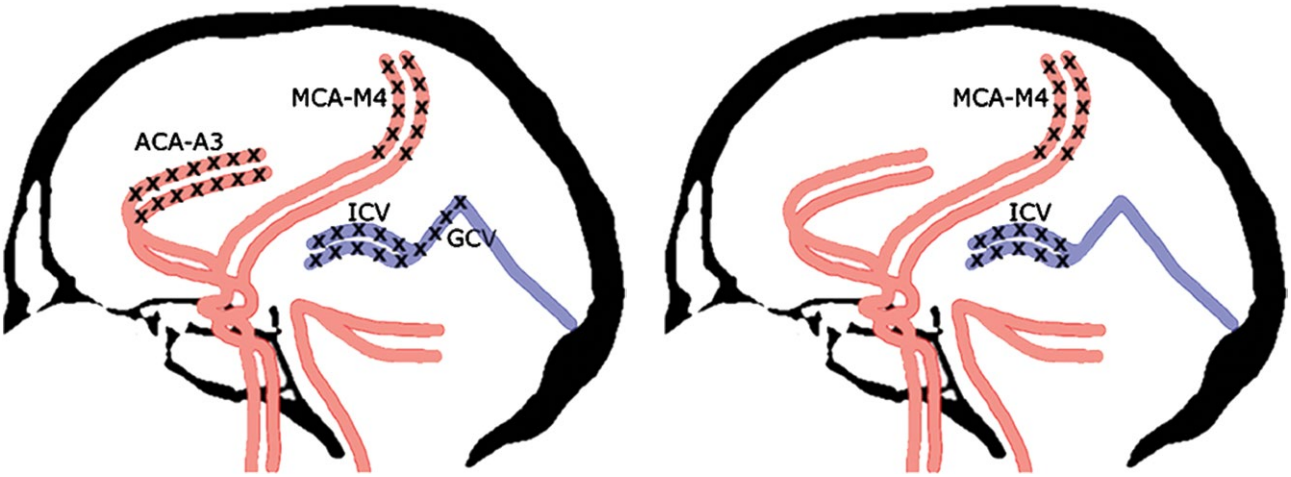
3.4.2. Electrophysiologic tests

3.4.2.1. *Electroencephalography*

An electroencephalogram (EEG) is a conventional and valuable test for diagnosing brain death using the evidence of electric cerebral (cortical layer) inactivity. Standard EEG measurements cover the electrical activity only of the cortex and not of the brain stem. Prerequisites such as core temperature above 35 °C and lack of sedative agents should be respected before testing. Otherwise, the results of the EEG recording cannot be validated.

The most accepted criteria when performing an EEG study for the diagnosis of brain death were approved by the American Electroencephalographic Society [48], which specified that a minimum of eight electrodes must be placed on the scalp, as well as a reference electrode (to detect electric interference in the environment of the ICU), with inter-electrode distances of at least 10 cm, placed in frontal, temporal, occipital regions with impedances under 10 000 ohms, but over 100 ohms. The EEG record must be obtained over a period of at least 30 minutes; sensitivity must be increased from 7 μV/mm to at least 2 μV/mm, with inclusion of appropriate calibrations. In order to avoid attenuation of low-voltage fast or slow activity, whenever possible, high-frequency filters should not be set below a high-frequency setting of 30 Hz, and low-frequency filters should not be set above a

Figure 3.2. **Criteria for the diagnosis of brain death by CTA**



(a) In the 7-point scale brain death is confirmed by a lack of opacification of the bilateral pericallosal artery (ACA-A3), the bilateral cortical segments of the middle cerebral artery (MCA-M4), the bilateral internal cerebral vein (ICV) and the great cerebral vein (GCV).

(b) In the 4-point scale brain death is confirmed when the bilateral MCA-M4 and the bilateral ICV are not opacified.

Adapted from: Sawicki, M., Bohatyrewicz, R., Safranow, K. et al. *Neuroradiology* (2014) 56:609 [47].

low-frequency setting of 1 Hz. The high levels of sensitivity set on the electroencephalography machine increase the number of artefacts, which are plentiful in an ICU because of the presence of multiple devices.

In brain-dead patients, there should be no EEG reactivity to intense somatosensory, auditory or visual stimuli. A simultaneous electrocardiographic record should be made to detect electrical activity due to the cardiac activity (spike of QRS complex), co-existing with the EEG record. In the case of electro-myographic artefacts interfering during the record, these must be eliminated through the use of a neuromuscular blocking agent. Under these strict conditions, electro-cerebral inactivity or electro-cerebral silence (or other synonyms such as flat EEG), brain death can be diagnosed if no electrical activity of the brain is recorded. If any doubt persists about the electro-cerebral inactivity, another EEG should be performed after an interval of usually 6 h. In some countries, two EEGs are mandatory as a legal requirement for the confirmation of brain death.

The advantages of an EEG are performance at the bedside, no requirement for contrast medium and wide availability. Its main disadvantage is that it might demonstrate an absence of electrical activity in the presence of confounding factors, namely, severe metabolic disorders, hypothermia and CNS depressant effects. In this case, CBF imaging must be performed [17].

The existence of a flat EEG must not be considered as a synonym of brain death but must always be accompanied by a complete clinical examination to confirm brain death [19].

Table 3.3. **Advantages and disadvantages of ancillary tests for the diagnosis of brain death**

	Advantages	Pitfalls and disadvantages
Electroencephalography	• Bedside • Wide availability • No requirement for contrast medium	• Presence of artefacts • Examination of supratentorial structures, but not infratentorial • Influenced by depressants of CNS, hypothermia and hypotension
Multimodal evoked potentials	• Bedside • Allows monitoring • Less influenced by depressants of CNS and hypothermia than electroencephalography	• Examination of few structures of CNS
Transcranial Doppler	• Bedside • Non-invasive • No need to use contrast medium • Can be repeated frequently • Can show cerebral circulatory arrest as a process • Not influenced by depressants of CNS	• False positive flow in cases of non-hermetic cranium (big fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) • Lack of sonic window in some patients • Operator-dependent (high level of training) • Appropriate blood pressure required
Angiography	• Not influenced by depressants of CNS	• Invasive • Not available in all hospitals • Use of potentially nephrotoxic contrast agents • Need to move the patient out of ICU • False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains)
Angio-scintigraphy	• Less invasive • No use of iodinated contrast • Not influenced by depressants of CNS	• False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) • If negative for BD, it cannot be repeated until elimination of radiotracer • Need to move the patient out of ICU (except for portable gamma camera)
Computed tomographic angiography	• Not influenced by depressants of CNS • Operator-independent • Fast, widely available, technically uncomplicated	• False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) • Need to move the patient out of ICU

3.4.2.2. *Multimodal evoked potentials*

The multimodal evoked responses to luminous, sound and electrical stimuli examine the visual, auditory and somatosensory pathways at different levels. These give information regarding the integrity of the pathways or their exclusive functional extension to the peripheral nervous system. Among the different modalities of the evoked potentials, the auditory brainstem responses (ABRs) and somatosensory evoked potentials of short latency for median nerve stimulation (SEPs) have shown the best results in brain-death diagnosis [49]. In brain death, evoked potentials are characterised by the disappearance of all waves corresponding to intracranial nerve generators and the persistence of activities of extracranial origin. In the auditory evoked potentials of the brainstem, all evoked responses of encephalic origin disappear, with only the presence of wave I, generated in the auditory nerve in the extracranial area. On the other hand, somatosensory evoked responses that demonstrate the spinal cord as the highest level of nerve-signal processing are compatible with brain death (assuming that no isolated infratentorial devastating cerebral lesion exists).

One of the hypothetical advantages of evoked potential technique is its resistance to CNS-depressant drugs, such as barbiturates, and hypothermia. It is a non-invasive technique with a bedside approach that allows monitoring and follows the evolution of the patient. However, the accuracy of evoked potentials in the diagnosis of brain death is still open to discussion, possibly due to lack of experience with the method except in specialised centres [49].

3.4.3. Other tests

Other instrumental tests have been described as useful add-on tools for brain-death diagnosis, measuring cerebral electrical activity (e.g. bispectral index – BIS), intracranial and cerebral perfusion pressure, decrease in cerebral consumption of oxygen etc. However, their lack of accuracy makes them useless, since their role in brain-death diagnosis is not confirmed by appropriate studies.

3.4.4. Special circumstances

Ancillary tests, when used to confirm brain death, require caution in special situations: patients with non-airtight cranium, patients under the effects of CNS-depressant drugs, and infants and children (for infants and children, see §3.5).

3.4.4.1. *Decompressive craniectomy – skull defects – ventricular drains*

The absence of a cranial-airtight skull induces changes in the normal balance of extracranial/intracranial pressure. As a consequence, tests exploring CBF show a decrease in diagnostic accuracy, particularly in the following causes of persistent CBF in brain-dead patients [50]:

- infants with pliable skulls;
- decompressing fractures;
- ventricular shunts;
- ineffective deep brain blood flow;
- reperfusion;
- extracranial herniation of intracranial vessels;
- jugular reflux;
- emissary veins; and
- artefacts of excessive pressure in contrast injection.

For example, in the case of skull defects (decompressive craniectomy, external drains, infants, etc.), because the increase of intracranial pressure may be partially compensated, the use of CBF tests for brain-death diagnosis leads to false negative results. To avoid a delay in the diagnosis, the use of other tests such as EEG and multimodality evoked potentials (or angio-scintigraphy) is recommended.

3.4.4.2. *Drugs depressant of central nervous system*

The administration of high doses of barbiturates and other CNS-depressant drugs can interfere with the clinical examination. EEG is very sensitive to this confounding factor.

Thiopental administered in continuous infusion, as a result of the wide range of plasma concentrations corresponding to efficacy (25-50 mg/L) and toxicity (30-70 mg/L), does not have a well-established therapeutic range because of the overlap between the two [51]. Long-term infusion increases thiopental levels, which remain elevated for more than six days in cerebrospinal fluid and serum after termination of its administration. The value of serum levels of individual drugs is highly controversial; in many countries the use of ancillary tests (perfusion, electrophysiology) is mandatory in such cases.

But, in daily practice, correlation between quantitative CNS drug dosage and depth of coma is weak. There is no unanimous opinion about how to make the diagnosis in these cases of CNS-depressant drugs and there are different opinions on the best policy to apply: waiting until the plasmatic levels of barbiturates or other measurable depressant drugs decrease to infra-therapeutic levels (most reasonably),

or waiting for the diagnosis until these levels reach zero. Furthermore, all clinical evidence explaining the observations may be more important than just relying on some measurements of blood levels that do not well explain the clinical situation. On the other hand, considering cases of isoelectric EEG due to the effect of drugs, the use of other techniques – such as techniques that examine CBF – could help to confirm the diagnosis, since they are not affected by CNS-depressant drugs.

In summary, no test shows 100 % accuracy covering all situations of brain death. CBF studies are not influenced by confounders such as hypothermia or sedative agents, unlike EEG. In the case of non-air-tight cranium, it is better to use an EEG to confirm the clinical diagnosis of brain death. When available, four-vessel angiography, radionuclide CBF testing, TCD, CTA and EEG are currently the most widely used and recognised, with a legal value in confirming brain death. Choosing one test over another requires a good knowledge of the advantages and limitations of each test and also of their technical requirements (see Chapter 3). They should be performed and documented by qualified and competent physicians – radiologists and electrophysiologists. The final result of the confirmatory test should be documented in the medical report together with a checklist to ensure that each step of the brain-death diagnosis process has been validated beyond doubt.

3.5. Brain-death diagnosis in infants and children

Determination of brain death in term newborns, infants and children is a very sensitive field, with different national regulations in place. In preterm infants of less than 37 weeks gestational age, the concept and diagnosis of brain death lack sufficient accuracy and confidence to be appropriately applied. Clinically, brain immaturity as well as anatomical and physiological differences from adults must be considered; furthermore, young children may have increased resistance to ischaemic-anoxic insults and intracranial hypertension, recovering cerebral functions after prolonged neurological unresponsiveness, compared with adults. Consequently, a more prolonged observational period, a neurological examination targeted at newborn reflexes (i.e. sucking and rooting reflexes) and a mandatory ancillary test are all clinically recommended. Available recommendations refer mainly to the recently updated American Guidelines for the Determination of Brain Death in Infants and Children from 2011 [52].

Legally, in most countries a different procedure for children is defined, based on a longer observational period than in adults and mandatory ancillary tests. In some countries, the brain-death concept is only considered after 7 days to 2 months of extra-uterine life and the observational period may range from 6 to 24 hours depending on age. Adult guidelines can be used in children older than 1 month or 1-2 years depending on different rules in different countries.

EEG and radionuclide CBF testing are the most frequently used ancillary tests. In countries where whole-brain death concept is applied, EEG is the most frequently used ancillary test. In this case, two EEGs are often required together with two clinical examinations. EEG should respect the standards established by the American Electroencephalographic Society [53]. Other ancillary tests (CTA, somatosensory evoked potential studies, MRI – magnetic resonance angiography, perfusion MRI) still lack sufficient data for the purpose of brain-death diagnosis in infants and children.

Considering the wide variability in recommended procedures for brain-death diagnosis in children even in Europe, an effort should be made in the near future to define an international consensus, based on scientific evidence and best practices, that should properly be included in national guidelines and rules.

3.6. Implications of brain-death diagnosis

Once a brain-death declaration is made at the end of the observation period, an individual is pronounced legally dead. Certification of death is the final common result of the process of death determined by either cardio-circulatory or neurologic criteria. In most countries, mandatory procedures for certification are based on specific legal requirements, including continuous observation for a variable number of hours in the case of neurological criteria, or the documentation of cardiac arrest for 5-20 minutes in the case of circulatory criteria. This period is aimed at proving the irreversibility of detected signs and brain death. In most countries, an independent committee of specialists who perform the tests and finally sign the certificate is requested for brain-death declaration.

Death should be declared when it is confirmed by neurologic criteria, not at the time when the ventilator was removed or at the time of circulatory arrest. It should be made clear to professionals and relatives that, after a brain-death declaration, any legal or mourning procedures – including autopsy and

funeral – can now be performed and last wills can be probated.

As death (i.e. irreversible total brain failure) is unique but may be declared on the basis of two different mechanisms (i.e. following circulatory/respiratory arrest or direct devastating cerebral injury), clear pathways should be defined, balancing uniform policies to be followed after the death declaration with appropriate concern for the feelings of the family as well as for any religious and social considerations.

Establishing a clear course of action after the brain-death declaration is of paramount importance and its implication cannot be influenced by the significant differences in procedures for death certification among European countries [33], particularly when brain death is not followed by organ donation. In this case, physicians should act wisely and humanely, explaining the situation to the relatives, making it clear that withdrawal of mechanical ventilation will not make the patient die but that continued ventilation is unnecessary, and therefore inappropriate, for a patient already dead. The only reason for maintaining ventilation for a short time is to preserve organs if consent is available for donation. ICU personnel should be properly educated and prepared to face the moment of ventilator withdrawal and waning cardiac function, explaining – to relatives and others concerned – the possible occurrence of spinal reflexes and the clinical, ethical and legal significance of their act. Appropriate answers should be given to respond to any doubts concerning brain death coming from relatives and professionals, taking into consideration the personal and psychological concerns of critical-care personnel and clarifying roles and responsibilities in brain-death determination and *post mortem* procedures.

Nevertheless, some patients who fulfil brain-death criteria but present absolute contraindications or opposition to organ donation are not promptly disconnected from ventilation after brain-death declaration; death may thus follow by spontaneous circulatory arrest hours or days later. Surprisingly, this confusing situation still occurs, because of either family opposition or physicians' attitudes that reflect doubts about brain death as real death [54]. In the case of donation refusal after brain-death confirmation, the legal opportunity to withdraw life-sustaining therapies – mainly ventilator support – is an absolute right which should be clearly stated in the legal framework surrounding brain-death declaration. In two North American states, New York and New Jersey, hospitals must take into account the family's religious or moral views when deciding how to proceed in such cases; in all other US states, there is no requirement to consult the family on how to terminate care. Consequently, it is important to raise the public's awareness of brain-death implications: the public needs to fully understand that the declaration of death cannot be the family's decision and that brain death is completely equivalent to the irreversibility of the more traditional 'cardio-respiratory' death.

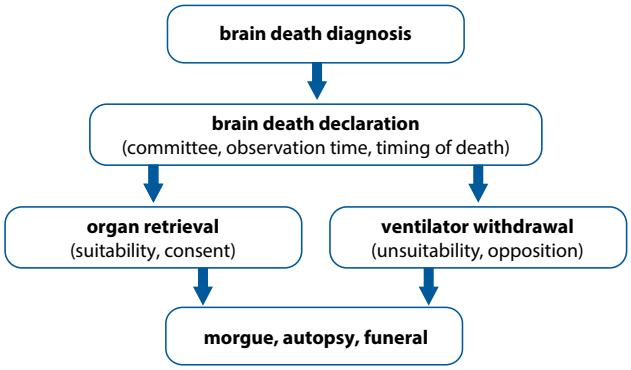
At the same time, practitioners should be sensitive to the feelings of families who suddenly have to face the death of their loved one. Thus, it seems reasonable to give the family some time to understand the process and absorb the concept of brain death, and to support the relatives during the whole process of diagnosis, observation and declaration of death, by honest, empathic, clear and understandable information and explanations. Nevertheless, hospital policies and practices should be as uniform as possible [55].

Brain death in a pregnant woman is an exception: intensive support can be prolonged after brain death for days and weeks, after ethical approval and family request, to allow adequate foetal maturity prior to delivery and organ donation [56]. In practice, as spinal cord function may recover after an initial 'shock' and primitive medullary reflexes can establish a level of circulatory integration and body metabolism, intensive care techniques can compensate in the dead person for the loss of brain function for months. This is accompanied by functions that are not strictly brain-dependent such as the immune response and the inflammatory responses, growth of the body and hair, wound healing and, finally, gestation of a foetus [57].

Only a few national laws (in seven European countries) indicate that death has to be determined by neurologic criteria regardless of potential organ donation, in all cases as soon as all the criteria of brain death are completely fulfilled. In other countries, according to the law, death determination by neurologic criteria is not mandatory if donation is not expected. In reality, even if national laws always require declaration according to brain death criteria, this procedure is rarely applied when unsuitability or opposition are already known. In reality, the number of brain-dead patients may be significantly underestimated because of end-of-life choices leading to cardiac arrest after withdrawal of life-support therapy, personal judgment of medical unsuitability for organ donation or unfavourable attitudes of individual ICU physicians towards brain death. In these cases, brainstem reflexes or apnoea may not be tested or documented [58]. An audit of all deaths in British

ICUs showed that brainstem tests had not been performed in over 30 % of persons in a likely brain-death condition [59].

Figure 3.3. **Management algorithm of brain death**



Public campaigns on organ donation could take advantage of public awareness of a clear and independent concept of death determination. National regulations and scientific guidelines should ideally include, in addition to a solid scientific basis for death determination, unambiguous procedures regarding all the possible implications of brain-death declaration and a clear indication about the time of death (see Figure 3.3). These recommendations could help in managing real situations in which the delicate relationship between medical practice and relatives, ethics and law may strongly affect the extent of social understanding of death declaration and organ donation possibility as normal parts of end-of-life care in an ICU [60].

Social confidence in brain-death diagnosis and the bereaved family's trust in the dead donor rule would benefit from brain-death declaration being standard practice in all subjects who fulfil brain-death criteria. This medical practice could support the fundamental idea that all citizens must be equal in death: there is no difference between potential donors and other patients.

3.7. References

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Chapter 4. Consent/authorisation for *post mortem* organ donation

4.1. Introduction

Donation of organs and tissues from deceased persons saves lives, or significantly improves the quality of life of patients with end-stage organ failure. However, before donation can take place, consent to donation – or absence of any objection as authorisation of donation – is needed, given either by the donor while alive (e.g. organ donor registry, organ donor card, non-donor registry, advanced directives) or given by the family of the potential donor [1-2]. The focus of this chapter is on the different legal systems for consent or authorisation to enable the donation of organs and tissues after death. Although the term 'consent' is used throughout this chapter, the Guide recognises that in some countries the term 'authorisation' rather than 'consent' is used to enable lawful procurement of organs and tissues.

This chapter also explains how different types of organ donor have an impact on the way the family is approached to support donation. It recognises that communication with bereaved family members requires clear and sensitive procedures or protocols, with consent obtained (or not) by appropriately trained specialists in donation, and it makes a number of recommendations as to how to communicate with families.

4.2. Consent or authorisation for organ and tissue donation

4.2.1. Legal consent systems

Consent for the donation of organs and tissues from deceased donors is subject to national legislation and regulation in each country. In general, there are two main legal consent systems to express individual consent: an opting-in system and an opting-out system. Although both systems are based on the self-determination of the individual, they have opposite starting points.

4.2.1.1. *Opting in or opting out*

According to the principle of the opting-in system, donation can only be initiated either if the deceased in life explicitly expressed his/her willingness to donate, or when the qualifying bereaved family member gives consent. The opting-out system starts from the idea that it is normal for people to donate organs *post mortem*, and therefore organ donation takes place as long as there is no evidence of any objection (of legally accepted type) by the deceased; note that some countries also accept evidence of previous oral objection by the deceased if the relatives present it. While an opting-out system presumes the consent for organ donation, the opting-in system states that donation can only take place after explicit consent. There are arguments for and against each system. From an ethical point of view, the two systems can

be considered equivalent because each has systematic ways to express positive or negative intent. In practice, operational variations exist within both systems, because bereaved relatives play a prominent role in the decision-making process.

Table 4.1 gives an overview of the different national consent systems in Europe. The information comes from a survey by the European Commission in August 2014 (Directive 2010/53/EU Implementation Survey) and was updated by the FACTOR study in 2016. From the 37 responding countries, the majority (22 countries) have an opting-out system, while 12 countries reported an opting-in system and three a mixed system. Mixed systems usually imply regional differences within a country with autonomous regions. For example, in the United Kingdom there is an opting-in system in three of the four United Kingdom administrations (England, Scotland and Northern Ireland), whereas Wales has an opting-out system. Other countries combine elements of both systems.

4.2.1.2. *Documenting people's wishes*

Irrespective of the type of consent system in place, many countries have procedures to help residents express their wishes regarding organ donation [3]. These include donor cards and organ donor registries that help make clear an individual's willingness or refusal to donate organs after death. People who have donor cards are often simultaneously recorded in the national donor registry. In some countries, the personal statement on consent to donation recorded on a donor card contains (or can be amended to include) detailed information, e.g. consent to specific types of donation – donation after brain death (DBD) or donation after circulatory death (DCD) – or to the donation of specific organs or tissues. In some countries, advanced wills documentation is popular. This enables people to state prospectively under which medical conditions they do not want to receive life-sustaining therapy. This does not conflict with the potential to become an organ donor. Advanced wills registries also allow documentation of people's wishes related to donating organs and tissues after death.

National legislation or operational policies need to make clear what evidence (i.e., written or oral) is valid in their country to confirm consent or objection to organ and tissue donation. However, consent to donation can take many forms, and many countries allow more than one way to express wishes regarding organ donation. All national systems should enable individuals to withdraw their consent or objection at any time. This ensures that the most recent information about an individual's wishes is recorded in some way and is available 24/7 for a doctor or a donor co-ordinator who is involved in the donation process.

4.2.2. Establishing consent in other circumstances

In countries with no legal framework for consent to donation, or where a potential donor is not able to express their donation preference during their life, for example a minor, the decision is, as a rule, left to the family of the potential donor, based on the assumption that the family would respect and represent the potential donor's wishes. Alternatively, power to consent can pass to those who are the nominated legal representatives of the potential donor, according to the national rules of the country.

In some specific cases, consent or authorisation to proceed with donation needs to be given by a coroner, judge or family court – for example, when death occurs in suspicious circumstances or because of an illicit act.

In other circumstances, if the expressed wish of the person is to become a donor but the relatives of the potential donor are absent, or it is impossible to contact them, national procedures should enable organ and tissue donation where possible, providing there is sufficient medical, social and behavioural information available to support safe donation and transplantation.

4.2.3. Specific consent for deceased tissue donation

Consent for deceased tissue donation should be obtained in accordance with applicable national law and internal hospital procedures and should not differ from the rules applied to organ donation (see the *Guide to the quality and safety of tissues and cells for human application*). When the identity of the deceased donor is unknown, donation cannot take place, as consent and medical history will be impossible to obtain.

4.2.4. Documentation of consent

Consent for organ donation should be documented [5]. The method of documenting and record keeping should be described in a hospital's quality system in accordance with national rules (see Chapter 16).

Table 4.1. **Legal provisions in European countries for consent to/authorisation of organ donation from deceased persons**

	Country	National consent system	Donor registry	Non-donor registry
1	Austria	opting-out		×
2	Belgium	opting-out		×
3	Bosnia Herzegovina	opting-out		
4	Bulgaria	opting-out		×
5	Croatia	opting-out		×
6	Cyprus	opting-in	×	
7	Czech Republic	opting-out		×
8	Denmark	opting-in	×	×
9	Estonia	opting-out	×	×
10	Finland	opting-out	NA	NA
11	France	opting-out		×
12	Germany	opting-in		
13	Greece	opting-out		×
14	Hungary	opting-out		×
15	Iceland	opting-in	NA	NA
16	Ireland	opting-in	NA	NA
17	Italy	opting-out	×	×
18	Latvia	opting-out	×	×
19	Lithuania	opting-in	×	
20	Luxembourg	opting-out	NA	NA
21	Malta	opting-out	×	
22	Montenegro	opting-in		
23	Netherlands	opting-in	×	×
24	Norway	opting-out	NA	NA
25	Poland	opting-out		×
26	Portugal	opting-out		×
27	Romania	opting-in	×	
28	San Marino	opting-out	NA	NA
29	Serbia	opting-in	×	
30	Slovakia	opting-out		×
31	Slovenia	mixed system	×	×
32	Spain	opting-out	×	×
33	Sweden	mixed system	×	×
34	'The former Yugoslav Republic of Macedonia'	opting-in	NA	NA
35	Turkey	opting-in	×	
36	United Kingdom	mixed system (opting-out in Wales)	×	×

NA: data not available. Note: some countries do not have registries, but advanced will directives fulfil this requirement.
Source: Adapted from European Commission's implementation survey regarding Directive 2010/53/EU [4].

4.2.5. Consent to deceased donation from non-residents

With increasing global mobility, the number of deaths of persons not residing permanently in the host country is likely to increase. These non-residents have the potential to become organ and tissue donors.

The diagnosis of death and donation assessment (health, social, behavioural and travel history) of a potential non-resident donor will follow the law, regulations and requirements of the host country. The establishment of consent should be performed in accordance with the general rules described in this chapter as well as with the legal rules of the hosting country. There are countries where the family will be asked to consent to donation in the case of a potential donor coming from a foreign country. Another practice is to consult the country of origin of the (non-resident) potential donor through, for example,

the competent authority or embassy, to ascertain the person's wishes in respect of organ donation (as recorded, for instance, in the national organ donor registry). An enquiry form (see Table 4.2) completed by both the host country and the country of origin might be helpful in establishing consent or objection. The embassy or other national representatives of a potential donor should be informed about organ donation.

Table 4.2. **Information needed in an enquiry form about possible organ donation from a non-resident**

Identification of the potential donor
• Family name, given name • Address • Date and place of birth • Passport number or personal identification number • Other useful information
Details of requesting organisation (host country) to donor's country of origin
• Organisation name • Address • Contact person • Contact details • Date/time
Record of response from potential donor's country of origin
• Consent to donation established – donation is possible • Objection to donation established – donation not possible • Contact person • Contact details • Date/time • Other useful information

4.3. Communication with family members involved in the donation process

The death (or ominous prognosis) of a potential donor is often sudden and unexpected. Communication with family members of the deceased may require multiple conversations with professional staff. The strategy must be to avoid unnecessary harm or distress. The best practice is to establish a stable relationship between family members and healthcare staff before the subject of organ donation is introduced. Skill enhancement of physicians has been advocated, to balance caring for grieving family members with raising the question of organ donation.

The following sections set out good practices in approaching families to enable a discussion about organ donation to take place at an appropriate time, in an appropriate place and with someone with the appropriate skills [6-8].

4.3.1. Importance and timing of the family discussion

The highly emotional conversations with relatives are a great challenge for doctors and nursing staff in the emergency departments and intensive care units (ICUs).

The need for early identification of potential organ donors, combined with experience in practice, has highlighted the importance of the discussion with the family, which should be structured into a series of successive and independent phases [7]. The preparation for a family approach to organ donation starts when the patient is admitted to hospital, but the type of information delivered must follow the changes in the patient's condition. The relatives have to face, sometimes very soon, the possible consequence of devastating brain injury, and they will have many doubts, questions and fears to discuss. The emergency department and ICU staff must inform the family about all relevant and new information as soon as it is available, including all the diagnostic and therapeutic life-saving attempts.

Participation of the donor co-ordinator in the family discussion significantly increases the probability of obtaining consent; therefore the donor co-ordinator should be notified before the family discussion occurs. Consent rates may be higher when the interview takes place after the brain death declaration, or when brain death is expected to occur within the ICU, compared with other clinical situations [9].

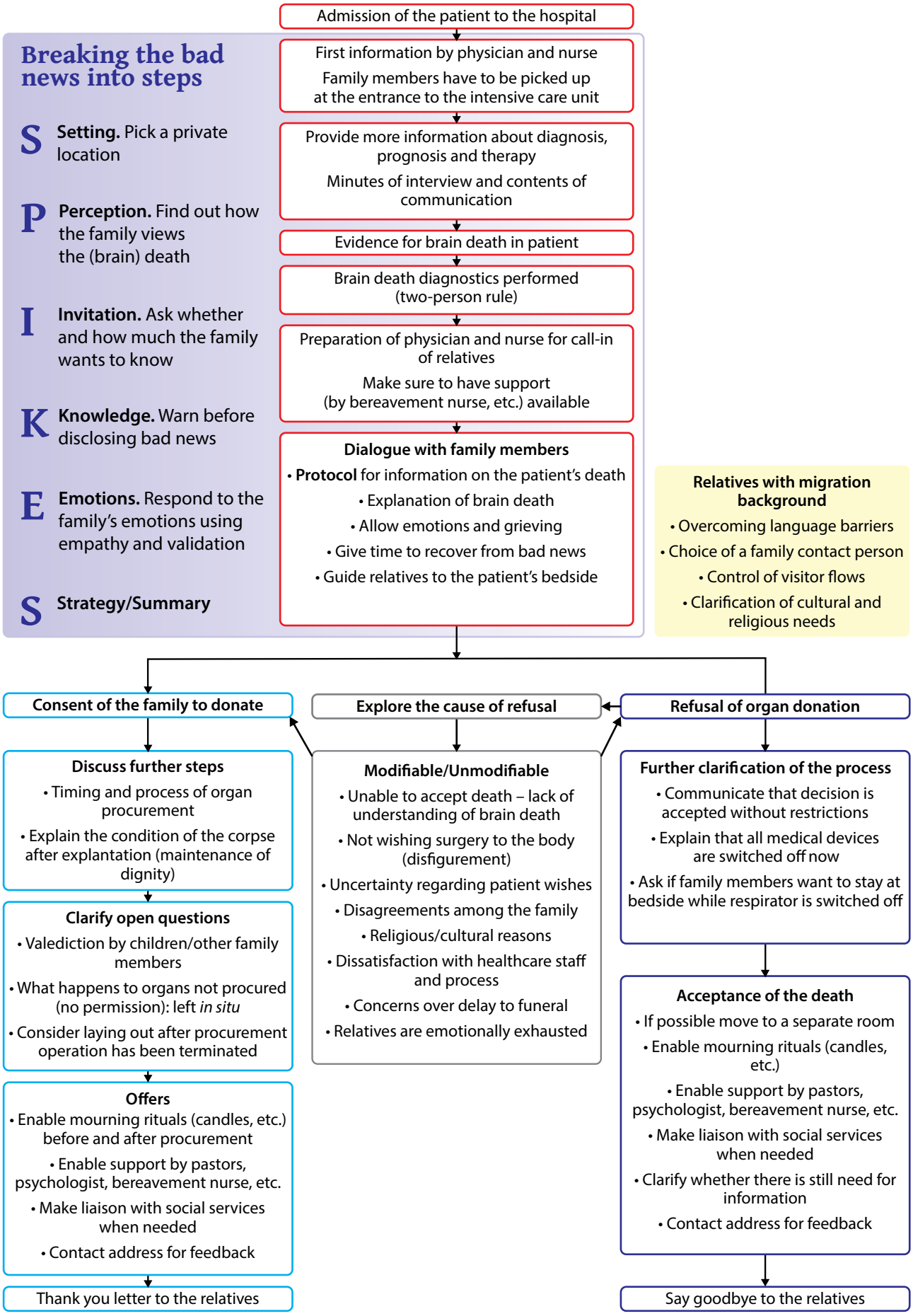
However, the possibility of organ donation should never be presented until the family has understood and recognised the inevitability of the death of the potential organ donor [10]. It is very important to establish a professional helping relationship that facilitates the necessary trust so that the relatives are willing to accept the option for donation [7].

Depending on the specific point in time when it happens, the discussion with the relatives of potential organ donors deserve a step-by-step approach:

a. development, progression and prognosis of the illness/critical injury, considering the initial diagnostic and therapeutic measures,
b. death after confirming brain-death diagnosis,
c. clarification of the expressed and presumed will of the deceased to organ donation,
d. information about the donation procedure.

Parallel to the mediation of medical and nursing specialist information, obtaining the empathetic support of relatives in the processing of these messages is a priority task of doctors and nurses.

Figure 4.1. **Standardised sequence of dialogue with bereaved family of potential brain-dead organ donors** [12-13]



4.3.2. Interprofessional task

In principle, discussions with relatives should be performed only by staff who have been trained to carry out such discussions. A doctor will be required to provide medical information. Caregivers, however, also have a decisive role to play in communicating with relatives, since they have the most intensive contact with the patient or their relatives. The conversation with the relatives is considered as an interprofessional task, because:

- relatives are in an extreme situation and grieving reactions can be better ameliorated by a team approach,
- the relationship and trust building between relatives and caregivers has often already taken place,
- the flow of information is guaranteed when the families turn to the nurses later.

If necessary, pastoral counsellors or clinical psychologists can be consulted. Given the evolution of our domestic and global society, it is paramount to attend to the individual needs of families from diverse cultural backgrounds.

4.3.3. Giving bad news

Bad news may be defined as 'any information which adversely and seriously affects an individual's view of his or her future' [11]. In the preparation phase of giving bad news, some questions must be answered: where, to whom and when to provide the news. The venue for discussion should help and support the conversation, perhaps located close to the place where their loved one died, to give family members the opportunity to say goodbye. It is important to provide a quiet, separate room for the family, where they can speak freely. It is also advisable to have resources that meet their minimum needs (telephone, handkerchiefs, water, seating).

It is frequently impractical to discuss organ donation with a large number of family members and it is recommended that participating family members should be limited to those who are key to the decision-making process, taking into account the legal framework in place and cultural practices or religious traditions. This should be explained to the other family members.

A supportive relationship is established by reflection of emotion and active listening. The empathetic response consists first of observation, looking for any emotion on the part of the relatives (silence, crying, denial, fear, anger); then help to express the emotion verbally; and help to identify the cause of emotion. Active listening is useful, but is an underused communication technique; it involves asking questions (open-ended, closed, inquisitive) to seek clarification, the use of paraphrasing and the appropriate use of silence. To facilitate decision-making and bereavement that is uncomplicated by questions about brain injury and subsequent death, families need time to understand the information given, with care in the way and context that information was shared and attention to their emotional needs [12].

A Six-Step Protocol for Delivering Bad News (SPIKES) is a model for giving bad news, which may be adapted from general medicine to approaching the family about donation [13]. It divides the task of giving the bad news into steps, rather than making it one big procedure that can be confusing. Each step represents an individual, learned and practised skill and the steps can then be put together into an overall package (see Figure 4.1).

The NURSE model can be used to structure the discussion (see Table 4.3) [14]. The basis for this approach to communication is to adapt the information to the relatives' capacity to take it in. It is about taking breaks, allowing reactions, expressing emotions and understanding. The formulation of respect for the situation of the relatives also serves the important purpose of strengthening their resources.

Table 4.3. **The NURSE model [14]**

1	**N**aming	Emotions	Name the perceived mood
2	**U**nderstanding	Understanding the emotions	Existing understanding expresses appreciation
3	**R**especting	Respect or recognition for the relatives	Opportunities to cope with the burden should be emphasised by the intensive staff
4	**S**upporting	Offer support to family members	In the form of an offer
5	**E**xploring	Find other aspects of emotion	Clarify ambiguous or missing feelings

The NURSE model provides a collection of helpful responses to the verbal or non-verbal emotions expressed by the affected person. The points are applied to specific situations, so they are not necessarily all applied each time or in the same order.

4.3.4. Dealing with grieving and aggressive reactions

Information about the sudden death of a beloved family member can lead to various grieving reactions among relatives, such as aggression and rage. The CALM model as a communicative technique can offer a way out of difficult interactions [15].

Table 4.4. **The CALM model for de-escalation in dialogue with bereaved family members [15]**

Step 1	C – Contact	• Remain calm and matter-of-fact (do not get infected by the aggression of relatives) • Respect that the relative is in a difficult situation • Show friendly behaviour (verbal and non-verbal) • Admit possible own mistakes, without giving up justifications • Clarify relationships that have led to the unpleasant situation
Step 2	A – Appoint	• Directly address the emotions (anger, disappointment, etc.) shown by the relatives • Wait for a possible short-term escalation in the expression of emotions, wait before responding to aggression (anxiety, worry, etc.)
Step 3	L – Look ahead	• Clarify the professional relationship between doctor and patient • Suggest the option of choosing how to proceed • If necessary, define the limits and the communication rules with which further co-operation can take place
Step 4	M – Make a decision	• Offer a 'contract' that the family members can accept or not • Make alternative offers (if possible) • Postpone continuation of the discussion to a specific later date

Grief can be described as 'a cognitive process of confronting a loss, of going over the events before and at the time of death, of focusing on memories and working toward detachment' [16].

The person leading the conversation with the family can meet with various emotional reactions that are characteristic of people in grief (see Table 4.5). It is very important to understand the possible reactions connected with grieving. For a conversation about potential organ donation, it is essential to establish good rapport with the relatives of the deceased. The donor co-ordinator is responsible for adjusting the conversation to the family's needs and expectations. This can be summarised as 'establishing a therapeutic relationship'.

The healthcare professional or donor co-ordinator who is leading the conversation with the relatives should respect their grieving. This type of conversation requires interpersonal skills, sensitivity and empathy. In situations when there is pressure on healthcare staff, the conversation with the family can become difficult, rushed or insensitive.

4.4. Approaching the family about donation after brain death

A multidisciplinary team should be responsible for planning the approach and discussing organ donation with the family. This allows all members of the team to be clear about how the discussion will proceed: when, where and with whom. This multidisciplinary team should include the clinical team involved in the care of the potential donor, the donor co-ordinator and where necessary the local faith representative [8].

The team should determine:

a. any clinical issues to be clarified,

b. any evidence of the will of the deceased, such as registration on national donor registries, and next of kin or key family members to be involved in the consent process,

c. specific cultural need, family or faith issues to be taken into account.

4.4.1. Information about brain death diagnosis

Irrespective of the consent system for organ donation, and differences in practice across countries [16-17], a conversation with the family of the potential DBD donor is required to convey information about brain death and the potential for organ donation [6].

The conversation with the family of a potential DBD donor will aim to do the following:

a. inform relatives of the patient's death,

b. support the family by focusing on their emotions and current needs,

c. explain the current situation (with the concept of brain death and other aspects of death and donation),

d. inform relatives about the potential of donation,

e. establish the wishes of the deceased about organ donation,

f. obtain additional information from relatives on medical, social and travel history and risk behaviours,

g. obtain family consent or support for organ donation.

Table 4.5. **Bereaved family and donor relatives' grief reactions to bad news**

Grief reactions	Remarks
Basics	Grief is a personal and unique experience. Healthcare professionals must respect the various displays of grief, taking into account unexpected emotions and behaviours. The sudden death of an apparently healthy person, which is frequently the case with a potential donor, finds the family unprepared. This extreme situation triggers a wide variety of reactions. All of them occur in combination with a variable degree of expression. This requires appropriate feedback to each individual reaction in order to avoid harm.
Shock	Shock is the initial reaction after receiving bad news. The person is unable to react and becomes emotionally paralysed. The person's non-response to the environment is an attempt at self-protection while being faced with uncontrollable feelings. This may be manifested in confusion (inability to assimilate information and/or to make decisions).
Denials and displacement	Denial and displacement are associated with lack of acceptance of an irreversible loss. Observed statements include 'It's impossible', 'It's not true', 'How could he have died, if he is breathing?' or 'You've made a mistake'. Relatives use denial as a protection against having to deal with reality. This requires patience, since forcing the information about reality only increases this defence mechanism in the family and further complicates adaptation to the new situation, or it may cause escalation of arguments and negative emotions on both sides with misunderstandings. This should be avoided. Inability to accept the loss of the loved one is often accompanied by a feeling of surrealism. This is stronger in cases of unexpected or sudden deaths. The emotional impact makes it difficult to assimilate information and increases the refusal to accept facts.
Anger and rebellion	When someone realises that a relative is dead, a feeling of undeserved harm and great injustice may arise. The typical reaction is anger and rebellion shown by asking such questions as: 'Why?', 'Why did he die?', 'Why did it happen to us?' In this early stage of grieving, relatives intensively look for an explanation for the reasons of death and may accuse medical staff. These reactions of the family, especially claims or allegations against a healthcare professional, are difficult to deal with. If the healthcare professional perceives them as threatening and tries to defend herself or himself, then it may be seen as confirmation of guilt. This should not be taken personally by the healthcare professional or the clinical team but seen as an essential part of the grieving process that might lead to an acceptance of death and an agreement to organ donation in time.
Rage and blame	Rage and blame are natural feelings born out of frustration when faced with the impossibility of changing what has happened. Therefore, this emotional thunderstorm should be allowed while the safety of relatives and clinical staff is ensured. It can be directed to the deceased, the medical team, God or even the person suffering. Rage and blame, when directed towards a healthcare professional, may be difficult to accept and cause confrontation. Blame is closely linked to rage. For the bereaved person, it may be necessary to find someone responsible for what has happened.
Bargaining	Another reaction is to negotiate the extension of a deceased person's life. This is described in the literature as 'bargaining'. In response to information about the death, the relatives try to deny the inevitability and irreversibility of this fact. They sometimes try to find a way to turn things round – 'If the brain is not working, isn't it possible to transplant the brain?' or 'To whom and how much do I have to pay, to make him alive?' Although sometimes a family's questions may cause impatience or indignation, it means that relatives are still willing to pay any price to regain the loved one.
Depression	Depression, as a short or long-lasting episode of disillusion, hopelessness, sadness and grief, is a common reaction to death. Depression is observed as 'family plunged into grief'. Relatives of the deceased are often withdrawn or submissive in conversation with clinical staff. They ask only a few questions. In comparison with a reaction of denial or anger, such muted behaviour or reaction from the family may seem to be an acceptance of death and organ donation. However, clinicians should proceed cautiously when observing such reactions because they are associated with increased risk of susceptibility to long-term trauma.
Acceptance	After some time, acceptance of death might be signalled. Reconciling oneself to the death of a close person usually occurs after an exhausting fight, when the family starts to think it is a 'better solution, than …'. Still they need to find a deeper meaning in the death and its circumstances, e.g. religious arguments or considerations such as 'Thanks to organ donation, the life of our relative is symbolically extended in a positive sense' or 'He died but his heart may save somebody's life', 'Although she suffered so much, she let someone else enjoy life', 'Though I lost my son, he let another mother still have her son thanks to the transplanted organ'. If relatives of a potential donor want to know who receives the donated organs, it can be said that they will be transplanted into a person 'similar' to the donor in the biological sense. This information may translate into a conviction of the meaningfulness of the gift.

Table 4.6. **Aspects to consider in communicating with members of the potential donor's family**

Persons attending	Try to limit the number of family members who take part in the donation conversation to those who are legally allowed to make a decision on donation and family members who take the lead in the family network. Explain clearly to the other family members that the intention is to talk first with the key persons responsible, to simplify the communication process. If this is based on the social and cultural background of the donor family, most people will accept this, as long as they are informed properly. When there are social, cultural or language barriers or difficulties, consider seeking the support of interpreters or friends of the possible donor who have a greater level of understanding, integration or knowledge of religious references and whose co-operation may be beneficial for the family. These interpreters or friends should be previously informed about the donation, so they can support the family and maintain a favourable attitude, and not be limited to making a simple translation.
Place of conversation	The conversation should be carried out at the right time, in the right place by the right people. Proper preparation reduces the risk for errors, especially when important information is not available. The place of conversation should provide ease, and should be located close to the place where their loved one died, to enable sight of the deceased again and the chance to say farewell. It is important to provide the family with a quiet room, where they can speak freely and unobserved. They should be provided with at least basic needs (e.g. telephone, handkerchiefs, water and food).
Establishing good contact	Persons conducting conversations with families will encounter different emotional reactions (see Table 4.5). It is important to understand such mourning reactions. Further conversation about potential organ donation requires a good therapeutic relationship with the families.
Sensitivity and empathy	Everyone should respect the mourning of families. A check should be made whether organ donation is consistent with the will of the deceased person, in accordance with national regulations. This requires interpersonal skills, sensitivity and empathy, without psychological pressure, to avoid complications.
Family acceptance of organ donation	The conversation about organ donation aims to fulfil the will of the deceased donor and obtain the acceptance of the family of organ donation. Regardless of the legal position, acceptance of organ donation by relatives must be agreed, and this must not be achieved under pressure. Neither financial nor any material benefit can be offered, and nor can donation be conditional on the deceased donation being directed to a specific recipient or group of recipients.
Family refusal	The family has the right to express their opinion about organ donation, but the will of the deceased, expressed during life, should be respected if possible.

Once the diagnosis of death using neurological criteria is established, the family should be informed in clear and simple words following the KISS rule (Keep It Short and Simple). Any questions about brain death, which can be difficult for medical non-professionals, must be answered objectively and simply. In the conversation, it must be clear that the patient is dead. The word 'life' must be avoided. Keeping it short and simple means there is more time to meet the needs of the affected relatives.

Most ICU clinicians will not have received specific training in approaching the families of potential donors. Although the available evidence is conflicting, consent rates might be higher when donor co-ordinators are involved in family discussions [18]. The donor co-ordinator should first ensure that the family understands what is meant by death as determined by neurological criteria. Only when the family understands that the patient has died – or that death is inevitable – should organ donation be discussed.

4.4.2. Information about organ donation

Conversation about organ donation aims to fulfil the will of the deceased and to obtain family consent or support for donation. Regardless of the legal position, conversations must aim to achieve an acceptance of organ donation by relatives. This acceptance cannot be forced or conditional, nor should it be achieved under pressure or by offering any financial or other material benefit.

It is difficult to proceed with donation when a family is strongly against it, even if there is evidence that their deceased family member wished to be an organ donor. The family has the right to express their opinion about organ donation, and clinicians need to make a balanced decision whether to continue with the donation without the support of the family – with the risk of damaging the emotional health of the relatives and possibly incurring bad publicity and a loss of public confidence in the organ donation programme – or whether to follow the wishes of the deceased and continue with the donation.

It might be helpful to use the following when discussing a refusal with the family:

a. If the family claims that the deceased (or dying patient) did not agree to organ donation or had changed their mind, explore the basis on which the family gives such a statement.

b. When the family does not know anything about the attitude of the deceased to organ donation, discuss whether their deceased relative helped people generally, e.g. as a blood donor or by

giving to charity, and how donation could help many people to benefit from a transplant.

c. If family members are concerned that the body will be disfigured, reassure them that the deceased's body will be fully respected and offer them the possibility of seeing their relative once the donation procedure has been completed.

d. In a case of religious concerns, offer a consultation with a religious leader or representatives.

e. In cases of dissatisfaction with the healthcare provided, record the complaints, but explain that the issue of organ donation should be kept separate.

f. Identify the persons involved in the refusal to donate and their role within the family, and attempt to communicate with them separately to understand and try to address their concerns.

g. Identify whether a disagreement to donation by individual family members is based on conflicts between family members, conflicts which can come to light when a person has died. In this case, try to separate the conflict from the issue of organ donation.

It is helpful to ensure that, following organ donation, the family receives the appropriate care they need. In many countries, hospitals have dedicated bereavement teams to provide psychological support, access to social services, administrative support or religious counselling. The clinical team should establish whether there are any specific religious or spiritual requirements of the family and whether the family wishes to retain keepsakes such as locks of hair or hand and foot prints (usually of children). Finally, establish whether the family wishes to assist with the final preparation of the body following donation, such as washing or dressing in certain items of clothing.

Figure 4.1 provides a suggested sequence of family care and communication with family members, adapted from the Swisstransplant donation pathway [19]. Table 4.6 summarises some key aspects to consider during communication with potential donor family members.

4.5. Approaching the family about donation after circulatory death

4.5.1. The family in controlled donation after circulatory death

Any decision on the withdrawal of life-sustaining treatments (WLST) should be totally independent of any consideration of the potential for controlled donation after circulatory death (cDCD) (see Chapter 12). The guiding principle is that the decision on WLST is made in a transparent, consistent manner and independently of the intentions and plans for organ donation [20-23]. This eliminates any conflict of interest. No investigation focused on organ donation (including consent) can take place before a decision on WLST has been taken. However, it may not always be possible to separate discussions about WLST and donation, if the family members raise the issue of donation themselves. In such cases it must be clarified that the treatment of the patient and any decision about WLST must come first, before any discussion of organ donation.

Although cDCD cases naturally have to follow the same general donation principles with regard to consent, there are some differences and specificities of donation before death occurs. Usually families have a longer stay in the ICU, so there is a closer relation with ICU workers; normally the emotional shock is resolved because, when the consent for donation is going to be given, the fatal prognosis is assumed. We must be aware that donation is a possible situation, not a certain one, and families need to be informed about this.

It is vital that the family be fully involved in discussions about the cDCD process. In addition, the family must be given the following information:

a. reassurance that all healthcare at the end of life will be provided during the process,

b. the location where the withdrawal of treatment will be carried out,

c. the procedure after death diagnosis,

d. the expected time of death (the family need to be aware that the dying process could be prolonged),

e. the possibility that the person will not die within a time frame consistent with organ donation,

f. reassurance that, if the timing of death prevents organ donation, then tissue donation will still be possible following death.

g. reassurance that, if tissue donation is to happen after death, the donor will be transferred to a

room where the family can remain with the dying patient and privacy will be provided.

4.5.2. The family in uncontrolled donation after circulatory death

General rules of consent for uDCD are similar to those of DBD, applied according to national regulations. However, in the case of organ donation after irreversible cardiac arrest, more negative reactions of relatives might be expected, but obtaining acceptance of death might be easier because death is visible according to the traditional perception of death (the cessation of a heartbeat) when compared with DBD [24].

In uDCD, two different situations can be found:

a. The family is present when cardiopulmonary resuscitation (CPR) was performed.
In this situation the family sees all the efforts that have been made to save their relative's life, so this situation can lead to a better understanding of the patient's situation. But sometimes it can be difficult for the family to understand why the patient has not been transferred to the closest hospital.

b. The family is not present when CPR was performed.
In this situation families do not know what care was given, and what was the real situation of their relative; the first information that they receive is about the relative's death.

Sudden death usually provokes strong reactions of denial, impotence or guilt, which requires understanding. During this first phase, donation should not be a raised during the discussion, unless the family initiates talk about donation. This first discussion should be arranged in the emergency department, following the recommendations on good practice [10], e.g. in a private place, with staff allowing grief and accompanying the family to see their deceased relative. In this situation, clinical staff must be aware that the time available to introduce organ donation is shorter than for DBD.

4.6. Approaching the family about tissue donation

Conversations with the family on planned tissue donation (DBD and DCD) do not generally differ from the conversations related to organ donation, described above. Therefore, it is best practice to discuss donation of organs and tissues within one conversation with the family.

The experience of working with families suggests that some difficulties and possible opposition may occur in donation of tissues like skin, bones and eyes when family members may fear disfigurement of the body. In these situations, special emphasis should be put on the legal and medical obligations to respect the body's appearance. If necessary, some technical aspects of donation should be explained, for example the use of specific surgical incisions and sutures, or suitable prostheses or artificial eyes or bones. (See also Chapter 3 'Recruitment of living donors, identification and referral of possible deceased donors and consent to donate' in the *Guide to the quality and safety of tissues and cells for human application*, 3rd edition).

4.7. Successful intercultural communication

4.7.1. Solutions to cultural and language problems

Because of the heterogeneous nature of migrant populations in Europe – in terms of social position, education, occupation, age, residence status, ethical and religious identities, economic conditions, family, friends and not least individual experiences – the range of social realities, affiliations and identities within this group is enormous.

The transmission of bad news (diagnosis, prognosis, brain death, organ donation) is always difficult for the ICU staff. For those families with a migration background, additional factors such as family size, increased visitor frequency and language barriers require further preparation for the delivery of bad news. In extreme situations, cultural and religious factors are particularly important. Ultimately, this can lead to a reduction in organ donation.

Clinical staff often underestimate the difficulty that laypeople can have in understanding information about hospital care. What applies in general also applies to people with an immigration background. Difficulties in communication with them are often attributed only to the lack of a common language. Above all, the mediation of emotional content and dealing with incriminating situations in the treatment of foreign-language relatives may demand new solutions, such as professional translation services. Only then can the information be correctly transmitted and the right questions be asked.

Professional translators have:

- good oral language skills in two working languages,

- knowledge of translation technology,
- communication skills,
- knowledge of ethical guidelines,
- knowledge about cultural respect,
- ways of dealing with incriminating conversation situations,
- willingness to train regularly and, if necessary, to request supervision [25].

In contrast, individual relatives acting as interpreters can present a challenge. Ideally, it is best practice to work with educated interpreters who are familiar with the necessary terminology and who can explain and translate medical terms [26].

Frequently, patients with a migration background belong to large family groups with several generations. The close contact among family, kinship and friends gives each person individual support and security so that no one feels alone or isolated. In various cultures, the medical visit also represents a religious and social duty, which also explains the high number of hospital visits and long visits.

Since visitor flows in the ICU are a major problem, finding a family principal is recommended. Through accurate observation or in conversation, it will become clear who is the family leader. This main contact person is responsible for the regulation of visitor flows, the transfer of information to the family circle and so on.

After clarification of possible problem areas, family members' care can be directly linked to the SPIKES, NURSE and CALM models.

When there are social, cultural or language barriers or difficulties, the support of interpreters or friends of the potential donor with a greater level of integration or knowledge of religious beliefs may be beneficial for the family. These persons should be previously informed about the donation, so that they can support the family and also champion a favourable attitude towards donation, rather than be limited to making a simple translation. The conversation should be planned, and then carried out at the right time, in the right place by the right people. Proper preparation for the conversation reduces the need for improvisation and the likelihood of errors [28-30].

4.7.2. Religious-cultural aspects in the organ donation process

Aside from race/ethnicity, religion plays a key role for many in the decision whether to become an organ donor. Although all major religions support organ, tissue and eye donation, within each religion there are different schools of thought. Most religious texts allude to the concept of helping the needy, which can be extrapolated to include organ donation [31].

There is a general consensus in the major religions that:

- organ donation is an act of charity,
- everyone should make a personal decision during their lifetime for or against deceased organ donation,
- a just distribution of donor organs is necessary,
- organ trafficking is rejected,
- relatives should be involved in the decision about organ donation.

Table 4.7. **Issues and solutions in family members' care**

Issue	Solutions
Overcome language barriers	• Clarify possible language barriers • If a member of the family does not sufficiently speak the language of the country, an interpreter or a colleague who is a native speaker must be consulted
Choose central family contact person	• Clarify who is the family principal partner (family head, family interpreter) • Forward all information about the patient's health to the contact person, who then informs the family group
Clarify if patient belongs to a faith community	• The faith and the religious rituals must be determined • Clarify whether a religious representative should be consulted
Control visitor flows	• Make arrangements and assume responsibility (visitor flows, number of visits, attendance) • Clarify that the time window for visits is restricted by the needs of intensive care unit (ICU)/rest for the recovery of patients • Lay out condolence books for visitors (relatives, friends, etc.) to document their participation
Respect cultural and religious differences	• Respect religious norms and values, as far as compatible with operation at the ICU • Create opportunities for prayer and meditation • Offer farewell facility to the relatives

Source: Development of this model in the Intercultural Workshop of Austrian Public Health Institute [27].

Whether brain-death diagnosis and organ donation are accepted in individual cases depends on the personal, religious and ideological attitudes of the relatives and on their cultural connections. If during the lifetime of the deceased no written declaration of intent has been made, the oral or the supposed will of the deceased should be ascertained in the family discussion.

There is no Europe-wide religious statement from churches on organ donation, but each country may have or should ask for statements from all existing religious groups [31]. The Christian churches accept the death of the brain as a defined death of humans and describe organ donation as an act of charity. In some other religions and cultures, brain death and the ethical basis of organ donation are controversial, or even rejected [32].

This is also the reason why ICU professionals are met with incomprehension and contradiction from relatives with other cultural-religious backgrounds, regarding both the acceptance of observed brain death and the acceptability of organ donation [33].

It is crucial to know the religion, culture and worldview of patients and their relatives in order to minimise possible conflicts.

4.8. Communication training

The training of all professionals – doctors, nurses, co-ordinators and staff from the ICU, especially those involved in family interviews, communication of bad news and discussion of organ donation – is essential. Their skills in verbal and non-verbal interpersonal communication are vital in establishing a relationship with the family. It is also important for the professionals involved to receive specific training to help them avoid the emotional overload that this type of work may induce.

It is recommended that hospital quality systems in organ donation should promote specific communication training of professionals in critical care units through continuing professional education.

The basics and techniques of interviewing must be offered during training through practical exercises, including simulated exercises such as breaking bad news, dealing with the fears and grief of relatives and dealing with dying, death and organ donation. It is helpful to use specialised, trained actors to take on the role of family members in specific situations. The feedback of the member–actor, doctor and nurse will provide effective and fundamental learning to overcome any conflicts in the organ donation process.

4.9. Conclusion

The sudden death of a family member is associated with profound sadness, insecurity and anxiety. This makes communication with the relatives a challenge for doctors and nurses. In addition to medical expertise, social and emotional skills are also required. This chapter has set out the key mechanisms for establishing consent – or at least minimising the refusal rate for organ and tissue donation – and for communication with bereaved families. It also recognises the specific skills required to respond to the issues raised by families.

4.10. References

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Chapter 5. Management of the potential donor after brain death

5.1. Introduction

Brain death (BD) status, as a fatal consequence of devastating cerebral damage, is responsible for pathophysiological events and clinical conditions that should be promptly identified and treated.

Aggressive donor management (ADM) protocols include early identification of possible donors, management at the intensive care unit (ICU) by dedicated personnel and early, aggressive use of fluid resuscitation, vasopressors and hormone therapy. Implementation of standardised ADM protocols gives priority to the management of all critically brain-injured patients identified as possible organ donors, allowing for a timely determination of brain death. ADM protocols result in increased rates of organs procured per donor [1]. Therefore ADM is an essential component of the process of donation after brain death (DBD).

Organ-protective intensive care therapy is the first step towards successful and durable transplantation. To protect organs intended for transplantation from damage and to maintain functional organ quality at the time of procurement, optimal therapy should be based on specific targets and well-defined donor-management goals, particularly in the case of expanded-criteria donors (see Chapter 7) [2-8]. The basic standards of appropriate intensive care medicine and therapy aimed at saving a patient's life already include all aspects of ADM protocols and organ-protective intensive care therapy after brain death, providing continuous protection to any tissue or organ. Deceased organ donor hospital volume has an impact on organ yield, as demonstrated by Patel *et al.* [9], suggesting that centralisation of donor care can increase the number of organs transplanted per donor.

5.2. Pathophysiological changes induced by brain death

Significant brain injury of any aetiology causes systemic pro-inflammatory response syndrome (SIRS) prior to the occurrence of brain death, with such responses as leukocyte mobilisation and release of inflammatory mediators, generation of reactive oxygen species, increased vascular permeability and organ dysfunction. Brain death then also creates a variety of inflammatory, haemodynamic and endocrine effects, which induce significant organ injury prior to organ procurement.

Brain death produces a typical haemodynamic pattern with consecutive dysregulation as a result of the loss of central afference to the cardiovascular system, the respiratory command, the baro- and chemo-receptors and the hypothalamic-pituitary axis. The pathophysiological changes evolve in two successive phases:

a. The agonic phase occurring just before brain death, a stage which is characterised by a catecholamine surge (autonomic storm) responsible for transient episodes of tachycardia–tachyarrhythmias and hyperten-

sion: a physiological response to maintain cerebral and coronary perfusion, associated with redistribution of regional blood flow, increased afterload and visceral ischaemia/injury.

b. The agonic stage is followed by the cessation of central regulatory mechanisms as soon as residual brain-stem functionality disappears because of the gradual arrest of central sympathetic adrenergic regulation.

As a consequence of the irreversible loss of brain function, the most common clinical pattern in brain-dead patients is [10] a combination of:

a. haemodynamic instability and cardiovascular dysfunction, caused by gradual cessation of central sympathetic adrenergic cardiovascular regulation, which is often compared to a sepsis-like or post-cardiac arrest syndrome due to the inflammatory response (up-regulation of pro-inflammatory cytokines) and ischaemia–reperfusion phenomena,

b. hypothermia due to the loss of hypothalamic thermoregulation,

c. the development of central diabetes insipidus as a result of hypothalamic-pituitary-axis loss of function,

d. reduced CO_2 production as the overall metabolism slows down.

These complications should be dealt with early and aggressively, because the number of organs procured can be increased by optimised management of brain-dead patients. Cardiovascular, pulmonary and metabolic management form the cornerstones of potential organ-donor management. The organ-protective strategy requires rigorous care and continuous monitoring to achieve the defined goals. The patient should be reviewed regularly to adapt therapies to the many changes that may occur during donor maintenance.

Treatment regimens of the potential DBD donor aim to avoid a potential negative impact on organ function and should take into consideration the pathophysiological changes caused by:

a. The catecholamine surge (autonomic storm), which occurs during the short period just before brain death and is characterised by:

i. hypertension,
ii. tachyarrhythmias,
iii. pulmonary oedema,
iv. raised vascular resistance,
v. disseminated intravascular coagulation,
vi. capillary damage,
vii. myocardial dysfunction.

In a few cases, hypertensive crisis needs to be primarily treated with Urapidil i.v. or Nifedipin i.v. and, secondarily, with short-acting beta-blocking agents like Esmolol if the heart rate must be reduced. It must be noted that the use of beta-blockers may lead to increased peripheral resistance and risk of left ventricular insufficiency and, after this crisis, a severe hypotension can occur.

b. The cessation of central regulatory mechanisms, which occurs as soon as residual brain-stem functionality disappears and is characterised by:

i. reduced cardiac output,
ii. hypovolaemia,
iii. hypotension,
iv. hypokalaemia,
v. hypernatraemia,
vi. hypothermia,
vii. hypocapnia,
viii. diffuse inflammatory response,
ix. diabetes insipidus.

Therefore it is important to:

a. detect and correct the signs of shock, i.e. hypotension, cardiac dysfunction and vasoplegia, which are responsible for hypovolaemia, oliguria and hyperlactataemia;

b. detect and correct metabolic and endocrine abnormalities, e.g. dysnatraemia, dyskalaemia, blood glucose abnormalities, dyscalcaemia–dysphosphoraemia;

c. prevent hypothermia.

5.3. Monitoring and target parameters

Organ-protective intensive care therapy based on standardised critical care end-points (see Table 5.1) aims to achieve an increase in both the quality and the number of transplanted organs [10].

Basic monitoring (pulse oximetry, invasive arterial pressure measurement, central venous pressure (CVP) measurement, core temperature measurement, urinary output) is not enough whenever the potential donor is haemodynamically unstable or a thoracic organ may be retrieved: in these cases additional parameters (see Table 5.2) should be monitored, using any of three methods – echocardiography, minimally invasive cardiac output monitoring or pulmonary-artery catheterisation – so as to improve the quality and the number of utilised organs [11].

Table 5.1. **Basic monitoring parameters and target range in adults**

Basic parameters	Target range (adults)	Suggested frequency
Central body temperature	35 °C to 38 °C *	Continuously
Invasive mean arterial pressure (MAP)	60-110 mmHg	Continuously
Heart rate **	70-100/min **	Continuously
Urine output	> 0.5 to 1 mL/kg/h	Hourly
Central venous pressure	4-12 mmHg (4-8 mmHg in potential lung donors)	Continuously
Peripheral arterial oxygen saturation (SpO_2)	> 95 %	Continuously
Arterial blood gas, pH	7.3-7.5	Every 2 to 4 hours or as needed
Na	135-145 mmol/L	Every 2 to 4 hours or as needed
K	3.5-5 mmol/L	Every 2 to 4 hours or as needed
Blood glucose	< 150 mg/dL (8.3 mmol/L)	Every 2 to 4 hours or as needed
Plasma biochemistry, urine sediment, C-reactive protein		Every 12 hours or as needed
Calcium level	Normal range	Every 2 to 4 hours or as needed
Haemoglobin/haematocrit	≥ 7-9 g/dL (≥ 4.4-5.6 mmol/L) / ≥ 20-30 % (≥ 0.2-0.3)	Every 12 hours or as needed
Platelets	> 50 G/L	Every 12 hours or as needed
Prothrombin time/partial thromboplastin time	within acceptable range to avoiding bleeding †	Every 12 hours or as needed

Notes:

* Mild hypothermia (34 to 35ºC) may be considered to reduce the rate of delayed graft function in kidney recipients of organ donors after declaration of death according to neurologic criteria [12].

** Due to failure of the vagus node, sinus tachycardia will be observed; if there are no actual or expected cardiac complications, heart rates up to 120/min can be accepted, especially when inotropes or catecholamines are applied.

† Reference range depends on methods of measurement as well as type of documentation of coagulation parameters; this varies between countries and therefore must be checked locally with the target documented.

Regular evaluation of the fluid balance (input–output) and laboratory monitoring of urine gravity and ionograms (both on plasma and urine samples) are required to ensure electrolytic balance. Further revaluation should be done according to the donor instability; however, for potential lung donors, PaO_2/FiO_2 should be checked at least every 2 hours and recruitment manoeuvres should be performed hourly from brain death until organ procurement [13-14].

Table 5.2. **Additional monitoring parameters in haemodynamically unstable donors and donors of thoracic organs**

Additional parameters	Target range
Cardiac index	3.0-5.0 L/min/m^2
Stroke volume index	40-60 mL/m^2
Pulmonary arterial occlusion pressure	< 12 mmHg
Systemic vascular resistance index	2000 ± 500 dyn × s × cm^{-5}/m^2
Intra-thoracic blood volume index	850-1000 mL/m^2
Extravascular lung water index	3-7 mL/kg
Central venous oxygen saturation ($ScvO_2$), %	65-80 %

5.4. Specific considerations

5.4.1. Hypotension due to hypovolaemia and fluid replacement

Hypovolaemia, absolute or relative, is frequent in brain death because of cessation of central stimulation of the vascular bed and up-regulation of proinflammatory cytokines. Large volumes of fluid replacement may be necessary to stabilise the circulatory system and to maintain organ function. The choice of i.v. fluid and rate of administration should also take into account any volume restrictions or prior dehydrating measures to treat cerebral oedema or cardiac complications before brain death, as well as uncontrolled diabetes insipidus. Measures should be taken to evaluate the response to fluid resuscitation and to avoid fluid overload effects on the respiratory system, guided by a monitoring system ensuring the precise haemodynamic profile and left ventricular filling pressure.

Administration of crystalloids or colloid solutions aims to correct intravascular deficit. If large volumes of crystalloid solution are given, balanced salt solutions may help avoid hyperchloraemic acid-

osis and confusion if base excess is being used as an index of the adequacy of resuscitation.

There are still controversies about the use of hydroxyethylamidons in case of distributive shock. According to some authors, new-generation rapidly degradable hydroxyethyl starch solutions with a low degree of substitution seem to have less risk of nephrotoxicity (osmotic nephrosis) on donor kidneys and can be administered with a restriction of maximal dose of 33 mL/kg/day on the first day and 20 mL/kg/day on subsequent days. This complication was initially described with the first-generation hydroxyethylamidons in brain-dead kidney donors [15-17]. The European Society of Intensive Care Medicine recommends colloids not be used in patients with head injury, and gelatins and hydroxyethyl starch not be administered in organ donors [18]. Though this issue is currently the focus of considerable debate, the use of colloids may be acceptable as bolus infusion to solve as quickly as possible maintained hypotension [19]; several ongoing trials are likely to provide new data in the very near future – until then, colloids are usually not recommended in organ donors.

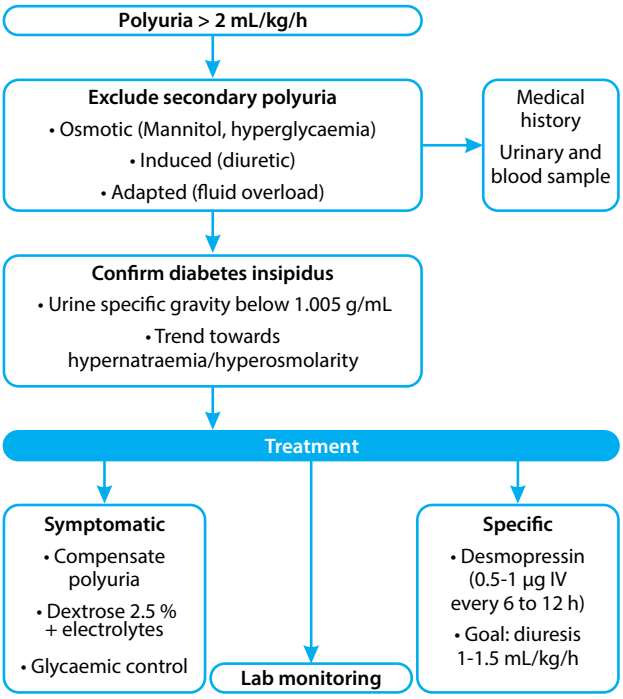
Competing requirements for organ perfusion may produce antagonistic strategies such as fluid replacement or a high value of positive end-expiratory pressure (PEEP). Attentive bedside multi-organ donor management supports adequate perfusion to vital organ systems even with CVP < 6 mmHg. A strict fluid balance can avoid volume overload, increasing the rate of lung grafts available for transplantation without impacting either kidney graft survival or delayed graft function development [20]. Thus, implementing an intensive donor-treatment protocol focused on increasing lung retrieval rates does not have a negative impact on the retrieval rates of other grafts or on early survival of heart, liver, pancreas or kidney recipients.

5.4.2. Central diabetes insipidus and endocrine management

5.4.2.1. *Central diabetes insipidus*

Central diabetes insipidus is commonly observed (in approximately 70 % of all donors). Its management should be initiated promptly, as shown in Figure 5.1 [21]. Diabetes insipidus is caused by a lack of anti-diuretic hormone (ADH) produced by the hypothalamic-pituitary axis. Diabetes insipidus is characterised by polyuria, with a urine volume > 2 mL/kg/h and a specific gravity of < 1.005. Rapid development of hypernatraemia in the form of hypertonic dehydration and hypokalaemia can also occur. When left untreated, it causes rapid and significant renal fluid loss (water deficiency) and a severe electrolyte imbalance (especially hypernatraemia) [2, 4-5, 7, 22-23].

Figure 5.1. **Management of polyuria in the potential donor after brain death**



Source: Cheisson G, Duranteau J. Modalités de la prise en charge hémodynamique [21].

Treatment of central diabetes insipidus (see also Figure 5.1) includes the following steps [22]:

a. Anti-diuretic hormone replacement: first-line medication is desmopressin (0.5-4 µg as intravenous bolus and check after 30 min):

i. If diuresis falls sharply (possible anuria), a lack of fluid volume is symptomatic and fluid balance must be restored. No indication for diuretics.

ii. In persistent polyuria, the blood sugar level must be checked to exclude osmotic diuresis (and corrected if necessary) before further administration of desmopressin.

iii. Repeated titrated application of desmopressin is necessary if symptoms of diabetes insipidus recur.

As an alternative to desmopressin, vasopressin may be continuously administered at a dosage of 0.8-1 U/h (anti-diuretic effect).

b. Sufficient fluid volume replacement, with mandatory monitoring of electrolyte and blood glucose levels:

i. In cases of hypernatraemia with hypovolaemia, water should be administered through nasogastric tube, and intravascular volume should

be restored with isotonic sodium chloride prior to water-deficits correction by 5 % glucose solution combined with insulin, while monitoring blood glucose levels.

ii. In cases of hypernatraemia without fluid depletion, administration of electrolyte-free solutions alone should be avoided because of the risk of over-hydration. In these cases, furosemide should be administered and the volume of urine excreted hourly should be replaced with 5 % glucose solution (alternatively, haemodialysis or haemoperfusion should be considered).

5.4.2.2. *Further endocrine substitution*

The benefit of additional exogenous hormonal supplementation continues to be regarded as controversial because of conflicting evidence. Until confirmative results are available, hormone-replacement therapy should be reserved for unstable patients, even those undergoing optimal haemodynamic care [2-3, 23].

Especially in haemodynamically unstable donors, methylprednisolone should be administered immediately after brain death causing septic shock-like symptoms, given the anticipated up-regulation of pro-inflammatory cytokines due to its ability to increase production of endogenous epinephrine, and the positive impact on lungs and liver transplant functioning. The use of methylprednisolone (bolus 15 mg/kg) at the time of brain death is commonly recommended for haemodynamic and lung-protective effects and has been shown to improve donor oxygenation and lung utilisation, although further research is needed to assess the effect of steroids in lung donors.

Alternatively, early substitutive administration of hydrocortisone can be performed (100 mg bolus initially, 200 mg/day continuous administration) [24-27]. Early substitutive administration of glucocorticoids in a potential DBD donor with circulatory failure allows significant reduction of the cumulative dose and of administration duration of vasopressors.

Given the lack of information from prospective randomised studies, the benefit of routine administration of tri-iodothyronine (T3) is still not clear and this treatment is currently not recommended. However, it may be useful in unstable potential donors unresponsive to volume loading and restoration of vascular tone as a rescue therapy combined with vasopressin and methylprednisolone [28]. In cases of steroid supplementation, glucose dysregulation must be corrected by insulin administration (target blood glucose < 150 mg/dL) to exclude polyuria due to glucosuria. Insulin infusion may provide benefits of anti-inflammation and reduced cytokines in addition to the benefits of good glycaemic control.

5.4.3. Persistent arterial hypotension and use of vasopressors

A target mean arterial pressure of 60-110 mmHg should be achieved in adults, with diuresis of > 0.5 mL/kg/h. This can be achieved by:

a. ceasing to administer all medication with hypotensive effects or side-effects,

b. replacing fluid volume with crystalloid/colloid solutions up to CVP 4-12 mmHg (4-8 mmHg in potential lung donors).

Administering fresh frozen plasma to replace fluid volume is only indicated for cases of simultaneous coagulation disorder. Erythrocyte concentrates should be maintained at 20-30 % haematocrit (see below). If adequate mean arterial pressure cannot be achieved by fluid replacement, then vasopressors are indicated.

5.4.3.1. *Vasopressors*

Despite fluid replacement, administration of vasopressors frequently becomes essential. The most common tool to target the fluid management of an organ donor has been the CVP value, though as a single indicator of fluid status it can be misleading: CVP values may not correlate with values of the pulmonary-capillary wedge pressure and could therefore increase the gradient of alveolar to arterial oxygen in the lung donor [29]. However, most organ procurement organisations and most ICU physicians rely heavily on the measurement of CVP as an indirect indicator of fluid status [30]. Nevertheless, extended haemodynamic monitoring (e.g. echocardiography, minimally invasive cardiac output techniques using a PiCCO® or equivalent monitor, pulmonary catheter) should be highly recommended in donors with maintained hypotension. This will facilitate determination of the precise haemodynamic profile and causes of hypotension, whether caused by hypovolaemia, vasoplegia or cardiogenic components (see Figure 5.2) [31-33]. The use of invasive haemodynamic monitoring and other parameters, such as extravascular lung water, for monitoring lung oedema at the bedside, have been recently proposed to improve the lung grafts available for transplantation [14, 34].

a. Norepinephrine is often the first-choice medication in this case and should be administered until the target mean arterial pressure is reached. An ongoing dose exceeding 0.2 µg/kg/

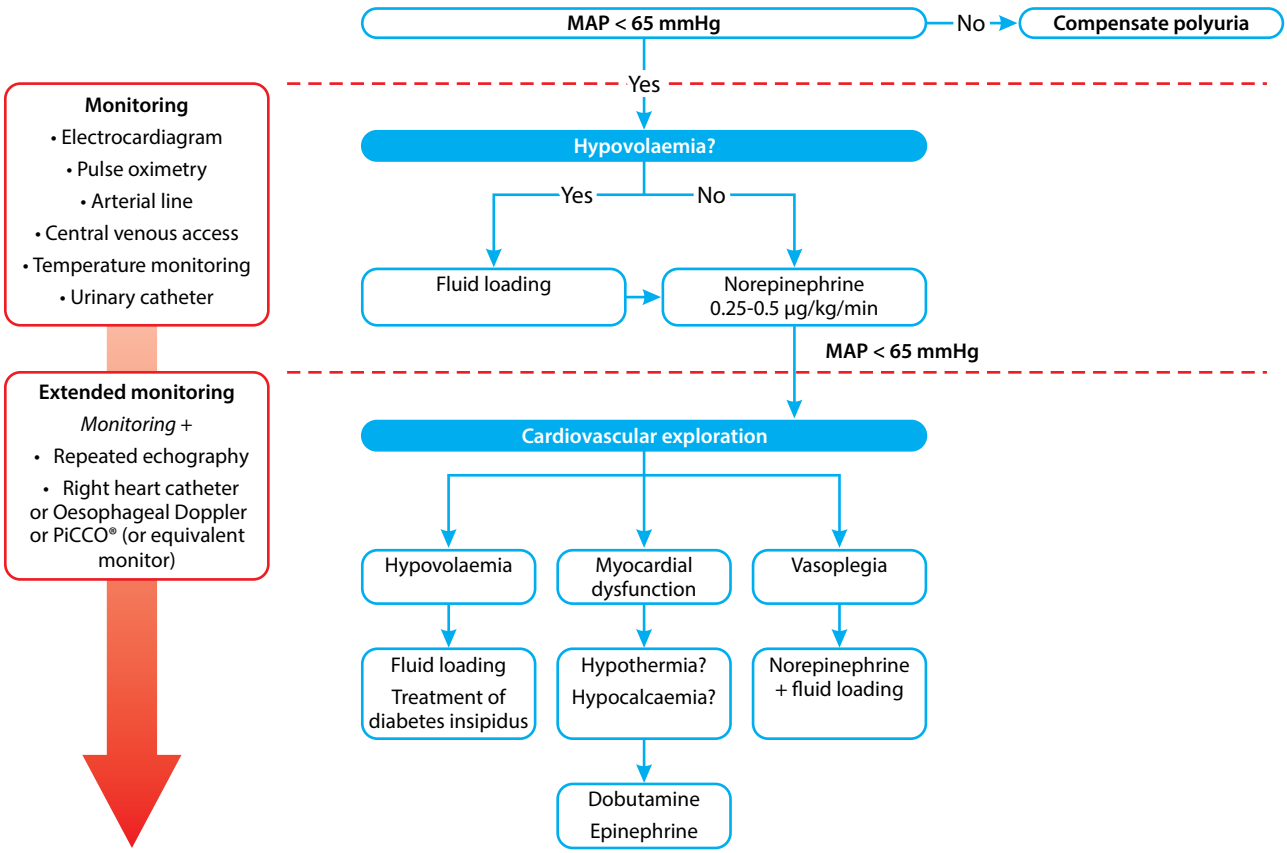
min should raise serious concerns about the possible complications mentioned below.

b. Myocardial dysfunction can be easily assessed and quantified by Doppler echocardiography. In such cases, administration of an inotropic drug, such as dobutamine in association with norepinephrine, is recommended.

c. Vasopressin (1 U as bolus, 0.5-4 U/h as a recommended dose) is still under evaluation for its use in DBD donors as a way to gradually reduce vasopressor administration, while maintaining target parameters after appropriate correction of all other issues to decrease vasopressor dosages. Given vasopressin's lack of cardiotoxicity and as a result of normalisation of systemic vascular resistance, cardiac function can be improved. As a result, in a study, the number of transplantable hearts (most of which had initially been evaluated as unsuitable for transplantation) rose by 35 % [31-32].

d. The pre-treatment of donors with low doses of dopamine (< 4 µg/kg/min) has been shown to reduce the need for dialysis after kidney transplantation without a significant clinical impact on graft or patient survival as well as to mitigate cold preservation injury to cardiomyocytes in heart grafts [33, 35-36]. Since dopamine directly interacts with the cellular membrane and is capable of protecting endothelial cells from oxidative stress during cold storage, the application of low-dose dopamine is intended to protect kidney grafts from damage related to prolonged ischaemia time exclusively (and not as vasopressor). This was confirmed by the randomised trial of Schnülle *et al.* in the sub-cohort of grafts exposed to long ischaemia times, by reducing the rate of delayed graft function [36]. On the contrary, high doses of dopamine (> 10 µg/kg/min) must be avoided because, due to its action on α-adrenergic receptors, it can induce a progressive renal and systemic vasoconstriction, as well as the depletion of endogenous norepinephrine and of ATP reserves in the organs, and it can affect their function after transplantation, especially in the case of the heart.

Figure 5.2. **Haemodynamic objectives and care in the management of the potential donor after brain death**



MAP = mean arterial pressure.

Source: Charpentier J, Cariou A. Objectifs et moyens de la prise en charge hémo-dynamique [33].

Whenever the administration of cathecholamine is guided by direct cardiac output measurement (minimal dose to maintain an ideal cardiac output and systemic vascular resistance), transplant coordinators and ICU physicians should not be worried about dose requirements.

5.4.4. Hypokalaemia/hypernatraemia

Hypokalaemia can be corrected by replacing potassium. Normalisation of elevated serum sodium levels may be difficult. When hypernatraemia exists in combination with volume deficiency – CVP < 7 mmHg (see §5.4.2.1) – water, through nasogastric tube, and a 5 % glucose solution (together with insulin) may be administered as an infusion (after isotonic sodium chloride to restore intravascular volume). Blood glucose and potassium levels should also be monitored. As there is a sharp decline in the metabolic rate of donors, administration of large volumes of 5 % glucose solution may lead to severe hyperglycaemia, with consequent osmotic diuresis, if not properly monitored. In the case of hypernatraemia with adequate blood volume or hypervolaemia (CVP > 10 mmHg), administration of electrolyte-free solutions alone will cause overhydration. In such cases, furosemide should be administered and the volume of urine excreted hourly should be replaced with 5 % glucose solution. Administration of clear water through the nasogastric tube may help to achieve normonatremia.

5.4.5. Hypothermia and dysregulation of body temperature

A minimum body temperature of 35 °C should be maintained in DBD donors. This can be achieved by:

a. reducing passive heat loss by covering the donor with, for example, metal foil,
b. using electric blankets and hot-air blowers,
c. heat-infusion solutions in water baths or special infusion heaters.

Untreated and/or uncontrolled hypothermia (< 35 °C) causes numerous complications that impair the transplant success of organs, such as:

a. In general, metabolic activity, energy and oxygen consumption of the organs fall at lower body temperatures. This causes adaptive impairment of organ function (heart, liver and/or kidneys), which may have a negative impact on organ-related functional diagnoses. At the same time, hyperglycaemia may increase as insulin production and insulin efficacy are reduced and the rate of glucose metabolism decreases.
b. Cardiac contractility declines and the risk of arrhythmia increases, both resulting in under-perfusion of the organs.
c. Erythrocyte flexibility declines, causing disruption to micro-circulation in the organs and reducing oxygen release into the tissues.
d. Hypothermia enhances coagulation disorders.

In some cases, hyperthermia (> 38 °C) may occur because of failure of central temperature regulation and SIRS without infection, or because of SIRS combined with a relevant infection (in which case the cause should be sought and proper treatment should be initiated).

5.4.6. Spinal vegetative dysregulation and movements

The typical indicative parameters are hypertension, tachycardia and massive reflex movements.

During organ procurement, administration of opioid drugs and muscle-relaxing agents may be advisable to avoid spinal reflexes and hypertension caused by surgical stimulation and to reduce bleeding (see Appendix 5).

5.4.7. Lung-protective treatment and ventilation

Lung grafts are procured in only 15-20 % of all multi-organ donors. Lungs are susceptible to damage by a number of factors, e.g. resuscitation manoeuvres, neurogenic oedema, pneumonia and aspiration of gastric content, SIRS (occurring before, during and after brain death) and suboptimal mechanical ventilation. Alveolar recruitment measures should always be carried out regularly in all potential donors, not only for reversing pulmonary deterioration, but also as a preventive management measure in cases with PaO_2/FiO_2 higher than 300 mmHg (40.0 kPa) or a normal chest X-ray.

Nowadays a lung-protective strategy [13, 38] in donor ventilation is recommended, which is equivalent to standard patient care, with the goal of increasing the number of lungs eligible for transplantation. It has been shown that lung-protective protocols of this kind are easily applied in all types of centre, without requiring any specific training [14], and may therefore help to relieve the organ shortage. A lung-protective strategy is based on:

a. protective ventilation with low tidal volume, ventilator recruitment manoeuvres, high PEEP value, fluid restriction with reduced target extravascular lung water values (see Table 5.3),
b. invasive haemodynamic monitoring to optimise haemodynamic parameters,
c. use of steroids.

This strategy includes methods to prevent atelectasis and infection through these precautions:

- continuous mucolysis,
- humidification of respiratory gases,
- aspiration of secretions,
- changes of body position and head-of-bed elevation (if no contraindications),
- disinfection of the hands preceding measures on the respiratory tract,
- oral care and oral decontamination,
- avoidance of oral aspiration (e.g., by using cuff pressure measuring and subglottic secretion drainage).

The targeted parameters, particularly if lung procurement is planned, are:

a. $PaCO_2$ of 35-40 mmHg (4.6-5.3 kPa),
b. PaO_2 of 80-100 mmHg (10.6-13.3 kPa),
c. PEEP ≥ 5 cm H_2O, even in cases of adequate oxygenation levels,
d. pH of 7.3-7.5.

Uncorrected hypocapnia in a donor, due to prior hyperventilation to lower cerebral blood volume and intracranial pressure, causes severe respiratory alkalosis. This has an impact on circulation and oxygen-binding curve because of reduced metabolism of the donor after brain death.

A lung-protective strategy aimed at improving lung function and protection in order to enable lung donation is summarised in Table 5.3 [13-14, 34, 38].

5.4.8. Nutritional support

Patients in the ICU are usually submitted to enteral nutrition as early as possible (when there are no contraindications), which may be helpful also to prevent bacterial translocation. In the DBD donor with missing vagal stimulation, if this approach is contraindicated, in cases of intestinal, pancreas and perhaps other organs donation, sterile fluid should be administered through the gastric tube [43]. Total parenteral nutrition should not be initiated but may be continued.

5.4.9. Haemostasis during organ transplantation

Abnormalities in haemostasis, which frequently occur in DBD donors, are linked to the destruction of cerebral tissues (by disseminated intravascular coagulation, fibrinolysis).

Platelets and haemostatic factors should be monitored and maintained until the end of the procurement procedure, at the following levels:

a. platelets > 50 G/L,
b. fibrinogen > 1 g/L (>100 mg/dL),
c. prothrombin time > 40 % and/or TCA ratio < 1.5.

Transfusion of erythrocyte concentrates should also be planned to maintain oxygen transport capacity. The critical haematocrit for the organs of donors after brain death depends on the age, previous medical history and progression of disease in the individual donors. International guidelines and other sources recommend taking surrogate parameters (central venous saturation > 70 %, normal range for serum lactic acid concentration) as a basis. Haematocrit levels of over 20 % should be targeted in cases where circulation is stable, and over 30 % in cases of circulatory instability (transfusion of packed red blood cells in organ donors after neurologic determination of death is associated with a lower rate of delayed graft renal function [44]). However, these transfusional targets have to be considered with precaution as it is possible that haemodilution increases the risk of false negative results in serology of donors; other risks are inflammatory activation related to the time of the blood collection (either for red blood cells or fresh frozen plasma), donor's lung injury and transmission of virus diseases to organ recipients [45].

Cytomegalovirus (CMV) transmission is prevented by transfusion of leukocyte-depleted blood products (particularly erythrocytes and platelets concentrates), a treatment which is consistent with the fact that CMV is a leukocyte-associated pathogen. CMV is a major concern when it comes to transfusing to organ donors or to immunocompromised organ recipients. For this reason, organ recipients, but also organ donors, are given CMV-seronegative or leukocyte-depleted blood products, even where this risk is generally considered negligible; however, this is still not the usual transfusion practice in many countries and hospitals through Europe [46]. The residual risk of transfusion-transmitted CMV infection can be significantly reduced by use of leukocyte-depleted blood components [47].

Table 5.3. **Interventions for a lung-protective strategy**

Intervention	Comment/Recommendation
Apnoea test	It should be performed with ventilator on continuous positive airway pressure mode. It is recommended to perform a single recruitment manoeuvre immediately after testing with attention to haemodynamic instability
Mechanical ventilation	Lowest FiO_2 possible Plateau pressure < 30 cm H_2O PEEP 8-10 cm H_2O (a high PEEP prevents lung oedema and helps prevent atelectasis)* Tidal volume 6-8 mL/kg
Recruitment manoeuvres**	Once per hour and after every disconnection from the ventilator
Bronchoscopy	With bilateral bronchoalveolar lavage, immediately after brain death
Close monitoring of haemodynamics [25-26]	With PiCCO or equivalent monitor EVLW < 10 mL/kg (administering diuretics, if necessary) CVP < 8 mmHg
Methylprednisolone	15 mg/kg after brain death declaration
Semi-lateral decubitus position	In lung donors with PaO_2/FiO_2 <300 mmHg
Closed circuit for tracheal suction	Any loss of pressurisation caused by tube disconnection must be avoided to decrease the risk of atelectasis
Avoid any decrease in oxygenation	Appropriate ventilation should be ensured during stay at ICU, during any transfer within the hospital and during surgery in the operating theatre at procurement with a target PaO_2/FiO_2 > 300 mmHg (> 40.0 kPa)

Note: CPAP: continuous positive airway pressure; CVP: central venous pressure; EVLW: extravascular lung water; FiO_2: fraction of inspired oxygen; ICU: intensive care unit; PEEP: positive end-expiratory pressure.

* Optimal ventilator settings in a protective mechanical ventilation include lowering the driving pressure (ΔP=plateau pressure minus PEEP), appropriate target being probably < 14 cm H_2O [39] or a bit higher < 19 [40-42].

** Suggested technique: controlled ventilation (plateau pressure limit of 35 mm Hg) with PEEP of 18-20 cm H_2O for 1 minute, and decreased 2 cm H_2O each minute; after that we increased 50 % tidal volumes for 10 breaths [13-14, 34, 38].

5.4.10. Multi-organ management of donation after brain death

Multi-organ DBD management should be approached as a global strategy requiring careful bedside management to avoid losing donors due to inadequate protocols. Implementing an intensive donor-treatment protocol that considers the DBD donor as a critical patient is cheap, is available in all ICUs all over the world and increases the organ procurement rate [48].

Some principles of donor management are generally applicable, whereas others are targeted to a specific organ. Competing requirements for organ perfusion may call for antagonistic strategies such as fluid replacement or high PEEP. A restrictive fluid balance is associated with higher rates of lung procurement, whereas aggressive volume repletion facilitates the maintenance of kidney function. Moreover, consistently high PEEP (> 10 cm H_2O) or alveolar recruitment manoeuvres with PEEP over 16-20 cm H_2O may limit the formation of lung oedema and prevent atelectasis but might produce a haemodynamic instability in unmonitored organ donors.

However, a strict intensive lung-donor-treatment protocol based on protective mechanical ventilation, advance cardiac monitoring and hormonal therapy affected neither the number of other grafts procured (heart, liver, pancreas and kidneys) nor the rates of graft and patient survival. Moreover, in grafts as sensitive to restrictive fluid balance as the kidney or heart, no negative effect was observed in rates of graft procured or recipient outcome due to inadequate perfusion to vital organ systems with this bedside treatment [20].

5.4.11. Optimising the timing to perform organ procurement

Some authors have proposed increasing the time from brain death until organ procurement to more than 20 hours, because in thoracic grafts longer treatment times have been associated with enhanced gas exchange, reduced lung water, inotropic weaning and improved lung and heart transplantation rates [49-50]; this option to delay organ procurement has been included in several national guidelines, e.g. Canada [51], Ireland [52]. Prolonged management of the brain-dead is not necessarily associated with reduction in organs retrieved. However, it has not been demonstrated that time is the factor that improves the grafts after brain death, rather than appropriate and early treatment by skilled personnel immediately after brain death declaration.

This approach is very complicated to implement because of the logistical complexity of multi-organ donation and the risk of cardiac arrest or deterioration of other organs [53].

There is no minimum time range. However, left ventricular systolic dysfunction detected by echocardiography in the absence of a history of heart disease is the single most common cause for non-transplantation of an organ. The phenomenon of ventricular cardiac dysfunction in the donor, just after brain death diagnosis, may be transient [54-56] and, with proper treatment, hearts could be resuscitated to transplantable status [57]. Therefore, advanced cardiovascular monitoring, with serial echocardiograms – preferably transoesophageal (TOE) rather than transthoracic (TTE) – separated by several hours and until weaning of cathecolamines, should be performed to monitor the response to medical management when early cardiac dysfunction is identified in potential donors.

5.4.12. Donor management during organ procurement

Multi-organ procurement [58] is an extensive procedure with wide exposure of surgical field, including incision from suprasternal notch to pubis. It may be up to 3-4 hours long. Proper anaesthetic treatment during this period may help to avoid organ damage prior to explantation.

Donor monitoring during the procurement should be similar as previously in the ICU (see Appendix 4, Appendix 5). Central venous line should be preserved for CVP monitoring and delivery of vasoactive drugs. Large-diameter venous catheters for rapid infusion might be useful in case of sudden unexpected bleeding from damaged large vessels. Active warming of organ donor should be considered in advance if prolonged procedures including liver and pancreas procurement are planned. This may prevent hypothermia and subsequent circulatory disturbances.

Ventilation should be similar as in ICU, with FiO_2 not exceeding 40% if procurement of lungs is anticipated. Although brain-dead patients do not have pain perception, spinal somatic and sympathetic reflexes may appear. Therefore long-acting non-depolarising muscle relaxants should be used to facilitate surgical exposure. Hypertension and tachycardia should be controlled with volatile anaesthetics and opioids. Severe bradycardia, if it appears, is resistant to atropine and should be treated with a directly acting chronotrope such as isoproterenol, or even by intravenous pacing. Dextrose-containing solutions should be avoided at this stage because they may aggravate already existing hyperglycaemia and be the reason of osmotic diuresis and electrolyte disturbances.

An anaesthesiologist may be asked by surgical teams to collect blood samples for several laboratory tests and for administration of heparin, phentolamin or any other medication according to current protocols. In the case of heart and/or lung procurement, central venous catheters and pulmonary catheter have to be withdrawn prior to aorta cross-clamping. After cross-clamping, all supportive treatment should be terminated and the ventilator should be switched off, with the exception of cases of lung procurement, when manual ventilation should be maintained according to the procurement team's suggestions.

5.5. Conclusion

To conclude, the period between brain death and organ procurement is one in which organ function can deteriorate rapidly. Optimal management of the DBD donor during this period remains critical to the successful outcome of transplantation. The impact of meeting donor-management goals [8], defined as normal cardiovascular, pulmonary, renal and endocrine end-points, is associated with an increase in both the quantity and quality of grafts. Implementation of preset donor-management goal protocols to improve outcomes is highly recommended. Once the donor-management goals are achieved and well maintained, the optimal timing for organ procurement is still a question for debate along with consideration of, for example, 'spontaneous' heart recovery with time [56].

Progress in organ transplantation technologies and the development of *ex vivo* organ perfusion systems, which mimic physiological conditions and allow prolonged preservation and better graft survival rates, are very promising and can be actively incorporated into *ex vivo* pre-transplant reconditioning of donor organs.

With time and more successful interventions, it may be possible to further address the ongoing shortage of donor organs. Understanding the molecular inflammatory responses and utilising interventions that can reduce haemodynamic instability, inflammation and SIRS are the keys to further advancing donor management.

5.6. References

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Related material

- Appendix 4. Procurement surgery in brain-death donors: tasks for the anaesthesiologist
- Appendix 5. Checklist for the anaesthesiologist in the operating room

Chapter 6. General donor characterisation, assessment and selection criteria

6.1. Introduction

In order to minimise the risks of transplantation, it is necessary that donors and all organs procured – or to be procured – are characterised properly before transplantation, as extensively described in this chapter, which focuses on deceased donation after brain death (DBD). Firstly – after all relevant information on the characteristics of the donor and of each organ has been collected from a variety of sources (the 'donor and organ characterisation') – a general assessment of the donor helps in drawing conclusions about the risks of disease transmission associated to the potential future recipient. Secondly, the quality of each potentially donated organ based on all data obtained during the organ-specific characterisation process must be considered too – this second step is covered in Chapter 7. Based on the conclusions extracted from characterisation of the donor in general and of the single organs, decisions can be made on whether any particular recipient might benefit from the transplantation of each single organ or not.

The general selection criteria for donors and specific selection criteria for organs intended for transplantation have changed in recent decades. This is based on knowledge that rigid selection criteria limit the transplantation of organs that may not be beneficial for one particular recipient while being life-saving for another [1-11]. It is difficult to determine where the absolute limits are. Therefore the wording 'absolute contraindication' may be used only in the context of allocation of any organ to any recipient. There are medical conditions that justify transplantation of a graft in a particular recipient at a high risk of complications when the medical condition of the recipient requires such therapeutic intervention. In such cases beyond informed consent it is best practice to document why such decisions have been taken, within an appropriate study protocol or in exceptional cases in a reproducible intervention protocol that can be followed up by the methods of biovigilance (Chapter 15).

Identification of possible organ donors is the starting point for donor evaluation. Thereby inappropriate exclusion a priori by the treating physician should not occur. Any patient who meets specific clinical triggers, e.g. a Glasgow coma scale ≤ 6 [12], should be referred to the donor co-ordinator for the start of the evaluation process and consideration for DBD (see Chapter 2).

The same applies to any patient for whom withdrawal of life-sustaining therapy is planned because therapy is no longer in the best interests of the patient: then controlled donation after circulatory death (cDCD) should be considered, when allowed within a given jurisdiction. In cases of termination of unsuccessful cardio-pulmonary resuscitation, uncontrolled donation after circulatory death (uDCD) can be considered when allowed by national law. In both types of DCD, some aspects of donor evaluation may vary from what is described in this chapter and as outlined in Chapter 12. For the additionally required details relevant to living organ donors, see

Chapter 13. The characterisation of tissue and cell donation is described in the *Guide to the quality and safety of tissues and cells for human application*. In order to avoid repeating information, details about donor transmission risks are covered in chapters 8-10 of this Guide.

There are three major categories of risk factor limiting the outcome of transplantation:

a. The general risk of donor's disease transmission to the recipient, e.g. infections or malignancies (§6.1.1 and chapters 8 to 10).

b. Donor or organ characteristics that increase the likelihood of failure (§6.1.2 and Chapter 7).

c. Risks related to recipient characteristics, the transplantation process, immunology etc. (§6.1.3).

One challenge in donor characterisation, assessment and selection is that the investigating physicians may focus pre-emptively on risk factors that limit the outcome of transplantation of single organs instead of reviewing all details firstly. Sections 6.1.1 to 6.1.3 summarise the impact of donor and organ characterisation and selection on the outcome of transplantation, while sections 6.2 to 6.8 and Chapter 7 review the principles of donor and organ characterisation, assessment and selection.

6.1.1. Risk assessment of general donor-disease transmission risks

According to the EU-funded Alliance-O project, 'non-standard-risk donors' are defined as those in whom the risk of disease transmission to the recipient is estimated as unacceptable, or increased but acceptable, or calculated or not assessable [1]. Based on data collected in 11 European countries within the EU-funded Dopki project, it can be concluded that non-standard-risk donors have not been uniformly considered throughout the EU [2]. Some member states have prevented the transplantation of organs from such donors by means of legal or technical provisions, whereas others have followed specific protocols for using organs from these donors. Based on the knowledge gathered in countries where such donors are used, it can be concluded that more organs from non-standard-risk donors could be used than has actually been done [1-2].

The vast majority of deceased donors nowadays suffer from severe cerebral damage due to different kinds of cerebro-vascular diseases/accident. In many countries, more than 50 % of deceased organ donors are above the age of 55 years. There is an increased risk of transmission of non-detected and untreated malignancies in this older donor group, beyond the calculated risks based on growing knowledge that selected donors with confirmed malignant diseases can be accepted (see Chapter 9). In the case of a malignancy known or detected in a donor, it will be graded as minimal risk, low to intermediate risk, high risk or unacceptable risk regarding the assumed probability of transmission (see Table 9.3).

The risk of transmission of infections is modified with climate change and with higher global mobility of both people and goods, as well as with the availability of new drugs (see Chapter 8). Regarding the risk of infectious disease transmission in non-standard-risk donors, physicians have to carefully balance whether pre-emptive and/or post-exposure treatment to the pathogen is possible in the recipient without harm or not – especially taking into account whether currently an appropriate therapy for such infection is available or not. Here we must be aware of rapidly changing inclusion or exclusion criteria for donors or particular donor–recipient combinations.

Other rare disease-transmission risks that may also exist are outlined in Chapter 10.

Based on careful assessment of donors, transplant physicians have to weigh the risk of disease transmission against the risk of the patient dying while remaining on the waiting list. By refusing an allocated organ, the patient might die or his/her clinical condition might deteriorate to the extent that transplantation is no longer feasible.

In non-standard-risk donors the Alliance-O classification of risk levels will not be used any more for grading disease-transmission risk [2-3]. Experience from the previous editions of this Guide [13] has shown that this static classification does not help to describe the most appropriate consideration of all individual donor and recipient factors for final risk assessment. After proper risk–benefit analysis based on the needs of an individual recipient, a generalised statement about assumed absolute contraindication to organ donation or classification as unacceptable risk [1] becomes very difficult. Taking into account the limited number of organs available, compared to the number of patients requiring a life-saving transplantation, accepting a life-saving organ in the absence of other therapeutic options is justified on a case-by-case basis if this is the only reasonable option for possible survival of the recipient. Therefore two groups of donors may be defined:

a. Standard risk donor: After donor characterisation, no clinical evidence exists for increased disease-transmission risks beyond the population-adjusted average risks for undetected diseases.

b. Non-standard-risk donor or increased-risk donor: After donor characterisation, clinical evidence exists for an increased transmission risk of a particular disease beyond the population-adjusted average risks for other undetected diseases. In this case a targeted risk–benefit assessment of each matched donor–recipient combination is required in order to identify whether transplantation of this graft into this particular recipient will be without harm, or with acceptable harm, to the recipient when compared with the risk associated with not transplanting to the recipient. In this context, informed consent of the recipient is requested (which is beyond the scope of this chapter).

6.1.2. Risk assessment of likelihood of failure associated to a specific graft

The assessment of the increased risk of failure of a particular graft donated is discussed in more detail in Chapter 7 and is beyond the scope of this chapter. However, general donor assessment and selection is biased by the focus put on the limited function or quality of one or more single organ(s). The best practice is

a. firstly to assess the issues discussed in sections 6.2 to 6.8, and then

b. secondly to proceed to the assessment of each individual organ as outlined in Chapter 7.

Whenever there is a chance that at least one organ may be finally transplanted, assessment of the donor should proceed. The issue of assumed reduced graft quality is summarised by the wording 'expanded-criteria donors' (ECD). Unfortunately, donors with otherwise optimal organ quality, but with the above-mentioned 'non-functional' disease transmission risks (§6.1.1), are also included in this ECD category.

The concept of ECD was initially developed by the United Network for Organ Sharing (UNOS) to recognise the fact that not all deceased donor organs provide a similar outcome for transplant recipients. Despite the well-documented risks of disease transmission, malignancy, toxicity or inherited diseases (see chapters 8-10), there is no clear and unambiguous definition of ECD. Difficulties arise on how to define ECD [6, 10, 14-18]. Currently the Eurotransplant region uses a set of parameters to define ECD criteria for liver donors [19], but over 50% of the donor livers are classified as marginal when following these criteria [20].

ECD is a yes/no score, and the quality of the graft depends on many donor factors (see Chapter 7). Besides, graft quality is difficult to measure because outcome after transplantation also depends on many transplant and recipient factors. The broad spectrum of graft quality runs from optimal quality to not-transplantable, with much variation in between. Therefore, graft quality would be best described by a continuous score. Such continuous scoring tools have been developed in the US using data derived from the national transplantation registry (UNOS/SRTR), e.g. the donor risk index (DRI) for livers, the kidney donor risk index for kidneys and the pancreas donor risk index for pancreas [4-5, 11]. But the overall donor quality in the US seems to be less optimal than in Europe [6, 14, 20-21]. Therefore data retrieved from registry studies in the US may not be transferable to the European context [21]. While some studies were able to confirm the usability of such donor risk indices, others could not find a clear correlation between outcome and DRI [6, 20, 22-28].

As an example of taking into account some of the above-mentioned issues, the Eurotransplant Senior Program matches kidneys from donors above the age of 65 to recipients above the age of 65 years: because kidneys procured from advanced aged donors are at increased risk of long-term failure, these are preferentially used for elderly recipients. In such a way the assumed limited duration of graft function can be matched to the assumed limited life expectancy of elderly recipients [7-8]. This concept takes also into account the fact that kidneys procured from elderly donors will be compromised by further exposure to long ischaemia times by the use of specific allocation rules.

6.1.3. Risks not associated with the donor or the graft donated

Further risks for transplant recipients are those associated with the transplantation procedure (including the issues of organ preservation and ischaemia times), their condition before the procedure, the operation itself and the subsequent intensive care period. Moreover, acute or chronic rejection of organs can occur. Presentation of complications due to immuno-suppressive therapy can increase, particularly if extended immuno-suppressive protocols (using mono- or polyclonal antibodies as induction therapy) are used, such as re-activation of *cytomegalovirus* as well as complications from pre-existing (and presumably cured) malignancies.

Little is known about the frequency of, or the reasons for, recurrence of primary diseases leading to organ failure. There are very well-known diseases, such as primary focal and segmental glomerulosclerosis, with a high risk of disease recurrence in the kidney graft. However, there are no data available on what kind of donor- or recipient-related factors influence the rate and risk of recurrence of primary diseases.

6.2. General evaluation of deceased organ donors

Once a potential donor has been identified, the priority is to establish his/her suitability by appropriate donor evaluation. To do that, the following sources of information should be used, with the aim of reconstructing the donor's current and past medical history as accurately as possible:

a. interviews with the family and/or friends and all other relevant sources,
b. interview with the attending physician and nurse, as well as other healthcare providers and the general practitioner,
c. detailed review of current and past medical notes/electronic files,
d. assessment of the donor's medical and behavioural history by review of all written reports about previous diseases (e.g. including histological tumour diagnosis and stage) etc.,
e. full physical examination, including exact measurement of height (and weight if possible),
f. laboratory tests, including all microbiological testing (specific note should be made of assays with pending results and followed up post-procurement),
g. complementary investigations (e.g. ultrasound, echocardiography, ECG, CT scan, etc.) as indicated,
h. autopsy if performed (not possible before procurement, but results must be communicated to the organ procurement organisation [OPO] immediately).

6.2.1. Medical and behavioural history

6.2.1.1. *Donor evaluation*

The history of an organ donor must be obtained with respect to all kinds of transmissible diseases and any disease that may affect organ quality. An interview with relatives of deceased organ donors should be undertaken (see appendices 6 and 7), bearing in mind that, under emotional stress, they might forget or mix up details. However, adding any stress to grieving relatives should be avoided. Contact with the general practitioner of the donor has been proved helpful, alongside a review of hospital archives for historic data or other sources of information (e.g. tumour registry). Finally, written reports clearly describing details of previous diseases should be obtained to perform an objective risk assessment.

In order to minimise the risk of unexpected disease transmission, it is important to obtain data on history of travel or residence, including information about living conditions, migration background, refugee status (e.g. stay in camps or elsewhere, or refugee route) and work places (e.g. sewage plant, woodlands, farm, airport, hospital, foreign countries). This may help to identify risks related to places/countries with inferior hygienic standards or with a high prevalence of certain infections, or where the environment poses other risks to health. With the same aim, information should be obtained about hobbies (e.g. home, garden, animals, woodlands), drug abuse (e.g. intravenous drugs, needle sharing, intranasal cocaine sniffing, oral or recreational drugs consumption, alcohol, smoking) and secondary effects on lifestyle (e.g. multiple sexual partners, commercial sex worker, sexual contacts or imprisonment) – beyond the standard questions about cardiovascular risks etc. This information may require further investigations.

The donor profile should document the donor's medical and behavioural history, including general data such as age, gender, body weight, height, cause of death, intensive care unit (ICU) admission and results of examination (see §6.2.2, §6.2.3 and Table 6.1).

6.2.1.2. *Clinical evaluation*

As well as the information in the donor profile, the clinical evaluation should also include the haemodynamic status, in particular, hypotensive episodes, need for mechanical cardiac resuscitation, use of inotropic or vasoactive drugs and duration of mechanical ventilation (see §6.2.3 and Table 6.1).

These parameters are all needed to assess, firstly, the suitability of the deceased person as an organ donor and, secondly, the suitability of a specific organ (see Chapter 7). This evaluation includes all diagnostic investigations performed, such as X-rays (especially thorax), CT scans (especially head, thorax and abdomen), ultrasounds (especially abdomen), echocardiography, coronary angiography and bronchoscopy, according to the need for such investigations (see §6.2.3 to §6.2.5). In this context it is helpful to document the results of any investigations performed previously, beyond the scope of donor

evaluation, in order to clarify current findings (see Appendix 10).

It is the responsibility of the person or team performing the procurement to document any abnormal anatomical findings observed during the procurement procedure (see §6.3 and Chapter 11).

Proper donor maintenance should start as soon as possible and especially after completion of death certification, while appropriate consent is being obtained, to maximise the chance of successful organ procurement (see Chapter 5). As dramatic changes in organ quality are associated with the quality of donor maintenance, the data outlined in Table 6.1 and section 6.2.3 should be documented precisely.

A comprehensive summary should be prepared of all clinical data and information obtained, to be easily understood by a third party (e.g. transplant centre performing risk–benefit assessment for an organ offered); for an example of an information form for this purpose, see Appendix 9. In cases of abnormal findings, with further investigations having been undertaken, results must be included in the donor documentation as described in sections 6.2.2 to 6.2.5.9. The inverse, i.e. no abnormal findings within the investigations, is difficult to document, but at least it should be clarified what has been done to rule out such abnormalities.

6.2.1.3. *Checks and pitfalls*

Finally, verify the blood group and confirm the investigations that characterise the donor's infectious status. The detailed guidance in sections 6.2.2 to 6.2.6 will help to characterise the donor properly. There are four pitfalls to bear in mind:

a. Any uncertain encephalitis or neurologic/mental/psychiatric disorder, as well as any fever, rash or discomfort, should be understood to signal the risk of a transmissible disease (see Chapter 8). This risk assessment should not be restricted to donors with a history of travel abroad.

b. Intracranial metastases should always be taken into account in donors diagnosed with intracranial haemorrhage, especially if no evidence of hypertension or arterio-venous malformation exists. Intracranial tumours have a different biologic behaviour than solid organ tumours or haematological malignancies (see Chapter 9). When in doubt, a brain biopsy or autopsy can be performed.

c. After all data have been collected and cross-checked against the donor and the organ-specific selection criteria, as outlined in Chapter 7, a plan must be set up to organise the procurement and to decide which complementary tests must be performed during or after procurement to ensure safety and quality (e.g. a space-occupying lesion in the kidney should be confirmed by histopathological examination of the whole tumour, but some organs – like the heart – will have to be transplanted because of obstacles due to ischaemia time, and other organs – like the liver or kidney – will have to be kept under quarantine until the result is available).

d. When, during general donor assessment, signs are detected (e.g. unexplained weight loss, hepatitis co-infection, lifestyle, unexplained mental alteration) that may raise suspicions of transmissible infections or malignancies, refer to the detailed guidance in sections 8.2, 8.3, 8.4 and 9.2.

Standardised questionnaires should be used to obtain the information outlined in Table 6.3, as shown in the examples of appendices 7, 9 and 10. The information obtained must be merged into the clinical data outlined in section 6.2.5 (see chapters 8, 9 and 10 for further details). If the information is not available or cannot be obtained properly, then the transplant teams must be informed in order to assess the risks associated to this information gap. We must also be aware of one other issue: even if donor relatives trust the interviewer, they may minimise, overlook or not disclose this information, or they may not know the entire truth, for multiple reasons.

6.2.2. Physical examination

Physical examination can take the form of a recent *ante mortem* or *post mortem* external examination of the donor, or a limited autopsy during/after procurement to look for evidence of high-risk behaviour, unexplained jaundice, hepatomegaly, hepatitis or other infection, neoplastic disease or trauma (e.g. check for old/new scars, healed/purulent wounds, exanthema, rash, injections, palpable space-occupying lesions). Nowadays tattoos and piercing are common; the sole issue is whether they were applied under sterile conditions or not recently (see §8.2; check when, where and how the tattoo was performed). The information obtained through physical examination is complementary to the comprehensive summary of clinical data as outlined in section 6.2.5.

There are three important points to notice:

a. Scars can tell you more than any lost and forgotten medical file, e.g. they can hint at previous operations which neither the relatives

nor the general practitioner were aware of and which may have been previous oncologic operations.

b. Exact measurements of body height (always possible) and body weight (if possible) help to avoid size mismatch during allocation for recipients.

c. Physical examination can be completed by adequate exploration of all organs in thoracic and abdominal cavity during the organ procurement (e.g. oesophagus, lungs, prostate, uterus, adnexa; see section 6.4).

An international protocol of physical examination in tissue donation is shown in Appendix 8 of this Guide (equivalent to Appendix 13 in the 3rd edition of the *Guide to the quality and safety of tissues and cells for human application*). This protocol was released by the American Association of Tissue Banks [29] and it may also be applied to organ donors. In the case of abnormal findings, further investigations should be carried out. The limited sensitivity and specificity of physical examination for discovering pathologies must be taken into account. Therefore additional investigations before and/or during procurement are mandatory (see sections 6.2.2 to 6.2.5).

6.2.3. Laboratory tests

All laboratory (lab) tests should be carried out before cessation of circulation. It is advisable to report the time when samples were taken, as well as medical interventions and clinical data. For appropriate interpretation of changing lab parameters in summary during the actual course of disease, see section 6.2.5.

All data collected since ICU admission should be reported continuously. For the assessment of organ function, a representative set of data at different time points is sufficient so that the course of disease can be reproduced (e.g. admission, every second day, most recent value). For cognitive reasons no more than four or five columns of data should be documented for all values of clinical chemistry investigation, and expanded – if needed for proper characterisation of an organ – by more single values. It is also helpful to know any lab data obtained before hospital admission in a stable condition of life, for describing temporary impairments of organ function during evolution to brain death (e.g. describing normal kidney function and no albuminuria in an elderly donor with diabetes now exposed to acute kidney injury after prolonged cardio-pulmonary resuscitation).

In the case of lab parameters, the units of measurement should be clearly communicated. Although many parameters are standardised in their measurement, deviations from assumed reference ranges in general exist even between hospitals within one region, and between countries. Furthermore, the range of values typical for organ donors with all their organs used for transplantation varies dramatically from the reference range assumed for healthy individuals not hospitalised in an ICU.

6.2.3.1. *Screening and available data*

The informative value and clinical relevance of lab parameters are summarised in Table 6.1. Some remarks about screening for infectious diseases and other lab data are necessary:

a. If a deceased donor received *ante mortem* transfusions (whole blood or blood components), colloids or crystalloids during the 48 h preceding death, a qualified specimen without dilution should be used for testing for infectious diseases. For further details about handling this issue refer to Chapter 8. It is important to remember that some trauma victims arrive at hospital in an already haemodiluted state. In the course of subsequent intensive care therapy, a significant degree of haemodilution by crystalloids is standard. Replacement of a relevant acute blood loss should be considered in this context. Nevertheless, haemodilution should never be used as an excuse to discard a donor unless there are other risk factors, as outlined in Chapter 8. Further antibody reactivity may be acquired by blood products post-transfusion.

b. Not only in cases of fever, specimens drawn from various sites (and the blood) for microbiological investigation may help to explain or exclude bacterial or fungal infections. The culture technique used to investigate specimens drawn for microbiological investigations should allow for the growth of aerobic and anaerobic bacteria and fungi. The results should be documented in the donor record and must be communicated to the OPO and recipient centres immediately upon arrival.

c. Every donor must be screened for HIV, HBV and HCV. The results must be available before procurement or before any organ of the donor is released for transplantation (see Chapter 8 and Table 6.3 for further details). Additional tests can be mandated according to national regulations and depending on the type of transplantation. Nuclear acid testing (NAT) is encouraged, where appropriate and available. In many institutions, 'fourth-generation'

serological testing is available. Its additional value or safety compared to NAT is not yet known. Importantly, even when using the best screening method available, the diagnostic window period for any infection cannot be reduced to zero. Other tests are required in specific situations, in the case of an immunosuppressed recipient or according to national provisions (see Chapter 8).

d. There is a long list of infectious diseases that have been transmitted with organs, as outlined in Chapter 8. The presence of a transmissible disease should not be an automatic reason for excluding a potential donor: once known, it is an element in the allocation process, an element in the correct decision by transplant teams to proceed (or not) with transplantation and an element to be carefully monitored in the different patients transplanted with organs from this same donor, within connected vigilance systems. For further details about best practice in donor screening, see Chapter 8.

e. ABO blood group, Rhesus Rh(D) group and human leukocyte antigen (HLA) typing: in cases of HLA typing, molecular-biologic techniques should be used which allow a low, as well as high, resolution of all HLA loci needed to provide appropriate information for a virtual cross-match.

f. The routine screening of tumour markers is not recommended. In the case of a confirmed malignancy in the donor history and tumour marker values available from previous examinations, a current update may help to assess the state of disease (see Chapter 9).

g. The other laboratory parameters outlined in Table 6.1 contribute further to donor characterisation. Please note that this table contains all laboratory data informative for general donor characterisation or organ-specific issues. Many hospitals use point-of-care systems as well as specific profiles covering a set of specific investigations (e.g. admission status, liver profile, kidney profile, heart profile). Such profiles are in line with the parameters needed to characterise an organ in detail. Depending on the infrastructure of the hospital, not all investigations will be available on a 24/7 basis. This should not be used as an argument to delay a donation procedure.

Table 6.1. **Informative value and clinical relevance of laboratory parameters in donor and organ characterisation**

Lab values are informative only after serial measurement in context of all other clinical data for assessment of organ function: +++ important, + helpful, R see comment. If not otherwise stated, all measurements refer to the blood compartment.								**Hospitals apply individual lab reference ranges adjusted to their local environment. Age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
Parameter	Basic	Kidney	Liver	Pancreas	Intestine	Heart	Lung	Comment on informative value and pitfalls associated with measurement
Hb	+++							In intensive care, medicine transfusion threshold is lowered to 7-9 mg/dL (4.4-8.6 mmol/L) according to age and cardiac status; down to this range, haemodilution is acceptable
Hct	+++							In intensive care, medicine transfusion threshold is lowered to 20-30 % (0.2-0.3) according to age and cardiac status; down to this range, haemodilution is acceptable
Leukocytes	+++							Acute elevation due to brain-stem coning (therefore, not representative for monitoring of infection); elevation if inflammation occurred for multiple causes (e.g. SIRS in brain death)
Platelets	+++							Elevated after brain damage, decreased due to bleeding or coagulation disorders or sepsis; substitution indication exists only in cases of bleeding due to thrombocytopaenia
Erythrocytes								
Na^+ *	+++							Consider diabetes insipidus
K^+ *	+++							Consider kidney function

Table 6.1 (continued)

Lab values are informative only after serial measurement in context of all other clinical data for assessment of organ function: +++ important, + helpful, R see comment. If not otherwise stated, all measurements refer to the blood compartment.								**Hospitals apply individual lab reference ranges adjusted to their local environment. Age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
Parameter	Basic	Kidney	Liver	Pancreas	Intestine	Heart	Lung	Comment on informative value and pitfalls associated with measurement
Ca^{2+}								
Cl^{-}								
Glucose	+++							Acute decompensation during intensive care therapy, not representative for time before hospital admission
Creatinine	+++	+++	+					Dependent on fluid load; elevated in kidney failure or due to muscle damage or cardiac failure (chronic)
Urea	+++	+++						See Creatinine
LDH (IFCC 37 °C)	+++	+	+	+	+	+		Tissue damage (necrosis, unspecific)
CPK (IFCC 37 °C)	+++	+++						CPK is released by muscle damage and may secondarily harm the kidney
CKMB		+				+		Troponin more sensitive/specific for myocardial damage; CKMB also elevated by brain damage
Troponin						+++		
ASAT/SGOT (IFCC 37 °C)			+++	+++	+++	+++		Myocardial damage or liver damage; see ALAT
ALAT/SGPT (IFCC 37 °C)			+++	+++	+++			Liver cell damage
γGT (IFCC 37 °C)			+++	+++	+++			Liver: indicator of biliary tract damage e.g. acute hypoxaemia, chronic alcoholic / non-alcoholic steatohepatitis (cholestasis)
Bilirubin tot.			+++					Consider if increased in cases of trauma and poly-transfusion due to bleeding or liver damage (cholestasis)
Bilirubin dir.			+					
Alk. Phos. (IFCC 37 °C)	+							Liver or bone damage or: physiologically elevated in growing children
Amylase								Unspecific (infusion, head trauma); reference range varies between hospitals as measurement is not standardised; only pancreas-amylase is specific
Lipase				+++	+++			Reference range varies between hospitals as measurement is not standardised, but more specific than amylase
HbA1c				+				Not generally available 24 h/365 days
Tot; Protein	+							Consider haemodilution
Albumin	+							Consider haemodilution; must be viewed in the context of donor management as well as liver function
Fibrinogen	+							Increased due to brain damage or inflammation
Quick/PT	+++							Distorted by bleeding and coagulation disorders due to brain damage or therapeutic anti-coagulation after correction by FFP transfusion
INR (international normalised ratio)	+							Measurement not adjusted to liver function; used in anti-coagulation therapy in people with normal liver function

Table 6.1 (continued)

Lab values are informative only after serial measurement in context of all other clinical data for assessment of organ function: +++ important, + helpful, R see comment. If not otherwise stated, all measurements refer to the blood compartment.								**Hospitals apply individual lab reference ranges adjusted to their local environment. Age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
Parameter	Basic	Kidney	Liver	Pancreas	Intestine	Heart	Lung	Comment on informative value and pitfalls associated with measurement
APTT	+++							Distorted by bleeding and coagulation disorders due to brain damage or therapeutic anti-coagulation after correction by FFP transfusion
AT III (antithrombin III)	+		+					Must be viewed in the context of bleeding disorders as well as liver function
CRP (C-reactive protein)	+++					+	+	Acute elevation due to brain-stem coning; not representative for monitoring of infection
FiO_2	+++						+	Must be viewed in the context of respiration therapy as well as other acute events
PEEP	+++					+	+++	
pH (acidity)	+++							
$PaCO_2$	+++						+	
PaO_2	+++	+	+	+	+	+	+	
PaO_2/FiO_2							+++	Oxygenation index representative for quality of lung
HCO_3	+++							Must be viewed in the context of respiration therapy as well as other acute events
BE (barium enema)	+++							
O_2 saturation	+++							
Lactate	+++		+	+	+	+		Indicates tissue damage due to anaerobic metabolism, sepsis, metformin-medication, shock, acute liver or kidney failure
Cholinesterase			+++					Liver synthesis
Procalcitonin	+							Acute elevation due to brain-stem coning, so not representative for monitoring of infection
Pro-BNP	+							Not evaluated in DBD populations; can be indicative of right heart failure, but distorted by fluid overload or acute kidney injury
Blood culture	+	+	+	+	+	+	+	Bacteria and fungi; anti-microbiological resistance pattern
Urine culture	+	+						Bacteria and fungi; anti-microbiological resistance pattern
BAL culture	+						+	Bacteria and fungi; anti-microbiological resistance pattern
Other cultures	+							Bacteria and fungi; anti-microbiological resistance pattern
Multidrug-resistant bacteria	+	+	+	+	+	+	+	Screening useful
Urine glucose								Depends on blood glucose; kidney damage

Table 6.1 (continued)

Lab values are informative only after serial measurement in context of all other clinical data for assessment of organ function: +++ important, + helpful, R see comment. If not otherwise stated, all measurements refer to the blood compartment.								**Hospitals apply individual lab reference ranges adjusted to their local environment. Age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
Parameter	Basic	Kidney	Liver	Pancreas	Intestine	Heart	Lung	Comment on informative value and pitfalls associated with measurement
Urine protein		+						Slight proteinuria possible due to urethral-catheter; kidney damage; only data of pre-hospital time during steady-state care can be informative; according to KDIGO Guidelines, albuminuria should be investigated instead of total proteinuria [30]; also the ratio urine protein/urine creatinine is a simple parameter resistant against sampling errors compared to collecting urine for 12 h or 24 h
Ratio urine-protein/ urine-creatinine		+						< 500 mg Protein/g Creatinine in urine normal, > 1000 mg Protein/g Creatinine indicative of kidney damage if measured in a steady state outside ICU [30]
Urine albumin		+++						For assessment of glomerular function more indicative than protein (KDIGO Guidelines) [30]
Ratio urine-albumin/ urine-creatinine		+++						< 30 mg albumin/g Creatinine normal; > 300 mg albumin/g Creatinine indicative of kidney damage if measured in a steady state outside ICU [30]
Urine Hb		+						Slight micro-haematuria possible due to urethral-catheter
Urine sediment		+						Exclusion of relevant haematuria, bacteriuria or glomerular or tubular damage
Urine nitrite		+						Bacterial infection of urinary tract possible
Estimated creatinine clearance or eGFR		R						Estimates of creatinine clearance or glomerular filtration rate (eGFR) have been developed for screening outpatients in a stable state without haemodynamic changes; therefore, estimates may be inappropriate for use in organ donors; according to KDIGO Guidelines, only measurements in a steady state (probably not during donor care) are reliable [30]
Measured creatinine clearance or eGFR		R						After haemodynamic stabilisation of a donor, recovery of kidney function can be assessed by this measurement (after one hour); further estimates may be inappropriate for use in organ donors; according to KDIGO Guidelines, only measurements in a steady state (probably not during donor care) are reliable [30]

Table 6.1 (continued)

Lab values are informative only after serial measurement in context of all other clinical data for assessment of organ function: +++ important, + helpful, R see comment. If not otherwise stated, all measurements refer to the blood compartment.								**Hospitals apply individual lab reference ranges adjusted to their local environment. Age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
Parameter	Basic	Kidney	Liver	Pancreas	Intestine	Heart	Lung	Comment on informative value and pitfalls associated with measurement
Anti-HIV-1/2	+++							See Chapter 8
HIV-NAT								
Anti-HCV	+++							
HCV-NAT								
HBsAg	+++							
Anti-HBc	+++							
Anti-CMV; Anti-EBV; Anti-Toxoplasma	+++							
Syphilis test	+++							
Further tests for infections	+							
Microbiological cultures	+							

ALAT: alanine amino transferase; APTT: activated partial thromboplastin test; ASAT: aspartate amino transferase; BAL: broncho-alveolar lavage; BNP: B-type natriuretic peptide; CKMB: creatine kinase MB isoenzyme; CMV: *cytomegalovirus*; CPK: creatinine phosphokinase; EBV: Epstein–Barr virus; γGT: gamma glutamyl transferase; HbA1c: haemoglobin A1c; HBsAg: surface antigen of hepatitis B virus; IFCC 37 °C: measurement according to methods of International Federation of Clinical Chemistry and Laboratory Medicine at 37 °C; KDIGO: Kidney Disease Improving Global Outcomes; LDH: lactate dehydrogenase; SIRS: systemic inflammatory response syndrome.

6.2.4. Other complementary tests

Complementary tests can contribute further to characterising the donor when an indication for the particular investigation exists and the results are communicated within standardised questionnaires as outlined in Chapter 7. One common language should be used by the investigator performing the test and the recipient centres interpreting the results.

For any organ procurement, as a minimum, abdominal imaging is strongly suggested. For abdominal organs the investigations concerning thoracic organs are not of primary interest, but for exclusion of other diseases (e.g. malignancy) or co-morbidities (e.g. arterial hypertension), they are helpful. For thoracic organs a specific indication should exist for performing invasive investigation (e.g. coronary angiography in a donor with relevant risk for coronary artery disease: see Chapter 7. When signs of unexpected atypical findings, space-occupying lesions, changes susceptible for infection etc. are detected in imaging studies, then special consideration must be given to further exclusion of malignancies (see Chapter 9, e.g. whole-body CT scan[1]), infections (see Chapter 8) or other transmissible diseases. Depending on the organs considered for transplantation and also on indications for general donor assessment, then chest X-ray, bronchoscopy, electrocardiogram, echocardiography (see §7.2.5.2) and abdominal ultrasound (see §7.2.1.1) are performed in the multi-organ donor as the basic set of imaging (see Appendix 10).

In cases where an examination cannot be performed in a particular hospital, individual decisions become necessary before any organ or donor is lost due to this limitation (e.g. coronary angiography). For safety reasons it cannot be recommended to transfer a donor to another hospital just to perform a complementary test. In special cases beyond the standard set of complementary tests, additional investigations become valuable (e.g. whole-body CT scan for exclusion of space-occupying lesions in a donor with or without a history of malignancy).

In cases of cDCD as well as DBD, these tests can be performed early in the work-up as long as they

1 In whole-body CT scan including head, contrast opacification of cerebral arteries or veins should not be interpreted for the diagnosis of cerebral circulatory arrest because of fundamental technical differences between whole-body CT scan and CT angiography dedicated for the diagnosis of cerebral circulatory arrest. Otherwise, discrepant results may occur, providing false positive or false negative diagnoses of cerebral circulatory arrest on the basis of whole-body examination.

are not invasive, without harm to the patient and as part of the repertoire of high-quality intensive care medicine according to the treatment protocols. Investigations performed early in the work-up should be re-evaluated according to the principles outlined in Chapter 7. In uDCD only a limited set of investigations is possible in the emergency room according to the standards of emergency medicine. In such cases the quality of measurement results represents the needs of investigations required to decide on further therapy and they do not represent a more detailed and qualified examination as applied in cDCD or DBD.

6.2.5. Histopathological examinations

Any suspect mass should be investigated by histopathology. The mass should be resected *in toto* (not only parts of it) to rule out or investigate malignancy properly, whenever possible without sacrificing a graft otherwise suitable for transplantation (e.g. Ro-resection in space-occupying lesions in a kidney). The pathologist should be informed about all donor data and the macroscopy surrounding the suspicious mass (see Chapter 9). In consultation with the investigating pathologist, it should be clarified which medium can be used for transport of the sample sent in for histopathologic examination (based on the assumed transport time).

A question frequently asked is whether, in cases of suspected brain tumours, imaging or biopsy will be sufficient for an appropriate diagnosis, allowing a release of organs after procurement. Only in urgent and dire circumstances may this be done. The best practice is to have brain autopsy performed with a histopathologic examination (e.g. the brain can be procured for autopsy during or after organ procurement).

It is recommended that in every country a network of pathologists is created for the purpose of a 24/7 service to assess biopsies of organ donors. Regional solutions with one centre on duty, e.g. a centre associated with a university hospital that has a transplantation facility, might be helpful. Appropriate reimbursement should be ensured by the national healthcare system. Exclusion of malignancy in space-occupying lesions and assessment of liver quality are especially pivotal in minimising organ wastage. Agreement on standardised wording in documentation is suggested (see Appendix 11).

6.2.6. Summary of clinical data

For the comprehensive description of the donor and specific characterisation of the organs, the clinical data shown in Table 6.3 should be collected, including the information obtained already or later on during the donation process. Organ exchange and/or allocation can be performed once this information has been provided as completely as possible, enabling proper assessment. Whenever data cannot be provided properly, despite best efforts, this must be indicated clearly; when donor evaluation has found no evidence for a risk factor, this also should be documented. These data should be updated by the most recent information available, even after transplantations have been carried out.

6.3. General donor selection criteria (pre-procurement)

At present there is almost no medical reason to justify why a deceased person could not donate organs. Therefore only a few absolute exclusion criteria exist for organ donation, while more and more 'critical donors' become actual donors. Thanks to this experience, knowledge of transmission risks is expanding. However, according to national regulations, in some countries individual cases may need expert local advice to evaluate the suitability of some donations; for example, donors with specific infections or malignancies (see chapters 8-9).

Careful consideration should be given to the following conditions, which are considered as general exclusion criteria because no appropriate life-saving treatment after transmission in the recipient is possible:

a. Active malignant neoplasia with spread to multiple organs (for exceptions: see Chapter 9).

b. Severe systemic infections that are untreated or of unknown origin (especially any case of uncertain encephalitis of viral origin or febrile meningo-encephalitis of unknown origin), as well as ongoing sepsis or disseminated, uncontrolled infection (bacterial, viral, fungal, parasitic, active [disseminated] tuberculosis, acute Chagas disease) or infections without option of treatment in a recipient (e.g. rabies). Specific details are outlined in Chapter 8.

It is highly recommended to refer to chapters 8 to 10 in order to perform a proper assessment of transmission risks due to infections, malignancies and other rare systemic diseases.

There is a long list of infectious diseases that have been transmitted with organs, as outlined in Chapter 8. On the other hand, the presence of a transmissible disease should not be the only reason nor an automatic reason for excluding a potential donor: once known, it is an element in the allocation process,

an element in the correct decision by transplant teams to proceed (or not) with transplantation and an element to be carefully monitored in the different patients transplanted with organs from this same donor, within connected vigilance systems. There is no reason to believe that a disease could not be transmitted with an organ/tissue, independently of how well the graft has been perfused during preservation. For further details about best practice in donor screening, see Chapter 8 and the *Guide to the quality and safety of tissues and cells for human application*.

When considering transplantation with a risk of disease transmission, the approach should be to solve the problems associated with pre-existing malignancies in a donor, as described in Chapter 9 in detail.

The factor of age and its associated co-morbidities should be evaluated according to the organ-specific selection criteria (see Chapter 7). Adding other avoidable risk factors on top of the existing ones should be avoided (e.g. prolonged ischaemia times).

For any other systemic disease, the pragmatic approach shown in Table 6.2 can be used as guidance on how to handle the case when a rare disease is not covered within the scope of chapters 8-10.

Infections, malignancies and other diseases transmitted with a graft expose the recipient to unexpected and/or unwanted complications. Whether or not it is possible to transplant an organ/graft to a suitable recipient with an associated acceptable risk must be considered before excluding an organ/graft for infectious or other risk reasons. Especially for deceased organ donors, there is insufficient time to perform exhaustive investigations and for results to become available within a few hours, so strategies have to be applied to reduce the risks. However, any deviation from 'normal circumstances' should be considered indicative of an undetected risk. Further details are outlined in chapters 8-10. Table 6.4 provides a summary of risk factors limiting successful donation. These should be considered when deciding final conclusions about general donor suitability.

Table 6.2. **List of pragmatic questions that might help in assessing whether donors and grafts are suitable for transplantation in cases of a rare disease where insufficient data are available**

Question 1	Was a successful transplant previously carried out where the donor was known to have had such a disease? If so, what was the outcome and how were other organs affected in this recipient (e.g. www.notifylibrary.org)? Were all additional resources/sources of information checked (e.g. www.orpha.net for rare diseases, literature)?
Question 2	Is treatment by immune-suppression effective for the disease? Can harm to recipient and graft due to immune-suppression be excluded as a risk factor? Is specific, successful anti-infective treatment possible in the immunosuppressed recipient of the particular graft in the case of an infectious pathogen, or can disease transmission be prevented successfully?
Question 3	Was the organ itself damaged? Are the supplying vessels intact and suitable for anastomosis? Is the probability high that the organ will function properly in the recipient within an acceptable time interval?
Question 4	Are there any other donor-related risk factors that may compromise the outcome? How does the cumulative effect of all risk factors taken together impact the graft quality?

After going through the questions above, an individual risk–benefit assessment for each donor–graft–recipient combination must be discussed before a decision is made. The decision process should be documented for reproducibility and later sharing of the knowledge (e.g. by prospective application of biovigilance tools according to Chapter 15).

Tables 6.3 and 6.4 follow. Text resumes on page 127.

Table 6.3. **Data needed for a comprehensive characterisation of the donor and organs**
The minimum data set defined in Part A of the Annex to Directive 2010/53/EU is marked by an asterisk (*); the complementary data set in Part B of the Annex is marked by two asterisks (**). For further details, see §6.8.

Data	Donor	Comment, informative value and background	Cross-reference
General data (important for allocation)	Type of donor*	DBD, cDCD or uDCD donor	
	Establishment where the procurement takes place and other general data* Contact details of this establishment or of the organ procurement organisation in charge**	Necessary for co-ordination, allocation and traceability of the organs from donors to recipients and vice versa as well as for acute questions by transplant teams during risk–benefit assessment for a particular recipient.	
	Age,* gender,* height,* weight,* other demographic and anthropometric data**	Data may determine allocation of organs (e.g. age match). For heart, lung, liver and intestinal transplantation, the size/weight match between donor and recipient is important. Weight and height should be measured [31] whenever possible.	
	Blood group,* HLA-typing	Only relevant for organ allocation.	§6.6
	Virology/ microbiology	All details must be known about the risk of transmissible pathogens, which may determine further allocation of organs. Before any graft is transplanted, anti-HIV1/2,* anti-HCV,* anti-HBc* and HBsAg* must have been determined.	Chapter 8 and §8.1 for indication of additional tests
	The correctness of the data, e.g. blood group, virology, should be ensured when determined or whenever data are transmitted. Ensure that specimens for the above-mentioned investigations are drawn properly and in time.		§6.8
General data, medical history of acute event	Cause of death* Date/time of death*	It is imperative to know exact cause of death in order to identify additional risks associated with the brain injury. Occasionally, a central nervous system infection is obscured by other causes of death or by an overlap in imaging, with the risk of fatal disease transmission [32]. The following conditions should raise concerns: • Cerebrovascular accident without risk factors for stroke, etc. • Unexplained fever or illness or altered mental status at presentation/admission with or without unexplained cerebrospinal fluid abnormalities (e.g. pleocytosis, low glucose, elevated protein) • Immunosuppressed host (e.g. autoimmune disease, cirrhosis) and/or environmental exposure (e.g. animals)	Chapter 8 Chapter 9 §8.9
	Timeline: admission to hospital, admission to ICU, start of ventilation, death certification	It is helpful to estimate the chances of recovery from primary critical periods at admission and/or the risk of acquiring nosocomial infections.	Chapter 8
	Episodes of cardiac arrest/resuscitation	For each episode of cardiac arrest, information on its duration, duration of CPR and treatment provided should be collected (e.g. defibrillation, medication), as well as about the haemodynamic status afterwards.	Chapter 7
	Hypotensive periods/shock	Time of hypotension or shock should be reported with systolic and mean arterial blood pressure, as well as medication applied.	
	General information/ remarks*	Summary of key information about actual donor data and history. This should cover all information outlined below as well as important remarks or facts to be considered for the further planning of the donation procedure.	

Data	Donor	Comment, informative value and background	Cross-reference
General data, medical history before hospital admission	History of arterial hypertension	Duration, kind and quality/success of treatment may indicate or exclude organ damage (kidney, heart, pancreas, risk of arteriosclerosis). Extension of left ventricular hypertrophy in echocardiography is indicative of quality of long-term care.	Chapter 7
	History of diabetes	Diabetes type (insulin-dependent/non-insulin-dependent), duration, kind and quality/success of treatment may indicate or exclude organ damage (kidney, heart, risk of arteriosclerosis, risk of liver steatosis, obesity, pancreas, intestine). Valuable information may be obtained by contacting the general practitioner, especially for laboratory tests such as HbA1c, glucose tolerance, kidney function (albuminuria or proteinuria) and other medical interventions due to diabetes. Type II diabetes is a frequent diagnosis in elderly people when patients did seek medical advice. Insulin demand of a donor in an ICU is not indicative of pre-existing diabetes.	Chapter 7
	History of smoking	Duration and quantity of smoking (pack-years) may be indicative for cardiovascular damage and risk of smoking-related malignancies.	Chapter 7 Chapter 9
	History of alcohol abuse	Duration and quantity of alcohol consumption may be indicative for organ damage (liver, kidney, heart, pancreas, intestine, risk of arteriosclerosis). Chronic abuse combined with malnutrition or smoking is a risk factor for other diseases.	Chapter 7
	History of drug abuse* (IV-drug abuse)	It should cover past and current history: Extended virology testing is necessary in cases of drug abuse (e.g. intravenous drug abuse, needle sharing, intranasal cocaine sniffing, oral or recreational drugs consumption), with secondary effects on lifestyle (e.g. multiple sexual partners). Organ damage can be caused by substance abuse.	Chapter 8, in detail §8.2 to §8.3
	History of transmissible diseases,* HIV,* HCV,* HBV*	For transmissible diseases, current history is particularly relevant. HBV/HCV: pattern of infection, treatment (medication) and virological response to treatment are informative in concert with the medical history. New treatment regimes in HCV, HBV and HIV will change the exclusion and inclusion criteria for donors and organs with such infections.	For the principles of basic donor screening §8.2 to §8.3 and in detail §8.4.2.6, §8.4.2.7, §8.4.2.11
	Behavioural risk, commercial sex worker, sexual contacts, Imprisonment	This may indicate that organ function could be compromised or that an increased risk of infectious diseases exists. It is necessary to ask about sexual behaviour (e.g. prostitution, frequently changing partners regardless of their gender), use of intravenous drugs or cocaine, lifestyle or imprisonment.	§8.2 to §8.3
	Blood transfusions or transplant procedures; body piercing or tattoos; non-medical injections	Risk of blood-borne infections is increased if they occurred within the 180 days preceding death. Body piercing or tattoos are very common nowadays. If they have not been applied professionally under sterile conditions, then they carry the same risk as non-medical injections.	§8.2
	History of malignancies*	It should cover the detailed past and current history of malignancies. Records should be checked for any previously diagnosed neoplasms or tumours removed.	§9.2 to §9.3
	History of other diseases or risk factors for potential malfunction of an organ*	The following information helps in assessing the side effects of these diseases: duration, treatment, quality of treatment. Co-existing laboratory data are also helpful. Previous diseases or surgery hint at potential disease-transmission risks (infection, malignancy, etc.) as well as posing the risk of acquiring nosocomial infections (due to hospital or nursing home admission). This includes considerations about diseases originating from neuro-degeneration, intoxication, auto-immune – or congenital – or inherited disorders as well as unknown aetiology.	chapters 7, 8, 9, 10
	History of recent immunisation	Transmitting live vaccines from the donor into a recipient.	§8.3.4

Data	Donor	Comment, informative value and background	Cross-reference
	Travel history or residence abroad/overseas, living conditions, social contacts, job description, travel, immigration, living abroad, private hobbies, pets, contact with fauna, especially bites from pets, domestic or wild animals, birds, etc.	This should be evaluated to rule out the risk of tropical or endemic infections. Information on potential exposure to foreign diseases will guide individual decisions as to what additional and specific testing is required. In most countries there are only a few institutions dealing with testing of tropical or other rare diseases (often without operational 24/7). Timely requests for these additional tests are necessary. The history of travel or residence abroad should include information about living conditions, migration background, refugee status and work places (e.g. sewage plant, woodlands, farm, airport, hospital, foreign countries). This may help to identify risks related to places/countries with inferior hygienic standards or a high prevalence of certain infections. Information about hobbies (e.g. home, garden, animals, woodlands) should be obtained with the same intention.	Chapter 8
	Risk of transmitting prion disease	This includes diagnosis or high suspicion of any transmissible spongiform encephalopathy in the donor, a family history of Creutzfeldt–Jakob Disease, and whether the donor was recipient of human-pituitary-gland derived hormones, *dura mater* or corneal/scleral transplants.	§8.8
	Medications before hospital admission (long-term use)	Chronic medication may cause organ damage or it is applied because of it. This consideration also applies to any previous medical treatment, exposure to chemical substances/radiation or immuno-suppression.	Chapter 7 as well as chapters 8, 9, 10
	Uniform donor health questionnaire	This is a complementary checklist that can help to avoid missing important topics.	appendices 6, 7, 8, 9
Haemodynamic parameters and further monitoring	Body temperature	Decreased body temperature is common in DBD. Sometimes, fever may occur due to SIRS and/or infection. In such cases taking cultures may be considered for exclusion of bacterial infections.	chapters 5 and 8
	Heart rate	After failure of vagal stimulation in DBD, the autonomous sinus node of the heart takes over (at a wide range, tachycardia of about 100/min in adults). Arrhythmias occur during or shortly after brainstem coning.	Chapter 5
	Arterial blood pressure	Surrogate for quality of organ perfusion; to be considered in association with demand for vasopressors and diuresis. Consider age adjustment and the need for elevated organ perfusion pressure in cases of pre-existing arterial hypertension without proper treatment.	Chapter 5
	Diuresis in last 24 h – with review of last 72 h. Diuresis in last hour	Indicates quality of kidney function if donor is haemodynamically stable and if appropriate fluid balance exists. Polyuria may be due to diabetes insipidus, elevated serum glucose or recovery from acute kidney injury. Oligo-anuria may occur due to haemodynamic instability, volume depletion or acute kidney injury.	chapters 5 and 7
	Central venous pressure	Correction for PEEP is mandatory. It is a questionable surrogate marker for venous filling and right cardiac function. In cases of maintenance problems, invasive monitoring is more informative (PICCO® or similar monitor, echocardiography, A. Pulmonalis catheter).	Chapter 5
	Pulmonary artery pressure	Can be estimated via echocardiography when no invasive measurement is available.	Chapter 5
	Physical and clinical data**	Data from clinical examinations – which are necessary for evaluation of physiological maintenance of the potential donor as well as any finding that reveals conditions that remained undetected during examination of the donor's medical history – might affect considerations about the suitability of organs for transplantation or risk of disease transmission. Consider also for examination during and after procurement. It is important to check for scars from previous surgery in order to identify any missed previous therapy for eventual oncologic reasons.	§6.2.2, §6.4 and §6.5

Data	Donor	Comment, informative value and background	Cross-reference
Medication during current stay at ICU** (for any kind of medication, the timeline and dose should be known)	Adrenaline, noradrenaline, dopamine, dobutamine, vasopressin, other vasopressor or inotropic drugs**	Indicative for the kind of haemodynamic status achieved (dose over the timeline is of interest in terms of haemodynamic parameters). Medications used during cardiac resuscitation should be documented separately.	Chapter 5
	Blood transfusions**	Erythrocyte concentrate, fresh frozen plasma and thrombocyte concentrate. Units over timeline to be viewed in the context of haemodynamic parameters, coagulation and bleeding disorders. CMV status of the blood products used can be helpful for interpreting the result of CMV screening; but this is a sophisticated procedure and cannot always be provided.	Chapter 5 §8.4.2.2
	Plasma expanders**	Type, dose and duration of substitute may be informative about haemodynamic stabilisation or damage to kidneys.	Chapter 5
	Other blood products**	Medication for correction of coagulation status.	Chapter 5
	Antibiotics**	Indication, type and duration of antibiotic or anti-fungal or anti-viral medication and success in treatment of infections. Treatment according to resistance patterns should be confirmed.	Chapter 8
	Anti-diuretics**	Treatment of diabetes insipidus (context of diuresis and serum-sodium level).	Chapter 5
	Diuretics**	Requirements for initiating diuresis or correction of fluid balance due to overload should be recorded. Applications should be viewed in context with diuresis and kidney function parameters.	Chapter 5
	Insulin**	Glucose metabolism is frequently deranged after admission to ICU.	Chapter 5
	Steroids**	Treatment of SIRS.	Chapter 5
	Other medication**	Document of other relevant medication.	Chapter 5
Ventilation and pulmonary function	Respirator settings, blood gas analysis	Conclusive for protective ventilation and achieved gas exchange. Standardised interpretation of blood gas analysis for lung donation includes following procedure: (1) Suction the airway, (2) Perform lung recruitment, (3) Ventilate at PEEP ≥ 5 cm H_2O at FiO_2 = 1.0 for 10 minutes.	Chapter 7
	Chest X-ray (thoracic-CT), bronchoscopy, BAL	To be considered if pulmonary infection is suspected and to assess acute or chronic structural damage to the lung. BAL samples should be sent for microbiological tests.	chapters 7 and 8
Others	Laboratory parameters,** imaging tests** and other complementary tests	These data are complementary to the clinical data and explain, clarify and verify them regarding assessment of organ quality and risks of potentially transmissible diseases.	§6.2.3 and §6.2.4
Final documentation of success in donor maintenance	Haemodynamic	Monitoring and prevention of hypotension, hypertension, arrhythmias and cardiac arrest, and maintaining arterial pressure, volume substitution etc. aiming at preserving cardiac output and perfusion of other organs.	Chapter 5
	Electrolyte	Monitoring and correction of hypokalaemia, hyperkalaemia, hyponatremia and hypernatremia.	Chapter 5
	Body temperature	Kept within a physiological range (> 34 °C).	Chapter 5
	Endocrine	Monitoring of the clinical effects and prevention of changes in the hypothalamic-pituitary-thyroid and hypothalamic-pituitary axis (diabetes insipidus) and changes in glucose metabolism.	Chapter 5
	Coagulation	Monitoring and correction of major coagulopathies.	Chapter 5
Specific data to be provided in cases of uncontrolled DCD	Event of cardiac arrest leading to unsuccessful resuscitation and determination of death and procurement of organs with proper preservation	It is imperative to provide all data available *ante mortem* and before the event of cardiac arrest. Of special interest are: the particular time when last seen alive, start of CPR by both non-professionals and professionals including details of CPR, arrival in hospital, end of CPR, start and end of no-touch period, cannulation, preservation and procurement.	Chapter 12

Data	Donor	Comment, informative value and background	Cross-reference
Specific data to be provided in cases of controlled DCD	Detailed description of agonal period starting from the moment where full life-sustaining therapy is discontinued until determination of death and recovery of organs with proper preservation	It is imperative to provide all data available *ante mortem* and before the event of terminating life-sustaining therapy. In a few countries, donation after euthanasia is allowed. Then the same principles apply. Of special interest are: the particular time of withdrawal of therapy, kind and duration of agonal period, terminal cardiac arrest, start and end of no-touch period, cannulation, preservation and procurement.	Chapter 12

Note: Anti-HBc: hepatitis B core antibody; BAL: broncho-alveolar lavage; CMV: *cytomegalovirus*; CPR: cardio-pulmonary resuscitation; DCD: donation after circulatory death; D/R: donor/recipient; EBV: Epstein–Barr virus; HbA1c: haemoglobin A1c; HBsAg: hepatitis B surface antigen; HBV; hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; ICU: intensive care unit; NAT: nucleic acid testing; PEEP: positive end-expiratory pressure; SIRS: systemic inflammatory response syndrome; TPHA: *Treponema pallidum* haemagglutination.

The minimum data set defined in Part A of the Annex to Directive 2010/53/EU is marked by an asterisk (*); the complementary data set in Part B of the Annex is marked by two asterisks (**). For further details, see §6.8.

Cross-reference: Refer to the chapter or section (§) specified to see all details that need to be considered.

Table 6.4. **General conditions in the donor that can be risk factors for successful transplantation**

Condition	Conditions that might be limiting for successful donation	Cross-reference
Acute	***Unfavourable – but avoidable*** Avoidable are complications in management of a patient *ante mortem* or potential donor *post mortem* by proper intensive care medicine therapy and donor management. Recovery from initial periods of shock, resuscitation or complications during intervention can be monitored; while we know that severe cerebral lesions cause indirect damage to organs, especially without proper neuro-critical care. ***Irreversible*** Acute multiple organ failure without option of recovery or chronic organ failure with structural damage both require a case-by-case decision.	Chapter 5 and Chapter 7
Infections	The most frequent misunderstandings in donor inclusion and exclusion are: Bacterial infections: 48 h definitively effective antibiotic therapies are considered to be sufficient for acceptance (negative culture preferred). Existing local infections or colonisations do not exclude donation of other organs (e.g. pneumonia, urinary tract infection). Fungus, virus, parasites: caution if the pathogen is detected in the blood. These infections must be cured or, after a case-by-case decision, selected recipients may have an organ transplanted because either treatment is available or recipient-related infection requires mandatory treatment anyway. For CMV, EBV and toxoplasmosis: chemoprophylaxis in a recipient is mandatory if D^+/R^-. For management of acute donor infections with spread of the pathogen into the blood (e.g. confirmed by NAT) such condition may limit the use of grafts. Antibodies detected against a pathogen document only that the immune system has responded to the pathogen. Reactive IgM antibodies do not clarify whether the pathogen has spread to the blood stream or not.	Chapter 8
	Special consideration should be given to exclusion of asymptomatic infection by HIV, HBV, HCV, HTLV I/II virus, *Trypanosoma cruzi* and other pathogens in donors who originate from endemic areas for these infections or populations with increased risk for window-period infections or vertical transmission.	§8.2
Malignancies	Decisions on a case-by-case basis.	Chapter 9
Poisoning	For appropriate determination of brain death, detoxification becomes mandatory. After recovery from poisoning, each organ should be individually evaluated.	Chapter 10
Inherited or rare diseases	Decisions on a case-by-case basis: systematic reports are not available. Further information can be retrieved from the emergency guidelines at www.orpha.net for very rare diseases. Systemic diseases with possible effects on graft quality (e.g. collagen disease or systemic vasculitis, or metabolic disorders such as maple syrup disease, oxalosis etc.) require additional examinations.	Chapter 10
Age-related co-morbidities	With advanced age the frequency of arterial hypertension, diabetes, obesity and of the side effects of chronic alcohol abuse and smoking increases. Beyond cardiovascular risks, including progressive arteriosclerosis, irreversible organ damage may occur to different degrees which require an individual assessment. In contrast properly treated arterial hypertension and/or diabetes and a lifestyle including enough physical activity may compensate for or limit such changes. Therefore, in the advanced-age donor population (e.g. > 60-70-80 years), significant differences exist in the suitability of each individual organ for transplantation.	Chapter 7

CMV: *cytomegalovirus*; DCD: donation after circulatory death; D/R: donor/recipient; EBV: Epstein–Barr virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HTLV: human T-lymphotropic virus. NAT: nucleic acid test.

Cross-reference: Refer to the chapter or section (§) outlined for all details to be considered.

6.4. Examination during procurement

Prior to the procurement of any graft from a donor, a detailed macroscopic examination should be performed and documented (see Chapter 11). It is the responsibility of the professional who is performing the procurement to document any suspicious anatomical findings observed during the organ procurement procedure. During procurement, the whole abdominal cavity must be inspected for any suspicious lesion. The same is highly recommended for the thoracic cavity in every donor.

Systemic diseases with possible effects on organs to be transplanted (e.g. collagen disease or systemic vasculitis) may require additional examination. The final decision to use grafts also depends on macroscopic evaluation by the procuring surgeon and, if necessary, histology of an organ biopsy.

In cases of abnormal findings, further investigations should be made and the results must be

included in the donor documentation. For example any space-occupying lesion detected either during pre-procurement investigations or during procurement should be verified by histopathologic examination of the whole lesion, or samples from a suspected area of contamination should be sent for microbiologic examination (swab, fluids etc.).

In cases of donors with previous history of malignancy, it must be planned in advance how any space-occupying lesion detected incidentally can be examined and what consequences may result from the use of any organ recovered.

6.5. Examinations after procurement

Performing an autopsy after procurement, for final exclusion of undetected diseases, can be helpful. However, experience shows that obtaining permission for an autopsy can be more difficult than obtaining permission for donation, unless medical evidence exists that may persuade donor relatives to insist on an autopsy. Therefore it is recommended to carry out an inspection at least at procurement (see §6.2).

Any investigation initiated before or during procurement with pending final result must be integrated into the final donor characterisation (e.g. a frozen section of a space-occupying lesion will have to be followed by paraffin embedding). The results must be forwarded immediately to all relevant institutions (e.g. OPO, transplant centres, tissue establishment). These results might change the final conclusions of donor characterisation and they may cause the reporting of a serious adverse event in order to prevent further harm to other potential recipients (see Chapter 15). In cases where results are pending, grafts can be offered to those centres and recipients who are willing to accept the risks associated with unknown data. Indeed, the transplant team might assess the risks posed by nontransplantation as outweighing the risks associated with data partly unknown, and might choose to monitor the situation before and when results become available.

Whenever a procured graft is finally not transplanted, then it is best practice to perform histopathologic examination to exclude other undetected disease and to confirm the quality of the decision to not transplant the graft.

Donor and organ characterisation is a continuous process, and data collected before, during and after the procurement should be completed by other results (for example lab tests) as soon as they become available. Communication channels between the OPO and the different transplant centres involved, as well as between the transplant centres themselves, should not be neglected and are also critical in the case of cross-border organ exchange. The correct definition of these communication channels and their availability to medical teams are essential for traceability and vigilance purposes within well-established donation and transplantation systems.

Follow-up studies of all grafts transplanted are also recommended for vigilance purposes and for quality assurance of the donor characterisation process.

The principles summarised in this chapter are confirmed by the European Foedus project [33], which is evaluating the practice of donor and organ characterisation to establish the best data set needed for efficient organ exchange across the borders of the various European organ-exchange organisations. As a major additional benefit, this project provides valuable information on how we can collect data on donor evaluation for future analysis of donor characteristics in Europe.

6.6. Examinations helpful for recipient allocation

Examinations like HLA-typing or ABO-blood-group determination and anthropometric or demographic data do not characterise the donor or organ quality itself. They are implemented in order to allocate a particular graft to the recipient with the greatest benefit of transplantation, as well as to rule out serious avoidable complications (e.g. antibody-mediated rejection in kidney transplantation). These data are collected as part of the donor and organ characterisation, but their purpose is to benefit the recipient. In order to avoid unnecessary delays after procurement (see Chapter 11), it must be carefully considered which investigations can be performed during the time interval that starts with clarification of death and final consent and continues until the start of procurement and cross-clamp.

It is important that the extent of immunisation in recipients against HLA-antigens or -epitopes of the donor is properly identified and monitored. Proper prospective HLA-typing of the donor by molecular-biologic methods – i.e. polymerase chain reaction (PCR-SSO or PCR-SSP) in low and/or high resolution as indicative of at least HLA-A*, -B*, -C*, -DRB1*, -DQB1*, -DQA1*, -DPA1*, -DPB1*, -DRB3*, -DRB4*, -DRB5* alleles (equivalent to serologic antigens of HLA-A, -B, -C, -DR, -DQ, -DP) enables transplant centres to perform virtual cross-match and further compatibility evaluation without risk of

unnecessary organ loss. For example, such investigations help to reduce the risk of graft loss in the long term due to existing or newly developing donor-specific antibodies; this risk is not only relevant in sensitised kidney recipients [34]. Since there are ongoing changes in the established methods improving quality in terms of outcome, it is recommended to consider adoption of new technologies in the light of the most recent changes.

For all organs procured from deceased donors, it is preferred to transplant them into ABO-blood group-compatible recipients. In specialised (paediatric) centres ABO-incompatible transplants are performed in approved protocols [35]. By contrast, for living donation it is a safe procedure to evaluate whether ABO incompatibility can be overcome by desensitisation protocols [36].

6.7. Appropriate amount of evaluation

For the characterisation and assessment of the donor as well as the organ, an appropriate amount of investigation is necessary as indicated. The correct balance must be found between examinations performed and examinations not performed. Over-evaluation is frequently a symptom of defensive medicine. This ties down a lot of resources – not only in money – and it creates a lot of results, which may be confusing or uninterpretable and therefore may lead to rejection of a potentially suitable organ donor or grafts. Under-evaluation of the donor, on the other hand, may lead to overlooking a clinically relevant situation that may harm the recipient by transmission of a disease or by transplantation of a damaged organ. Both situations are harmful for the future patient.

It is important to follow the frequency of tumours and similar indicators in each age group. For example, the incidence of coronary artery sclerosis (CAD) is extremely low in people in the age range 20 to 30 years compared to those in the age range of 50 to 60 years. This does not exclude CAD in younger people, but it is very unlikely. Then excessive diagnostics would be harmful when balancing the benefit of increased knowledge obtained by coronary artery angiography *versus* the associated complications. But in elderly people it might be justified to perform such diagnostics, especially if risk factors for cardiovascular co-morbidities exist. Still this picture might change when we have the risk factor of insulin-dependent diabetes mellitus or exposure to certain immuno-suppressive drugs in a former kidney graft recipient at a younger age. Such situations require an individualised indication of the need for examination, which will not be covered well by strict adherence to protocols without assessing each case individually.

6.8. Formal issues and documentation

Among the member states of the Council of Europe, regulations on transplantation and the required documentation vary. Transplantation teams must follow national and/or regional laws. The rest of this section concerns European Union legislation.

According to Directive 2010/53/EU, Article 7 ('organ and donor characterisation'), EU member states shall ensure that all procured organs and the donors thereof are characterised before transplantation, through collection of the information set out in the Annex to the Directive. Part A of the Annex contains a set of minimum data that must be collected for each donation. Part B of the Annex contains a set of complementary data to be collected in addition, based on a decision of the medical team, taking into account the availability of such information and the particular circumstances of the case. If, according to a risk–benefit analysis in a particular case, including in life-threatening emergencies, the expected benefits for the recipient outweigh the risks posed by incomplete data, an organ may be considered for transplantation even where not all of the minimum data specified in Part A of the Annex are available. It should be added that, while the EU directive mandates common quality and safety standards, it does not prevent any EU member state from maintaining or introducing more stringent rules, including rules on organ and donor characterisation.

A database of donor information should be maintained that protects anonymity. Directive 2010/53/EU states in its Article 16 that 'Member States shall ensure that the fundamental right to protection of personal data is fully and effectively protected in all organ donation and transplantation activities'. All necessary measures must be taken to ensure that 'the data process are kept confidential and secure' and 'donors and recipients whose data are processed … are not identifiable …. Any unauthorised accessing of data or systems that makes identification of donor or recipients possible shall be penalised'.

Donor and recipient confidentiality should be maintained throughout the entire process. But for medical purposes such as traceability and vigilance, data concerning the organ donor procedure must be documented on standardised forms. The forms outlined in sections 6.8.1 and 6.8.2 should exist for every donor and organ. Directive 2010/53/EU also

prescribes that 'Member States shall ensure that data required for full traceability is kept for a minimum of 30 years after donation. Such data may be stored in electronic form'. Indeed, it must be ensured that all organs procured, allocated and transplanted can be traced from the donor to the recipient and vice versa in order to safeguard the health of (living) donors and recipients (also in the case of international organ exchange).

6.8.1. Donor information form

The donor information form should contain all relevant information about the donor to allow evaluation of eligibility for organ donation and to support the allocation process (examples used in the Eurotransplant area and Foedus project [33] are shown in Appendix 9). The person who refers the donor to the referring hospital should complete the form. The form should accompany the organs and be maintained in the donor file. It should be archived separately from recipient notes. In practice, for donors, this information should be maintained in the donor records of the OPO. The donor records should include the donor information form and the documents proposed in chapters 6 and 7, as well as the records allowing reproducibility of consent/authorisations and death certificates. The death certificate must not be in paper form when an appropriate electronic database exists.

The Foedus project [33] is aimed at facilitating exchange of organs donated in EU member states in particular, through cross-border exchange in cases where organs are not allocated in the country of origin and would be lost otherwise. To support these cross-border organ exchanges and facilitate the organ offer and allocation, dedicated forms have been developed.

Exchanging donor data between different institutions involved in the donation transplantation process must be done with care: errors can occur as a result of clerical issues, transcription problems (e.g. interface to transfer data from paper forms to IT systems) or limited human resources involved in the process. Such errors can cause avoidable serious adverse events or reactions (Chapter 15). Therefore it is recommended that critical data such as blood group or virological tests are reviewed face to face by two independent persons with reference to the original files and data exchanged electronically at key points. Verbal communication of key data without visual verification of the original files by both witnesses is discouraged.

6.8.2. Organ report

This form should contain all data on donor organs at the time of procurement (see Chapter 11).

6.8.3. Donor sample archive

Samples of relevant donor material (e.g. serum, remains from HLA-typing) should be stored for look-back studies if indicated at a period of 10 years (see chapters 11, 15 and 16).

6.9. Conclusion

Primarily, donor characterisation contributes to the safety and quality of organs. Risk evaluation of donor and recipient factors has to be carried out on an individual, case-by-case basis regarding the issues associated to a donor in general. In addition, the organ-specific selection criteria must be considered in this process too. There may be factors that make a given donor absolutely unsuitable for a specific recipient, whereas the same donor could provide a life-saving graft for another recipient. This is why there are almost no absolute contraindications against organ donation from a global point of view. Therefore all details outlined in Chapter 7 have to be taken into account before a decision can be made on whether to continue or not to continue with the donation process. Because organ donation procedures in DBD or DCD are carried out within some time constraints, as explained throughout this Guide, not all desirable aspects that we might like can be considered.

6.10. References

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Related material

- Appendix 6. Rationale document for medical and social history questionnaire (United Kingdom)
- Appendix 7. Donor patient history questionnaire (Germany, English-language version)
- Appendix 8. Physical examination of an organ or tissue donor (American Association of Tissue Banks)
- Appendix 9. Donor and organ information forms
- Appendix 10. Donor examination by various means
- Appendix 11. Grading for biopsies at histopathological examinations (English-language version)

Chapter 7. Specific organ characterisation, assessment and selection criteria

7.1. Introduction

Organ-specific assessment is intended to support the decision about which organs of a donor can be transplanted without unnecessary harm to a recipient, after the general assessment of the donor has been performed as outlined in Chapter 6. The summary of all data obtained during general donor and specific organ characterisation allows a prediction of whether transplantation of a particular graft will be of harm to a recipient or not. Only after this risk–benefit assessment is complete can the transplantation of a particular organ into a particular recipient be considered, while knowing the limitations of predicting outcomes after transplantation (see Chapter 17).

The health status of patients on the waiting list during the waiting period deteriorates continuously. The individual urgency of a recipient for transplantation correlates with the risk of not surviving on the waiting list. Owing to these changes, the acceptance criteria for risks related to an organ vary for each patient depending on the actual situation from one day to the next. The specific selection criteria of organs for transplantation have changed and will continually be changing according to the current state of the art and the condition of the potential recipients on the waiting lists.

Currently the majority of organs are recovered from donors whose death has been determined by neurologic criteria – donation after brain death (DBD). Selection criteria for DBD donors are reviewed here. For donation after circulatory death (DCD), the additional specific criteria are summarised in Chapter 12. Specific and additional criteria for living donors are outlined in Chapter 13. For the specific selection criteria for tissue or cell donation, please refer to the *Guide to the quality and safety of tissues and cells for human application*.

The three major categories of risk factors limiting the outcomes of transplantation are summarised in sections 6.1.1 (Risk assessment of general donor-disease transmission risks), 6.1.2 (Risk assessment of likelihood of failure associated to a specific graft) and 6.1.3 (Risks not associated with the donor or the graft donated).

The organ-specific diagnostics and selection criteria are reviewed in this chapter in this order: kidney, liver, pancreas, intestine, heart, lung and vascularised composite allografts (VCAs). You will find expanded information about VCAs in Chapter 14. Since some investigations may be useful for multiple organs, their description – although placed with the most appropriate organ – is also linked to the other relevant organs. For each organ, this chapter reviews the issues of donor age, clinical history, functional and morphologic description pre-procurement and assessment during procurement and biopsy, as well as subsections on interaction in donor-management issues and on the imaging technologies most frequently used during assessment.

In the future, organ assessment and selection processes may change due to introduction of new

organ-preservation methods where organ quality may be modified and can be assessed during preservation time (see Chapter 11). Since currently cold storage is the most frequent method used for organ preservation, the considerations about assessment and selection are based on this technology.

7.2. Organ-specific assessment and selection criteria

Acceptance criteria for organs are mainly based on an assessment of the function and morphology of the donor organ. These criteria may vary between transplant teams and may also depend on recipient characteristics.

Organ viability criteria are a set of clinical, analytical, morphological and functional characteristics that are intended:

a. to support the decision-making process of selecting which organs can be used,
b. to ensure that the transplanted organs will function,
c. to avoid the transmission of diseases to the recipient.

Theoretically, if organ preservation and the surgical techniques of procurement and transplantation have been appropriate, any organ functioning well in a donor should function after implantation in the recipient. But sometimes grafts fail to recover their function, and delayed graft function (DGF) or primary non-function (PNF) may occur. The first priority of organ-specific selection criteria and donor management is to avoid DGF or PNF, although these events are not always donor-related. The second priority is to avoid transplantation of a damaged organ, which may become a long-term harm. Daily clinical practice demonstrates that many transplanted grafts function well although originally they did not seem to fulfil the published selection criteria [1]. Therefore, organ viability criteria must be continually adjusted, based on state-of-the-art medical practice and on changes within the population constituting the current donor pool. Such an adjustment is not easy to perform since large randomised studies are not available for practical and ethical reasons [1]. To cover this issue the term 'expanded-criteria donor' (ECD) has been introduced in the field, as either a binary or a continuous risk index, as discussed in Chapter 6.

In organs with a specific disease related to the organ, the use of the graft for transplantation must be considered with care: when progression of the disease can be ruled out or if it can be estimated that terminal failure is more likely to occur after the assumed life expectancy of the recipient based on the data of organ function (see Table 6.2 as guidance for a decision pathway). Then transplantation can be considered with informed consent of the recipient [1-4]. In addition, the following further issues may apply to any organ and require case-by-case decisions, but none of these issues should be used as an exclusion criterion *per se*:

- Re-use of previously transplanted grafts is possible [1, 5-7] although, after many years of a graft *in situ*, adhesions due to prior surgery and/or complications due to chronic or subclinical rejection may limit successful procurement and transplantation [6].
- The same can be said for previous trauma where, without inspection during procurement, no final assessment is possible. An exact description of the trauma mechanism will help to inform correct decisions, e.g. in a motor vehicle accident a deceleration trauma to the mesenteric root may affect the quality of the pancreas and intestine [8].
- In cases of damage to the central vessels (e.g. aorta), techniques similar to the procurement of a graft in living donation can be considered too.

7.2.1. Kidney selection criteria

7.2.1.1. *Issues in kidney selection*

a. *Donor age*

No age limit applies in very young and elderly donors [9-14], although grafts procured from advanced age donors could preferably be used in elderly recipients because the limited duration of graft function (e.g. Eurotransplant Senior Program) may be acceptable based on the limited life expectancy of elderly recipients and their health deterioration while waiting for a kidney transplant [15-19]. Many studies have concluded that increased donor age is associated with an increased risk of graft failure, especially in cases where donor age exceeds the seventh decade of life [9, 20-23]. In some countries, an age-match between donor and recipient is considered so as to give grafts from young donors to younger recipients, after adjustment for co-factors, to allow longer graft survival [24-26]. Further protocols should exist which avoid the addition of risk factors on top of the age-related limitation of kidney graft function (e.g. prolonged ischaemia times, donor-specific antibodies in the recipient) [27].

b. Past and current medical history

Metabolic syndrome, arterial hypertension, diabetes mellitus, albuminuria (see below) and other chronic kidney diseases or systematic disease affecting the kidney are considered as risk factors for inferior outcome after kidney transplantation, after adjustment for donor age and quality of care and treatment for the above-mentioned problems [28-31] (see below).

Direct damage of the kidney after abdominal trauma (e.g. rupture) and irreversible acute kidney injury with persisting anuria for many days due to necrosis may limit the use of such grafts (see below). But full reversible acute kidney injury may occur as a complication of acute illness independently of chronic damage. Especially after periods of hypoperfusion or shock when diuresis is recovering, irreversible necrosis is unlikely despite the temporary use of a renal replacement therapy. Therefore final determination should be done during procurement (exclusion of necrosis).

c. Renal function and imaging of renal morphology

Consideration should be given to urine output, current and previous serum creatinine levels, estimated glomerular filtration rate or creatinine clearance obtained from a stable period of life before hospital admission, urea, albuminuria or proteinuria, urinary sediment, ultrasound of the kidneys (with quantitative measurement of: length × width × parenchyma thickness + structure) and urinary tracts.

In cases of chronically impaired kidney function, biopsies may be performed to determine the nature of the underlying disease. Advanced, irreversible, chronic renal failure is a contraindication for donation. This condition should be assumed when, during the previous three months, either severely decreased kidney function or severely increased albuminuria, or both moderately decreased kidney function and moderately increased albuminuria, existed in accordance with the KDIGO Guidelines [32]: albuminuria (> 30 mg albumin/g creatinine in the urine) in steady state outside an intensive care unit (ICU) or proteinuria (> 1 g protein/g creatinine in the urine) in steady state outside an ICU indicate severe kidney damage. Unfortunately, this cannot be concluded when only the data of the most recent hospital stay at an ICU are available.

Acute impairment in donor renal function may not necessarily be a contraindication, since it may be reversible. In cases of acute tubular necrosis without cortical necrosis, results are good [33-35]. Kidneys may not be used in the case of a persisting anuria for several days after intraoperative inspection of the kidney with the result of irreversible necrosis with or without histopathological confirmation (expert opinion). Otherwise, full reversible acute kidney injury is observed as a complication of acute illness independently of chronic damage. Then, after periods of hypoperfusion or shock, diuresis may recover despite the temporary use of renal replacement therapy. Such grafts will often show prolonged DGF in the recipient and require dedicated post-transplantation care.

For laboratory data that help to characterise the kidney, please refer to Table 6.1 in section 6.2.3. Creatinine levels may not be representative of renal function in cases of haemodynamic deterioration or volume depletion.

The morphologic description of the kidneys can be performed by abdominal ultrasound or, if performed, by computer tomography (CT), either abdominal CT or whole body CT scan, as outlined in section 7.2.1.1.

d. Macroscopic appearance at procurement

Consideration should be given to the macroscopic appearance (smooth surface or scars, evaluation of cysts, adhesions to adjacent perirenal fat due to antecedents of inflammation), colour after perfusion, individual evaluation of anatomical variants and vascular atherosclerosis of the organ(s). In the case of suspicious findings (e.g. space-occupying lesion), additional imaging or an expert's help may be recommended. Limited warm ischaemia may be acceptable for kidneys to some extent, as we know from experience with controlled DCD kidneys, especially if it stays well below 20 minutes; however, it becomes critical when exceeding 120 minutes (see Chapter 12). In every solid mass not equivalent to renal parenchyma or cysts, malignancy should be ruled out; the mass should be removed, with an appropriate safety margin and preservation of the rest of the graft, in order to permit later transplantation and proper investigation by histopathology (see §9.4.22 for further details).

A major issue is the degree of arteriosclerosis of the renal artery allowing anastomosis or not. However, this highly depends on the opinion

of the transplanting surgeon and should therefore be left to that surgeon's decision.

e. Biopsy

Most kidney biopsies are taken at procurement for clarification of space-occupying lesions. An Ro-resection should be attempted. The aim is to exclude any malignancy. Beyond the principles outlined above, there is no additional benefit obtained by assessment of the kidney graft quality through kidney biopsy. Pre-implantation biopsies are not done systematically in all countries because the added value of routine biopsy is limited when it comes to predicting intermediate or long-term function of donated kidneys [10, 17-18, 36-42]. Systematic reviews and other reports have concluded that the knowledge derived from biopsy does not contribute to the prediction of graft survival [10, 17, 38-43]. Therefore it is inappropriate to discard kidney grafts for transplantation exclusively on the basis of biopsy results.

In cases where a biopsy is performed, the number of glomeruli investigated should be reported. As a minimum, the degree of glomerulosclerosis, interstitial fibrosis, arterio-/arteriolosclerosis and tubular atrophy/necrosis should be documented. Currently, no consensus exists about the prognostic relevance of biopsies. It is recommended to adhere to the Banff classification so the results can be compared in a post-transplant evaluation of the recipient if necessary [38, 43-44]. On the other hand, the knowledge of age-adjusted normal results of a biopsy of donors older than 80 years might enhance the decision to accept such grafts for single or dual transplantation, especially for an older recipient. Currently we lack systematic research on this detail.

Other groups or countries rely on biopsy to be helpful for assessment of older donors and donors with cardiovascular risk factors (e.g. history of hypertension, diabetes). Mild histological changes with minor glomerular sclerosis, minor interstitial fibrosis, mild arteriosclerosis or minimal tubular atrophy, may be acceptable. Some transplant groups apply, as viability criteria, the histological score described by Remuzzi *et al.* that allows the classification of kidneys as unsuitable or suitable for transplantation as single graft or as double graft [22].

f. Other issues

En bloc and single kidney transplantation from small paediatric donors (e.g. 2.7-10 kg) has been demonstrated to be possible and successful [11-14, 45-48], even when the two small grafts are used in two different paediatric recipients [48]. Both kidneys can be procured *en bloc* or separately, and procurement/transplant surgical teams should be familiar with paediatric transplantation as well as micro-surgical technique (for implantation) of the two grafts in one or two recipients. In properly procured kidneys as *en bloc* graft from small paediatric donors it is inappropriate to discard one kidney just for the purpose of generating a vascular patch for the other graft.

In grafts procured from advanced age donors (e.g. > 80 years), a controversy exists whether they should be transplanted as two grafts for one recipient or as two grafts for two recipients [10, 17-18, 22].

In controlled and uncontrolled DCD, despite exposure to prolonged ischaemic episodes, functional recovery of the kidney is possible without impairment of long-term function [49-54] although DGF may occur (see Chapter 12).

Scoring systems for expanded donor criteria have been developed in other countries (e.g. US). They require adjustment to the donor and recipient populations in a country and they should not be abused as deferral criteria. Instead grafts with high score values may provide acceptable outcomes with a benefit for the recipient when a proper match between donor risk factors and recipient risk factors has been performed [18, 26-28, 41, 55-59].

7.2.1.2. *Imaging in the context of abdominal graft evaluation*

g. Abdominal ultrasound

Abdominal ultrasound can be performed as a bedside method in the ICU with the known limitations of the sensitivity and specificity of the investigation (see Table 7.1). A proposal for a standardised dataset to be communicated within the investigation is in Figure 7.1 and an example questionnaire can be found in Appendix 10.6. The abdominal examination includes all organs and the whole abdomen as this will help to verify the issues of kidney quality on the one side (e.g. severe arteriosclerosis of the aorta); in any case, the standard investigation always includes the whole abdomen for general donor assessment and the other organs (e.g. liver, pancreas).

Whenever a whole-body CT scan or abdominal CT scan or magnetic resonance imaging (MRI) has been performed, re-evaluation should be attempted for donation purposes. Beyond investigation for space-occupying lesions, the data obtained should be provided in the same grid as suggested for abdominal ultrasound. In donors with a previous history of malignancy, it is highly recommended to perform a whole-body CT scan according to the recommendations of Chapter 9.

Figure 7.1. **Reporting workflow for minimum dataset to be communicated for investigation of the abdomen by ultrasound, CT or MRI [60]**

Liver	size MCL (cm)	*only if not measured:* size in relation to MCL (medio-calvicular line): normal/small/large/enlarged/n.a.
	parenchyma	normal/slightly hyperechogenous/severely hyperechogenous (relevant steatosis)/cirrhosis/n.a.
	space-occupying lesion	no/yes/n.a. **if yes:** kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries) location: segments *further details*
	liver edge	sharp/blunt/n.a.
	intrahepatic bile ducts	normal/dilated/n.a.
	portal cava	open/thrombosis or obstructed/n.a.
	remarks	*only further information not described above should be added*
Gall-bladder	status	normal/cholecystectomy/cholecystitis/cholecystolithiasis/cholecystitis & cholecystolithiasis/n.a.
	space-occupying lesion	no/yes/n.a. **if yes:** kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries) *further details*
	extrahepatic bile duct	normal/dilated/choledocholithiasis
Pancreas	parenchyma	normal/lipomatosis/oedema/fibrosis/n.a.
	calcifications	none/yes/n.a.
	signs of pancreatitis	none/yes/n.a.
	space-occupying lesion	no/yes/n.a. **if yes:** kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries) location: head/corpus/tail/multiple lesions/n.a. *further details*
	remarks	*only further information not described above should be added*
Kidney right	measurements	**length (cm), length (cm), width (cm), thickness of parenchyma (cm)**
	only if not measured:	normal size & parenchyma/thin, atrophic parenchyma/atrophic kidney/nephrectomy/n.a.
	hydronephrosis	none/yes/n.a.
	nephrolithiasis	none/yes/n.a.
	space-occupying lesion	no/yes/n.a. **if yes:** kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries) location: upper pole/middle section/lower pole/multiple lesions/n.a. *further details*
	remarks	*only further information not described above should be added*
Kidney left	measurements	**length (cm), length (cm), width (cm), thickness of parenchyma (cm)**
	only if not measured:	normal size & parenchyma/thin, atrophic parenchyma/atrophic kidney/nephrectomy/n.a.
	hydronephrosis	none/yes/n.a.
	nephrolithiasis	none/yes/n.a.
	space-occupying lesion	no/yes/n.a. **if yes:** kind of lesion: tumour/abscess/angioma/contusion/cyst/n.a./unspecified (multiple entries) location: upper pole/middle section/lower pole/multiple lesions/n.a. *further details*
	remarks	*only further information not described above should be added*
Other	Aorta morphology	normal/abnormal/n.a. **if abnormal:** arteriosclerosis/aneurysm/stenosis *further details*
	Vena cava	
	free fluid or ascites	none/moderate/significant/n.a. **if free fluid:** location and amount in abdomen
	remarks	*only further information not described above should be added*

n.a. = not assessable.

Table 7.1. **Parameters to be considered in abdominal ultrasound investigation**

Abdominal ultrasound sonography	Comment, informative value
Safety warning	Conditions of investigations can be limited due to obesity, intestinal overlay (intraluminal gas) or inability to position the donor properly for investigation.
Space-occupying lesions	In any case of a space-occupying lesion, the findings must be verified by intra-operative inspection and histopathology when indicated. A CT scan might be helpful to search for possible metastases elsewhere (e.g. in case of a suspected primary renal cell carcinoma) or a primary tumour in another location (e.g. in case of suspected metastases).
Aorta/ vascular anatomy	Aneurysm and arteriosclerotic plaques are indicative of systemic arteriosclerosis. Within this examination there should be checks for vascular abnormalities and/or arteriosclerotic plaques in the arteries supplying the organs.
Kidney	Standard description plus quantitative measurement of length, width and parenchyma mass (thickness). Anatomic variants should be highlighted (e.g. horseshoe kidney).
Liver	Standard description plus size in medio-calvicular line (MCL), liver edge. The comparison of echogenicity of liver to kidney parenchyma (probability of macro-vesicular steatosis elevated in cases of non-homogeneous or enhanced echogenicity of liver parenchyma compared to kidney parenchyma). Also status of portal vein, perfusion in the liver, intrahepatic and extrahepatic bile ducts should be assessed. Statements about exact size are helpful for considering split liver transplantation.
Pancreas	Standard description should include statement about intra-parenchymal fat if possible.
Intestine	Standard description.
Fluid in the abdomen, pleura effusion, evidence for haematoma, lymphoma, abnormalities in lower pelvis (e.g. ovaries, prostate, urinary bladder), status of the spleen	This relevant information is for the general assessment of the donor.
Vena cava inferior	Information about fluid status of the donor (donor maintenance).

h. Abdominal CT-scan

This may not be required in the standard investigation of a donor unless a whole-body or abdominal CT scan is indicated, as outlined in Chapter 9, or for verification of an unexplained space-occupying lesion. If such investigations exist for any other indication, then re-evaluation should be attempted. With this more detailed information, the issues outlined in abdominal ultrasound (see 7.2.1.1.a and Table 7.1) can be examined.

7.2.2. Liver selection criteria

7.2.2.1. *Issues in liver selection*

a. Donor age

There is no age limit (in very young and elderly donors) although with increasing donor age the risk of failure may be elevated due to arteriosclerosis of the small vessels of the biliary tract and increased frequency of ischaemia-type bilary lesions (ITBL) [61-88].

b. Past and current medical history

Prior viral, alcoholic or fatty liver disease, previous hepato-biliary surgery, uncontrolled abdominal infections, long-term hepatotoxic or acute liver failure causing medication, intoxication affecting liver function, acute or chronic right heart failure and liver trauma are considered as risk factors for inferior outcomes after liver transplantation. Please consider lifestyle conditions, ethnicity, country of origin and travel history; beyond increased risks of infectious disease transmission these may be a hint of potential graft damage.

Systemic or other disease related to other organs may compromise the liver in quality and function, e.g. colitis ulcerosa might be an indicator for undetected primary sclerosing cholangitis.

Recovery from previous acute cardiac arrest or hypotensive periods, as well as an ICU Stay > 7 days or use of vasopressors or acute kidney failure, etc. do not preclude liver donation [1].

c. Liver function parameters

Consideration should be given to liver transaminases (alanine aminotransferase [ALAT] or aspartate aminotransferase [ASAT]: both non-specific liver function tests), gamma-Glutamyltransferase (γGT: cholestasis)

[89-92], serum bilirubin (cholestasis), alkaline phosphatase, lactate dehydrogenase (LDH: any necrosis), albumin and coagulation tests (e.g. INR: liver function). Evaluation of liver enzymes should take current and past clinical history into account with respect to hepatic and non-hepatic causes of deviation. Please refer to Table 6.1 in section 6.2.3 for more details.

d. Imaging and liver morphology

Liver ultrasonography (see §7.2.1.1 and Figure 7.1) may be used to exclude obvious fatty liver degeneration, cirrhosis and fibrosis or any morphological abnormality, while the low rate of sensitivity and specificity is well known. It is recommended to confirm the result by intra-operative inspection (including histopathologic confirmation of the result if indicated). It is very helpful to provide data about the perfusion status of the organ, status of portal vein, intra- and extrahepatic bile-ducts, and liver size (in particular of the left lateral lobe when a split procedure is intended). If available the abdominal CT scan should be re-evaluated with this question.

e. Macroscopic appearance and perfusion at procurement

It is important to evaluate the sharpness of the liver edge, and the colour and consistency of the liver before and after correct perfusion. Obvious liver fibrosis and cirrhosis or steatosis may exclude transplantation. The degree of macro-vesicular fatty degeneration as well as fibrosis (according to Ishak score) can be evaluated and confirmed by using peri-operative biopsies (frozen section) [61-63, 70, 77, 93-97]. A rose-like colour with change to yellow after cold flush during organ preservation is associated with a higher probability of macro-vesicular liver steatosis [79].

Some limitations exist due to inter-observer variation or due to unrepresentative samples caused by a more or less focal pattern of a lesion (e.g. sub-capsular biopsy) [98-99]. The degree of acceptable fatty degeneration may depend on the general conditions of the donor and recipient, and may vary with the urgency or hepatitis C co-infection of the recipient and the experience of the transplant team [100-101]. Unfortunately, there is no agreement about criteria for determining the extent of fatty degeneration of the liver. Most transplant surgeons rely more on their overall impression through the graft procurement process, than on histology. Nevertheless, histopathologically confirmed macro-vesicular steatosis exceeding 30 % to 60 % of the parenchyma surface is increasingly considered as an unacceptable risk factor for slow graft function (SGF), intermediate graft function (IGF) or PNF [97, 102-105], whereas other forms of steatosis (so-called micro-steatosis with small fat droplets not displacing the cell nucleus) are considered as a minor issue [94, 97-98, 105-109] unless the disease is associated with an underlying liver disease causing liver failure with fat accumulation in the cell in a kind of 'fat-foam' [99, 106-107]. The issue of micro-vesicular steatosis is outlined in section 7.2.2.*f* below.

Allocation of a liver with some (macro-vesicular) fatty degeneration might not be advisable for a recipient not surviving the risk of SGF or IGF, whereas allocation to another recipient in a clinical status to survive the risk of SGF, IGF or PNF, requiring re-transplantation in the worst case, may be acceptable, depending on the risks of waiting for the next available organ and avoidance of other risks, such as donor diabetes or long ischaemia time > 5-6 h [107, 110]. There is no consensus on the use of critical grafts and selection of the appropriate recipient.

In elderly donors the liver parenchyma may have a 'funny colour' [79] and it might rupture due to its fragile consistency when extensive traction is applied at surgical manoeuvres.

Severe arteriosclerosis may not harm the hepatocytes but it is a risk factor for damage to arterioles of the small bile ducts. In this case, an appropriate flush with preservation solution during procurement must be carried out. How far donor arteriosclerosis is a risk factor for causing postoperative complications, e.g. ITBL, needs further research.

In livers without morphologic changes the only limitation for a split liver procedure is the size and vascular anatomy, which requires careful inspection and description by an experienced surgeon.

f. Biopsy

Liver biopsy is usually performed during procurement as frozen-section. The result must describe the percentage of parenchymal area with cells affected by macro-vesicular steatosis and the extent of fibrosis (by Ishak score). In addition it is helpful to report steatosis regarding small fat droplets, micro-vesicular steatosis, signs of inflammation, necrosis, cholestasis [98, 107].

Beyond inter-observer variation the representative value of a biopsy may not be given due to sampling errors (e.g. nodular cirrhosis) or non-representative findings from biopsies taken from sub-capsular liver edge. Furthermore, it is detrimental to discuss with the examiner how to transport the specimen to the pathologist – as incorrect transport media will cause further inappropriate results.

Biopsy before procurement can be done when death has been certified and consent exists, and also where there are no coagulation disorders and the physician performing the biopsy is very experienced in doing this (because of bleeding risks) [111].

The wording used to describe steatosis should clearly distinguish between macro-vesicular steatosis – to be described either as large fat droplets or small fat droplets caused by risk factors responsible for non-alcoholic-steato-hepatitis (NASH) – and micro-vesicular steatosis, described as multiple tiny fat vesicles caused by other issues [98, 107-109]. Macro-vesicular steatosis refers to the percentage of liver parenchyma where in the hepatocyte one or a few large fat droplets displace the nucleus to the edge of the cell. Despite lack of consensus, grafts with a degree of such steatosis below 30 % are used for transplantation, whereas in graft where the degree of steatosis is above 30 to 60 % the risk of PNF increases and grafts with more than 60 % are deferred. In contrast, when one or a few small lipid droplets do not displace the nucleus then the finding should be described as small droplet steatosis, but often the term micro-vesicular steatosis is used. This finding can be ignored as a risk, because it seems not to affect the outcome adversely. Distinguished from this entity should be pure micro-vesicular steatosis either caused by severe diseases with acute liver failure or as a harmless finding in DBD due to agonal and or ischaemic changes. The morphologic finding is a foamy or vesicular-appearing cytoplasm of very small lipid droplets that surround the nucleus [108-109].

g. Other issues

In every graft macroscopically not compromised, it must be considered whether further splitting of the liver into two grafts for two recipients is possible according to the anatomy. At least in every donor younger than 50 years and a weight above 50 kg, splitting of the liver should have been considered [112]. Even broader criteria may be applied for splitting of livers depending on the expertise of the centres and recipients selected. This issue should be reviewed further by systematic research.

Scoring systems for ECDs developed in other countries (e.g. the Donor Risk Index in the US) [113] should be validated [90] and may even require adjustment to the population of the donor country [89]. Many studies confirm that ECDs do not limit the outcome of liver transplantation after proper recipient selection despite the known risk of increased graft failure rates [1, 6, 68-69, 72, 77-79, 82, 86-90, 114-116]. This requires proper matching of donor and recipient after critical risk–benefit assessment. In such grafts it is pivotal to keep ischaemia times as short as possible because this factor may even further increase the risk of ITBL [71, 79-80, 107, 115].

The issue of hepatitis C co-infection of the recipient and use of compromised liver grafts will have to be revised [87, 113] when more reliable outcome data become available due to new drugs in hepatitis C therapy. Then elimination of the problem of re-infection of the graft by circulating HCV-virus in the recipient might be possible.

In controlled and uncontrolled DCD the liver can be recovered and transplanted. Compared to DBD there is a more or less higher risk reported for SGF, IGF, PNF or ITBL [1, 117-122]. The warm ischaemia time is predictive for outcome, and decreases with every extra minute of asystolic warm ischaemia [118, 122]. Careful decision is mandatory with asystolic warm ischaemia times exceeding 25 minutes [122].

7.2.2.2. *Initial organ assessment and liver selection*

ECDs are assumed to be associated with an increased risk of SGF, IGF or PNF [123-124] since compromised liver grafts have a poor tolerance to ischaemia-reperfusion injury (IRI) [125] due to complex pathophysiological interactions [126]. From clinical experience, the ECD criteria associated with increased graft failure rates are donor age > 65 years, serum sodium > 155 mmol/L [127], macro-vesicular steatosis > 40 %, cold ischaemic time > 12 h [71, 79-80, 107, 115, 128], split-liver grafts [113, 129], DCD grafts or haemodynamically compromised donors. Nonetheless, experienced transplant centres overcome such restrictions and they successfully use grafts from donors with a hospital stay > 7 days, body mass

index (BMI) > 34.9 kg/m², maximum ALAT or ASAT > 500 IU/L and maximum bilirubin > 2.0 mg/dL [130].

Age-related atherosclerotic changes have a low impact on the function of the hepatocyte due to its double system of perfusion (arterial and portal-venous) in the absence of metabolic disease, e.g. diabetes or hyperlipidaemia. Literature supports the use of liver grafts from the upper extremes of age [131-132] when routine biopsy excludes relevant fibrosis, macro-vesicular steatosis etc. With advanced age the prevalence of obesity increases [133] as well as the risk of macro-vesicular steatosis of the hepatocyte – which is observed in 9 % to 26 % of the procured livers [134]. When biopsy reveals a macro-vesicular steatosis > 30-60 %, excessive cytoplasmic fatty acids may lead to increased lipoperoxidation yielding more free radicals, which in turn lead to damage of the cellular architecture and inappropriate Kupffer cell activation with concomitant pro-inflammatory up-regulation [104, 135]. This causes poor outcomes when grafts are used with such moderate or severe steatosis in addition to the above-mentioned IRI [136].

Hypernatraemia as a complication of diabetes insipidus has been reported to be associated with a high probability of PNF [127]. The critical effect on the graft is thought to be the result of cell swelling, increased osmolality during IRI. As a result, high sodium levels during the donor's stay in the ICU are a significant factor for PNF, and not only the last sodium value before procurement [127]. Whether only the single vector of avoiding hypernatraemia or the side-effect of including this issue in the concept of aggressive donor management (see Chapter 5) contributed to reducing the rate of PNF has not been confirmed well in studies. From a theoretical point of view the area under the curve caused by a timeline of hypernatraemia should be of a different impact compared to single peak values for a short time. Interestingly, large database researches in UNOS [113] and Eurotransplant [89] could not find any association between hypernatraemia and graft failure.

Abnormal liver biochemistry *per se* does not exclude the use of these organs for transplantation [8, 89, 91-92]. Very high levels of transaminases indicate a recent ischaemic insult probably due to hypoperfusion or hypoxia that is seen in patients with cardio-respiratory arrest. Adequate circulation and oxygenation by resuscitation helps compensate for this event, allowing recovery from dysfunction especially in younger donors [137]. Metabolic acidosis in the presence of abnormal liver biochemistry is generally an unfavourable combination. There are no definite guidelines on the upper limit of acceptable abnormal biochemistry, but a downward trend in liver enzymes is assumed to be indicative for recovery of the liver from such events. This can be measured by blood tests at least 12 h apart. It is possible that, with novel preservation techniques available, grafts with severe dysfunction prior to procurement can be resuscitated *ex situ* (see Chapter 11).

In summary, in a compromised liver graft, as outlined above, ischaemia times should be kept as short as possible.

7.2.3. Pancreas selection criteria

7.2.3.1. *Issues in pancreas selection*

a. Age and body mass index

This depends on local protocols. Traditionally many centres are reluctant to use pancreases from donors older than 50 years despite some good results after careful donor selection [138-140] taking well into account past and current medical history (see below). In some countries, donors below the age of 55 years and with BMI < 30 kg/m² are primarily considered for pancreatic whole organ transplantation, rather than islet preparation [138].

Although higher BMI is considered a risk factor in whole pancreas transplantation, these more obese pancreas grafts have higher yields for islets after isolation and are preferably being used for pancreatic islet transplantation [141].

Beyond the mentioned limits of age and BMI, pancreas transplantations have been carried out with success when appropriate retrieval technique, preservation and prophylaxis of ischaemia-reperfusion damage has been applied [142]. However, donor age is the highest single risk factor for failure in pancreas transplantation [143-145]

b. Past and current medical history

Prior pancreatic disease, alcoholism (risk of pancreatitis), diabetes mellitus, history of arterial hypertension, adipositas (increased risk for intrapancreatic lipomatosis), active abdominal infection, abdominal trauma (especially deceleration trauma of the mesenteric root), significant number of days spent in the ICU (increasing probability of development of oedema of the pancreas), cardio-respiratory arrest and resuscitation manoeuvres are considered as risk factors for inferior outcomes after pancreas transplantation.

Glucose metabolism is frequently deregulated during stay at ICU. Therefore insulin

requirements during ICU stay within donor-maintenance protocols are without explanatory value. On the other hand, manifestation of diabetes mellitus type II is possible at an age of over 50-65 years.

c. Pancreatic function

This may be assessed by factors other than glucose and insulin requirements, pancreatic enzymes and calcium levels during stay in an ICU. Some donor-maintenance protocols recommend insulin treatment, among other hormones. Many patients with severe head trauma become hyperglycaemic and require insulin therapy, despite normal pancreatic function and no history of diabetes.

For laboratory data contributing to characterise the pancreas, please refer also to Table 6.1 in section 6.2.3. In laboratory examination, amylase may be elevated for non-pancreatic reasons unless pancreas-specific amylase or lipase is measured. If available, HbA1c measurements may reflect the glucose metabolism of the past weeks more precisely.

d. Morphological study

This can be assessed by abdominal ultrasonography, magnetic resonance imaging (MRI) or other imaging, e.g. trauma CT on admission (see 7.2.1.1 and Figure 7.1).

e. Haemodynamic

Uncontrolled severe hypotension and cardiac/pulmonary arrest profoundly compromise the quality of pancreatic organs outside the issue of DCD.

f. Macroscopic appearance at procurement

Consideration should be given to the macroscopic appearance, vascular and anatomical changes, and correct perfusion of the pancreas. The macroscopic appearance should be without severe oedema, bleeding, fibrosis or pancreatitis (despite toxic causes and without evidence in imaging or laboratory parameter). Further risk factors for post-transplantation pancreatitis associated with graft failure are peri-pancreatic haematomas, capsular tears and elevated intra-capsular fat content or induration. Abnormalities of vascular in- and outflow often exist. This may compromise pancreas procurement in cases of simultaneous intestinal and liver procurement for other recipients (especially if an aberrant right hepatic artery, that branches off the arteria mesenterica superior, travels through the pancreatic head). Unexpected pancreatitis may be detected. A pivotal role is played by the procurement surgeon (with or without expertise in pancreas transplantation) who must procure the graft properly without damage to the pancreas (see Chapter 11) [146-147]. The specific details of pancreas procurement technique are summarised in reference [146].

The pancreas is a delicate organ that is easily harmed during procurement (and transplantation). Minor injuries may be repaired, but up to 13 % of procured pancreata are still withdrawn after back-table inspection at the receiving hospital [148-149]. Adequate training and certification of donor surgeons is mandatory [150], as successful pancreas transplantation highly depends on the quality of procurement of the graft [146-147].

g. Other issues

Although risk scores, such as the pre-procurement pancreas allocation suitability score (P-PASS) and the pancreas donor risk index (PDRI), predict the change of acceptance of the graft for transplantation, still an experienced pancreas surgeon should inspect the graft for a definite decision of transplantability of the graft. Note that the P-PASS does not correlate with outcome after transplantation, but the PDRI does [144].

Most risk factors considered critical for liver grafts coincide with risk factors for pancreas grafts (see §7.2.2).

Successful results with pancreata transplanted from selected cDCD donors have been reported [151]; see Chapter 12.

7.2.3.2. *Initial donor and organ assessment and pancreas selection*

Strict adherence to 'ideal donor criteria' – such as donor age < 40 years, BMI < 30 kg/m² or traumatic cause of death – is not in line with the average donor nowadays and therefore will unnecessarily limit the number of grafts available for pancreas transplantation [152]. There is a wide variation in the acceptation and transplantation of pancreata among European countries [153]. Centres with more expertise, reflected in higher volumes, tend to be willing to accept higher-risk organs [153].

Increasing donor age is associated with a higher failure rate after pancreas transplantation [143, 154], which should be seen in the context of remaining on the waiting list. A study reported that the 5-year unadjusted patient survival rate was higher for simultaneous pancreas–kidney transplant recipients from young donors (84.5 % v. 81.0 %). [155] However, the 5-year patient survival rate for those who remained

on the waiting list was 45.4 %. In this study, receiving a simultaneous pancreas–kidney transplant from an old donor was associated with a 72 % reduction in mortality compared with remaining on the waiting list. Similar results can be reported from other single centre or registry studies [156-161].

Adipositas is associated with the risk of intra-pancreatic fat accumulation. This intra-pancreatic fat accumulation may contribute to a higher rate of reperfusion damage and post-transplantation pancreatitis, although some centres report acceptable outcomes after utilisation of overweight donors [142].

Concepts under discussion that aim to overcome the burden of non-ideal donors [154] include allocation systems which decrease predicted ischaemia times and enable local experienced pancreas transplant surgeons to inspect the grafts without huge logistic efforts. Then metric donor assessment scores, such as the concept of the PDRI [143], may be helpful to guide decision pathways without increasing the discard rate of potential grafts [142, 161].

7.2.4. Intestinal selection criteria

7.2.4.1. *Issues in intestinal selection*

Up to now no standardised definition of ideal intestinal donor criteria exists. Based on a recent review and critical analysis of a national European donor population, the following inclusion criteria can be proposed [8]:

a. *Enteral nutrition*
Enteral nutrition should be initiated in the ICU patient as early as possible when there is no contraindication. In cases of intestinal donation, at least some sterile fluid should be applied to the intestine when passage is tolerated due to missing vagal stimulation of the intestine in DBD. This may be of benefit for the pancreas and other organs too.

b. *Age*
Depends upon local protocols. Some centres have successfully used grafts from donors older than 50 years [8, 162-164]. In any donor aged 0-50 years, intestinal donation must be considered [1, 8, 162]. In the group of donor age > 50-65 years the probability of manifestations of other chronic diseases is increased.

c. *Body weight and donor size*
Donor weight should preferably be lower than recipient weight because most recipients have retracted abdominal cavities. The major obstacle in intestinal transplantation is the size match, in terms of both weight and length, between donors and recipients [8]. In donors with a BMI > 28 kg/m² the probability of elevated intra-abdominal fat is increased.

d. *Past and current medical history*
The criteria are similar to those for liver and/or pancreas donation. Donors should not be obese, nor should they have a history of alcoholism or uncontrolled abdominal infections, prior exposure to toxins affecting small bowel function, severe blunt abdominal trauma (especially deceleration trauma to the mesenteric root), previous intestinal illness or unexplained diarrhoea. There is no evidence for other specific pre-treatment requirements during donor management except for the consideration of enteral nutrition (see Chapter 5) [8]. Recovery from cardiac resuscitation events does not limit donation of the intestine [8, 164]. Prolonged hospital stay (> 1 week) increases the probability of intestinal oedema.

e. *Gastro-intestinal and liver evaluation*
Serum electrolytes, liver function tests and liver enzymes should be considered to have trend towards normal values. Evaluation should be undertaken to assure that intestinal motility exists. The use of vaso-active drugs with a vaso-constricting effect should be avoided by aggressive donor management. Ongoing abdominal bleeding is a risk factor.
Prolonged hypotension and cardiac arrest may severely compromise the quality of intestinal grafts, but after recovery from such conditions intestinal transplants have been performed successfully [8, 163-164].

f. *Intestinal morphology*
This can be assessed by abdominal ultrasonography to exclude ascites, other lesions and tumours (see §7.2.2.1 and Figure 7.1). Abdominal X-ray or CT scan may be used when appropriate, especially to evaluate complications due to blunt abdominal trauma.

g. *Macroscopic appearance at procurement and perfusion*
Macroscopic appearance, intestinal peristalsis, exclusion of oedema, vascular and anatomical changes and correct perfusion should be examined. It must be remembered that most recipients of intestinal grafts require an individually tailored graft and that anatomical structures usually dissected from other standard organ recoveries must be preserved, e.g. colon ascendens-transversum and all mesenteric vessels. It is advisable to have the surgeon responsible for intestinal procurement and transplantation at the site of operation

from the outset. Assessment by an experienced intestinal transplant pancreas surgeon is mandatory from start until end of procurement (e.g. procurement procedure is different if colon is included in the graft).

h. Other issues

Very often intestinal grafts will be transplanted as a package that includes more than the small intestine with/without colon (e.g. liver, pancreas, stomach, duodenum). Therefore all these organs must be included in the allocation process regardless of donor age and other circumstances (except for legal issues like consent to donation restricted to specific organs).

Currently no reports about DCD and intestinal donations exist.

7.2.4.2. *Initial donor and organ assessment and intestinal selection*

There is widespread confusion over what is an ideal intestinal donor [8]. Current ideal donor criteria are [8, 163-164]: age 50-60 years, CPR below 10 min, ICU stay < 2 weeks, low doses of vasopressors, normal liver function tests and sodium level below 155-165 mmol/L. Very often, intestines from donors not fitting into this set of ideal donor criteria have been used successfully. Unfortunately, recipients' determinants such as size-match, ABO-match and immunisation in the HLA-system limit the chances for transplantation. An intestinal procurement requires a highly interacting multidisciplinary team [8]. For donor management, it is important to consider enteral nutrition if possible (see Chapter 5). The limitation is that intestinal paralysis occurs in many donors due to the lack of vagal stimulation.

7.2.5. Heart selection criteria

7.2.5.1. *Issues in heart selection*

a. Age

The probability of coronary artery disease (CAD) as well as other cardiac pathologies increases with age beyond the seventh decade of life. This limits the number of advanced-age heart donors [165-175], although some successful transplants have been reported [165, 168-170].

b. Past and current medical history

Myocardial infarct, severe valve abnormality (see below), coronary heart disease with diffuse sclerosis, severe stenosis of multiple vessels or stenosis at critical location, dilative cardiomyopathy, endocarditis without option for intervention etc., and chronic right and left ventricular dysfunction all exclude heart donation. Minor morphologic abnormalities (e.g. open foramen ovale, atypical venous drainage of coronary vessel, previous correcting heart surgery) require a case-by-case decision. Minor heart-valve disorders can be corrected before transplantation in some cases.

The risk of coronary sclerosis starts to increase at an age beyond 44-55 years in cases where there are other risk factors (high blood pressure, diabetes, tobacco use, even more in combination with alcohol abuse, age, hyperlipidaemia, cocaine abuse) to be verified by donor evaluation; minor stenosis and wall sclerosis detected by coronary angiography require a case-by-case decision. Minor luminal wall irregularities in coronary arteries or single-vessel stenosis of lower degree do not preclude heart donation for a recipient properly selected and assessed by an experienced heart centre when wall motion disorders and other risk factors can be ruled out.

Severe left ventricular hypertrophy (LVH) is a risk factor (IVSd >16 mm in adults), moderate hypertrophy a minor risk (IVSd 12-16 mm in adults). There is a correlation between quality in treatment of arterial hypertension and LVH.

Valve pathologies exceeding Grade 1 insufficiency are only an exclusion criterion after confirmation by an experienced heart transplant centre. Grade 1 insufficiency is a frequent finding in brain-dead donors.

Arrhythmogenic hearts without other morphologic alterations may not be used for every recipient since the risk of 'arrhythmia transmission' still exists despite consideration of implantation of automated implantable cardioverter–defibrillator.

Regarding acute events, proper recovery – from trauma, cardiac resuscitation, temporary arrhythmias or broken heart syndrome due to neuro-cardiac lesions (reduced left ventricular function, wall motion disorders, stunned myocard) or temporarily impaired right or left ventricular function – does not preclude heart donation. The recovery period might take a few days (consider serial monitoring by echocardiography) [176-179]. In the right ventricle, acute dilation caused by acute events of pulmonary hypertension might cause irreversible damage. In this context the use of inotropic catecholamines with an indication due to decreased cardiac output might not lead to a successful transplantation [180] (e.g. > 10 µg/kg/min

dopamine or dobutamine as well as > 0.2 µg/kg/min norepinephrine for longer time intervals pre-procurement) while the use of catecholamines with an indication due to peripheral vasodilation may not limit successful transplantation [178, 181-182]

Heart contusion due to direct thoracic trauma or after cardiac resuscitation manoeuvres detected during procurement or by imaging may preclude heart donation.

Critical assessment of recovery and successful detoxification is mandatory in donors with acute poisoning from carbon monoxide or other agents before a heart is excluded (see Chapter 10).

A proper size-match between donor and recipient improves the outcome of heart transplantation [183].

c. *Investigation for acute myocardial ischaemia*

This should include tests for enzymatic changes such as troponin (either I or T), which should take clinical history and evolution into account. Electrocardiograms should be normal. Atypical re-polarisation can be accepted, especially when clearly related to cerebral complications. Arrhythmia or diseases with arrhythmogenic potential (e.g. confirmed long QT-syndrome) limit the success of transplantation. In DBD, due to failure of the vagal tonus, sinus tachycardia of about 100 per minute is a normal finding and should not prevent further investigation of the donor.

d. *Morphological examinations pre-procurement*

Echocardiography should evaluate contractility of both ventricles, left ventricular ejection fraction (measurement of the ejection fraction or shortening fraction), wall motion disorders, valve anatomy and function of both ventricles and atriae. Hypertrophy should be measured quantitatively (e.g. diastolic thickness of intra-ventricular septum). The haemodynamic status of the donor should be stabilised before decisive echocardiography is performed [176, 184]. Coronary angiograms are advisable in donors aged above 55 years and if there is a significant risk factor for CAD, e.g. male donors over the age of 55 and females aged over 55 with one or more risk factors for CAD, as well as donors of either sex aged between 45 and 55 years if more than one risk factor for CAD exists [173, 176-177, 183-186]. However, the absence of coronary angiogram data is not necessarily a cause for excluding a potential heart donor. The indication for coronary angiography must be balanced against the risks associated with complications introduced by investigation and transfer of donor to laboratory.

Adenosine stress echocardiography may contribute to assessment of stress-induced wall motion abnormalities as an alternative diagnostic tool to coronary angiography [187-188].

e. *Haemodynamic during resuscitation and donor maintenance*

This should include evaluation of blood pressure, oxygen saturation, haemoglobin, hypotension, occurrence of cardiac arrest, use and dosage of inotropic and vaso-active drugs, central venous pressure and invasive haemodynamic measurements, where appropriate.

f. *Macroscopic appearance at procurement and perfusion*

Consideration should be given to macroscopic appearance, contractility, wall motion disorders, coronary artery palpation and morphology of valves or aorta.

g. *Other issues*

For organ preservation by cold storage in DBD, cold ischaemia times should not exceed 4-5 h (net transport time 2-3 h).

For the timing of procurement it is detrimental to adjust the procurement surgery with the transplant surgery when in the recipient previous heart surgery has taken place and/or removal of the assist device is necessary due to severe adhesion.

Procurement of hearts in DCD and transplantation is currently performed at a limited number of centres in Europe (see Chapter 12). This became successful with introduction of novel organ preservation technologies.

7.2.5.2. *Initial donor and organ assessment and heart selection*

The complications of temporary neurocardiac injury after devastating cerebral injuries, with or without cardiac arrest, must be taken into account as one reason for a reversible increase in heart enzymes. As the level of creatine phosphokinase in muscle/brain (CPK-MB) has no significant impact on patient survival, the suggestion of characterising donor hearts by determining CPK-MB may be outdated. CPK-MB values may be increased due to brain tissue necrosis or the fact that measurement differs between laboratories. Other more heart-tissue-specific parameters exist, e.g. Troponin [182], but increased donor Troponin levels themselves should not preclude heart transplantation because experienced centres achieve

acceptable results after appropriate recipient selection and short ischaemia times [175].

Further consequences of the autonomic storm are an imbalance between myocardial oxygen demand and supply, which triggers metabolic functional alterations and sometimes anatomical heart damage (myocytolysis and micronecrosis) [189]. Temporary electrocardiographic signs of myocardial ischaemia, conduction abnormalities and arrhythmias are also common during this period of intense catecholamine release and may require no treatment [178, 190-191]. Insufficient secretion of antidiuretic hormone after brain death is associated with haemodynamic instability and compromised organ function. Low-dose arginine vasopressin results in reduced inotropic requirements and has been associated with good graft function [192]. Methylprednisolone i.v. remains beneficial [193].

Many hearts are declined due to temporarily poor left ventricular function. But after optimal management, left ventricular function can completely recover over time in the donor and allow heart transplantation [166, 179]. Although echocardiography is very effective as a snapshot assessment of function, assessment can also be achieved by invasive haemodynamic investigations (see Table 5.1, Table 5.2) which may help in weaning off inotropes. Paradoxically, hypotensive periods in donors have not been associated with inferior graft and patient survival, and neither have many other factors – such as cardiac resuscitation, application of norepinephrine or other catecholamines, donor medication or anti-*cytomegalovirus* status – when the donor had been assessed and managed properly [174].

Careful donor and recipient selection should be carried out, especially in donors with recovery from cardiocirculatory instability while adhering to recommendations [194]. It should be decided at transplant centres whether an offered heart graft for a particular recipient will be of benefit or not, taking into account the actual health status of the recipient.

Concerning recipient parameters, a significant negative impact on patient survival may be observed for the following risk factors: increased age, increased serum creatinine before heart transplant, ventilator dependency, history of diabetes, pulmonary vascular resistance (PVR) exceeding 320 dyn*s*cm^{-5} at heart transplant, previous complex heart surgery, dependency on different cardiac assist devices. Size, weight and gender matches were without significant effect, probably because of adequate donor–recipient matching. Although undersized allografts in recipients with normal/low PVR did not adversely affect survival, in recipients with high PVR this should be avoided because there is clearly defined increased risk [183]. Extending donor criteria to include undersized hearts in recipients without elevated PVR and with gender match may be considered to expand the donor organ pool and reduce mortality rates for patients on the waiting list because, after careful adjustment for all risk factors, mortality seems not to be increased in selected recipients with a donor/recipient weight ratio outside the range < 0.8 to > 1.2 [183, 195].

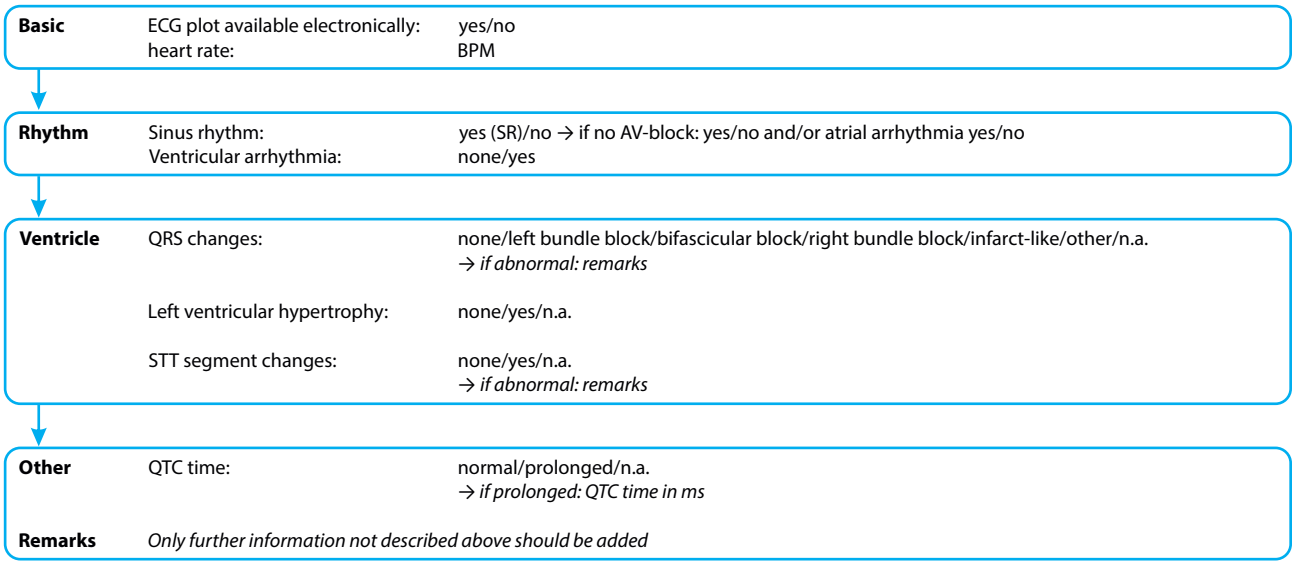
Currently, criteria for acceptance of ECD hearts for transplantation remain poorly standardised. Future evidence-based research and updated consensus guidelines on ECD donor heart acceptance are necessary, aimed at the development of novel and improved methods of donor heart resuscitation and preservation [196] and judiciously increasing utilisation rates, thereby making heart transplantation available to a greater number of patients dying from end-stage heart failure. The discrepancies in utilisation rates between countries may be due to differences between transplant centres' willingness to accept 'higher-risk' donor hearts and/or differences in organ procurement organisations' cardiac evaluation and allocation practices.

7.2.5.3. *Imaging in the context of heart graft evaluation*

a. Electrocardiogram

In any donor an electrocardiogram (ECG, 12-lead measurement at the bedside) may provide additional information as outlined in Table 7.2 (for reporting data, see Figure 7.2 and Appendix 10.4).

Figure 7.2. **Reporting workflow for minimum dataset to be communicated for electrocardiogram [60]**



n.a. = not assessable.

Table 7.2. **Electrocardiogram parameters to be investigated and standard data list**

Electrocardiogram	Comment, informative value
Sinus rhythm QRS-complex ST-segment T-Wave	Sinus tachycardia and supraventricular extra systoles are compatible with brain death. Arrhythmias not related to the acute event of brainstem coning should be excluded. After cerebral damage, QT-elongation, ST-deviation or negative T-waves may temporarily occur. Misinterpretation should be avoided caused by temporary T-Wave and ST-segment changes due to neuro-cardiac damage in direct timely association to the cerebral event. Atrial fibrillation, persisting ventricular extra systoles or QRS deformation, as well as other persisting abnormalities are indicative for cardiac damage not only related to a cerebral event. The most recent investigation is most representative.
Hypertrophy	(Left) ventricular hypertrophy should be confirmed by echocardiography.

b. Echocardiography

Echocardiography contributes to bedside assessment of the heart morphology and function (see Table 7.3) and to complementary haemodynamic monitoring. It is imperative to assure that the donor is in the best haemodynamic management condition before assessment by echocardiography if the resulting data are to be valid for the decision whether to use or not use a heart for transplant. In cases of impaired function that can be explained by temporary neuro-cardiac damage, it must be decided whether serial measurements can document recovery of the heart function [179, 197]. A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.3 and an example questionnaire can be found in Appendix 10.3.

Figure 7.3. **Reporting workflow for minimum dataset to be communicated for echocardiography [60]**

At time of echo	Haemodynamics: Inotropes, catecholamines:	MAP (mmHg), CVP (mmHg) , heart rate (BPM) yes/no → *if yes: kind and dosage* (µg/kg/min)
Basic	Type of examination: Visualisation:	TTE (transthoracic)/TEE (transoesophageal) normal/limited/severely limited
Left heart morphology	measurements: left ventricular hypertrophy (LVH):	LV-EDD & LV-ESD (mm), LV-PWd & LV-PWs (mm), IVSd & IVSs (mm), LA (diameter, mm) normal/moderate/severe/n.a.
Left ventricular function (LVF)	measurements: systolic LVF: diastolic LVF:	LV-EF (%, Simpson/Teichholz/estimated) or LV-FS (%) normal/moderately reduced/severely reduced/n.a. normal/abnormal relaxation/pseudo-normalisation/restrictive filling/n.a.
Wall motion disorders	any wall motion disorders: *if yes → description:*	yes/no/n.a. regional akinesia/hypokinesia/n.a. & *location*
Right heart	measurements: right ventricle function (RFV): right ventricle morphology: right ventricle dimension:	RV-EDD & RV-ESD (mm), RV-TAPSE (mm), RA (diameter, mm) normal/reduced/n.a. normal/hypertrophy (wall > 5mm)/n.a. normal/moderately dilated/dilated/n.a.
Aorta	measurements: morphology:	Aortic annulus (diameter, mm), Ascending aorta (diameter, mm) *description if abnormal*
Heart valves	aortic valve mitral valve tricuspidal valve pulmonary valve	*obtain following data for each valve:* - insufficiency: none/1°/2°/≥3°/n.a. - stenosis: normal/mild/moderate/server/n.a. - morphology: normal/thickened/calcification /
Other	pericardial effusion:	yes/no; → *if yes: thickness*
Remarks	*only further information not described above should be added*	

n.a. = not assessable.

Table 7.3. **Echocardiographic parameters to be investigated and standard data list**

Echocardiography	Informative value
Indication	Basic assessment of a heart considered for transplantation as well as haemodynamic status. Transthoracic (TTE) may be sufficient; transoesophageal (TEE) may be performed if indicated. In donors with tachycardia the heart rate should not be lowered for diagnostic purposes. Sometimes conditions for measurements are limited at bedside at ICU. Haemodynamic status and use of inotropes should be documented.
Right and left heart morphology and function	The function and morphology of all four chambers should be described as outlined in Figure 7.3. Left ventricular hypertrophy is indicative of the quality of treatment for arterial hypertension if other pathologies have been excluded. Good right ventricular function, with hypertrophy due to pulmonary hypertension secondary to lung disease, does not exclude transplantation because many heart recipients suffer from pulmonary hypertrophy. Right ventricular recovery from acute events causing pulmonary hypertension must be demonstrated (e.g. after pulmonary embolism). In elderly donors, slightly impaired diastolic relaxation is a frequent finding due to age-related 'stiffness' of the myocardium.
Regional wall movement disorders	Exact description is helpful to distinguish between temporary neurocardiac injury and other, irreversible damage. Minor movement disorders may not exclude the heart from transplantation – especially if improvement is observed during serial evaluation.

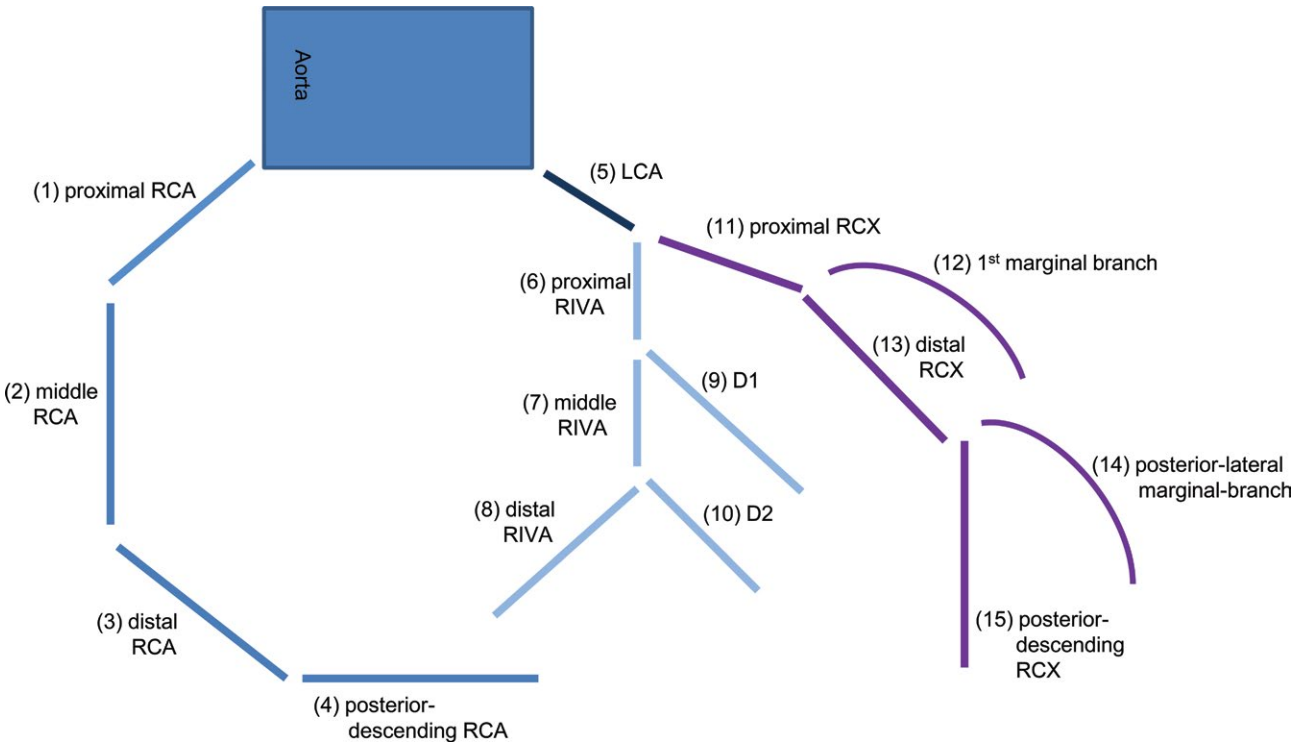
Echocardiography	Informative value
Aortic valve Mitral valve Pulmonary valve Tricuspidal valve	Insufficiency of 1st degree is seen often in hearts recovering from acute neuro-cardiac injury in DBD. This does not preclude transplantation. Any insufficiency exceeding 1st degree, stenosis, calcification or other morphologic changes (e.g. increased thickness of a valve leaflet) must be described properly. Pressure- or flow-velocity measurements (e.g. E/E´ or E/A) over the valves are not requested because most donors have tachycardia and measurement will be difficult.
Aortic root and ascending aorta	A dilated aorta is a risk factor for latent aneurysm. Plaques in the ascending aorta are highly susceptible to coronary artery sclerosis.
Pulmonary hypertension	If indicated, estimated (elevated) systolic pulmonary artery pressure should be validated by other methods.
Serial evaluation	Re-evaluations should be performed after haemodynamic stability has been achieved. Functional recovery from reversible neuro-cardiac damage should be assessed in cases of wall motion abnormalities and/or temporarily impaired left ventricular function.

c. Coronary angiography

This invasive investigation should be performed when death has been confirmed and consent for heart procurement exists. Additionally, echocardiography should not have confirmed major damage of the heart [197] and there should be an indication that justifies investigation (see Table 7.4). Also, it should not be assumed that coronary angiography mitigates donor-age-related cardiac risk factors [174, 198]. This investigation assesses the intraluminal status of the coronary vessels (see Table 7.4) and helps the procurement surgeon to rule out palpable plaques, as surrogate for intraluminal stenosis at procurement. Interventions like percutaneous transluminal coronary angioplasty or stenting may only be performed upon agreement with the recipient centre.

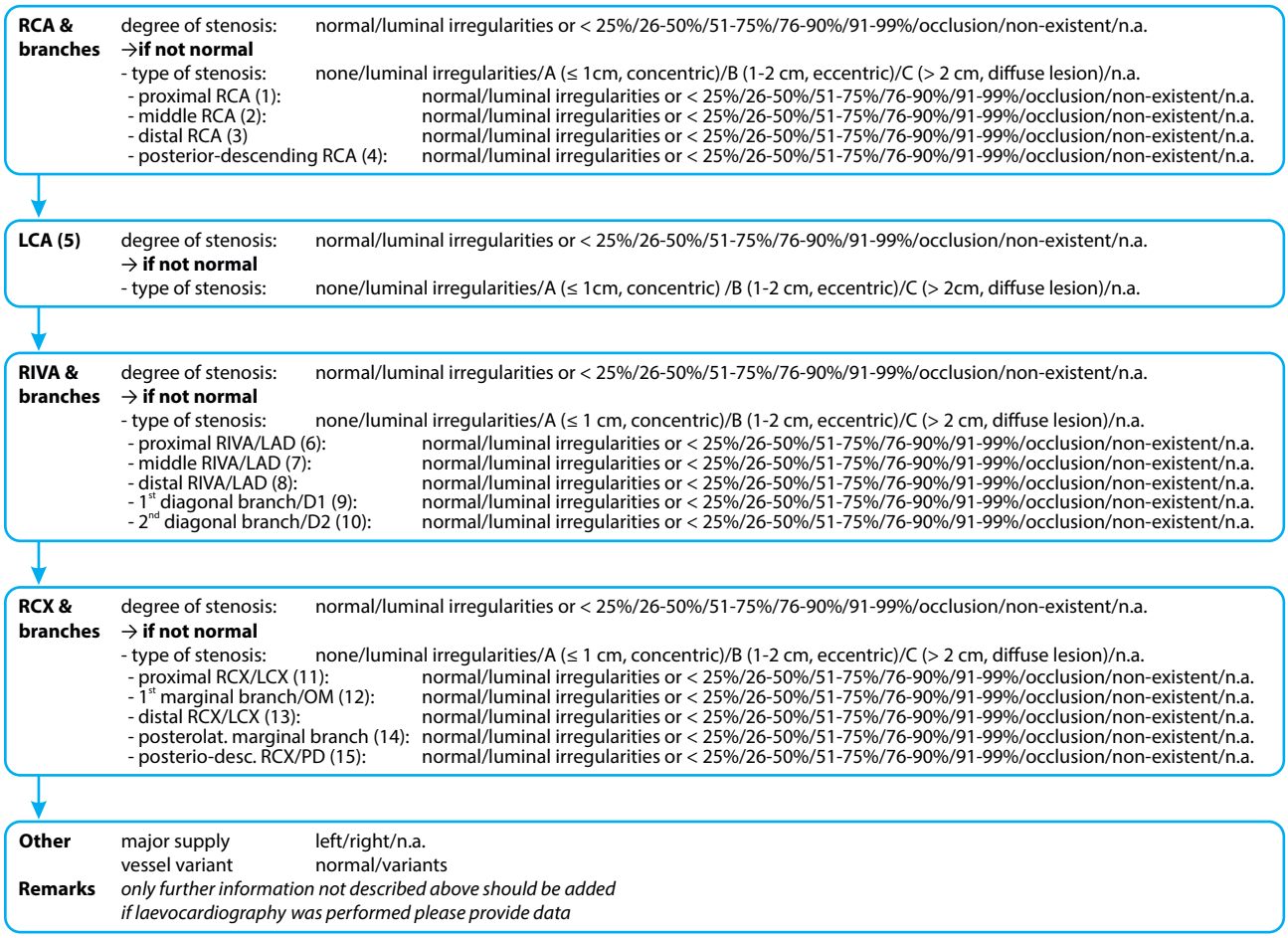
A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.5 and an example questionnaire can be found in Appendix 10.5. Data of a historic investigation may contribute to verify donor assessment in general. As an alternative to conventional coronary-angiography, CT-coronary-angiography may be considered if technically possible due to donor tachycardia.

Figure 7.4. **Coronary arteries and branches**



LCA = left coronary artery; RCA = right coronary artery; RCX = ramus circumflexis; RIVA = ramus interventricularis anterior.

Figure 7.5. **Reporting workflow for minimum dataset to be communicated for coronary angiography [60]**



Note: Coronary arteries may be graded according to the 15-vessel model of the American College of Cardiology/American Heart Association classification [198].
LCA: left coronary artery main stem; n.a.: not assessable; RCA: right coronary artery; RCX: ramus circumflexus; RIVA: ramus interventricularis.

Table 7.4. **Coronary angiography parameters to be investigated and standard data list**

Coronary angiography	Comment, informative value
Indication in donor evaluation	In donors with a heart clinically suitable for transplant but with existing risk for coronary heart disease after all other diagnostics have confirmed suitability: If donors are aged above 45 years and if there is a significant risk of coronary artery disease (CAD), e.g. all male donors over the age of 55 (with or without risk factors for CAD) or females aged over 55 with one or more risk factors for CAD, and donors of either sex aged between 45 and 55 years if more than one risk factor for CAD exists. Complications may occur during transfer and investigation (e.g. donor instability, worsening of lung function, vasospasm with cardiac arrest, rupture of vessel).
Coronary sclerosis and stenosis	The narrowing and shape of stenosis, its location and affection of the vessel should be described, as well as the shape of the intravascular structure of RCX, LCX, LCA, RIVA and their branches. In cases of a stenosis detected during investigation, interventions like PTCA or stenting may be done only upon agreement by the recipient centre.
Facultative laevocardiography	Functional parameters can be obtained if appropriate echocardiography is not available and if investigation of coronary vessels is indicated anyway (e.g. aortic valve, LVEF, LVEDV, LVEDP, LV-wall motion abnormalities, LV-hypertrophy).

7.2.6. Lung selection criteria

7.2.6.1. *Issues in lung selection*

a. Age

This criterion depends on individual donor/ recipient evaluation and individual transplant team assessments. Experienced centres have increased the upper age limit for routine lung donation to 80 years [1, 199]. In advanced-age donors, some limiting factors such as pleural adhesions, micro-emphysema or apical scars can only be ruled out by intraoperative inspection at procurement. At least in every donor younger than 80 with a PaO_2/FiO_2 of > 250 mmHg, lung donation should be considered after proper assessment and recruitment of atelectasis.

b. Past and current medical history

A history of pulmonary disease, active pulmonary infection, aspiration, purulent secretions, thoracic trauma and previous thoracic surgery are considered as risk factors for inferior outcomes after transplantation. Regarding the history of smoking expressed in pack-years, probably no limitations exist when smoking-related co-morbidities are ruled out (e.g. increased risk of malignancy, chronic inflammation/ infection). Other chronic lung diseases without structural damage to the lung parenchyma require a case-by-case decision (e.g. asthma, micro-emphysema). Lung grafts will not be used in cases of tuberculosis or chronic obstructive lung disease (COPD).

Acute deterioration of gas exchange with PaO_2/FiO_2 < 250 mmHg (< 33.3 kPa) with positive end expiratory pressure (PEEP) = 5 cmH_2O requires a careful work-up. When recovery from trauma/contusion, aspiration, inappropriate ventilation, fever, fluid overload or transfusion-associated lung injury can be demonstrated, then lungs can be used for transplantation.

c. Lung function

This should be assessed in order to exclude organs with inadequate gas exchange. A functional challenge test about gas exchange is the coupled measurement of the blood gases at baseline 1.0 FiO_2 at a minimum PEEP of 5.0 cm H_2O, and temporarily increment to 1.0 FiO_2 for 10 minutes. For this measurement, bronchial cleaning and recruitment of atelectasis must be performed in advance. The aim of this test is to identify the quality of gas exchange. Lungs should not be excluded for low PaO_2/FiO_2 until at least 2 h of adequate treatment (which includes protective mechanical ventilation, recruit manoeuvres and bronchoscopy to remove clots and sputum and improve lung function) has been given. Diuretics have been applied if there is low PaO_2/FiO_2 and pulmonary oedema, evaluated by extravascular lung water index > 10 ml/kg, if PICCO® or a similar monitor is used, or central venous pressure over 10 cm of water (see Chapter 5) [200].

Donors with persisting reduced lung function can still be considered for single lung donation. Many centres ask for acute ventilator settings and for data about all microbiological investigations, e.g. tracheal suction or bronchoalveolar lavage (BAL) sent in for investigation in order to know which pathogens are in the graft.

d. Morphological examinations

Chest X-ray is mandatory to rule out major pathologies (e.g. space-occupying lesions, structural changes of lung parenchyma) and, if indicated, a CT scan is preferred. Bronchoscopy is performed at an ICU for primary assessment (and cleaning of airways if necessary) as well as by the procurement teams for final assessment (for diagnostic reasons as well as to perform better intra-tracheal cleaning). Recovery from lung contusions should be considered after effective ventilator therapy for a few days. For details of the set of investigations, see section 7.2.6.3.

e. Macroscopic appearance at procurement

Consideration should be given to the colour of the lungs, presence of atelectasis, tumours, water content of the tissue, contusion marks, signs of early pneumonia, appropriate insufflations and pleural adhesions. Single lung transplantation is possible for selected recipients in the case of one lung being unsuitable. Sometimes pneumonia, structural changes or apical scars may not be detected until procurement surgery. Recruitment of atelectasis can be done under *in situ* control and care of the lung surgeon in collaboration with the anaesthesiologist in order to avoid barotrauma. Selective blood-gas analysis of the pulmonary veins helps to identify areas with good or impaired gas exchange (especially when the global arterial PaO_2/FiO_2 is below 250 mmHg or 33.3 kPa). Resection of compromised lung areas is at the discretion of the procurement team and

recipient centre. The same can be considered for size adaptation of oversized lungs or areas of localised emphysema.

f. Other issues

Lungs can be successfully transplanted from both uncontrolled and controlled DCD donors [1, 201-202]. See Chapter 12.

Single lung donation should always be considered when one lung is deemed unsuitable.

7.2.6.2. *Initial donor and organ assessment and lung selection*

It is well known that a series of injuries occurs in the donor lung from the time of devastating cerebral injury, during brain-stem coning, death declaration, preservation and transplantation until reperfusion in the recipient, which may cause primary graft dysfunction with recipient mortality [203-205]. Minimising such risks by adequate donor selection and management is critical.

The major concern when considering lung donors with a history of smoking is the potential for poor lung function due to an obstructive pulmonary disease and the risk of an undetected primary or metastatic cancer [206-207]. In some studies smoking history in lung donors is associated with decreased recipient survival [208], but this is still higher than when remaining on the waiting list [209]. Other studies could not confirm a relevant impact on long-term survival [205, 210-212]. Therefore a donor history of smoking should not prevent the use of lungs for transplantation when no objective risks exist.

Donors undergo multiple chest radiographs, after their admission to ICU, until procurement. In a retrospective survey, one-third of all donor radiographs had infiltrates, which improved or resolved spontaneously in more than 50-80 % of cases [213-214]. All patients transplanted with such infiltrates were alive after one year of follow-up. Plain chest X-rays taken at the bedside are of low sensitivity and only CT scans can properly estimate structural abnormalities like minor contusions or small infiltrates. Indeed, lungs should not be rejected because of minor abnormalities observed in CT scan, because a CT scan is too sensitive and most of these abnormalities could be reversed with proper treatment and they do not have negative influence on recipients' outcome [215]. Donors with strong unilateral abnormalities should not be excluded for donation of the contralateral lung [216]. Finally, evaluation of a donor chest X-ray is highly subjective, which limits its value for determining organ suitability [217]. No studies have been found that correlate chest radiograph findings and recipient infections.

Post-transplantation pneumonia and sepsis are serious concerns. Prospective analysis of donor airway cultures and bronchial tissue cultures revealed a < 1.5 % transmission rate of donor organ contamination [218-219]. Positive donor Gram stain did not predict post-transplant pneumonia, oxygenation or duration of post-transplant mechanical ventilation [220-223]. The Newcastle group reported decreased survival in a group of patients with positive cultures of donor BAL, suggesting that lower airway colonisation may be indicative of an increased risk for post-operative graft infection and dysfunction [224]. Therefore, the impact of microbial colonisation or subclinical infection in assessing the donor lung is not completely clear but important. Successful transplantation is possible with frequent post-operative microbial airway sampling and adequate antibiotic treatment against the identified organisms.

Potential donors on mechanical ventilation for prolonged periods are at increased risk of ventilator-associated pneumonia. It has been found that duration of donor ventilation correlates strongly with the presence of infection. In one study, 90.5 % of donors ventilated for more than 48 h were infected [225]. But in another study no increased rates of recipient infections with organisms identified in the donor lung were observed with donor lungs ventilated for up to 15 days after the initial intubation [226]. There is no evidence that donors should be excluded solely on the basis of the length of mechanical ventilation.

Arterial partial pressure of oxygen (PaO_2) is a tool for assessing lung function. The PaO_2/FiO_2 ratio can be easily affected by reversible processes such as retained secretions, pulmonary oedema and atelectasis. Several authors have shown that initial PaO_2/FiO_2 < 300 mmHg after brain death diagnosis does not make the donors ineligible for lung donation. Indeed, the initial PaO_2/FiO_2 can increase by nearly 100 mmHg with adequate treatment (see Chapter 5). In more than one third of lung donors with low PaO_2/FiO_2, that would otherwise have been not considered for donation, oxygenation value was increased over 300 mmHg and were finally transplanted without impact on recipient's survival [200, 227]. Donor management for improving initially poor gas exchange is important (see Chapter 5). Steroid administration after brain death is associated with an increase in PaO_2/FiO_2 [192-193].

Ex vivo lung perfusion is a new technique used to evaluate high-risk donor organs that allows careful visual inspection of the explanted lungs: reventilated and blood reperfused for functional assessment with measurement of gas exchange, haemodynamic and aerodynamic parameters, and indicators of lung

oedema. Many studies have demonstrated similar length of mechanical ventilation, rate of primary graft dysfunction, length of stay and mortality [228-233]. Dramatic changes in lung-selection criteria must be expected in the future by use of *ex vivo* lung perfusion and growing experience in repairing damaged grafts.

7.2.6.3. *Imaging in the context of lung graft evaluation*

a. X-Ray thorax

Chest X-ray can be performed as a bedside method in the ICU with the known limitations of the sensitivity and specificity of the investigation. A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.6; an example questionnaire can be found in Appendix 10.1. Small space-occupying lesions or minor changes of the parenchymal structure may not be detected. Lung size measurement is not required for standard matching of donor and recipient (exception: malformations of the thoracic cavity of the potential recipient or in extremely adipose donors). The investigation should not be outdated (e.g. older than 4-8 h).

Whenever a whole-body CT scan or thoracic CT scan or magnetic resonance imaging (MRI) has been performed, re-evaluation should be attempted for donation purposes. Beyond investigation for space-occupying lesions, the data can be entered into the same grid as suggested for chest X-ray. In donors with a previous history of malignancy, it is highly recommended to perform a whole-body CT scan according to the recommendations of Chapter 9.

Figure 7.6. **Reporting workflow for minimum dataset to be communicated for X-ray of chest/thorax or computed tomography of thorax [60]**

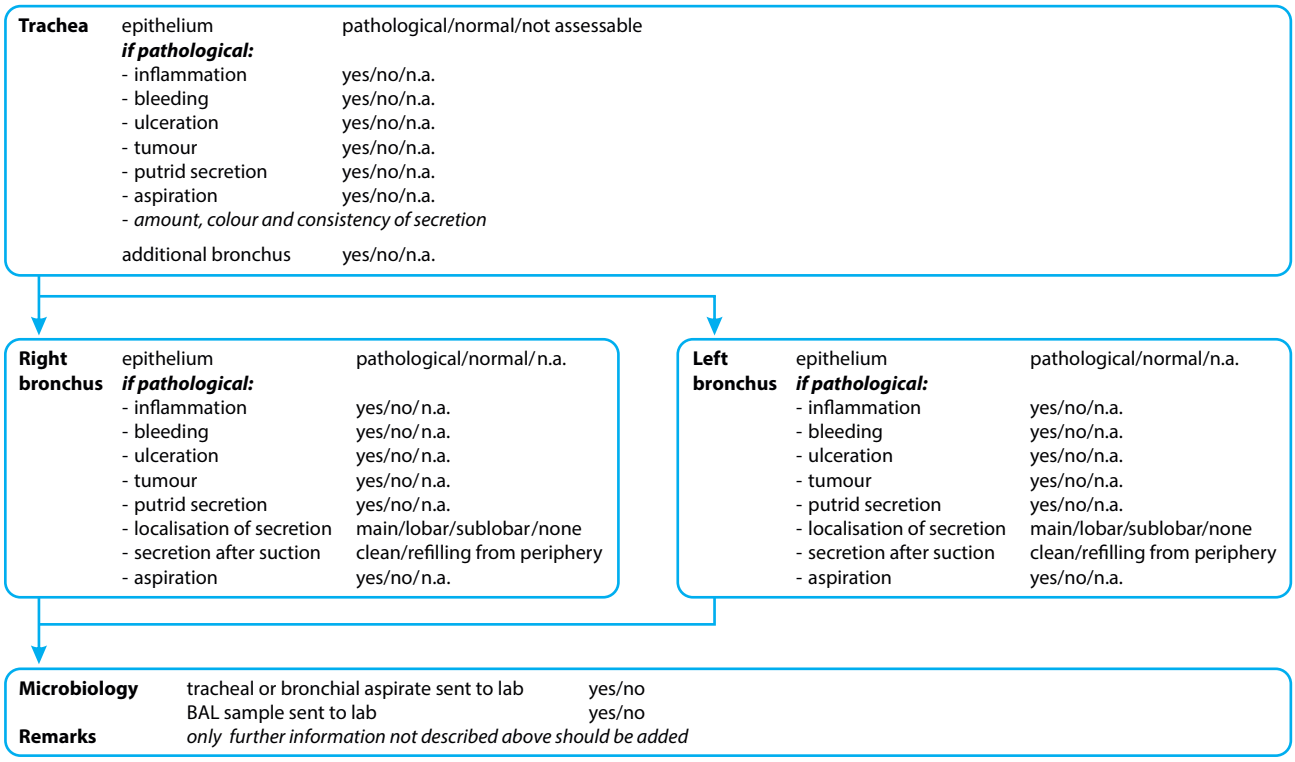
Trachea	deviation from midline	yes/no
	ET tube cranial to carina	yes/no
Right lung	clear (no changes)	yes/no/n.a.
	if not clear:	
	- rib fractures	yes/no/n.a.
	- pneumothorax	yes/no/n.a.
	- pleura effusion	yes/no/n.a.
	- pleural thickening	yes/no/n.a.
	- atelectasis	yes/no/n.a.
	- infiltrates	yes/no/n.a.
	- bronchial thickening	yes/no/n.a.
	- space-occupying lesion	yes/no/n.a.
	- emphysema	yes/no/n.a.
	- interstitial lung disease	yes/no/n.a.
Left lung	clear (no changes)	yes/no/n.a.
	if not clear:	
	- rib fractures	yes/no/n.a.
	- pneumothorax	yes/no/n.a.
	- pleura effusion	yes/no/n.a.
	- pleural thickening	yes/no/n.a.
	- atelectasis	yes/no/n.a.
	- infiltrates	yes/no/n.a.
	- bronchial thickening	yes/no/n.a.
	- space-occupying lesion	yes/no/n.a.
	- emphysema	yes/no/n.a.
	- interstitial lung disease	yes/no/n.a.
Other	foreign body	yes/no → *if yes description and exact location (left lung, right lung or trachea)*
	prominent hilum	yes/no/n.a.
	mediastinum enlarged	yes/no/n.a.
	heart shadow enlarged	yes/no/n.a.
Remarks	*only further information not described above should be added*	

ET: endotracheal; n.a: not assessable.

b. Bronchoscopy

Bronchoscopy can be performed as a bedside method especially for assessing the status of the bronchial system (see Table 7.5). A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 7.7 and an example questionnaire can be found in Appendix 10.2. The investigation should not be older than eight hours for assessment of lung quality if performed. Many lung procurement teams re-perform bronchoscopy during procurement.

Figure 7.7. **Reporting workflow for minimum dataset to be communicated for bronchoscopy [60]**



BAL: Broncho-alveolar lavage; n.a: not assessable.

Table 7.5. **Bronchoscopy parameters to be investigated and standard data list**

Bronchoscopy	Comment, informative value, background
Indication	In a potential lung donor before procurement or for exclusion of bronchial malignancy if suspected or for cleaning airways to improve gas exchange and pulmonary function (especially after suspected aspiration).
Status of bronchus and trachea	Blocked peripheral orifices or purulent secretions may indicate infection (pneumonia). Bleeding or ulceration may have multiple causes; consider additional chronic inflammation due to smoking history. Any tumour detected requires histology prior to transplantation of any organ. Secretions originating from the peripheral bronchial orifice indicate infection in peripheral tissue of the lung (purulent, blood, clean). Samples should be sent to microbiology for identification of colonisation or infection (e.g. bacteria or fungi and their resistance pattern against anti-microbiological agents).

c. Computer tomography or magnetic resonance imaging of the thorax

Whenever a whole-body CT scan or thoracic CT scan or MRI has been performed, re-evaluation should be attempted for donation purposes. These investigations can provide additional information on the issues outlined in Table 7.6.

Table 7.6. **Computer tomography or magnetic resonance considerations in thoracic donor evaluation**

CT-thorax	Comment, informative value
Heart/vessels	Identification of trauma or haematoma and description of coronary vessels are possible by angio-CT if coronary angiography is impossible and donor tachycardia is not limiting technically.
Lung	Check for smaller tumours and abnormal lymph nodes to exclude malignancies and pneumonitis. Highly sensitive for effusion, pneumonia, atelectasis, pneumothorax, embolism and vessel alterations as well as structural abnormalities. Pulmonary contusion: restorations possible after a prolonged time interval (days).

7.2.7. Vascularised composite allografts

Vascularised composite allografts (VCAs) are defined as heterogeneous tissues containing skin, muscles, bones, tendons and vessels, requiring surgical connection of blood vessels and nerves for allograft function. All the issues of VCAs in the donation process are discussed in detail in Chapter 14.

Notably, the donation and transplant process applied to VCAs has important similarities with that applied to whole organs. The main consideration is their essential vascularisation, in contrast to tissues in general. In particular, VCAs are subject to the same time constraints as organs due to their vulnerability to ischaemia, the absence of storage options and the need for immuno-suppressive therapy. Among VCAs, hand, forearm and facial transplantations have progressed. Currently, experience is limited to a few transplant centres.

7.2.8. Tissue- and cell-specific selection criteria

Please refer to the Council of Europe *Guide to the quality and safety of tissues and cells for human application*. These criteria differ from organ criteria, among other reasons because no one-to-one relationship exists between donor and recipient (allocation schemes are different) and because tissues and cells are processed further. Whenever organs (e.g. heart, pancreas) are assessed as unsuitable for transplantation before or during organ procurement, the use of these organs to obtain tissues/cells for human application should be considered (e.g. heart-valves, islets). This will require *ad hoc* collaboration with tissue/cell donation experts.

7.3. Donor and organ documentation

This issue is discussed in Chapter 6. Within the donor selection and organ-specific selection processes it is helpful to document clearly the reasons for each decision, based on the data levels recorded for the donor and/or organ being unacceptable, being either not suitable for any patient or not suitable for a particular donor–recipient combination. Only exact data about such decisions will allow future improvements in donor-selection criteria while monitoring transplant outcomes (see Chapter 17).

7.4. Conclusion

Appropriate donor and organ characterisation contributes to the safety and quality of organs used in transplantation. It has to be remembered that certain medical findings are indicative for using or not using a particular organ for transplant, e.g. severe macro-vesicular steatosis of the liver, even though other grafts of the same donor can be transplanted without increased risk. Other fixed factors cannot be eliminated by characterisation and therefore persist as risk factors after transplantation (e.g. donor age). The aim of donor and organ characterisation is to ensure adequate allocation of the organ to the recipient with the highest probability of benefit from a transplant, based on the data acquired during the process as outlined.

Organ donation and transplantation are procedures carried out within significant time constraints, especially in deceased organ donation, where most procedures are rapidly carried out to keep ischaemic times as short as possible.

Risk evaluation of donor and recipient factors is carried out on an individual, case-by-case basis. There may be factors that make a given organ from a donor absolutely unsuitable for a specific recipient, whereas the same organ could be life-saving for another recipient. This is why there are only few absolute contraindications against organ donation. Limits are even further stretched when there is urgency for transplantation among the increasing number of potential recipients on the waiting list. It is the duty of the transplant physician to carefully evaluate donor and recipient factors in an individual risk–benefit analysis, while it is a shared general responsibility of authorities in charge, and of the medical community, to organise transplant systems (including allocation schemes) in such a way that organ loss is prevented and organs donated are respected to the highest possible extent. By the same philosophy, it is important to document and assess when and why organs procured were finally not used, to learn from these findings and ensure optimised organ use for the future.

A 'customised' donor/organ profile of each patient enrolled on the transplant waiting list may facilitate planning of adequate donor/recipient risk assessments and the best use of all suitable organs.

Finally, the team of physicians performing the transplantation have the overall responsibility for its use in that particular recipient, regardless of the considerations and risks in donor and organ selection as presented above.

7.5. References

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Related material

- Appendix 10. Donor examination by various means
- Appendix 11. Grading for biopsies at histopathological examinations (English-language version)

Chapter 8. Risk of transmission of infectious diseases

8.1. Introduction

Acute or latent infections may be transmitted by the graft to the recipient and may result in morbidity or mortality [1, 2]. A decision to use donors with certain infections – e.g. *cytomegalovirus* (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) – may be considered for selected recipients, with an acceptable risk of morbidity and mortality that is mitigated by monitoring and pre-emptive or prophylactic interventions [1, 3-4].

In the context of deceased donation, despite collection of detailed clinical and epidemiological information, there is not sufficient time for exhaustive diagnostic investigations, except for tests for which results are likely to be available within a few hours [4-5]. In donation procedures without such time constraints (e.g. tissue donation), more extensive diagnostic procedures should be performed for safer risk assessments.

In addition to national guidelines, locally applicable current and updated epidemiology of infectious diseases should be taken into account [6-7]. Recent experience with emerging local or geographically restricted and pandemic infections highlights the changing nature of risk, and this risk is best addressed by *ad hoc* action plans on a national or international level – e.g. for chikungunya virus, West Nile virus (WNV), Zika virus, Yellow fever virus, Ebola virus or the 2009 pandemic influenza H1N1 virus [8-13].

Infectious agents transmissible by organs or tissues belong to five groups of pathogens:

- Viruses: by infection in the organs or tissues of donor, with or without current viraemia.
- Bacteria: by bacteraemia or colonisation/infection of organs or tissues.
- Fungi: by fungaemia or colonisation/infection of organs or tissues.
- Parasites: by latent infection or acute infection.
- Prions: by infection.

The timeline for primary infection in the donor can be categorised as follows:

a. The infection was acquired a long time before hospital admission (e.g. CMV, *Mycobacterium tuberculosis* or *Strongyloides*).
Diagnosis of these past infections in the donor is made by detection of an immunological response (e.g. serologic testing) or, if present, by other clinical signs or symptoms. Serological screening cannot differentiate whether a donor has cleared an infection or if a latent infection prevails in tissues or organs; when positive, such screening indicates previous exposure to the given pathogen. Latent infections in the donor can be transmitted by a graft and may be reactivated in immuno-suppressed recipients. If recipients are without previous immunological protection against the pathogen, the incidence and severity of illness is likely to be higher.

b. The infection may have been acquired shortly before hospital admission – e.g. HIV, HBV or

HCV – and the donor has not yet presented clinical symptoms of the infection or a serologic response to it.

The time interval between exposure to a pathogen and the point when assays are able to detect specific markers of infection is known as the window period. Another phase also exists, when specific target tissues, such as lymph nodes or the liver, can be infected, while a systemic spread has not yet occurred and neither the pathogen nor an immunological response to it can be detected in the blood; this is the so-called eclipse period. In the setting of eclipse or serological window period, despite negative screening results, the use of infected organs may transfer the infection from the donor to the recipient. During the serological window period, the pathogen is present in the blood circulation, but antibodies are not detectable because humoral immune responses have not yet occurred (see Figure 8.1).

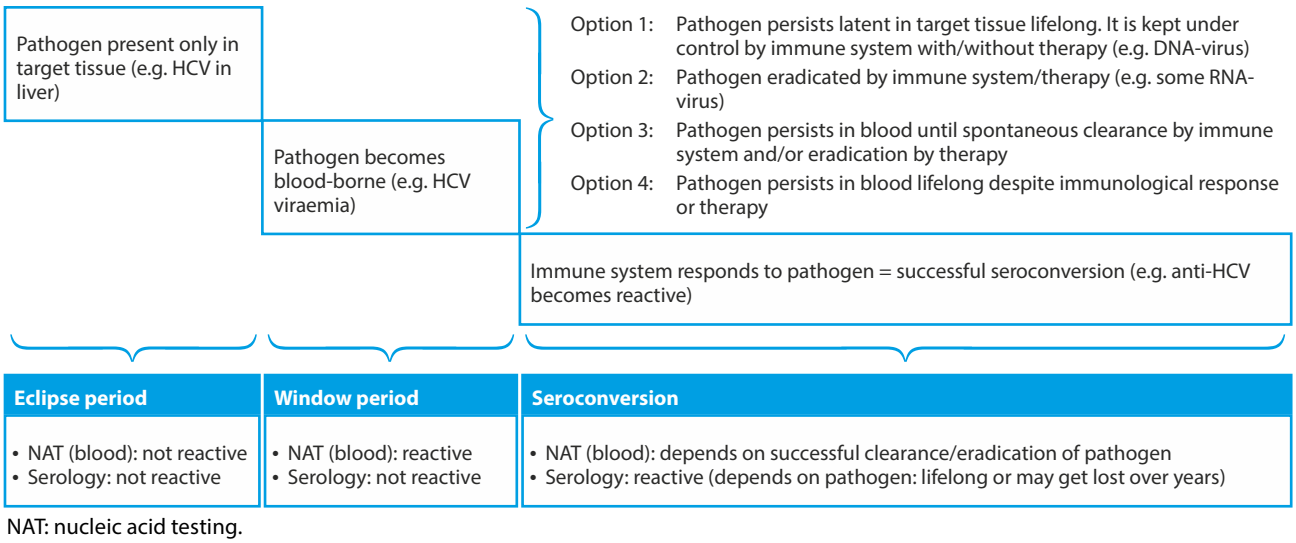
Since serologic assays may not be reactive during the serologic window period, and clinical signs may be absent, assessment of the pathogen in the blood by nucleic acid testing (NAT) may reduce the period between initial infection and possible detection (e.g. the window period for the detection of HCV is reduced from approximately 70 days using serology to 5-7 days using NAT). However, by definition, during the eclipse phase, NAT may also fail to detect the pathogen in the blood or plasma (≈ 5-7 days for HIV and HCV, and ≈ 20 days for HBV), and infection may be transmitted even with a non-reactive NAT [14-15].

The risk of disease transmission from a donor with an infection but non-reactive screening tests is referred to as the residual risk of disease transmission. If any risk factors for recent acquisition of an infection are identified, it is mandatory to report this information. NAT on donor blood or target tissue of the pathogen helps to decrease the diagnostic window period until seroconversion occurs, but this is not always available. Furthermore, even with NAT testing, the risk can never be completely eliminated [16].

c. The infection may have been acquired during the terminal hospital stay or due to contamination during the organ procurement, transportation and storage process.

This risk is greatest for nosocomial bacterial and fungal infections, although transmission of other infections (e.g. WNV) through blood products has also been described [17]. Diagnostic systems are more limited for detecting these types of infections; for example, organs may have already been transplanted before reactive bacterial/fungal cultures become available. Assays with pending final results at the time of procurement need to be carefully recorded, and timely follow-up of all results is mandatory. Any infection or new diagnostic information should be conveyed as soon as possible to all transplant centres that have accepted organs from the affected donor.

Figure 8.1. **Timeline from infection until final seroconversion, including the eclipse period and window period**



NAT: nucleic acid testing.

A review of the information available (e.g. case history, travel history, medical history, contacts and signs of infection) should guide the decision-making process as to which pathogens to screen for, over and above the mandatory markers, and a balanced approach is required. However, it is impossible to completely exclude all risks for unexpected disease transmission. Some further pitfalls or limitations exist in screening for infectious diseases in organ donors:

- Because of changing epidemiology and the globalisation of geographically restricted infections, laboratories are not capable of testing for all potential infections. For some rare pathogens, approved assays do not exist or have not been properly evaluated. Therefore national authorities should ensure that a national reference centre is established to provide expert information on potential disease-transmission risks. This information about epidemiology and risk factors for donor-derived infections should be shared with organ-procurement organisations (OPOs) and transplant centres. The performance, sensitivity and specificity of screening assays should be reviewed periodically. Unresolved false positive screening results, or inability to screen for relevant suspected pathogens, must be avoided in order to minimise unnecessary organ loss [6]. In this context, each OPO should regularly refer to the institutions mentioned in section 8.3 for monitoring of global changes in infections and vector monitoring. In addition, surveillance of local epidemiology requires the same process as for national and regional reports, because there may be significant differences.

Table 8.1. **Abbreviations used for the reporting of viral screening results**

Abbreviation (standardised)	**Other abbreviations still in use**	**Explanation**
HBsAg		*Surface* antigen of HBV
anti-HBc	HBc-Ab	Antibodies against the *core* antigen of HBV*
anti-HBs	HBs-Ab	Antibodies against surface antigen of HBV
anti-HBe		Antibodies against envelope antigen of HBV
HBeAg		Envelope antigen of HBV
anti-HCV	HCV-Ab	Antibodies against hepatitis C virus
anti-HIV	HIV-Ab	Antibodies against human immunodeficiency virus (HIV) without definition of the subtype
anti-HIV-1/2	HIV-1/2-Ab	Antibodies against HIV type 1 and 2
anti-HIV-1	HIV-1-Ab	Antibodies against HIV type 1 only
anti-HIV-2	HIV-2-Ab	Antibodies against HIV type 2 only
HIV-1-p24-Ag	HIV-p24-Ag	Protein p24-antigen of HIV type 1
anti-CMV	CMV-Ab	Antibodies against *cytomegalovirus* (CMV)*
anti-EBV	EBV-Ab	Antibodies against Epstein–Barr virus (anti-EBV-VCA and anti-EBV-nuclear antigen (EBNA) are usually tested in donors and it needs to be specified which test has been used)*
anti-Toxoplasmosis		Antibodies against *Toxoplasma gondii*
anti-*Treponema*	Lues AB	Antibodies against *Treponema pallidum*. Formerly the *Treponema pallidum* haemagglutination test (TPHA Test) was used
anti-HTLV-1/2		Antibodies against *HTLV-1/2 virus*
D+/R–		The donor is seropositive for the pathogen and the recipient is naïve (i.e. is seronegative)*
D+/R+		Both the donor and the recipient have been infected by the pathogen*
D–/R+		The donor is naïve (i.e. is seronegative) and the recipient is seropositive for the pathogen*
D–/R–		Both the donor and recipient are naïve (i.e. are seronegative) for the pathogen*
reactive	positive	Any 'reactive' or 'detected' test result indicates either a current or past exposure to an infectious agent. The medical community documents this as 'positive'
non-reactive	negative	Any 'non-reactive' or 'not detected' test result only indicates that the test did not detect the specific marker in the specimen investigated. The medical community documents this as 'negative', without knowing whether the pathogen was missed or whether it was not present.

*D/R-sero-status is driven by IgG-antibody status of donor and recipient. Most laboratories rely on IgG-tests for screening.

- Basic screening results must be available 3-6 h before organ recovery (see §8.3). This tight timeline may preclude confirmatory tests for certain pathogens – e.g. false positive results in human T-lymphotrophic virus-1 (HTLV-1) screening [18].
- In deceased donors, cerebral lesions can mimic a state of generalised inflammation. Parallel to failure of all brain-stem reflexes, collapse of the immune system can be observed, presenting as a sepsis-like syndrome. Careful interpretation and acknowledgement of this 'brain failure syndrome' is needed.
- In living donors, acquisition of infection between initial screening and actual organ donation can occur [19]. Ensuring screening or re-screening close to the time of organ recovery and educating the potential living donor on how to avoid acquiring infections between screening and procurement are essential [20].
- Abbreviations used in viral screening and interpretation of results should be standardised as summarised in Table 8.1. Alternative abbreviations commonly used in the regional/national language may also be used, but with proper explanations. In order to avoid misinterpretation, test results should be communicated properly, taking into account all the limitations of screening tests as outlined above (see §8.10.3). In that respect, written interpretation of results in the laboratory report is highly desirable.

Risk assessments of donors are moving from a graded to a more dichotomous system as the graded system was felt to be challenging to contextualise in the individual risk–benefit assessment based on all particular donor and recipient factors (see §6.1.1). Therefore, in so-called non-standard-risk donors, the clinician must determine case by case if post-exposure prophylaxis or treatment of the pathogen is possible in the recipient without harm or whether currently no appropriate therapy exists. This is especially important with regard to the changing epidemiology of resistance to anti-infective drugs and emerging new pathogens. Each donor–recipient combination must be assessed individually, based on their respective risks for infections and the risks related to spending a prolonged time on the waiting list. Information available on donor-derived transmission of rare pathogens includes individual case reports on fatal outcomes or cases treated successfully, in addition to critical reviews by national institutions or experts [1-2, 5, 21-22].

8.2. Medical history and behavioural history to inform about the risks of infections in the asymptomatic donor

The guidelines for excluding or including donors presenting certain risk behaviours for an increased risk of *de novo* infections vary between countries and regions. They are determined by local disease prevalence and risk assessments. This catalogue of risk criteria should be regularly reviewed. It reflects epidemiological changes and diagnostic developments.

Data to be obtained for detecting potential infectious disease-transmission risks are outlined in section 6.2.1 as well as appendices 6, 7 and 9.

One major concern is the risk of unintended transmission of HIV, HCV or HBV infection [23]. The incidence and prevalence of HIV and HCV infection varies depending on different risk factors [24-25], and the causes of *de novo* infections vary between European regions [26]. Unfortunately there are only a few studies based on adequate evidence that define the risks of window-period infections [16, 23]. Where such studies exist, data cannot be directly extrapolated from one population to another because the variables used for calculations differ.

In spite of these limitations, the evidence-based guidelines issued by the United States Public Health

Table 8.2. **Basic screening for infections in deceased organ donors**

Before organ recovery or transplant (1-3 h)	As soon as possible (not necessarily before organ recovery and transplant)	Retrospectively after transplant, if indicated at the recipient transplant centre
anti-HIV-1/2 (incl. HIV-1-p24-Ag) HBsAg and anti-HBc anti-HCV	anti-CMV IgG anti-EBV-VCA-IgG, anti-EBNA1-IgG anti-*Treponema pallidum* ELISA (enzyme-linked immunosorbent assay or VDRL/ RPR) anti-Toxoplasma IgG	Additional tests can be performed according to the recipient profile for targeting specific prophylaxis VDRL: Venereal Disease Research Laboratory RPR: rapid plasma reagin

Service (PHS), as updated in 2013, are recommended for assessing individuals at increased or non-standard risk for HIV, HCV or HBV infections [23]. According to these guidelines, donors should be considered at high risk for HIV, HCV or HBV infections if one of the following conditions exists:

a. People who have had sex with a person known or suspected to have HIV, HBV or HCV infection in the preceding 12 months.
b. Men who have had sex with men (MSM) in the preceding 12 months.
c. Women who have had sex with a man with a history of MSM behaviour in the preceding 12 months.
d. People who have had sex in exchange for money or drugs in the preceding 12 months.
e. People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months.
f. People who have had sex with a person who injected drugs by intravenous, intramuscular or subcutaneous route for non-medical reasons in the preceding 12 months (intra-nasal drug use should be interpreted as similar to the subcutaneous route).
g. A child who is 18 months of age or less and born to a mother known to be infected with, or at increased risk of, HIV, HBV or HCV infection.
h. A child who has been breastfed within the preceding 12 months and whose mother is known to be infected with, or at increased risk for, HIV infection.
i. People who have injected drugs by intravenous, intramuscular or subcutaneous route for non-medical reasons in the preceding 12 months.
j. People who have been in lockup, jail, prison or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months.
k. People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhoea, chlamydia or genital ulcers in the preceding 12 months.
l. People who have been on haemodialysis in the preceding 12 months (risk factor for HCV infection only).

In these increased-risk donors, extended screening by NAT for HIV and HCV is highly recommended to reduce the diagnostic window period [4, 23].

In the European setting, some deviations from PHS guidelines should be considered:

a. People who have been on haemodialysis in the preceding 12 months may be also at increased risk for HBV infection in certain European countries.
b. In the annual epidemiological report of the European Centre for Disease Control (ECDC) [24], acute HBV, HCV or HIV infection is reported to be transmitted by heterosexual contacts, MSM, injecting drug abuse, medical procedures or vertically, with a substantial variation in each geographic region or subpopulation of migrants and ethnic minorities. The conclusions from these data should be considered carefully too – e.g. frequently changing sexual partners or lifestyle (during youth) may vary the risk in certain populations.
c. Tattoos, ear piercings, body piercings and/or acupuncture are very popular in some European countries. Usually they are applied by sterile methods but in case of doubt the associated risk should be considered similar to that of non-medical injections.
d. The time intervals for defining increased-risk donors according to the PHS guidelines may be shortened to the duration of two window periods.

Additionally, with the advent of direct-acting anti-virals (DAA) for HCV and available data on the safety and efficacy of DAAs in treating HCV-infected transplant recipients, the consequences of HCV transmission have changed and should be taken into account in considering the use of donors at increased risk for HCV. There are currently several studies ongoing in the United States and elsewhere in which HCV-infected donors are intentionally used for HCV-uninfected recipients who receive DAA post-transplant [27].

Any recipient, particularly those having received organs from increased-risk donors, should be followed up for early detection of donor-derived infections, with initial serial testing performed between 0 and 3 months post-transplant [2]. Frequently, recipients who acquire donor-derived infections, particularly HCV, may not seroconvert due to immunosuppression. As a result, recipient screening should always include a direct measure of the virus (i.e. NAT or antigen detection). Additionally, it is important to remember that the majority of patients with donor-derived HIV, HBV and HCV will be either asymptomatic or have only transient liver-function testing abnormalities – therefore, symptoms should not be the driver for testing. Further serologic testing may be temporarily false positive due to transient activity of donor passenger lymphocytes.

Table 8.3. **Additional tests which should be considered for donors with certain geographic connections**

Test	Central & South America	North Africa	Sub-Saharan Africa	Indian subcontinent	Southeast Asia
HTLV serology	Always	Always	Always	Always	Always
NAT* for *Plasmodium* spp.	Central America and Amazon	No	Always	Always	Always
Stool examination**	Always	Always	Always	Always	Always
Urine examination***	No	Egypt	Always	No	No
Strongyloides stercoralaris serology	Always	Always	Always	Always	Always
Schistosoma spp. serology	Caribbean, Venezuela and Brazil	Always	Always	No	Always
Trypanosoma cruzi serology for screening; NAT or Strout test for exclusion of parasitaemia	Always (not Caribbean)	No	No	No	No
Leishmania serology	Always	Always	Always	Always	Always
Paracoccidioides brasiliensis serology	Brazil	No	No	No	No
Coccidioides immitis serology	Always	No	No	No	No
Histoplasma capsulatum see Table 8.7	No	No	Western Africa	No	No

Note: The above tests should be considered for screening of donors who have lived in and/or travelled to those geographically-restricted areas or are at risk for vertical transmission due to ancestors having lived there.

Source: modified according to [28].

* NAT is sensitive to rule out parasitaemia, but limited availability for routine diagnostics may require other tests.

** *Entamoeba histolytica*, *Clonorchis* spp., *Opistorchis* spp., *Schistosoma* spp., *Strongyloides* spp.

*** *Schistosoma haemeatobium*.

Screening for some parasitic and bacterial infections (e.g. Chagas disease, malaria, toxoplasmosis, strongyloidiasis) should be considered, according to their prevalence in the region or in the specific donor subpopulation. Insanitary living conditions (especially with respect to water) and certain outdoor activities may expose people to pathogens in different situations – e.g. Chagas disease, tick-borne encephalitis, rabies. Contact with wild animals, as well as animals living in or near households (e.g. birds, rats, reptiles), may be a source of infection. Zoonosis may also be transmitted via food. The occurrence of epidemic diseases in animals should be cross-checked with those of humans because this will help to develop preventive strategies at an earlier stage (e.g. the WNV endemic in animals).

A history of travel to, origin in or relatives from areas with endemic transmissible diseases such as malaria, trypanosomiasis, rabies, WNV, tuberculosis etc. requires further consideration (see Table 8.3). The history of recent immunisations with live vaccines should also be evaluated. If the donor has been previously deferred from blood donation, then the reason for deferral should be evaluated (see §8.3.4).

8.3. Basic screening for infections in organ donors

The basic screening for infections in deceased organ donors must include the serological tests shown in Table 8.2, with results being provided within the time frame specified in Table 8.2.

Based on regional prevalence or endemics, further tests may be performed. In cases where a donor has lived in endemic areas, additional tests listed in Table 8.3 should be considered in donor screening [28]. Further, the risk of vertical transmission from mother to child should be considered.

Donors having increased risk for HIV, HCV or HBV infection due to risk behaviours are discussed in section 8.2. They should be screened according to the algorithm outlined in section 8.3.1.

In the event of an anti-HCV reactive result, supplemental serologic testing – such as with the recombinant immunoblot assay (RIBA) – has been used to confirm the specificity of the screening tests by demonstrating to which HCV antigen there was reactivity. However, supplemental antibody assays are time-consuming and not widely available. Accordingly, use of high signal/cutoff ratios has largely replaced RIBA testing to improve the specificity of

enzyme immunoassay results. In clinical laboratories, enzyme immunoassay reactive samples with high optical density – e.g. > 3.8 for the Ortho and Abbott tests [29] – are nearly always RIBA-positive or contain HCV RNA. As a first-line test, HCV-NAT should be performed as a complementary test to assess whether clearance of viraemia has occurred (spontaneous or due to sustained virological response after therapy). Even if a negative result for HCV-NAT is obtained, HCV may still persist in the liver tissue [30]. With wider use of DAAs for the treatment of HCV, a large number of HCV-seropositive, NAT-negative donors will be available. Recent US guidelines suggest that use of such donors can be done safely with close recipient monitoring [31].

Reactive anti-*Treponema pallidum* screening should be verified by complementary diagnostics for final conclusions and discrimination between past and acute infection. It is preferable to have the results of anti-*Treponema pallidum* screening available before procurement in order to detect additional infection risks related to blood-borne viruses.

Samples for further microbiological investigations should be drawn at organ recovery, as indicated. It is always important to perform a critical review of all relevant pathogens as outlined in the following sections, together with all results available – e.g. blood cultures, broncho-alveolar lavage (BAL), urine cultures.

Screening should be extended to NAT for donors with an increased risk of HIV-1, HBV or HCV infection [32] (see §8.2 and §8.3.1). The results of these tests must be made available before organ recovery or transplantation. However, even with NAT-negative results, these donors must still be considered at increased risk because of the residual risk posed by the eclipse period. Accordingly, recipients should be tested as described in section 8.1.

Screening should be performed with the latest-generation assay available, according to the manufacturer's instructions and as licensed by the national health authorities [7]. Each centre should have a plan for how to handle reactive or unexpected results (§8.3.1 and §8.10.1) [7]. For basic screening, serologic tests should detect IgG antibodies. Only in special cases is IgM detection necessary. The use of IgM for donor screening is not advocated on the basis of the little information gained and the high rate of false positive results. Donor sera or plasma samples should be stored for at least 10 years by the OPO, according to the methods available and national recommendations [6].

Screening protocols must be reviewed regularly because of the rapid development in testing repertoires. The recommendations of this Guide are based on the technology available in 2017 in most Council of Europe member states and on the basis of 24 h a day, 365 days a year availability with regard to the needs of deceased organ donation. In some countries, multiple different techniques are employed for NAT testing according to their local certifications. In such cases, appropriate sensitivity, specificity and turn-round time must be ensured when using NAT testing under the specific circumstances of organ donation, i.e. as single-specimen runs outside standard working hours and without routine staff availability.

Multiplex NAT-screening assays for HIV, HBV and HCV can be used when individual donor screening (ID-NAT) is performed and if sensitivity as well as specificity is equivalent to individual NAT. Reactive triple or multiplex NAT results must be confirmed according to manufacturer's instructions so as to reduce the frequency of false positive results. For further confirmation, individual NAT has to be performed as indicated.

Serologic markers may not be reactive during the window period and viraemia may not exist during the eclipse period. Further viral infections may not be detected by NAT unless a specimen has been drawn from the appropriate tissue, e.g. rabies from specific areas of the brain, cardiotropic virus from the myocardium. Therefore, organs should not be transplanted from a donor if there is strong clinical evidence or strong suspicion of an infection in the donor, especially when there are no suitable treatment options for organ recipients.

The requirements for serologic testing of donors vary between European countries due to the variability in specific/endemic prevalence of viral diseases [7]. For example, prevalence of HTLV, HBV, hepatitis D or hepatitis E varies regionally, due to different immigration patterns from endemic areas and epidemiological changes. Also geographic diversity among and within European countries in the prevalence of indigenous hepatitis E infection is likely to be attributable to the cultural background and dietary habits of the population. In some regions, the seasonal endemic occurrence of certain viruses (e.g. WNV) requires extended screening during certain time periods [2, 5]. Up-to-date information about new and emerging, seasonally occurring or regionally endemic virus infections (e.g. WNV, Usutu, chikungunya, dengue, Zika, Yellow fever, influenza virus) can be obtained from the references listed below. The relevance of these data should be discussed within the member states for regional strategies in updating local screening algorithms.

Websites

For more specific information about infections, see:

- 'Travel and Health' pages at www.who.int/ith/en
- Centers for Disease Control (CDC) in the USA: the yellow book at wwwnc.cdc.gov/travel
- European Centre for Disease Prevention and Control (ECDC) at www.ecdc.europa.eu/en
- other reference centres within member states (e.g. for Germany, see www.rki.de)

For each pathogen discussed in the following sections, the reader is advised to refer to the websites of the above-mentioned organisations where the most current epidemiological information can be obtained.

8.3.1. Initial screening algorithms in organ donors for HIV, HCV and HBV

Criteria that define donors as having increased risk for HIV, HCV or HBV infection due to risk behaviours are discussed in section 8.2. In donors at increased risk for HIV, HCV or HBV, a screening algorithm is required which minimises the diagnostic window period including prospective NAT testing. It may be discussed whether retrospective NAT testing can be considered for all other donors as this is done for tissue donors without time constraints in some European countries anyway. Therefore, different screening algorithms should be used, based on the recognised risk of the donor, as appropriate (see Figures 8.2, 8.3 and 8.4).

In the near future the rate of donors infected with HCV but without viraemia due to sustained virological response after successful therapy, or due to spontaneous clearance, will increase. HCV-seropositive, NAT-negative donors pose an exceptionally low risk for HCV transmission, and current guidelines recommend the use of such donors (see §8.4.2.7) [31, 33-34]. For the issue of new DAA against HCV, refer to section 8.4.2.7.

For HIV, HCV and HBV screening, the possibility of an initially reactive result must be considered for any organ donor. As this initial reactive result may be a true positive or a false positive result, a pragmatic algorithm for verification of the initial result must be used due to the time constraints in organ donation (see Figures 8.2, 8.3 and 8.4 for an algorithm at first initial testing). Any initially reactive result in tissue or cell donors without time constraints must be verified according to local protocols (e.g. proper handling of specimen by high-speed centrifugation and repeat double testing in cases of unexpected results).

Initial screening

Initial screening algorithms for donors at standard risk for HIV-, HCV- and HBV-infection are shown in the left diagrams of Figures 8.2.a, 8.3.a and 8.4.

Initial screening algorithms for donors at increased risk for HIV-, HCV- and HBV-infection are shown in the right diagrams of Figures 8.2.b, 8.3.b and 8.4.

NAT and diagnostic window

The use of simultaneous NAT screening for HCV and HIV decreases the diagnostic window period to a few days (HIV-1 NAT screening only, unless otherwise requested).

NAT for HBV is not necessary, except for occult HBV infection.

The utility of NAT screening in donors lacking identified risk factors is that it also decreases the diagnostic window period. However, access to NAT for prospective single donor screening is very limited in many European countries and the risk of missing an early infection may be very low.

Anti-HBc/anti-HCV results

Donors that do not present elevated risks for infection as outlined in §8.2, but are HBsAg non-reactive and anti-HBc reactive, should be considered at risk for potential HBV transmission for liver grafts (see §8.4.2.6).

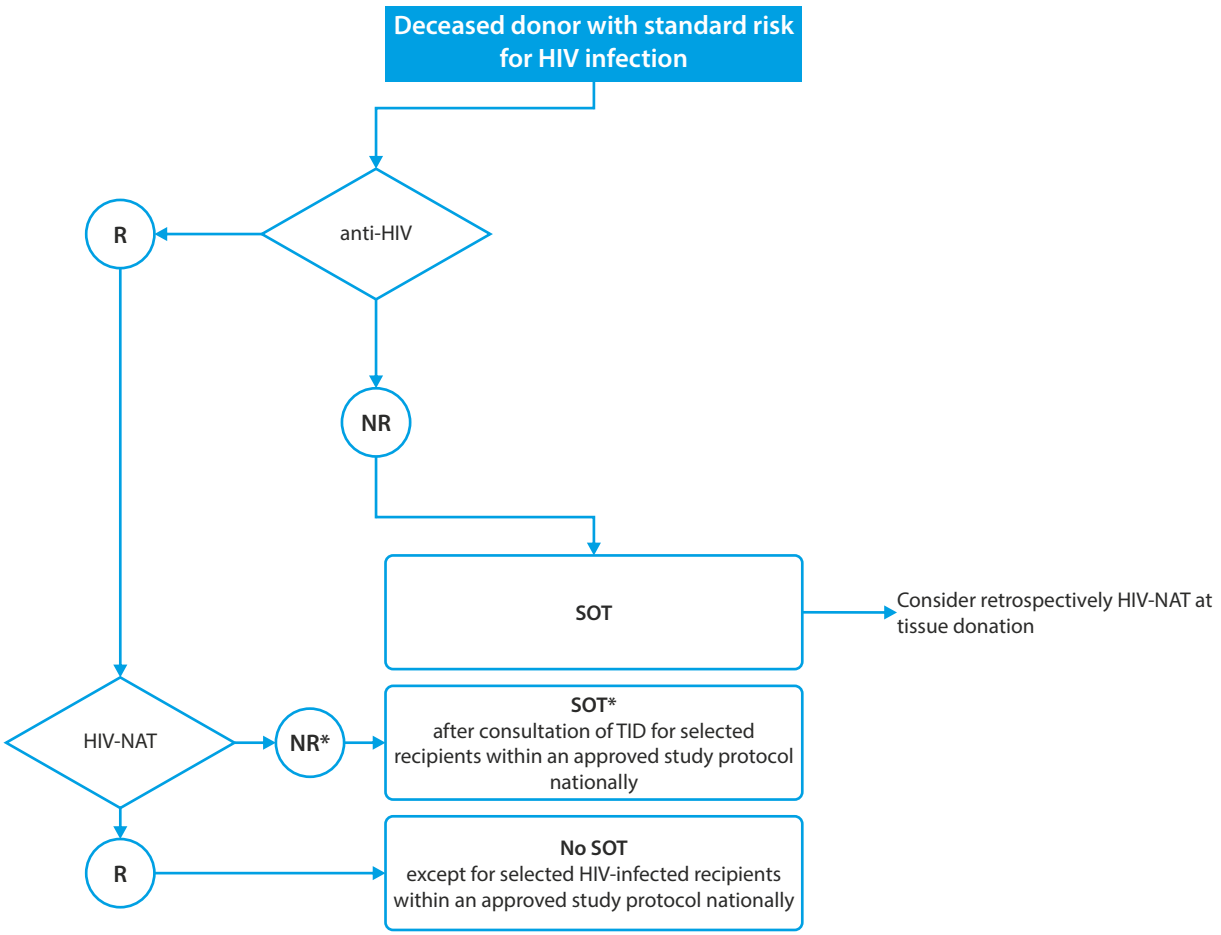
In donors with anti-HCV reactive results, HCV-NAT may clarify whether the donor is viraemic or not, with relevant consequences regarding the use of organs (see §8.4.2.7).

Figures 8.2, 8.3 and 8.4 follow.

Text resumes on page 177.

Figure 8.2. **Screening algorithms for HIV infection in potential organ donors during first initial testing**

8.2.a. Standard risk donor

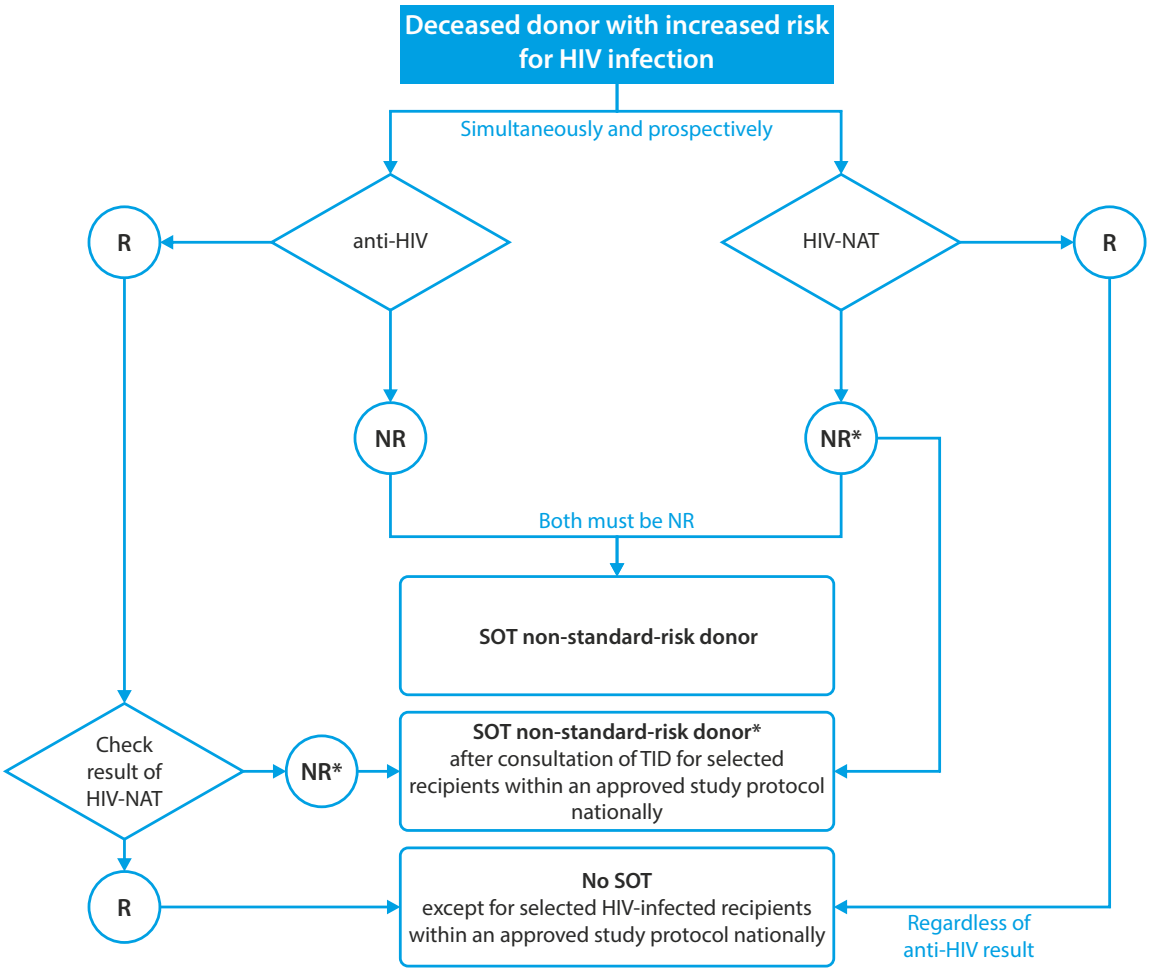


R=reactive; NR=not reactive; SOT=solid organ transplantation; TID=transplant infectious disease expert; anti-HIV=anti HIV 1/2 incl. HIV-1 p24Ag.

* It must be ensured that donor was not on active treatment for HIV with suppressed HIV (if uncertain, proceed as if HIV-NAT is R).

Note: In the case of an anti-HIV reactive result, confirmation of the result is recommended before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For further consideration about protocols of HIV-to-HIV-transplantation (D+/R+), see section 8.4.2.11.

8.2.b. Increased risk donor



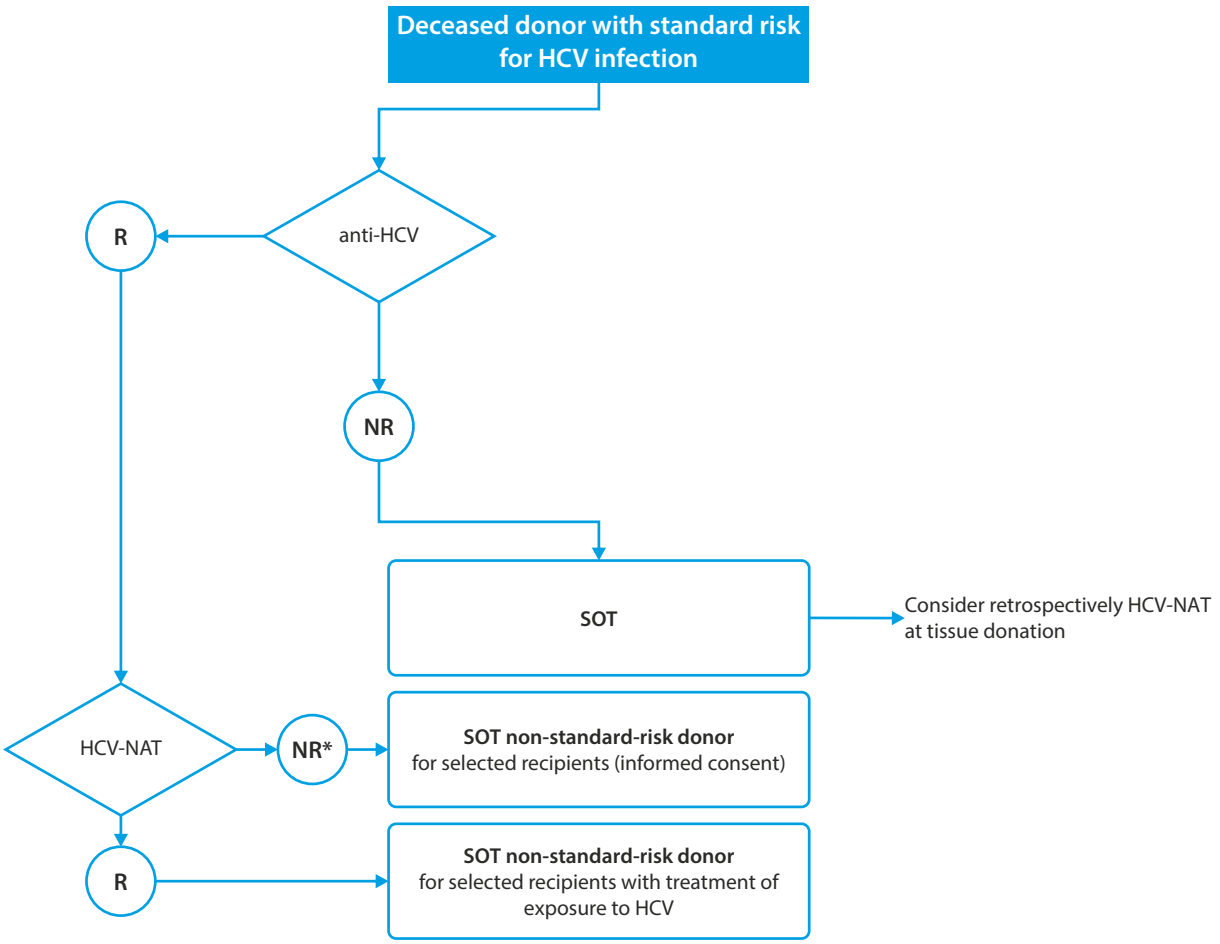
R=reactive; NR=not reactive; SOT=solid organ transplantation; TID=transplant infectious disease expert; anti-HIV=anti HIV 1/2 incl. HIV-1 p24Ag

* It must be ensured that donor was not on active treatment for HIV with suppressed HIV (if uncertain, proceed as if HIV-NAT is R).

Note: In the case of an anti-HIV reactive result, confirmation of the result is recommended before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For further consideration about protocols of HIV-to-HIV-transplantation (D+/R+), see section 8.4.2.11.

Figure 8.3. **Screening algorithms for HCV infection in potential organ donors during first initial testing**

8.3.a. Standard risk donor

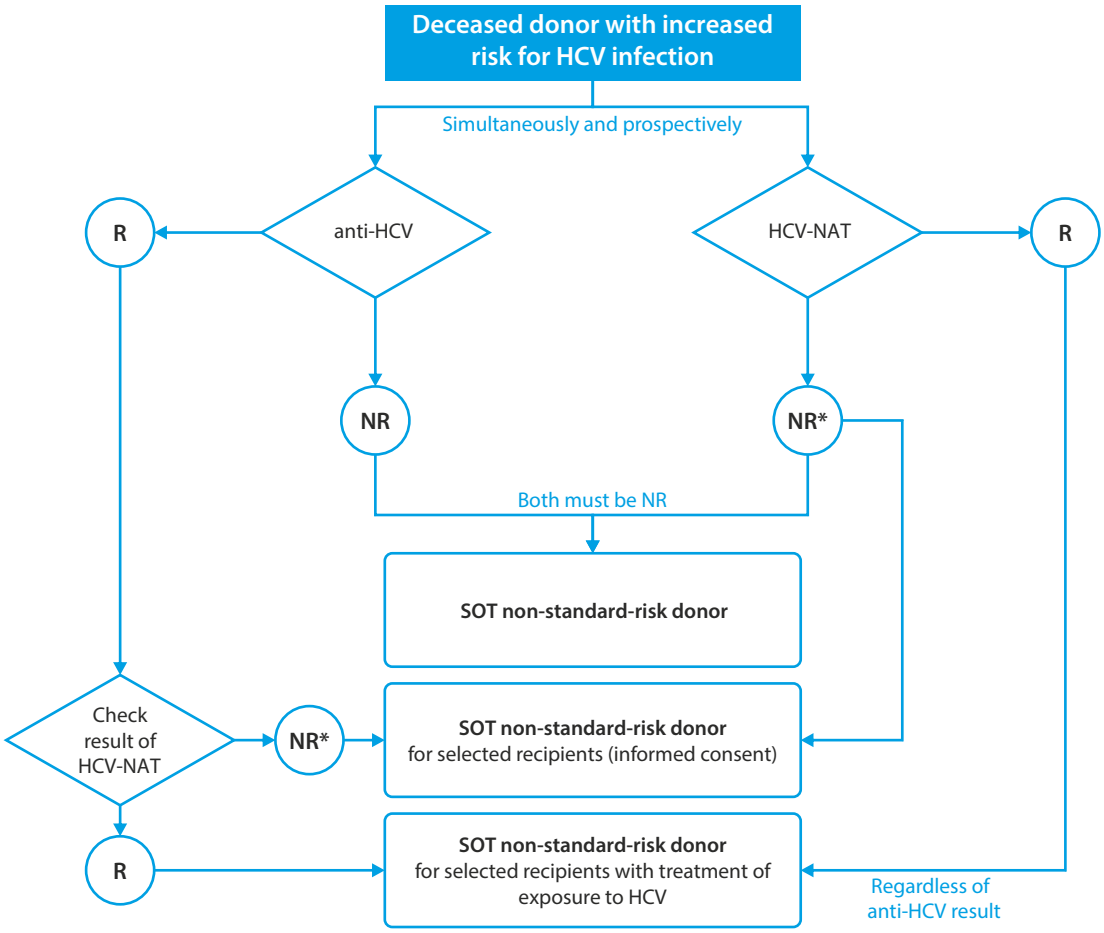


R=reactive; NR=not reactive; SOT=solid organ transplantation.

* Consider ongoing HCV treatment: without sustained virological response or spontaneous clearance, proceed as if HCV-NAT is R.

Note: In the case of an anti-HCV reactive result, confirmation of the result is desirable before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For details about HCV infection in donors, see §8.4.2.7.

8.3.b. Increased risk donor

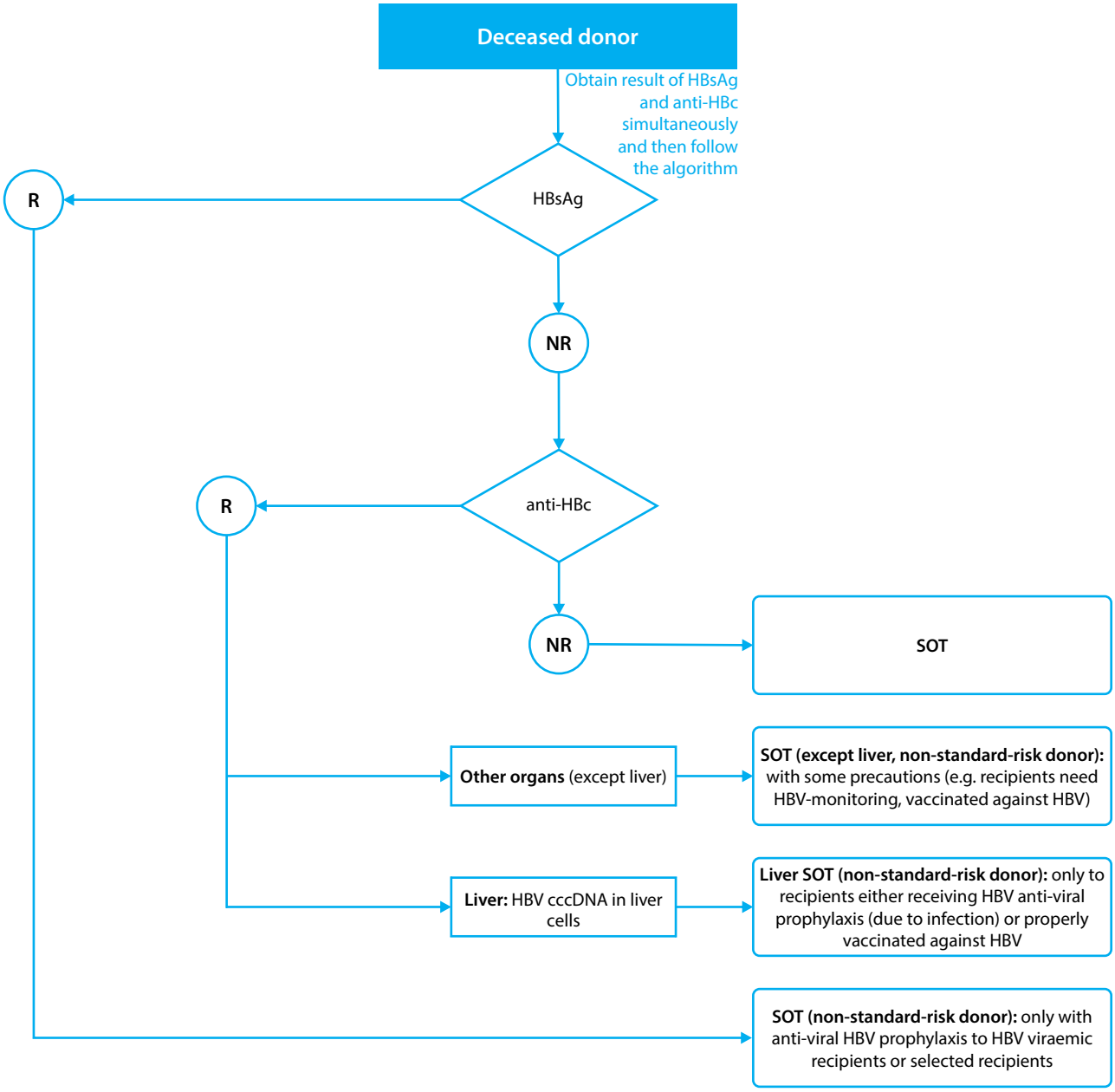


R = reactive; NR = not reactive; SOT = solid organ transplantation; TID = transplant infectious disease expert

* Consider ongoing HCV treatment: without sustained virological response or spontaneous clearance, proceed with HCV-NAT as R.

Note: In the case of an anti-HCV reactive result, confirmation of the result is desirable before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and organ procurement organisation, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For details about HCV infection in donors, see §8.4.2.7.

Figure 8.4. **Screening algorithms for HBV infection in potential organ donors during first initial testing**



R = reactive, NR = not reactive, SOT = solid organ transplantation.

Note: In Figure 8.4, the screening algorithm for donors with increased risk for HBV infection is equivalent to the one for donors at standard risk for infection. Accurate communication of the risks is required. It should be considered that, depending on the prevalence of HBV mutants, testing algorithms might miss HBsAg reactivity in some populations – depending on the country where infection occurred – and hence laboratories should select appropriate testing platforms. Such cases should be discussed with a transplant infectious disease expert for proper indication of additional testing (e.g. if HBV-NAT is available, then measurement in liver tissue and blood may provide more specific information). In the case of an HBsAg or anti-HBc reactive result, confirmation of the result may be preferable before a donor is rejected or the organs are discarded on the basis of a result obtained through this screening algorithm. The donor hospital, donor co-ordinator and OPO, as well as the laboratories performing investigations beyond the pathway shown here, should discuss all the options and risk-assess the situation based on an agreed protocol. For details of HBV infection in donors, see §8.4.2.6. In the case of an HBsAg+ result, exclude HDV infection.

8.3.2. Basic screening for infections in living organ donors

Basic screening should be performed at initial counselling for living organ donors, as well as at final counselling and/or before organ procurement, and results must be available before an organ is removed for transplantation. The repeat testing should be performed as close to the donation procedure as possible, the interval not to exceed 4 weeks because greater intervals have been associated with disease transmission [35]. Counselling of the donor and recipient should include the information that infections may

be acquired during the period from initial to final screening and up to the day of transplantation [20]. This requires education about avoiding infections like HIV, HCV, HBV and regionally endemic infections (e.g. tick-borne encephalitis), which may help to reduce risks. For further details see Chapter 13.

8.3.3. Basic screening for infections in deceased or living tissue and cell donors

Please refer to the *Guide to the quality and safety of tissues and cells for human application*.

8.3.4. Previous vaccinations of the donor

Vaccinations with live attenuated vaccines may result in transmission of a vaccine-derived pathogen to an immuno-suppressed recipient. This may give rise to a disseminated life-threatening disease. In contrast, inactivated vaccine or passive immunisation of the donor is unlikely to pose harm to the recipient, but may confound screening testing in paediatric donors.

Therefore, it is imperative to determine if the donor has received live vaccines during the previous 4 weeks. Live vaccines include: inhaled, attenuated influenza (not injectable, inactivated influenza), varicella–zoster (VZV), rotavirus (below 6 months of age), measles, mumps, rubella, bacillus Calmette–Guérin (BCG), smallpox, oral cholera (not injectable), oral polio (not injectable), yellow fever or oral *Salmonella typhi* (not injectable). In this case, an individual risk assessment of the immune status of all prospective recipients is mandatory.

If the donor has been vaccinated in the last 4 weeks pre-donation with live vaccines, a risk assessment should be carried out and the recipient should be monitored post-transplant because there is the risk of transmission of an acute infection by a live vaccine.

Live vaccines include vaccination against the following pathogens:
- Influenza (inhaled = live, injectable = inactivated)
- Varicella, including VZV
- Rotavirus
- Measles
- Mumps
- Rubella
- BCG
- Smallpox
- *Vibrio cholerae* (oral = live, injectable = inactivated)
- Yellow fever
- *Salmonella typhi* (oral = live, injectable = inactivated)
- Polio (oral = live; injectable = inactivated)

For some vaccines, the risk of transmission is limited to specific organs:
- Inhaled influenza vaccine: lung, face
- Rotavirus: intestine
- Cholera: intestine
- Salmonella: intestine

8.4. Viral infections

8.4.1. Basic screening for viral infections in organ donors

The basic screening for viral infections in deceased organ donors must include at least the serologic tests recommended in section 8.3.

8.4.2. Specific viral infections

8.4.2.1. *Chikungunya virus*

Chikungunya virus (also known as CHIKV; RNA-virus of the *Togaviridae* family) infection is imported from endemic areas; currently these correspond to tropical Africa, parts of Asia, Central and South America, islands in the Indian Ocean, Western and South Pacific and the Caribbean. Up-to-date information about affected areas needs to be checked, due to possible changes in epidemiology. Transmission occurs by bites of infected *Aedes* species mosquitoes (*aegypti* or *albopictus*), which are diurnal (day-active). If competent mosquito vectors are present, imported cases can trigger an outbreak of locally transmitted chikungunya infection, as in northern Italy in 2007. Since *Aedes albopictus* mosquitoes without infection have been detected all over temperate European regions, it is important to monitor whether they will become infected through movement of infected humans or through importation of infected mosquitoes by international transport. *Aedes aegypti* has recently been re-established in Madeira and around the Black Sea in southern Russia, Abkhazia and Georgia. In 2011, 55 cases of chikungunya fever were reported by 22 European Union (EU) and European Economic Area (EEA) countries [24].

Infection may manifest through fever, arthralgia or exanthema and rarely as meningoencephalitis, uveitis, retinitis, myocarditis, hepatitis, nephritis, haemorrhage, myelitis or Guillain–Barré syndrome.

Viraemia exists approximately 4 days to 3 weeks after the mosquito bite, during which time transmission by organs can occur. Detection of viraemia by NAT is possible.

Chikungunya infection in solid-organ transplant recipients has rarely been reported but clinical

disease does not appear to be more severe in transplant recipients [36-38]. Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks. Organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to perform a close monitoring of the recipients of organs from donors with documented infection in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for chikungunya virus should not be used without consulting a transplant infectious disease expert.

8.4.2.2. *Cytomegalovirus*

Between 20 % and 100 % of the adult population (increasing with age) in Europe are latently infected with *cytomegalovirus* (CMV: DNA virus, *Herpesviridae* family), with significant geographic variation. Following primary infection, most immunocompetent individuals remain asymptomatic. No contraindications exist for organ donation in the case of a donor with latent CMV infection [5].

De novo infection by a graft in naïve recipients, as well as reactivation of a latent infection in the recipient should be avoided by specific anti-viral prophylaxis or virological monitoring and pre-emptive therapy. Most CMV-active anti-viral agents are, at least partially, effective in preventing/treating other herpes viruses – including *Herpes simplex* virus (HSV) and VZV – but not all, e.g. letermovir. Recipient morbidity increases in the case of donor-seropositive and recipient-seronegative (D^+/R^-) combinations.

Organs can be accepted independently of the anti-CMV IgG status of the donor. Suitable prophylaxis or virological monitoring with pre-emptive treatment should be adopted in recipients, particularly in donor-positive/recipient-negative (D+/R–) cases.

8.4.2.3. *Dengue virus*

Dengue virus (DENV: RNA-virus, *Flaviviridae* family) is transmitted by mosquito bites of various *Aedes* species (*aegypti* or *albopictus*). Distribution of *Aedes aegypti* or *Aedes albopictus* without infection in the European region is described in section 8.4.2.1. It is important to monitor whether these *Aedes* spp. will become infected by blood meals on infected humans migrating from affected areas of infected mosquitoes by international transportation, in order to identify new risks.

Imported cases of dengue fever in travellers returning from endemic countries are frequently reported. Sporadic locally transmitted cases have been recorded recently in areas of France and Croatia where *Aedes albopictus* is present. In 2012-13, a dengue outbreak involving *Aedes aegypti* transmission was reported in Madeira [39].

Infection may be asymptomatic or may manifest as febrile disease, haemorrhagic fever or shock syndrome due to variable immunological response, endothelial failure and vasculitis. After 3-7 days of incubation, viraemia persists for up to 21 days with a risk of transmission through blood or organs. NAT or NS1-antigen-test can confirm viraemia [40].

Transmission of dengue via organ transplantation has rarely been reported [41-43]. Given the limited number of transmissions, biology of dengue transmission via this mode is unknown. Further data are needed to assess the effect of dengue virus on graft function and the effect of immuno-suppression on the presentation of dengue.

Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks. Organs from these donors might be used before the results of the tests are available. It is recommended to monitor recipients of organs from donors with documented dengue infection in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for dengue virus should not be used without consulting a transplant infectious disease expert.

8.4.2.4. *Epstein–Barr virus*

In Europe, more than 90 % of all adults are infected with Epstein–Barr virus (EBV: DNA virus, *Herpesviridae* family). After primary infection with or without disease, people may remain asymptomatic if not immuno-compromised.

EBV transmission to immunologically naïve transplant recipients increases the risk of post-transplant lympho-proliferative disorders (PTLD). This risk requires regular follow-up of all transplant recipients and consideration of specific therapies if viraemia or malignancy is identified.

In the case of EBV D^+/R^- (for instance, most paediatric transplant recipients), protocols for close monitoring of such recipients contribute to reducing the fatal complications of PTLD by earlier diagnosis. It should be noted that there is no prophylactic treatment which can prevent primary EBV infection. Still EBV-DNA monitoring and early treatment should be considered for all D^+/R^- recipients.

In case of suspected acute mononucleosis, EBV infection can be ruled out by an investigation of the

presence of EBV-DNA and EBV nuclear antigen in peripheral blood.

Organs can be accepted independently of the anti-EBV IgG status of the donor. Proper follow-up and/or surveillance for PTLD is required particularly in children and D+/R– cases.

8.4.2.5. *Hepatitis A virus*

Hepatitis A virus (HAV: RNA-virus, *Picornaviridae* family) infection is not a risk for transplantation unless in cases of acute infection in the donor. A case of donor-derived transmission through pancreas and intestinal transplantation has recently been described [44]; of note, the donor was retrospectively found to be viraemic with HAV and the paediatric recipient had very prolonged viraemia and faecal shedding, with diagnosis made due to transmission to two healthcare workers. Recovery from HAV infection or prophylactic vaccination status is indicated by anti-HAV-IgG reactivity. In 2012/2013, a HAV outbreak in EU member states, linked to frozen berries, was responsible for an increased number of cases [45].

More recently, since February 2016, growing numbers of confirmed hepatitis A cases infected with three distinct strains of sub-genotype IA virus have been reported in EU countries. Most cases are reported among adult men who have sex with men (MSM), with only nine women affected [46]. As of June 2017, at least 16 EU member states had reported approximately 1 434 cases infected with one of the three cluster strains. An additional 2 660 cases probably (or suspected to be) associated with this outbreak have been reported [47]. In the case of a donor belonging to the above risk population or with suspected acute infection, consulting a transplant infectious disease expert is suggested. Potential recipients should have been vaccinated against HAV also before being put on a waiting list [28].

Organs can be accepted independently of the anti-HAV IgG status of the donor, except in cases of acute HAV infection in the donor.

8.4.2.6. *Hepatitis B virus*

At least 10 % of the European population, with significant geographic variation, have been in contact with hepatitis B virus (HBV: DNA virus, *Hepadnaviridae* family) [3].

In the case of donors with HBV viraemia (indicated by an HBsAg-reactive result or detectable HBV DNA in the blood), HBV will be transmitted by any organ or tissue. Such infected donor organs may be used in special circumstances, when either the recipient receives HBV prophylaxis by anti-viral therapy in addition to hepatitis B hyperimmunoglobulin (HBIG), or when the recipient is already immune [48-51]. Lifelong monitoring for HBV is necessary. However, a breakthrough HBV infection may occur despite the prophylactic use of anti-virals and HBIG (especially in liver transplantation).

Individuals who have controlled and cleared their natural infection usually become HBsAg non-reactive, anti-HBc reactive and anti-HBs reactive (> 10 IU/L). Except for the liver, the use of organs from such individuals rarely results in transmission of HBV [48, 52-53]. However, grafts from such donors should preferably be used in recipients with current or previous HBV infection or successful vaccination. Lifelong monitoring is recommended [50]. Except for the liver, organs may also be used in HBV-naïve recipients after informed consent and when combined with special monitoring of the recipient, including HBV-NAT and HBsAg screening at least during the first year after transplantation [54]. In recipients of non-hepatic grafts HBV prophylaxis with anti-viral agents may be considered but it is most likely unnecessary.

In anti-HBc reactive donors (with non-reactive HBsAg and irrespective of anti-HBs titres), the hepatocytes remain latently infected with the virus – by viral covalently closed circular DNA (cccDNA) located in the nucleus and/or viral DNA integrated in the genome of the hepatocyte – and reactivation of latent infection can occur in the setting of immuno-suppression, especially in such liver-graft recipients. In such cases, in liver recipients without initial protection against HBV, lifelong treatment with HBV-specific anti-viral therapies (± HBIG) will be required [55]. Such infected liver grafts may also be transplanted into recipients that have their own immunological control of HBV infection through previous vaccination or infection. Most transplant centres use HBV-specific anti-viral agents in recipients with previous HBV infection and virus replication [55]. Any recipients of HBsAg-reactive or anti-HBc reactive donor livers should be monitored throughout life [55] for HBV reactivation or rare breakout due to mutation of HBV acquired from the donor via the graft. HBV vaccination does not always prevent this due to escape mutants [56]. The epidemiology of HBV mutants is not well studied in all European countries, but there must be awareness of the different HBV variants that can pose difficulties in HBsAg screening. Moreover, HBIG prophylaxis or previous immunity in the recipient will be ineffective against escape mutant strains.

Table 8.4. **Potential risks of organs used for transplantation from HBV-infected donors**

Hepatitis B tests	Conclusion	Liver: transmission risks to be considered and possible recipients to be selected for transplant	Non-hepatic organs: transmission risks to be considered and possible recipients to be selected for transplant
HBsAg+ Anti-HBc–	HBV viraemia (exceptional case)	HBV transmission occurs: transplantation of organs in vital cases, HBV-infected recipients or vaccinated recipients with HBV prophylaxis*	
HBsAg+ Anti-HBc+	HBV viraemia		
HBsAg– Anti-HBc+	Hepatocyte infected, usually no viraemia but low-level viraemia to be considered	HBV transmission occurs with liver transplant: transplantation of organs in HBV-infected recipients or vaccinated recipients with HBV prophylaxis*	Transmission unlikely: transplantation of organs in vaccinated or infected recipients May also be used in other recipients with (or without) HBV prophylaxis* and with lifelong monitoring

+ = reactive; – = non-reactive.

* HBV prophylaxis = anti-viral treatment (and HBIG) as well as lifelong monitoring (serology and NAT) required. In recipients with appropriate own immunological protection against HBV after vaccination, discontinuation of anti-viral treatment can be considered casewise, but evidence is lacking [54-55].

Note: only in donors with anti-HBc reactivity, anti-HBs might be determined for additional information in case of unreliable anti-HBc tests (unless HBV-NAT of blood and liver tissue is available).

The clinical relevance of isolated anti-HBc reactivity, without reactivity of any other HBV serological marker, is uncertain [57]. This is suggestive of prior, long past, HBV infection in the donor with undetectable anti-HBs and anti-HBe, false positive serological reactivity or passively acquired anti-HBc.

In the case of an anti-HBc reactive donor, only negative HBV-NAT from liver tissue would exclude HBV infection. This could be done as a complementary investigation after transplantation. Unfortunately such measurements are not yet standardised. Thus, further recommendations cannot be provided at this stage.

HBV infection with HBV pre-core mutants is frequent (> 60 %) in some areas of Europe [58]. These mutants lack the genetic information for the production of HBeAg. Therefore, determination of HBeAg or anti-HBe is of limited informative value. After transplantation of organs from donors with isolated anti-HBc reactivity, seroconversion to anti-HBc has been documented in recipients. Furthermore, HBV escape mutants occur (despite anti-HBs prophylactic treatment); these donors are usually HBsAg negative, anti-HBs and anti-HBc reactive and HBV DNA reactive [59-61].

It should be considered whether, depending on the prevalence of HBV mutants, testing algorithms might miss HBsAg reactivity in some populations – also depending on the country where infection occurred. Hence, laboratories should select appropriate testing platforms.

In the case of a donor with known HBV infection, it will be helpful to provide recipient centres with all known data, similar to the form suggested for HCV (see §8.4.2.7). Then, even a liver graft from a HBsAg-reactive donor may be used with proper safety precautions [62].

In every donor, HBsAg and anti-HBc must be determined. In any case of a reactive result for HBsAg or anti-HBc, follow the algorithm in Figure 8.4 in order to provide all information needed. Table 8.4 summarises the potential risks of organs used for transplantation from HBV-infected donors according to their screening results.

8.4.2.7. *Hepatitis C virus*

Hepatitis C virus (HCV: RNA-virus, *Flaviviridae* family) infection is transmitted by any donor with an HCV-NAT reactive test result, irrespective of antibody status [4]. In donors with anti-HCV reactive results and viraemia ruled out definitively by HCV-NAT this may not occur [33], with a remaining risk due to occult HCV infection or inappropriate sensitivity of the HCV-NAT test. Potentially, about 0.5-18.5 % of all donors are HCV-infected globally, with extensive variation according to geographic prevalence and occurrence of risk behaviours, e.g. intravenous drug abuse, intra-nasal cocaine sniffing, medical procedures [24, 63].

Although viral load may fluctuate in chronically HCV-infected individuals, it generally remains above 1 000 IU/mL. Still the detection level of the NAT test used should be < 15 IU/mL. The fluctuation of viral load can also be caused by acute reinfection of people who were able to clear previous acute HCV infection spontaneously [64].

Spontaneous clearance of viraemia can occur in up to 25 % of the people with acute HCV infection. Which factors enhance or restrict this chance of clearance is a matter of extensive research. Due to improvements in HCV treatment, more people will achieve a sustained virological response with no

viraemia detectable by HCV-NAT after therapy regardless of the HCV genotype. The issue of potential HCV-persistence in such patients with sustained virological response is controversial and unresolved, with no evidence of transmission in such circumstances.

Organs from donors with HCV viraemia should only be transplanted into recipients with HCV viraemia or recipients with an otherwise life-threatening condition, since HCV transmission is very likely, or into recipients receiving pre-emptive/post-exposure treatment within an approved study protocol until appropriate evidence is available. In the case of donors with anti-HCV reactive results and viraemia ruled out definitively by HCV-NAT due to sustained virological response after effective treatment or spontaneous clearance after acute infection, transmission is unlikely to occur [33]. Such grafts can be used in recipients willing to accept the risk after informed consent and compliance with follow-up by HCV-NAT screening and HCV-therapy if infection occurs.

Determination of the virus load or genotype does not help in decision-making about the risk of transmission. The prevalence of certain HCV genotypes varies across Europe. The only rationale for determining HCV genotypes in HCV-infected donors would be to avoid using organs with one genotype in recipients infected with a different genotype. Whatever the benefits of knowing the donor HCV genotype may be, logistics preclude its determination at the time of organ donation. In addition, mixed HCV infection has not been associated with increased mortality [65-66]. One study has reported that, in recipients where the donor viral strain predominated, HCV recurrence was less frequent than in cases where the recipient viral strain was predominant [67-68]. With the currently available pan-genotypic DAAs the issue of the genotype is less relevant [69]. It might be useful for better understanding of the prevalent genotype in the recipients, but it has no impact on the post-transplant treatment as pan-genotypic DAAs are recommended as therapy in patients after transplantation according to the guidelines of the European Association for the Study of the Liver [70] (see Appendix 12).

With the newly available treatment options, policies on the use of organs from HCV donors should be reconsidered [71]. Furthermore, all previous conclusions about the risks associated with transplantation of grafts procured from expanded-criteria donors into HCV-infected recipients must be revised since effective treatment of HCV infection is possible and this should not be withheld for such recipients. In addition, due to the current availability of pan-genotypic DAA, the issue of genotyping at the time of organ procurement becomes much less relevant.

NAT testing of recipients should be used post-transplant to detect donor-derived HCV transmission because most patients with donor-derived HCV fail to develop serologic evidence of infection despite persistent high-level viral replication. Testing should be done optimally within the first month post-transplant to allow early initiation of DAA.

The new DAAs against HCV have provided an opportunity for reassessment of organ transplantation from HCV-positive donors to HCV-negative recipients. In fact, clinical trials in kidney and thoracic organ transplantation have just commenced in the United States (ClinicalTrials.gov Identifier: NCT02781649 and NCT03086044) to assess the safety of this approach. In addition, a few anecdotal reports have been recently published [72-74]. Current guidelines recommend that such HCV D^+/R^- transplants take place in a research setting until all of the chal-

Table 8.5. **Potential risks of organs used for transplantation from HCV-infected donors**

Hepatitis C tests	Conclusion	Liver: transmission risks to be considered and possible recipients to be selected for transplant	Non-hepatic organs: transmission risks to be considered and possible recipients to be selected for transplant
Anti-HCV+ HCV-NAT not available	HCV viraemia cannot be ruled out*	HCV transmission occurs by the graft: vital cases or viraemic recipients with mandatory HCV-prophylaxis/pre-emptive treatment, as well as lifelong monitoring by serology and NAT required. In HCV-naïve recipients, known use of grafts from HCV-viraemic donors should currently only be done in approved study protocol and/or with informed consent in dire recipient conditions.	
Anti-HCV+ HCV-NAT+	HCV viraemia		
Anti-HCV– HCV-NAT+			
Anti-HCV+ HCV-NAT–	HCV viraemia unlikely*	HCV transmission may not occur; transplantation after informed consent of recipient in study protocol possible for D+/R–. In D+/R+ no restrictions.	

+ = reactive; – = non-reactive.

* HCV viraemia may be below the detection threshold of HCV-NAT. This causes a non-reactive result. Therefore appropriate data should be collected (about the course of HCV treatment or evidence for spontaneous clearance).

Note: prospective HCV-NAT is only recommended for donors with an elevated risk of HCV infection or anti-HCV positive donors.

lenges associated with this type of transplant are understood [31].

The available drugs for interferon-free anti-viral treatment should be applied according to the established therapeutic regimens, taking into account the genotype of the virus and previous treatments as well as current recipient's hepatic and renal function [69-70] (see Appendix 12 for additional information). When using grafts from HCV-viraemic donors, a pan-genotypic regime will have to be applied within the pre-emptive therapy of *de novo* HCV-exposure. In end-stage renal disease patients, impaired renal function (e.g. eGFR < 30/mL/min/1.73m^2) might raise the question whether to treat the recipient before or after transplantation of allografts from HCV-viraemic donors in case of assumed short waiting times. Since waiting times are unpredictable (e.g. due to HLA immunisation) and DAAs will be available for use in patients with impaired renal function, preference can be given to early eradication of HCV to avoid further complications.

In every donor, anti-HCV must be determined:

1. In any case of a reactive result, follow the algorithm in Figure 8.3.
2. In the case of an anti-HCV reactive result, HCV-NAT should be performed to assess whether viraemia clearance exists or not (spontaneous or due to sustained virological response after therapy).

Table 8.5 summarises the potential risks of organs used for transplantation from HCV-infected donors according to their screening results.

For the appropriate selection of transplant recipients, it is helpful to obtain the following information in a donor with a HCV infection:

a. Has there been previous HCV infection?
b. Was any HCV treatment given before?
   i. If yes: what kind of medication was used? What kind of virologic response was achieved or did resistance develop? How was the effectiveness of treatment monitored and what were the results of NAT (qualitative)? Was the genotype determined? Was the therapy complied with throughout its duration?
   ii. If no: what was the reason for not treating the infection?
c. Is there any information about the source of infection?

8.4.2.8. *Hepatitis D virus*

Hepatitis D virus (HDV: RNA-virus, the only agent of the genus *Deltaviridae*) infection, as with HBV infection, is mostly an issue for countries with a high prevalence of HDV.

Defective HDV requires the HBsAg for replication. Donor-transmitted HDV infections must be avoided by adequate screening of HBsAg-reactive donors because therapeutic options do not currently exist [75-76].

Organs from donors with HDV infection are usually not accepted because we still lack effective treatment for HDV. Organs from HBsAg+ with HDV infection can be used only in HBsAg+, HDV-RNA+ recipients.

8.4.2.9. *Hepatitis E virus*

Currently, the impact of Hepatitis E virus (HEV: RNA-virus, *Hepeviridae* family) infection in solid-organ transplant recipients cannot be fully assessed because of the variable endemic occurrence in European organ or blood donor populations.

At least four genotypes cause infections in humans (HEV-1 to 4). HEV-1 and HEV-2 infect only humans, transmission is mainly oral-faecal, occurring in tropical endemic areas and causing acute, self-limited illness apart from infections in pregnancy when morbidity is significantly increased; materno-foetal transmission has been described and no chronic infection has been reported with these types. On the other hand, HEV-3 and HEV-4 have animal reservoirs and are responsible for autochthonous cases in industrialised countries; the main source of zoonotic HEV transmission is the consumption of raw or undercooked, infected pork and game meat or direct contact with infected animals; transmission via blood components has also been documented. Genotype 3 is prevalent in some EU member states, where it causes mostly asymptomatic and sometimes symptomatic, self-limited infection. HEV-3 is known to cause persistent infection in immuno-compromised individuals, and in particular, recipients of solid organs where it appears to be linked to progression to cirrhosis [77].

The pathogenesis of hepatitis E is still poorly understood. Negative strands of HEV RNA, indicating virus replication, have been detected in the small intestine, lymph nodes, colon and liver of pigs, indicating extra-hepatic HEV replication [78]. HEV then replicates in the cytoplasm of hepatocytes and is released into both blood and bile. The liver damage induced by HEV infection may be immune-mediated by cytotoxic T-cells and natural killer cells since HEV is not cytopathic. HEV first infects the intestinal tract (with excretion via faeces) and then the blood and the liver (with excretion via bile). After an immunological response, HEV is cleared from the blood and, after a maximum of 120 days, from the intestine. Chronic HEV infection (by HEV-3) is usually observed in patients with profound immuno-suppression.

HEV infection has been observed in liver, lung, kidney, haematopoietic stem cell, heart and simultaneous kidney–pancreas recipients. Reactivation of HEV infection has been reported without association to the donor [79]. As of June 2017, three cases of transmission have been reported: one case through liver transplant [80] and two through kidneys from a common donor; the kidney recipients were managed by modulation of immuno-suppression and Ribavirin [81]. When management of infection is required, cautious modulation of immuno-suppression may be considered; oral Ribavirin is efficient in controlling HEV replication. Ribavirin is the drug of choice and seems to be effective in immuno-suppressed recipients [82-83].

In cases of acute infection in the donor with viraemia, organs should not be transplanted without proper risk–benefit assessment and application of pre-emptive therapy protocol. After recovery from HEV infection, organs can be transplanted. In HEV-endemic countries, retrospective screening of donors by HEV-NAT should be considered for further management of recipients.

Organs can be accepted independently of the anti-HEV-IgG status of the donor, except in cases of acute HEV infection in the donor with known viraemia where consultation of a transplant infectious disease expert is recommended.
In HEV-endemic countries, retrospective screening of donors by HEV-NAT should be considered. In cases of HEV-viraemic donors, the treatment option with ribavirin should be taken into consideration. However, some recipients (especially kidney-transplanted patients) may have viral rebounds even after an aviraemic interval. In such cases, continuous monitoring of HEV RNA is recommended.

8.4.2.10. *Herpes viruses (Epstein–Barr virus and cytomegalovirus excluded)*

No contraindication to organ donation exists for donors presenting with only latent herpes-family viral infections [5]. No specific donor screening is required [5]. Some members of this family of viruses have oncogenic potential. However, it is important to be aware of fatal *de novo* infections in naïve recipients by grafts recovered from latently infected donors, as well as reactivation in latently infected recipients.

Some transplant centres perform retrospective, additional donor tests for latent HSV or VZV in cases of sero-negative recipients (mostly children) in order to decide on specific anti-viral prophylaxis or treatments and follow-up. However, no evidence exists to suggest this, based on a few case reports [84-87], while it is recommended not to overlook symptomatic infection.

Some cross-effectiveness exists between some anti-viral prophylaxis for CMV, HSV and VZV.

Donors with successfully treated herpes encephalitis infection can be used with some precautions (e.g. avoid D^+/R^- combination, for which see section 8.9).

Organs can be accepted from donors with latent α-herpes-family viral infections, but not in the case of acute herpes viraemia in the donor without effective anti-viral treatment.

8.4.2.10.1. Kaposi sarcoma associated herpes virus or human herpes virus-8

Kaposi sarcoma associated herpes virus (KSHV) is a double-stranded DNA herpes virus belonging to the gamma *Herpesviridae* subfamily; the other human herpes virus in this group is the Epstein–Barr virus. Human herpes virus 8 (HHV8) has been associated with the development of three neoplastic diseases: Kaposi sarcoma, primary effusion lymphoma and multicentric Castleman disease. As is the case with all herpes viruses, the KSHV life-cycle includes both latent and lytic phases.

Unlike most herpes viruses, human infection with KSHV is not ubiquitous. Sero-prevalence is estimated to be between 0 % and 5 % in North America, northern Europe and Asia; between 5 % and 20 % in the Mediterranean and Middle East; and > 50 % in some parts of Africa.

Transmission of KSHV from organ donor to recipient has been documented through assessment of sero-status before and after transplant and by molecular epidemiologic studies [88-98]. In immuno-compromised persons, fever, splenomegaly, lymphoid hyperplasia, pancytopaenia and occasionally rapid-onset Kaposi sarcoma have all been described in association with apparent primary KSHV infection [93, 95-98]. However, in immuno-compromised transplant recipients, KSHV is more often associated with neoplastic diseases. Early identification of primary or reactivated infection offers the possibility of careful alteration of immuno-suppression, where appropriate, or pre-emptive anti-viral treatment; this is associated with more favourable outcomes when compared to late diagnosis of symptomatic disease.

Various assay formats have been developed to detect antibodies against latent and lytic proteins: immunofluorescence, Western blot and ELISAs. Some of these assays have been used for sero-epidemiologic studies, but there are limitations to their usefulness in clinical daily practice, such as the lack of standardised methodologies and international controls. Moreover, the sensitivity of serological assays is variable and ranges from approximately 80 % to greater than 90 %. The optimal serologic assay technique cannot be determined at present, with few commer-

cially available tests and several assays developed in house. It has been suggested that a combination of whole virion ELISA and lytic immunofluorescence assay may be the most sensitive and specific serological method for diagnosing KSHV infection.

HHV8 serology is generally unavailable prior to deceased donor organ transplantation, and a donor screening policy may be adopted almost exclusively for living donors. Many studies have suggested the potential utility of the screening of KSHV antibodies among organ donors and recipients. These studies have argued in favour of KSHV screening, sometimes even in low-KSHV infection-prevalence countries. Organs should not be excluded but information on the KSHV status provides the opportunity to monitor, clinically and biologically, patients at risk for KSHV-related disease development. Therefore, targeted antibody screening according to risk could be done in the days following transplantation with the results transmitted retrospectively to physicians.

Universal screening of donors for KSHV is generally not necessary. However, since donor-derived primary KSHV infection may be associated with severe disease, screening of donors for KSHV anti-lytic and anti-latent antibodies is recommended for donors and recipients coming from areas with high prevalence. In cases of D+/R– mismatch, close monitoring of the recipient for KSHV-DNA in blood is recommended in order to identify infection early.

8.4.2.11. *Human immunodeficiency virus*

Organs from donors with HIV (RNA-virus, *Retroviridae* family) infections have so far been utilised intentionally only in a limited number of cases. This includes the experimental protocol for HIV-infected recipients in South Africa. The protocol requires strict adherence of the recipient to highly-active anti-retroviral treatment [99]. More recently, liver and kidney transplantation from HIV-positive donor to HIV-positive recipients has been reported in Switzerland [101], UK [102], USA [103] and Canada [104]. Further HIV-infected donors have been inadvertently used after false negative testing, resulting in unintended transmission into previously uninfected recipients [105-106].

With the aim of generating evidence-based, research-driven data to put forth criteria that would facilitate the feasibility of HIV-to-HIV transplantation in the United States, the US Congress approved the HIV Organ Policy Equity Act (HOPE) Act (42 U.S.C. §274f-5b) in November 2013, mandating a revision to the 1988 National Organ Transplant Act (NOTA) prohibition of transplanting organs from HIV-positive donors. The US Department of Health and Human Services was charged with developing guidelines for clinical research involving HIV-positive organs and, on 25 November 2015, the final HOPE Act safeguards and research criteria were published [107-108].

Donors who present with evidence of HIV-viraemia or 'HIV-related diseases' should never be used. However, if HIV-RNA is undetectable (under anti-retroviral treatment) and there are no relevant co-infections, organs from HIV-infected donors may be used for HIV-infected recipients within an experimental context with appropriate results [100]. The specifically designed protocol has to be approved and permitted by local regulation and national law. However, anti-HIV-1/2 reactive status in potential donors is still regarded as a contraindication for organ donation in most European countries.

Organ transplantation using organ from HIV-positive donors poses further challenges. In addition to the risk of transmitting opportunistic infections or malignancies, there is the potential risk of HIV superinfection in the recipient, i.e. transmission of HIV strain with resistance to antiretrovirals that may preclude HIV suppression after transplantation. However, in the UK case, despite the transmission of a different strain, responsible for an HIV viral load rebound on day 2 after transplantation, resuppression of the recipient's viral load occurred within the first seven postoperative weeks without a change in the highly-active anti-retroviral treatment (cART regimen). His viral load has subsequently remained undetectable throughout the first five years after transplantation. Of note is that in some populations the target organs for HIV infection are the kidneys (e.g. HIV-nephropathy in South Africa). Nonetheless, transplantation of HIV-infected patients receiving highly-active anti-retroviral treatment before and after transplantation has demonstrated excellent recipient survival when they were carefully selected and monitored by experts, with particular emphasis on the complex drug interactions between the anti-HIV and anti-rejection medications [109-110].

Although transplantation from HIV-positive to HIV-positive is promising, it remains unclear whether or not patients may be inadvertently harmed. Accordingly, as experience increases, ethical practice will demand measures to ensure that risks are identified and minimised [111].

The serologic HIV test should detect antibodies against HIV-1 and HIV-2, as well as group O of HIV-1. Fourth-generation assays include the test for the p24 Antigen of HIV-1, which acts as a marker of early infection during seroconversion. For increased-risk individuals, NAT is recommended prospectively

(see sections 8.2 and 8.3). Although NAT currently focuses on HIV-1, NAT screening should be extended to HIV-2 for specific populations in HIV-2 endemic areas or European sub-populations with immigrants coming from HIV-2 endemic areas.

Physicians need to be aware of the diagnostic challenges posed by the growing use of HIV post-exposure prophylaxis following sexual exposure, whereby serological responses are modified and viral load measurements are affected. This may need to be considered and taken into account when obtaining donor history, as and when appropriate with the known limitations of obtaining data precisely.

Organs from anti-HIV-reactive donors should not be used for HIV-naïve recipients. Such organs may be offered, under careful surveillance, to selected HIV recipients under a specifically designed protocol.

8.4.2.12. *Human T-lymphotrophic virus*

Retrovirus infection by human T-lymphotrophic virus-1 (HTLV-1: RNA-virus, *Retroviridae* family) results in insertion of the viral genome into T-lymphocytes. HTLV-1 is transmitted through similar routes to those for HIV. HTLV-1-associated T-cell leukaemia develops in 2-5 % of cases, usually 20-30 years after infection. HTLV-1 may also cause spastic tropical paraparesis (also called HTLV-associated myelopathy or HAM) in 0.25-4 % of cases, with onset of disease following soon after the initial infection. No proven treatment for HTLV-1 infection exists, although chemotherapy may treat associated leukaemia [18].

Human T-lymphotrophic virus-2 (HTLV-2) has not been definitively associated with human disease [18].

In Spain, the general prevalence of HTLV-1/2 was reported to be below 1 % and, in blood donors, below 0.1 %. In an unpublished series from Germany in the early 1990s, HTLV prevalence was essentially 0 % in organ donors. In first-time blood donors in Europe it is only in Romania that a higher prevalence of 5.3/10 000 exists [112]. For the Middle East region (Asia) the same must be assumed. However, transmission of HTLV by blood or organs has been reported in a few cases globally.

Unfortunately, current screening methods cannot differentiate between HTLV-1 and HTLV-2 infections. Furthermore, many screening methods have a high rate of false positive results and confirmatory tests are usually only available through reference laboratories [18].

HTLV screening can only be recommended for endemic areas and in endemic populations, [113] since a risk of infection may exist [114]. The recently reported cases in the UK, of two recipients of kidneys from a common HTLV-1-infected donor, demonstrated infection in both individuals; incidentally, no risk factors were identified for the donor [115]. A group in Japan reported 100 % transmission rate in D^+/R^- living-donor kidney transplant (16/16), with 62 % incidence of HAM [116]. Because of further limited follow-up on recipients of HTLV-infected organs, no conclusive recommendations are possible [18]. In donor populations where HTLV is endemic – the Caribbean, most parts of South America, Africa, Asia (particularly the southern islands of Japan and Oceania, and also Iran) and Romania, as well as some higher-prevalence spots in some Chinese provinces, native populations in north Australia and some US states [112] – the risk assessment for donor-derived HTLV-infection should balance the following considerations: the likelihood of true HTLV-1 infection; the low likelihood of subsequent disease in recipients of such organs; the general shortage of organs; and the specific needs and wishes of patients.

In 2010, the US ceased mandatory testing for HTLV-1/2 [18]. Japanese experts suggest that HTLV-infected organs can be transplanted into previously infected HTLV recipients [117]. In Europe, HTLV-1/2 screening is mandatory only in France – despite a mere 0.0056 % sero-prevalence in new French blood donors [118] – and it is advised in Portugal. In Spain, it is only recommended for donors at higher risk for HTLV-1 infection (i.e. immigrants or sexual partners of immigrants from endemic areas, children at risk of maternal vertical transmission) [112-113, 119]. An ECDC *ad hoc* expert panel recently suggested that if HTLV-1/2 screening is implemented in a member state or its regions for blood donations (e.g. due to high prevalence of HTLV-1/2 infections, exceeding 1 % in the general population or 0.01 % in first-time blood donors), it should also be implemented for tissue and cell donations [119].

Any initial reactive test result must be confirmed as a true positive for HTLV-1 before further conclusions can be drawn [119].

Anti-HTLV-1/2 screening should be attempted in donors coming from geographic regions with a high prevalence of HTLV-1/2 infections. D+/R– combinations are usually not accepted.

Caveat: a high rate of false positives has been documented with this test and should not result in organ wastage.

8.4.2.13. *Human polyoma viruses*

The *Polyomaviridae* are a family of DNA viruses that infect a variety of hosts. BK polyomavirus (BKPyV) and JC polyomavirus (JCPyV) are human polyomaviruses that cause severe disease in

immunocompromised patients. In case of JCPyV and BKPyV, primary asymptomatic infection occurs early in life and persists as latent infection in the kidneys with occasional virus shedding in urine. When immunity is decreased, these viruses can reactivate, posing a threat to solid-organ transplant recipients.

BKV-associated nephropathy is a leading cause of renal allograft dysfunction and loss after kidney transplant [120-121]. However, it is still unclear whether BKPyV replication is a result of reactivation in the recipient's native kidneys or whether the virus originates from the allograft [123]. Though BKV sero-prevalence is too high to exclude seropositive donors from kidney donation, the potential high-risk constellation (BKV shedding in donors) should be analysed for clinical outcome in comparison with other risk factors for reduced transplant survival in future. Currently this issue is under investigation. The issue of progressive multifocal leukoencephalopathy is addressed in section 8.9.

8.4.2.14. *West Nile virus*

West Nile virus (WNV: RNA-virus) is a member of the *flavivirus* genus and belongs to the Japanese encephalitis antigenic complex of the family *Flaviviridae*, which includes Japanese encephalitis virus and Usutu virus. It is one example of an arbovirus causing sporadic cases and seasonal outbreaks of neuro-invasive disease (e.g. meningitis, encephalitis, acute flaccid paralysis), combined with febrile illness. Infection is asymptomatic in up to 80 % of cases.

WNV is transmitted through bites of infected mosquitoes (*Culex* sp.), so the risk of infection transmission correlates with the season with the highest probability of mosquito bites, i.e. whole year in southern Europe or late summer/early autumn in the rest of Europe. WNV is becoming established in some south-eastern EU member states, with over 200 cases reported in 2012 from Greece, Hungary, Italy and Romania, and more than 600 from countries bordering the EU [24]. WNV has been a recurrent seasonal problem in some areas of Italy [124-125]. Whenever locally increased rates of WNV infections are detected, either in humans or animals, it is appropriate to consider screening since many cases of transmission occur from donors without febrile neuro-invasive illness.

Viraemia may be detected by NAT, and fatal transmission to organ recipients has been described when WNV NAT-reactive and NAT-negative donors have been utilised [125-128]. Transmissible WNV may be present in potential donors in the absence of positive serology or NAT [127]. There is some evidence that WNV viral nucleic acids and infectious virus remain associated with blood cells after the clearance of virus from plasma [129]. Viraemia may persist after incubation for 2-4 weeks or exceptionally for a few months [130-132]. Detection of antibodies confirms an antecedent infection, but does not clearly identify the risk of transmission through transplantation. Furthermore, positive serology may result from cross-reacting antibodies from other prior flavivirus infections in the donor.

Some data are available on the urinary excretion of WNV following neuro-invasive disease but this issue is completely unexplored in the case of asymptomatic or mild infections. The kidney is a well-established site of active WNV replication in animals [133]. WNV shedding in urine has been reported in humans, not only early post-infection [134], but even years later [135]. Because of longer shedding and higher viral load, urine samples may be more appropriate than blood for WNV testing in blood and organ donors [136]. It was thought that urine might become a specimen of choice to identify WNV in asymptomatic carriers. However an unpublished study of the US-CDC failed to confirm these results [137].

As with other closely-related flaviviruses, serological cross-reactivity within the JE complex is known to occur and results must always be interpreted with caution. Genetic similarity has also led to cross-reactivity in NAT assays, as evidenced by the case reported from Germany in 2016 [138].

Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks (e.g. using NAT; see §8.3 above). Organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to perform monitoring of recipients of organs from donors with documented infection in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for WNV should not be used without consulting a transplant infectious disease expert.

8.4.2.15. *Zika virus*

The Zika virus (RNA-virus, *Flaviviridae* family) is transmitted mostly by *Aedes aegypti* mosquitoes. Mild illness (e.g. fever, rash, arthralgia or conjunctivitis) with more than 80 % asymptomatic infections may be observed after an incubation period of up to a week with symptoms resolving after one week where viraemia may be detected by NAT. In the genito-urinary tract the virus may persist for a longer period.

It is now accepted that ZKV infection during pregnancy is linked to foetal infection and congenital Zika Syndrome. ZKV infection is also associated with other neurological presentations such as Guillain–Barré syndrome (GBS). The whole spectrum of disease caused by ZKV remains to be elucidated, but haematological abnormalities such as thrombocytopaenia seem to be one of the findings.

Outbreaks of primary infection are possible in regions with the presence of competent vectors, permissive climate and intense movement of people. This may explain the emerging endemic character of the Zika virus infection (even into temperate regions globally).

Few data exist regarding the clinical characteristics of ZIKV infection in immuno-compromised hosts. Laboratory screening protocols for transplantation to differentiate ZIKV infections from other endemic viral diseases and for the detection of possible donor-derived infection have not been stated. The diagnosis of ZIKV infection remains a challenge, fuelled by the lack of standardised commercially available diagnostic tests and validated reference diagnostic laboratories, as well as the limited duration of ZIKV viraemia [139]. *Flavivirus* serology is complex, as a high degree of cross-reactivity is seen among closely-related viruses; in the case of ZIKV, separation between ZIKV and dengue virus immune responses is very difficult.

The first case series of ZIKV infection in solid-organ recipients, with a description of clinical and laboratory features and therapeutic management, has been recently published [140]. This report did not demonstrate more severe disease in transplant recipients. A case of transfusion-transmitted Zika virus infection in a liver transplant recipient was published in 2016 with no indication of a more severe course of infection [141]. The risk of transmission by solid-organ transplantation at the date of publication of this Guide is currently unknown, but it is theoretically possible.

Since *Aedes* species as vector may transmit other viruses too, e.g. dengue or chikungunya viruses, considerations about Zika virus overlap with concepts of how to minimise the risks associated with possible infection by these viruses. In cases of travel to or living in Zika-endemic areas 28 days prior to donation in symptomatic donors, targeted NAT screening may be helpful to identify the correct pathogen. In asymptomatic deceased donors, the risk of donor-derived infection should be balanced with the benefits of transplant in each potential recipient. In living donation during pre-donation counselling, the risks can be discussed with the donor and recipient for proper timing of the procedure.

Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks. Organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to perform monitoring of recipients of organs from donors with documented infection according to updated protocols in order to identify future risks due to this emerging pathogen.

Organs from donors viraemic for Zika virus should not be used without consulting a transplant infectious disease expert.

8.4.2.16. *Yellow fever virus*

Yellow fever is an African mosquito-borne infection of primates. It is caused by a virus of the *Flavivirus* genus of the *Flaviviridae* family. In its natural habitat, it is transmitted between monkeys by forest-dwelling primatophilic *Aedes* mosquitoes. The virus and its vector (*Aedes aegypti*) were introduced to the Americas, where it is also enzootic in forest habitat, with the slave trade. Sylvatic infection of humans occurs when they enter the forest to hunt, gather food, harvest timber and so on. Forest-infected persons can initiate human-to-human transmission if suitable peridomestic vectors are present in towns and villages. In the urban environment, *Ae. (Stegomyia) aegypti* (Linn.), a forest species that has adopted the human domestic environment, is a highly effective vector for yellow fever virus. This mosquito is also the principal urban vector of dengue and chikungunya viruses.

Yellow fever is distributed in west, central and east Africa and in South America, from Panama to the northern part of Argentina. It has never been detected in Asia. Catastrophic epidemics, with tens of thousands of deaths, have been recorded in rural Africa. The vector *Aedes aegypti* was once endemic in Europe, and responsible for large epidemics of yellow fever and dengue. The reason for its disappearance after the Second World War has never been explained. It is still present in the United States and has been recorded in 21 states. It is conceivable that the vector could become re-established and widespread in Europe, as has happened in recent years with another putative vector, *Ae. albopictus*.

There are no specific criteria for the deferral of a prospective donor with a history of yellow fever. Therefore, it is suggested that the same general rec-

ommendation, applied in cases of non-specific acute viral illnesses, be applied in these cases: donors must have recovered, be afebrile and asymptomatic on the day of donation and may donate 14 days after full recovery. Deferral of living donors returning from areas affected by malaria will be sufficient to prevent yellow fever infectious donations: precautionary deferral is suggested for 28 days of non-vaccinated living donors returning from an area affected by yellow fever but non-endemic for malaria. In deceased donation, a case-by-case decision after consultation of a transplant infectious disease expert is required.

If an organ donor has received yellow fever vaccine during the four weeks before donation, an individual risk assessment of the immune status of all prospective recipients is mandatory. Yellow fever vaccination is contraindicated for immunocompromised patients after solid-organ and haematopoietic stem-cell transplantation because it is a live attenuated preparation. Potential transplant patients living in countries endemic for yellow fever or planning travel to endemic countries in the future should be immunised before transplantation [142].

8.4.2.17. *Other viruses*

Donor-derived infections caused by rabies [1, 3] and lymphocytic choriomeningitis virus (LCMV, RNA-virus) [1, 3] have been reported. These rare infections cause life-threatening or fatal complications in recipients, without any possibility of curative treatment. Typical childhood infections may still occur in adulthood and can be transmitted through organ donation. Transmission of Parvovirus B-19 infection has been documented through bone marrow, blood and organ donation.

In many cases, no appropriate tests are available for screening. Some specialised laboratories can provide useful investigations, but only after a potential virus has been identified. The risk can only be assessed by careful donor evaluation, including the careful examination of travel and social history. Special attention must be paid to any unexplained behavioural or disease patterns (e.g. recent mental changes, unexplained fever, myalgia). This may be indicative of a rare or endemic infection restricted to a specific geographic area or population. In these cases, an awareness of unusual or rare infections is more important than the introduction of further screening assays without any benefits for recipients.

Please refer to section 8.10.6 on additional infectious diseases that can be transmitted by solid-organ transplantation.

The risks are too low to justify uniform testing for rare or exceptional viral diseases. On the basis of information about the donor's recent behavioural/disease patterns and the present endemic situation in relevant regions, as well as the possibility of recent exposure, targeted testing and individual exclusion of donors should be considered.

Donors with encephalitis of unknown cause – especially when febrile – represent an exceptionally high risk of disease transmission and should be excluded until the cause of encephalitis has been identified for sure (e.g. see section 8.9).

8.4.2.18. *Handling of acute emerging new viruses: influenza and Ebola*

In 2009, pandemic A/H1N1-influenza virus infection occurred. This required a rapid action plan for an approach to potential organ donors possibly infected with the virus. Firstly, all available information was collected. Secondly, a guideline was issued. This initially occurred at a national level. Without proper testing methods, it was difficult to determine with enough sensitivity and specificity whether donors were not viraemic as in any case of influenza, and if a target organ was infected (e.g. lung or intestine). Therefore, it was assumed that, in the case of flu-like symptoms, this condition might have existed. Persons in contact with symptomatic people were considered at risk. Clinical symptoms guided the use of organs, as well as prophylactic anti-viral treatment, in donors and recipients, with oseltamivir (depending on resistance patterns).

When reliable screening methods became available, an appropriate diagnostic pathway was developed, which was still limited by the capacity for further investigations. Ultimately, donor inclusion or exclusion had to be done according to the newly developed pathway [11-12]. The next influenza virus pandemic may require new or adapted pathways. Such pandemic influenza infections will have to be distinguished from seasonal influenza.

For seasonal influenza in Europe, viraemia is unlikely. Therefore organs from donors with seasonal influenza can be used, with the exception of lungs and intestine.

For non-novel viruses (i.e. all RNA-respiratory viruses currently circulating) in immuno-competent patients, no appreciable risk of transmission exists via the blood compartment. Respiratory viruses are only a reason for excluding lungs for transplantation. Screening of donors for respiratory viruses is only recommended if there is clinical concern.

For novel viruses, i.e. in the setting of the next pandemic influenza, organ donation should be excluded until information is available on the tissues where the virus replicates and on the prevalence of extra-pulmonary dissemination.

In 2014 the Ebola virus emerged as a pathogen which has become endemic in some regions of Africa, raising concerns for the healthcare systems in other

continents. Again, proper surveillance and obtaining of appropriate information were the key issues for avoiding infection spread as well as the safety precautions of hygiene and deferral intervals including the time of incubation in persons at risk of acquired infection [143-144]. The minimum recommendation is to defer donors at risk due to exposure in the countries where Ebola is endemic, or related to other contacts, for two incubation periods (21-25 days doubled to 60 days). Donors who recover from Ebola virus infection should be deferred for one year due to lack of proper evidence on viral persistence in the body.

Meanwhile the Middle East respiratory symptom coronavirus (MERS-CoV) is on the watch as another pathogen expanding the list of risk factors [145].

8.5. Bacterial infections

8.5.1. Acute infections

In accordance with standard good clinical practice, intensive care units (ICU) monitor patients – regardless of their being a potential organ donor or not – for bacterial infections, with special attention to multidrug-resistant (MDR) micro-organisms (see §8.5.5) [146-148]. Before administering antibiotics, a culture or smear should be taken from the site of infection or target area for identification of the pathogen and a suitably effective antibiotic agent should be validated. Antibiotic treatment should be based on determination of the pathogen/subtype and resistance pattern. Appropriate follow-up cultures should be obtained to demonstrate that the infection is under control: urine-, tracheal- and blood-cultures should be taken [22] even if final results may not be available until after transplantation of an organ. In cases of an assumed, uncertain infection, microbiological work-up of central venous access lines, etc. may be helpful. The OPO should have clear policies and procedures for following up results of any outstanding test made prior to procurement and should ensure that, when available, results are efficiently communicated to all recipient centres.

Some transplant centres routinely take smears from the abdomen or thoracic cavity or from bronchial-alveolar lavage (BAL) during organ recovery, as well as from the organ preservation solution before transplantation [149]. Investigations should cover bacteria and fungi, as well as analysis of resistance patterns.

Most positive bacterial cultures or microbiologic assays lead to a diagnosis [3, 51]. However, active infection has to be differentiated from colonisation, which may not require treatment, but could influence prophylactic antibiotic selection for the recipient. Knowledge of the local, epidemiologic background (at hospital level) helps to evaluate risks, to select appropriate antibiotics and to detect shifts in nosocomial flora and resistance patterns. The use of prophylactic antibiotics, without apparent infection or specific indication, is not recommended. If bacterial infection is detected, therapy must be initiated as soon as possible. Therapy should be continued until inflammation parameters are indicative of remission or until serial cultures confirm clearance of infection. However, it must be remembered that, in brain-dead donors, inflammation parameters may rise exponentially in relation to the event of terminal brain-stem coning.

Donors with bacteraemia may be used if appropriate antibiotics have been utilised for at least 48 h (some countries consider 24 h as sufficient) and if recovery from signs and symptoms of infection is demonstrated. Nevertheless, antibiotic treatment for a longer period may be necessary (e.g. for endocarditis). Treatment of the recipient for an appropriate duration post-transplant is strongly recommended, with careful attention to evidence of embolic infection. Organs from bacteriemic donors should be accepted on a case-by-case basis, in direct consultation with the transplantation team for appropriate post-transplant care and monitoring. The focus (organ) of such infections should not be transplanted. On the other hand, bacterial growth from blood cultures may be contamination and not true infection (e.g. coagulase-negative *Staphylococcus*).

Localised infections without systemic spread do not contraindicate donation [6], but antibiotic treatment should be given for more than 24-48 h or until full recovery from signs and symptoms of infection has taken place. Then, use of a previously infected organ may be considered [6], but this should be confirmed by sterile cultures. Continuation of antibiotic treatment in the recipient should be considered.

Colonisation by MDR bacteria is not a contraindication for organ procurement as long as the colonised tissue remains sealed from the rest of the body, i.e. trachea or external wounds. In some cases (e.g. *Pseudomonas* or *Acinetobacter*), infection should not be confused with colonisation. Such colonised tissues and their adjacent organs may not be used for transplantation due to the risk of donor-derived pathogen transmission. Transmission of MDR bacteria has been demonstrated even when appropriate therapy was given to the donor and continued for a 2-week

course in the recipients. As such, recipients of organs from donors with confirmed MDR organism infections require special attention with adequate therapy and close post-therapy monitoring.

When *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *paraphrophilus*), *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella klingae*, *Streptococcus viridans* or *Staphylococcus aureus* (MRSA) are detected in blood cultures, then endocarditis should be ruled out (see §8.5.2).

Translocation of intestinal bacteria may occur in patients without enteral nutrition. Feeding via a nasogastric/duodenal tube using uncontaminated fluids decreases this possibility.

During organ recovery, inappropriate ligation of intestinal vessels may cause translocation of bacteria. Opening of the trachea or gastro-intestinal tract should be avoided or, if necessary, should take place as the very last step during recovery so that other organs or tissues are not contaminated.

Bacterial infections are a frequent problem in donors and, although there is only a low rate of donor-to-recipient transmission, significant morbidity and mortality may result when it occurs [150]. This is particularly true in the case of MDR pathogens.

Organs with active bacterial infections limited to the organ should not be used unless adequate antibiotic therapy of at least 24-48 h has been initiated in the donor and, subsequently, in the recipient. In this context, bacteraemia must be considered as an active bacterial infection affecting all organs.

8.5.2. Bacterial sepsis, -meningitis, -endocarditis and -osteomyelitis

Although organs from bacteraemic donors can be transplanted without complications if appropriate anti-microbiological agents are applied in the post-transplant recipient [3], the following issues should be considered:

a. Bacteraemia due to nosocomial pathogens (e.g. multi-resistant *Enterococci*, *Staphylococci* (MRSA), *S. pneumoniae*, *Pseudomonas*, *Escherichia coli*, *Serratia*, *Acinetobacter* spp. and *Klebsiella* spp. or other ESBL-producing *enterobacteriaceae*) is often related to the use of intravenous access and other medical support systems [1, 3]. Following transplantation, these pathogens can cause serious infections, particularly at anastomotic sites by colonising fluids and by forming abscesses or mycotic aneurysms [1, 3]. Despite negative blood cultures, infections may be transmitted in cases of unsuspected endocarditis or pneumonia (e.g. *S. pneumoniae*). Even with transmission, most patients survive whenever effective specific antibacterial therapy is available and administered for a sufficient time.

b. The use of organs from donors with endocarditis remains controversial because of the risk of metastatic infection, although they may be used at the discretion of the transplant centre. Treatment in the donor is highly recommended [151].

c. Donors with ongoing sepsis (and positive blood cultures) should not be accepted, especially if effective therapy cannot be confirmed. However, grafts from donors without sepsis, but incidentally-detected bacteraemia, have rarely resulted in disease transmission under correct antibiotic prophylaxis in the recipient.

d. If it is impossible to have the results of blood cultures available, despite treatment in the donor having been started 48 h before organ donation and when clinical data suggests therapy is effective, then the case should be discussed with a transplant infectious disease specialist before the donor is discarded. In most cases a preliminary result becomes available. Some specialists consider at least 24 h of appropriate treatment based on the antibiogram acceptable. It is always recommended that the same treatment be continued in the recipients until the final results of the blood cultures collected immediately before organ procurement are available.

There is significant evidence that donors with proven bacterial meningitis caused by *N. meningitides*, *S. pneumoniae* or *Haemophilis influenzae* can safely be used, even if bacteraemic, as long as the bacteria are confirmed to be susceptible to the antibiotics used to treat the donor. Optimally the donor should be treated for 48 h prior to donation [5-6], although many experts consider 24 h of active therapy to be sufficient to consider donation. Recipients should undergo treatment for the infection post-transplant. In some cases of bacterial meningitis, successful treatment can be confirmed even if bacterial growth of liquor cultures fails. When in such cases the pathogen can be identified by PCR (polymerase chain reaction), this will provide sufficient information about the infection. Meningitis caused by *Listeria* may disseminate systemically. Treatment by targeted antibiotics is possible, but management of immuno-suppressed patients with *Listeria* infec-

tion is troublesome and can lead to non-acceptance of such donors by recipient centres.

In the case of an osteomyelitis, systemic spread must be ruled out.

Generally, organs should only be considered for use after 48 h of targeted and effective antibiotic therapy as well as appropriate evidence of clearance of the infection. After evaluation of the case with a transplant infectious disease expert regarding the option of effective treatment in the recipient, the time interval may be shortened.

8.5.3. Pulmonary infections

Most deceased donors require emergency intubation. Aspiration and consequent pneumonia must be ruled out and treated [5]. Coincident with the amount of time spent in an ICU, the rate of confirmed bronchopulmonary infections increases from 10 % to 40 % [6]. Following at least 48 h of effective antibiotic treatment and unimpaired pulmonary function, lungs (or at least unaffected lobes) may be considered for donation [6]. Transmission of MDR bacteria or fungi by colonisation of the lungs should be ruled out. Tissue biopsies of transplanted lungs may document pathogens not previously detected by BAL. If adequate antibiotic therapy according to the resistance pattern of the isolates is provided, lung recipients should not suffer complications due to donor-derived bacteria, as long as the transmitted pathogens are not MDR [152].

In the case of pneumonia without bacteraemia, all other organs can be used safely for transplant. Lungs may be used after adequate and effective antibiotic therapy of pulmonary infections.

8.5.4. Urinary tract infections

Urinary tract infections (UTIs) and pyelonephritis are common due to bacteria ascending along the urethral catheter [5]. A UTI may be considered cured after adequate antibiotic treatment (48 h in duration), but a final decision should be taken at the time of organ recovery. Post-transplant treatment of the recipient may reduce the risk of donor-derived infection. In case of a UTI restricted to the lower urinary tract, kidneys may be used as they are not infected.

In the case of UTI without bacteraemia, all other organs can be safely used for transplant. In most cases, uncomplicated UTI/bacteriuria is not a contraindication for the use of kidneys if adequate antibiotic treatment is given to the donor and/or recipient. Any suspected UTIs in donors should be confirmed by urine culture.

8.5.5. Multi-drug-resistant bacteria

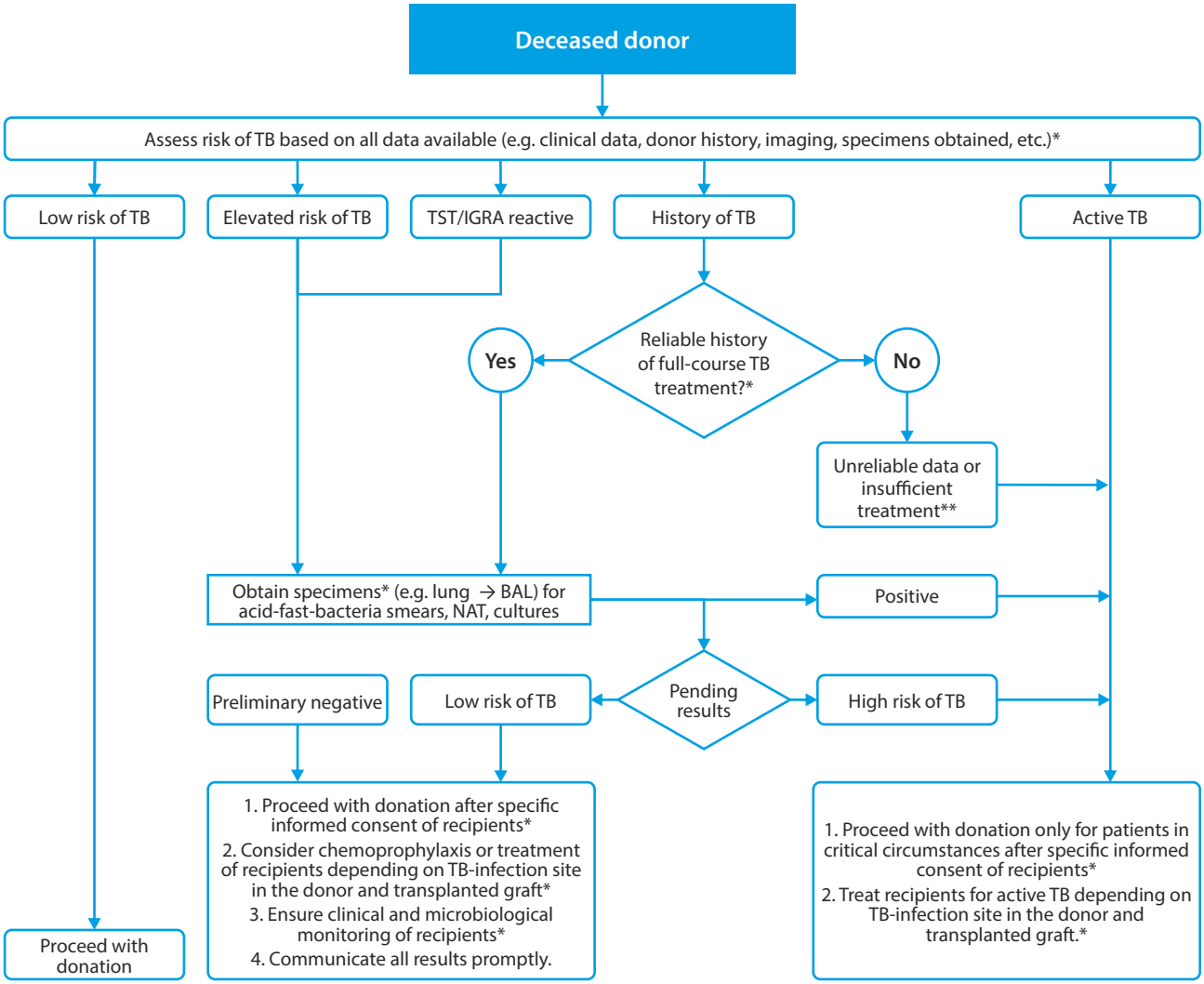
An increasing number of patients admitted to ICUs are exposed to infections with MDR organisms, in particular ESBL-producing *enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Klebsiella pneumoniae* (CR-KP) and other carbapenem-resistant *enterobacteriaceae* (CRE). Carbapenem-resistant Gram-negative bacteria are of particular concern because of their difficulty to treat which, in turn, results in significant morbidity and mortality, particularly among solid-organ transplant recipients [153-155]. No specific donor risk factor may predict the infection or colonisation by MDR organisms. Prolonged (> 7 days) ICU stay, vasopressor use and need for cardiopulmonary resuscitation have all been reported as independent risk factors for predicting potentially infected donors [156]. However, others have demonstrated that a period of hospitalisation as short as 2 days is, unfortunately, long enough to acquire a MDR nosocomial pathogen that can be transmitted through transplantation [157].

Anecdotal reports suggest that with prolonged treatment after transplantation, recipients of organs from donors with MDR infection may have a favourable outcome [158]. In addition, the current availability of new drugs with activity against some MDR pathogens might allow in the future a more liberal use of organs from donors with CRE or *Pseudomonas aeruginosa* [159].

The very limited available experience suggests that, in well-defined conditions, organs from donors who are CRE- or CRAB-positive, in respiratory secretions or rectal swabs, may be considered for transplantation. Close recipient follow-up is mandatory in order to validate this approach. In this setting, it seems prudent that lung transplantation should not be performed if the lungs are colonised. Similarly, if the donor has a positive urine culture for CRE or CRAB, transplantation of the kidneys should be avoided. However, it appears that the transplant of all other organs could be permitted.

In the presence of MDR bacteraemia, transplant of any organ should not be considered, because outcomes in such circumstances are still unknown and because the accumulated literature deals with different types of organisms. In any case, consultation of the transplant infectious disease expert is strongly recommended.

Figure 8.5. **Algorithm for management of deceased donors for suspected risk of infection with tuberculosis**



* Consult transplant infectious disease expert for proper assessment.
** Obtain specimen to confirm diagnosis and communicate results promptly.
TB: Tuberculosis; TST: Tuberculosis skin test; IGRA: Interferon gamma release assay; NAT: Nucleic acid amplification test; BAL: Bronchoalveolar lavage.

Source: adapted from Morris MI, Daly JS, Blumberg E *et al.* Diagnosis and management of tuberculosis in transplant donors [161].

8.5.6. Tuberculosis

Late infections by *Mycobacterium tuberculosis* are troublesome for recipients [1, 3, 6]. Organs from donors with disseminated tuberculosis (TB) should not be utilised. Organs from donors with a history of TB and with successful treatment for at least 6 months have been transplanted with success. Prophylaxis and/or empiric treatment of the recipient should be considered in such cases, according to the guidelines [160].

Whereas in living donation evaluation of the donor can be performed according to the recommended guidelines, in deceased donation this is challenging [160-163]. There are no proven methods for screening deceased donors for TB, but interferon-gamma release assays (IGRAs) may be helpful, although not validated for this purpose. The use of organs from donors who have travelled to, or previously lived in, regions with high rates of TB may be at higher risk of transmitting infection or having had acquired latent TB infection (LTBI). In such cases, monitoring or treatment of the recipient for LTBI should be considered. Donors suffering from meningitis caused by *M. tuberculosis* may only be considered exceptionally because dissemination of TB must have occurred for infection to be localised to the central nervous system. Donors with residual pulmonary lesions can donate other organs

[160-163]. For lung donors, histopathological and microbiological studies should be performed to rule out active infection (e.g. BAL for acid-fast staining smear, culture and PCR) [160-163]. Since the global prevalence of TB changes annually, in many countries it is recommended to check the web page of the WHO for further information (see www.who.int/tb/data).

For assessment of the risk of TB transmission in detail, refer to the consensus conference report of the American Society of Transplantation, the Canadian Society of Transplantation and The Transplantation Society [161]. In summary, the following considerations are important in deceased donors:

a. Stratify into low, moderate or increased risk of LTBI or active TB according to:
   i. country of prior residence and/or exposure (epidemiological history);
   ii. social risk factors (homelessness, incarceration, alcohol, known TB-contact, refugee camp);
   iii. medical factors (history of untreated or insufficient treatment, especially for the high risk of relapse in the past two years; investigative imaging with evidence for prior TB – especially chest X-ray and upper lung lobes; lymph nodes; cachexia; BMI < 18 kg/m² in adults; diabetes mellitus; cigarette smoking; immuno-compromised, reactive IGRA or other TB-screening test); and
   iv. organ (consider extra-pulmonary manifestation in immuno-compromised donors; check for unexplained apical fibrosis during lung procurement).

b. In donors at moderate risk, be sure not to miss active TB or disseminated TB.

c. Obtain a specimen for testing of mycobacteria (e.g. BAL, urine in suspected genito-urinary TB), consider IGRA (though the test might not provide a clear result for further conclusions). There are often pending results when procurement is performed. Therefore ensure that all data are forwarded as soon as they become available so it can be decided whether therapy, chemoprophylaxis or surveillance in the recipient will be appropriate for mitigation of risk.

d. Perform risk–benefit assessment according to the pathway provided in Figure 8.5. It is helpful to distinguish between grafts that are remote from the active TB-site and those affected by the active TB-site.

e. Targeted imaging studies are recommended in cases of suspected or documented past TB.

All recipients documented to have LTBI should receive treatment to prevent reactivation, ideally pre-transplant or (if this is not feasible) post-transplant. The problem of MDR TB may complicate treatment of recipients.

Active, disseminated tuberculosis is a contraindication for organ donation. Organs (except lungs) from donors with a history of tuberculosis may be used if successful treatment has been carried out for at least 6 months.

8.5.7. Other bacterial infections

Treponema pallidum infection is detectable by standard serology [6]. Donors with positive rapid plasma reagin test (RPR) should have infection confirmed by a *Treponema*-specific test because false positive rates are high; if reverse screening is utilised, confirmation of positive initial results is also recommended [164]. Generally, organs from donors with newly diagnosed syphilis can be safely used if the recipient is treated, because latent syphilis appears not to be transmitted in this case [5]. Follow-up testing for syphilis transmission should be conducted. Any newly diagnosed syphilis should raise serious concerns about an increased risk for HIV, HBV or HCV infection in the window period.

For bacteria that cause infections commonly known as 'tropical diseases', many of which now exist in Europe, for example leptospirosis, the basic considerations mentioned below for parasites (see §8.7) apply.

Intestinal infection by *Clostridium difficile* has not yet been reported to be an issue in organ donation, although it is an important consideration for immuno-compromised patients.

Infections by *Coxiella burnetti* (Q fever) are possible in many European regions and may be transmitted by substances of human origin. A case of Q fever transmission following bone marrow transplant has been reported. Donors presenting with symptoms such as fever, pneumonia and/or hepatitis, and association with local outbreaks or farming activities, should elicit further investigations.

In immunosuppressed patients (e.g. lung transplant recipient), fatal hyperammonaemia can be caused by disseminated infection of *Ureaplasma* species. Usually this pathogen is restricted to the urogenital tract, but disseminated colonisation in donors and/or recipients cannot be excluded. Whenever hyperammonaemia is detected, infection by *Ureaplasma* species should be considered. Special cultures, NAT screening and further tests will be required as well as the start of empiric antibiotic treat-

ment effective against *Ureaplasma* or *Mycoplasma* species.

Ureaplasma and *Mycoplasma* species belong to the category of Mollicutes – which are bacteria without cellular wall and which adapt well to their host as parasites. Unfortunately, standard microbiologic diagnostics fail to detect these pathogens [165-168]

8.6. Fungal infections

Disseminated fungal infections (or fungemia), confirmed by blood cultures, must be eradicated completely before donation [3, 5]. For localised infections, a case-by-case consideration is necessary; for example, the trachea is often colonised by *Candida* spp.

Undetected fungal infections are a concern for lung transplant, so BAL during bronchoscopy prior to donation is recommended. Fluconazole-resistant *Candida* sp. or *Aspergillus* spp. are particularly problematic, especially among lung recipients. Dissemination of *Aspergillus* spp. infections must be ruled out.

In certain geographic areas, *Histoplasma*, *Coccidioides*, *Blastomycosis* and *Scedoporium* spp. are endemic, and screening may be necessary to rule out active infection in at-risk donors [1, 3, 5, 169-171] (see Table 8.3 and Table 8.7).

Cryptococcus infection may be associated with HIV infections, other immuno-suppressive conditions and liver failure.

In persons hospitalised for long periods in the ICU, under anti-microbial therapy and invasive procedures, the risk of colonisation or infection by *Candida* increases. In persons receiving immuno-suppressive therapies, there is increased risk of colonisation or infection by opportunistic pathogens, e.g. *Aspergillus* or *Pneumocystis jiroveci* (*carinii*) [169-172]. Another substantial risk factor for acquiring fungal infections is renovation work in the home or hospital. Unfortunately fungal infections are becoming less and less geographically restricted [173]. In some donation procedures, contamination of preservation solution before implantation by various *Candida* spp. has been detected [173].

The reported rate of fungal infections transmitted by organs is low, with the exception of the lungs, although under-detection or under-reporting may occur. In countries with limited medical resources, fungal infections represent a big problem in transplantation procedures.

Disseminated fungal infections must be eradicated before any organ is considered for use. In the case of lung donations, pulmonary fungal infection/contamination represents a particular problem that must be investigated and properly treated. Proven *Pneumocystis jiroveci* (= *carinii*) infection of the donor is a contraindication for the use of the lungs.

8.7. Parasites, protozoans, nematodes

Active parasitic disease of the donor is a contraindication for organ donation. Exceptions may be possible if unacceptable risks for the recipients have been ruled out by transplant infectious disease specialists.

Prophylactic use of trimethoprim-sulfamethoxazole, atovaquone or combined anti-microbial therapy (including pyrimethamine dapsone and folinic acid, or pyrimethamine-sulfadiazine and other combinations) is known to be effective against *Toxoplasma gondii* as well as *Pneumocystis jiroveci* (*carinii*) and should be provided to organ recipients who are at risk of infection (generally, recipients of heart and vascularised composite allografts, which include muscle transplants) [3-174]. Serology for toxoplasma is included in the standard screening of heart donors in order to avoid *de novo* infection through dissemination in a seronegative recipient [174]. More than 70 % of the adult population in Europe has had contact with *Toxoplasma gondii*.

Persistent diarrhoea, colitis, etc., in donors – in combination with risk factors, for example recent foreign travel – should lead to investigations to exclude intestinal parasites. Usually, symptomatology is absent.

Donor-derived parasitic infections are rare in Europe, but must be considered for donors having contact with (i.e. through travel), or coming from, other areas. Details of tropical and geographically restricted infections during solid-organ transplantation have been previously published [175], and they are summarised in Table 8.7. For the most recent data about tropical and geographically restricted infections, especially in the case of donors with a history of foreign travel or a background of migration, transplant personnel are referred to the websites listed in section 8.4.1, where the most current epidemiological information can be obtained.

Detailed discussions of malaria (§8.7.1), Chagas disease (§8.7.2) and echinococcosis (§8.7.3) are provided below. In many parts of the world, endemic parasites such as *Strongyloides* (e.g. Indian subcontinent, Africa) or *Schistosoma* exist, with an elevated risk for donor-derived infection [176-177]. Due to migration and global travel or employment there are sizeable

populations at risk living in Europe. Screening of donors and/or empiric treatment of recipients and/or donors should be considered in all at-risk cases (see Table 8.7). Unfortunately, donors are often asymptomatic for such parasitic diseases.

Active parasitic disease in the donor is a contraindication for the use of organs. The possibility of parasitic infections should be considered in donors coming from, or having travelled to, endemic areas (see above-mentioned references and box entitled 'Websites', as well as Table 8.7) and in the case of persistent diarrhoea or other unexplained signs of illness.

For other infections by protozoans and nematodes, the risk-assessment approach for potential donors is equivalent to that applied to parasitic infections.

8.7.1. Malaria

Active malaria may be detected by blood smears, liver biopsy, PCR or antigen assays. In some donors, symptoms may not be detectable. There should be no delay in the initiation of anti-malarial treatment if malaria is suspected in either a donor or a recipient. Donors at risk of malaria infection include residents of, immigrants from and travellers to endemic areas.

Parasitaemic donors are usually rejected by transplant centres. Grafts can be used after successful treatment and recovery, but it must be remembered that some species (*P. vivax* and *P. ovale*) may survive in the liver. Therefore, differential diagnosis of any fever in the recipient within the first weeks after transplant should consider the possibility of reactivation of malaria in recipients of grafts from donors at risk of acquired malaria. Proper treatment of the recipient must be initiated immediately [178]. Treatment recommendations are dependent on the *Plasmodium* species and the geographic region where malaria was acquired. Consultation of a transplant and malaria/tropical medicine specialist is recommended.

In asymptomatic deceased donors with residency or travel to endemic areas, antibody tests should be performed if the history of return falls in the last 4 to 12 months. If the test is reactive, PCR should be performed. If history of travel or residency is within the last 4 months, PCR should be performed always. The result should be available within 24 h post-transplant in order to initiate further measurements [179].

8.7.2. Chagas disease

Trypanosoma cruzi, the parasite responsible for Chagas disease or American trypanosomiasis, has a predilection for muscle, heart and neurological cells. Screening is important for residents of, immigrants from or travellers to endemic areas (Latin/South America; check for latest epidemiological data at websites given in §8.3). Due to the common vertical route of transmission in endemic areas, donors whose mothers are at risk for Chagas disease should also be tested.

Asymptomatic parasitaemia is more common than symptomatic disease in potential donors [174, 180-181]. Antibodies against *Trypanosoma cruzi* indicate previous exposure and current infection, unless treated. Due to significant variability in sensitivity and specificity, appropriately validated tests must be used. Acute parasitaemia may be detected by PCR and Strout test (microscopy of blood after blood con-

Table 8.6. **Key questions to be asked of any potential donor to mitigate the risk of missing an unsuspected central nervous system infection**

Donor characteristic	Comments
Cerebrovascular accident in a patient without risk factors	Especially in young adults or paediatric patients without known risk factors for severe complications due to cerbrovascular damage, CNS infection may be associated with a cerebrovascular accident
Fever at presentation of illness or at admission without clear explanation	Early fever with changes in mental status would be higher-risk; fever is common after hospitalisation and non-specific in critically ill patients
Altered mental status/seizure at presentation illness/admission	Higher risk would include potential donors with new and otherwise unexplained seizures or mental status changes
CNS Imaging characteristics	There may be significant overlap with non-infectious causes of CNS disease
Cerebrospinal fluid abnormalities	Higher-risk findings include unexplained CSF pleocytosis, low glucose and elevated protein; low cellularity in CSF does not exclude an infectious process and can be often seen in viral encephalitis, particularly in the early stages
Immuno-suppressed host	Examples include treated autoimmune disease, cirrhosis (risk factor for cryptococcosis)
Enviromental exposures	Examples include exposures to bats or other potentially rabid animals, heavy mosquito exposure

CNS: central nervous system; CSF: cerebrospinal fluid.

Source: Kaul DR, Covington S, Taranto S *et al*. Solid-organ transplant donors with central nervous system infection [188].

centration), but these are generally not sufficiently sensitive for screening of organ donors because of intermittent parasitemia. For screening purposes, serology with validated antibody assays must be used.

Prophylactic treatment (benznidazole) in D^+/R^- combinations is considered controversial but it has had some success [182]. All recipients of organs from Chagas disease-positive donors should be closely monitored for disease transmission by PCR or microscopy of blood [183-184]. Treatment (benznidazole, nifurtimox) should be initiated promptly upon recognition of parasitaemia. Some experts recommend avoiding certain immuno-suppressive therapies (e.g. thymoglobine or mycophenolate) in recipients of organs from Chagas disease-positive donors [162]. Cardiac or intestinal grafts should not be used from donors with a history of *Trypanosoma cruzi* infection, whereas other organs can be considered [162-164, 169-178, 180-181, 183-184].

8.7.3. Echinococcosis

Echinococcosis (critical in liver or lung donations) requires an individual-based decision [6]. If there is evidence of disseminated echinococcosis in the donor, then organs should not be considered for transplant. Even if previous surgery and therapy has been successful, some transplant centres do not recommend the use of affected organs (e.g. an affected liver lobe), while other organs may generally be used with a low risk of transmission. *Echinococcus* has been detected in rural areas throughout Europe, with donors being unaware of antecedent infection. Extra-hepatic manifestation of hydatid cysts should be ruled out [6].

8.7.4. Helminths: nematodes, trematodes, cestodes

Intestinal nematodes either stay in the intestine (e.g. *Trichinella*) or, during their life-cycle, they can disseminate via the blood from the intestine to the lungs or other tissues (e.g. *Ancylostoma*, *Ascaris*, *Strongyloides* or *Schistosoma*) with an increasing number of cases donor-transmitted [185]. In addition, some nematodes can be transmitted by *Culex* or *Anopheles* mosquitoes (e.g. lymphatic filariasis through *Wuchereria bancrofti* and *Brugia* spp., *Mansonella*), black fly (e.g. *Onchocerca*) or tabanids (e.g. *Loa loa*) and may persist in the body for months (e.g. filariae) [186]. Nematode infections are endemic in tropical countries, so a history of travelling to or coming from such areas, plus reported visual impairment and itching, may suggest infection. As long as the life-cycle can be interrupted by preventing the transmission of microfilariae via the blood from donors to non-immuno-suppressed recipients, no disease development may be expected. Active infection should preclude donation, although evidence on how to manage donors with these infections is limited.

There should be a high index of suspicion for parasitic infections not only in donors and recipients coming from endemic regions in the world but also in Europe. Therefore screening should be considered in potential donors at elevated risk. The prevalence of *Strongyloides* infection of 12.4 % has been reported among farm workers in a Mediterranean region in Spain [187]. Infections by one of the multiple trematode species (e.g. *Schistosoma*) are most common in Asia, Africa, South America or the Middle East. In 2014, 11 cases (6 from France and 5 from Germany) of uro-genital schistosomiasis were reported. All cases were exposed to fresh water in a natural swimming area in southern Corsica (Cavu River) [188]. There have been isolated cases of *Schistosoma mansoni* transmission through infected liver transplantation and a possible reactivation of schistosomiasis in patients with chronic infection originating from endemic areas, who received uninfected liver transplants [189]. In both situations, transplant recipients were successfully treated with praziquantel.

Infections by cestodes (e.g. *Cysticercosis*, *Echinococcus*) or other tapeworms are common in underdeveloped countries, or those having poor sanitary conditions, or endemic in specific geographical regions (see §8.10.6).

Recently, in the UK, a rare case of fatal donor-derived nematode transmission (*Halicephalobus gingivalis*) to kidney recipients was the subject of a lay press release [190]. Also, parasitic infection by pathogens unknown in Europe may occur in donors coming from distant countries or having lived there (e.g. clonorchiasis in a donor having migrated from Kazakhstan to Europe [191].

Target organs of active infection by helminths should not be used for transplantation. Since knowledge is limited, it is recommended to consult transplant infectious disease experts.

8.8. Prion-related diseases

Transmissible spongiform encephalopathies are rare, but exclusively lethal, degenerative diseases of the central nervous system [6]. Creutzfeld–Jakob Disease (CJD) and variant Creutzfeld–Jakob Disease (vCJD) are transmitted by prions. Prions result from abnormally-folded proteins, so there are no NAT

assays available, nor are there sensitive Western blot or ELISA assays for the detection of prion proteins in the blood. Diagnosis can only be made, if at all, *post mortem* on autopsy material. It is suggested that transplant teams should adhere to CDC recommendations (www.cdc.gov/prions/) and consider the risk of transmissible spongiform encephalopathies being transmitted in cases where:

a. CJD or vCJD has been observed frequently within the family;

b. treatment has occurred with pituitary gland hormones or growth hormone of human origin;

c. *dura mater* has been used during an operative procedure.

Currently, there are no definitive conclusions about the risk of people being infected in Europe. Living in or having travelled to the UK is associated with this risk, but evidence is lacking about the extent. It is recommended to obtain informed consent of the recipient about this when such at-risk grafts have to be used. Future monitoring of this issue will be required for further evidence.

Dura mater should not be procured and used as graft material due to an unpredictable risk of prion transmission.

8.9. Cerebral infections (meningitis/encephalitis) by various pathogens

Any meningitis or encephalitis caused by an unknown pathogen is an absolute contraindication for organ donation. A brain abscess is not *per se* a contraindication. Nevertheless, the potential causes of the brain abscess should be evaluated before accepting the organs.

Extreme precaution should be used in cases of donors with presumed bacterial meningitis with negative cultures, especially when no pathogen can be identified in liquor or blood by culture or PCR. All of the data on the 'safety' of donors with meningitis is in the context of positive cultures as outlined in section 8.5.2. Further, there have been transmissions of malignancies and infection (e.g. TB, fungi) when donors with culture-negative, presumed bacterial meningitis were used. Therefore donors should only be used when there is a proven bacterial or possible Naegleria infection.

In the case of a non-reactive culture but where the bacteria are confirmed by PCR as the pathogen causing the meningitis (e.g. Liquor-PCR), it can be assumed that after 24-48 h of antibiotic treatment, infection will not be transmitted – as long as all other clinical data fit. Still a residual risk of unconfirmed disease exists.

If there is no pathogen identification, including by PCR, organs should not be used for transplantation. Before the donor is discarded, the particular case should be discussed with a transplant infectious disease expert.

As already outlined in the section about specific virus infections (see §8.4), donors with encephalitis, particularly febrile encephalitis, present an exceptionally high risk for disease transmission and should generally be excluded unless the pathogen is identified and viraemia can be excluded, and treatment options in the recipient exist.

In the case of a potential donor who dies of confirmed herpes encephalitis and received initial treatment, the use of the organs can be recommended, provided that the donor is not viraemic (viraemia is rarely found in HSV encephalitis) and provided that the recipient is HSV-seropositive pre-transplant. If the recipient is seronegative, specific anti-viral prophylaxis is recommended for 6 months.

Progressive multifocal leukoencephalopathy (PML), caused by JC virus and its mutants, is typically observed in immuno-compromised patients and is associated with high viral load in the cerebrospinal fluid (and urine) but in general without viraemia. Currently there are not enough data to endorse acceptance of organs from a donor with PML. The number of potential donors with PML is very limited and they should be excluded from donation until more reliable data become available.

Acute disseminated encephalomyelitis is always diagnosed by exclusion of other causes. But unfortunately it has been associated with donor transmissions, including rare pathogens, e.g. *Balamuthia mandrillaris* [193].

A special donor population is represented by those with unrecognised central nervous system (CNS) infection. Unrecognised CNS infection in donors has been associated with high rates of transmission to organ recipients, with subsequent morbidity and mortality. These events are of great concern due to the absence of effective treatments for most of these pathogens. To help OPOs and transplant centres to differentiate CNS infections from stroke in potential donors, the Donor Transmitted Advisory Committee created a document to outline indicators of possible meningo-encephalitis in potential deceased organ donors. Concerted efforts to improve screening of donors with suspected encephalitis, to carefully consider risks and benefits of transplanting organs from these donors and to better monitor transplant recipients for rapid recognition of infection may improve patient management and prevent further transmission [192].

The key questions summarised in Table 8.6 should be asked about any potential donor [192] in order to mitigate the risk of missing an unsuspected CNS infection.

There is still a considerable overlap between findings in donors with and without CNS infection (e.g. fever), but one upshot in most cases of donor-derived transmission of CNS infection was that suspicion of it was missed. Most reports about unintended transmissions of CNS infection result from cases where either the diagnosis had been missed or where the pathogen was not identified for further risk assessment. In cases of a known pathogen with curative treatment performed, either in the donor or recipient, a low rate of adverse outcomes can be postulated, as data from a UK Transplant registry study show [194].

Any meningitis or encephalitis caused by an unknown pathogen is an absolute contraindication for organ donation. Before the donor is discarded, the particular case should be discussed with a transplant infectious disease expert.

8.10. Pitfalls of serologic screening

8.10.1. Unexpected results

In the case of an unexpected result (e.g. reactive anti-HIV-1/2 testing), the appropriate response depends on the risks for the patients (both donor and recipient) and staff involved:

- the donation procedure must be interrupted and no organ or tissue should be recovered until confirmatory test results are available (e.g. reactive anti-HIV-1/2 testing), or
- the donation procedure may be continued under the assumption that the donor is infected and will transmit the virus with acceptable harm to other patients after appropriate recipient selection (e.g. D+/R+ combinations). This requires time for a new organ-allocation procedure, but without the need to wait for confirmative tests, or
- the donation procedure may be continued, including procurement, under the assumption that an infection can be managed at the recipient transplant centre (e.g. reactive anti-CMV testing).
- However, if a donor has recently received transfusions of blood, blood components or intravenous immunoglobulin preparations, then antibodies may be acquired passively, which may cause false positive results. If no pre-exposure specimen is available, it is impossible to provide an unbiased result. Then reactivity might be assumed without knowledge whether this is associated with the donor or a blood product.

8.10.2. Haemodilution and quality of specimen investigated

Whenever possible, a donor blood sample collected before administration of any transfusions and infusions should be used for testing purposes.

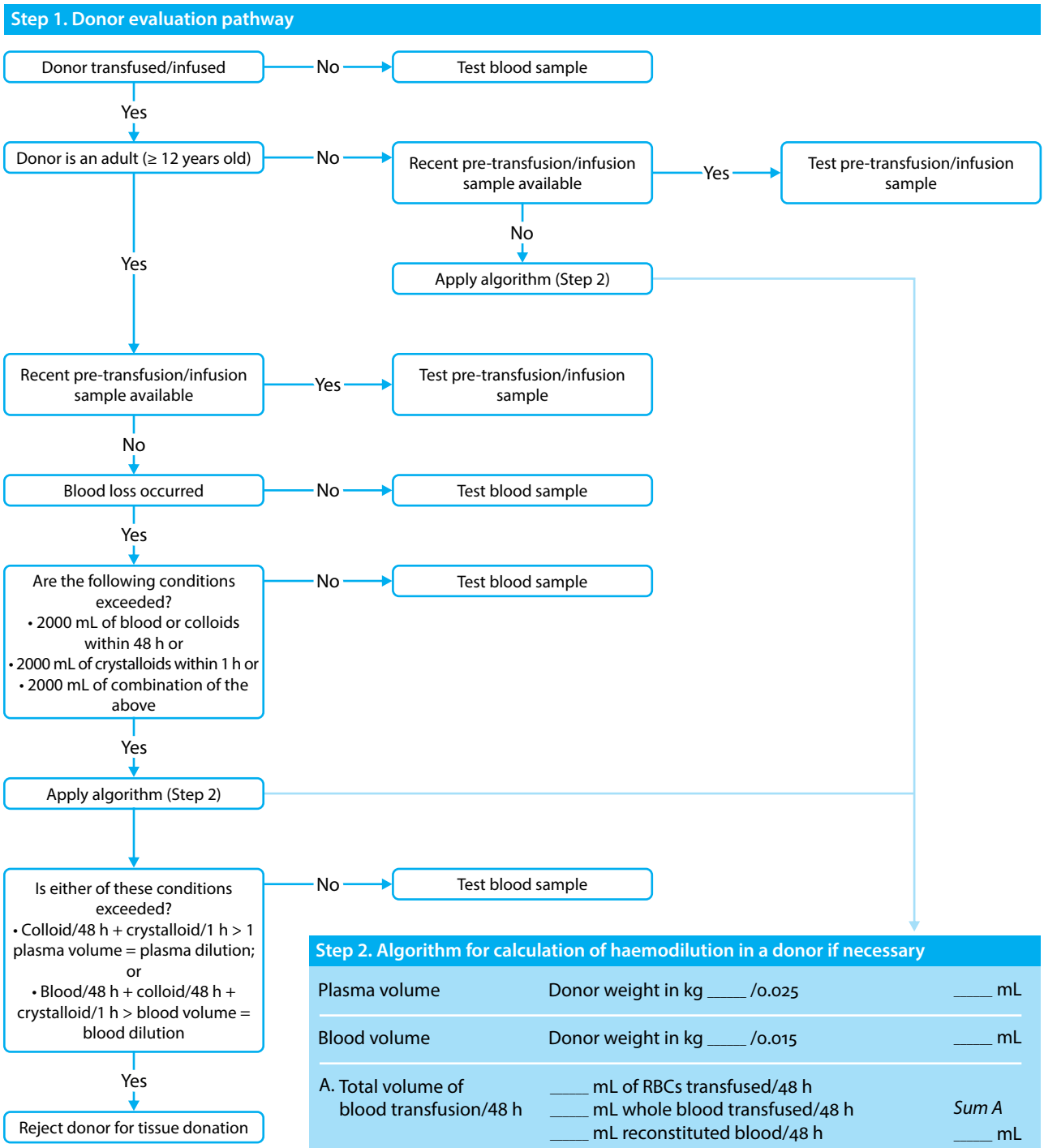
If a donor has recently received transfusions of blood or blood components, or infusions of colloids or crystalloids, and has lost substantial volumes of blood, testing of donor blood collected post-transfusion or post-infusion may not be valid due to haemodilution or plasma dilution of the donor's blood and, thus, of any samples taken from the donor.

Careful assessment of the extent of the donor's dilution that might render any test result invalid includes the use of a formula to calculate dilution of the donor's original circulating blood volume (and circulating levels of antigen and/or antibody, if present). Examples of when a haemodilution calculation may need to be carried out include:

- *ante mortem* blood sample collection: if blood, blood components and/or colloids were administered in the 48 h preceding blood sampling, or if crystalloids were infused in the hour preceding blood sampling;
- *post mortem* blood sample collection: if blood, blood components and/or colloids were administered in the 48 h preceding death (circulatory arrest), or if crystalloids were infused in the hour preceding death (circulatory arrest).

Refer to Figure 8.6 for an example of a commonly used formula to assess the donor's potential haemodilution or plasma dilution that can be applied when the donor has lost blood [195-199]. Adaptations of the algorithms may be needed for body sizes outside the normal adult range. Allowances may need to be made for very large or very small adult donors, or for paediatric donors.

Figure 8.6. **Recommended steps for the calculation of haemodilution**



Based on the algorithm developed by the Food and Drug Administration, USA [198].

Ultimately, it is important to consider that calculating the degree of dilution only by one of the currently used formulas [196-197] does not take into account pathophysiological changes due to blood and volume replacement in organ donors. In deceased organ donors, maintenance protocols encourage replacement of the blood volume by fluids, which results in a lower haematocrit than in healthy adults according to the standards of intensive care medicine accepting haemodilution (see Chapter 5). Therefore, the recipient team should perform a proper risk–benefit assessment to evaluate the risk of a false negative result due to haemodilution judged against the potential benefit to the recipient [198] after being properly informed about which assays have been used to determine the results.

Finally, the quality of the specimen sent for testing is important (no haemolysis, proper storage, no dilution when sample is drawn from donor) [199].

8.10.3. False negative and false positive results

A false negative result means that a test does not detect infection where an infection exists, because of haemodilution, a window-period infection, incorrect sampling or inappropriate test quality.

A false positive result means that a test wrongly indicates reactivity to infection where an infection does not exist and may arise due to contamination, quality control issues, cross-reactivity or inappropriate test quality.

8.10.4. Blood samples drawn after cardiac arrest

Blood samples taken for screening before cessation of circulation, in donors after circulatory death, are always preferable to those obtained afterwards (see Chapter 12). A procedure should be in place to ensure identification and easy access to stored donor samples at each hospital. If such blood samples are not available, samples should be taken as soon as possible after the cessation of circulation, i.e. within 24 h. To avoid further haemolysis, the samples should be centrifuged and the serum or plasma separated as soon as possible after collection. Whenever such blood samples are investigated, the test employed has to be validated for such samples and the laboratory must be informed of the nature of sample collection.

8.10.5. Procurement from newborns

In infants younger than 6 months old, serologic screening may be unreliable due to the transfer of maternal IgG. Maternal IgG may persist up to 18 months after birth. Complementary serologic screening of the mother or NAT of the infant donor will clarify the risk of vertically-transmitted diseases. If this is impossible, the donor should be used with caution or infection should be ruled out by NAT. IgG antibodies may also be transferred from mother to child by breast-feeding. Due to the limited amount of blood specimen available for testing in newborns, each centre should have a protocol on how to handle such situations.

8.10.6. Geographic restrictions

Table 8.7 is a non-exhaustive overview of geographically restricted, rare or critical infectious diseases that can be transmitted by solid-organ transplantation; the table is modified from the original sources [4, 175]. As therapies for infections change, it is recommended to discuss with an infectious disease specialist the status of each donor presenting with a suspected infection. The 'Remarks' column provides information as to what risks exist, whether donors may be used in cases of infection, what to do in case of transmission and comments on the relevance in Europe.

Beyond these geographic considerations, risks for infections should also be evaluated according to lifestyle, living and sanitary conditions, vertical transmission, vaccination record, etc. (see Table 8.8). Finally, surveillance of disease-transmission vectors contributes to detecting new transmission risks.

Table 8.7 follows.

Text resumes on page 207.

Table 8.7. **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	**Geographic distribution, endemic zones and risks**	**Remarks**	**Transmission reported***
Aspergillosis (*Aspergillus* spp.)	Worldwide Risk for long-term and immuno-suppressed patients in ICUs	Risk factors: prolonged stays in hospital, immuno-compromised, building renovation, damp conditions; donors with invasive and disseminated Aspergillosis should not be used	Yes
Bacterial infection (various): a) *Staphylococcus aureus*, *Pseudomonas* sp.; b) *E.coli*, *Yersinia enterocolitica*, *Brucella* spp., *Bartonella* spp., *Enterobacter* spp., *Acinetobacter* spp.; c) *Bacteroides fragilis*, *Klebsiella* spp.; d) other species	Worldwide	a) Risk of mycotic aneurysm a) to d) Pulmonary and other infections d) See specific pathogen	Yes
Babesiosis (*Babesia* spp.)	Worldwide, Europe, eastern and western USA; subtropical climates	Transmission from infected blood and organ donors described No precise exclusion criteria for organ donation	Yes
Blastomycosis (*Blastomyces dermatitidis*)	North America (Mississippi and Ohio river, Great Lakes), Central America and Mexico	Serologic tests and urine antigen assays may distinguish between acute or reactivated infection in donors and recipients from endemic areas. Probably no risk for previously infected recipients. No precise exclusion criteria for organ donation described. Prophylactic use of azole anti-fungals may reduce the incidence of donor-derived disease if infected donors are used	Yes [200]
Lyme disease (*Borrelia* spp.)	Endemic in areas with ticks (northern hemisphere), different species in Europe	Check donor history: tick bites, *erythema migrans*, neurologic failures, neuroborelliosis, arthropathia. After successful treatment, donation may be possible	?
Candidiasis (*Candida* spp.)	Worldwide	Donors with disseminated or invasive disease should not be used	Yes
Chikungunya fever (chikungunya virus)	Africa, India, Southeast Asia, emerging in many European regions with warm climates	Transmission via diurnal *Aedes* sp. mosquitoes. Monitor graft recipients from donors with reactive serology. NAT available; viraemia for ≈ 2 weeks after first symptoms. Donors with viraemia should not be used	Theoretically possible; not described yet
CMV infection (*cytomegalovirus*)	Worldwide, contact with virus varies from country to country (60-100 % prevalence)	Virological monitoring and pre-emptive treatment or anti-viral prophylaxis should be considered in all patients (new infection of naïve recipients must be avoided). Donors without active CMV disease (viraemia) can be used	Yes
Coccidioidomycosis (*Coccidioides immitis*)	Southern USA, Mexico, Guatemala, Honduras, Nicaragua, Venezuela, Colombia, Argentina, Paraguay	Serologic tests and urine antigen assays may distinguish between acute or reactivated infection in donors and recipients from endemic areas. Probably no risk for previously infected recipients, but provide azole prophylaxis Lung transplant: if donor comes from endemic areas, initiate azole prophylaxis in recipients for 6 months unless infection excluded	Yes
Q fever (*Coxiella burnetii*)	Worldwide, regional variation in Europe: localised occurrences around farms with infected animals (e.g. sheep, goats). Migrating herds contribute to further spread	Targeted antibiotic therapy might prevent outbreak No reported cases yet. Spread occurs easily by aerosol over many kilometres or after preservation in any medium over months PCR (polymerase chain reaction) and serology at specified laboratories	?

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

Table 8.7. (continued) **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	Donors who died with meningo-encephalitis caused by *Cryptococcus* should not be used. *Cryptococcus* antigen tested in blood or by ligase chain-reaction assays. No precise exclusion criteria for organ donation described in other cases	Yes
Cryptosporidiosis (*Cryptosporidium* sp.)	In slums: 65 % prevalence in developing countries, 20-30 % in developed countries	Faecal-oral infection; suspected if profuse, watery diarrhoea occurs. No known effective therapy. Indirect immuno-fluorescence, antibody-ELISA assays	No
Cystoisosporiasis (*Cystoisospora belli* syn. *Isospora belli*)	(Sub)-tropical South America, Africa, Southeast Asia	Causes diarrhoea. Trimethoprim-sulfamethoxazole and reduced immuno-suppression resolve infections in recipients	No
Dengue virus infection	Temperate areas of Asia, Africa and America	Transmission by *Aedes* mosquitoes. NAT or NS1-antigen test for detection of viraemia. Transmitted infection may results in fatal complications. Viraemic donors should not be used	Yes
Ebola virus	Tropical Africa	Significant risk of transmission in persons at risk for acquired infection during incubation period (21-25 days)	?
EBV infection (Epstein–Barr virus)	Worldwide, > 90 % of all adults latently harbour the virus	PTLD is a major risk; *de novo* infection of naïve recipient must be avoided. Donors without active EBV disease (infectious mononucleosis) can be used. PCR monitoring of recipients	Yes
Echinococcosis (*Echinococcus* spp. e.g. *Echinococcus granulosus*)	Worldwide, Mediterranean and rural areas of Europe, South America, southern Russia, central Asia, China, Australia, Africa	No precise exclusion criteria described. Without active infection and dissemination beyond the liver (calcified cysts), organs can be used. Therapy possible. People are often unaware of antecedent infection	Yes
Amoebiasis (*Entamoeba histolytica*)	Insanitary conditions (food, water) especially in Central and South America, Asia, Africa	No precise exclusion criteria for organ donation described. Check donors living in insanitary conditions (food, water) and/or coming from areas of risk and/or with a history of dysentery or diarrhoea or colitis (serology, faecal PCR, microscopy; parasite mostly limited to intestines, but liver abscess or dissemination possible). Critical organs: liver, intestine	No
Hantaviral diseases (*Hantavirus* spp.) Worldwide: the different species are grouped as old-world (causing hantavirus haemorraghic fever with renal syndrome: HFRS) and new-world (causing hantavirus cardiopulmonary syndrome: HCPS)	Europe: *(Puumala-, Dobrava-Belgrade-, Saaremaa-, Seoul- and Tula-virus)* endemic in many regions. Rodent faeces contain the virus (aerosol transmission), infection causes HFRS of variable degree [201-203]. Europe/Asia: *Hantavirus* species often associated with HFRS; Other regions: hantavirus species often associated with HCPS	Europe: Consider specific diagnostics in case of acute renal damage (reversible) associated with fever, pain, thrombocytopaenia and/or capillary leak (± nonrenal organ failure) [201-202]. After recovery from acute infection, organ transplant should be possible. Worldwide: Depending on the virus species, different organ systems are affected with risk of human-to-human transmission in a few species	?
HAV infection (hepatitis A virus)	Worldwide, poor sanitary conditions. Recurrent ongoing outbreak (in MSM population) due to sexual transmission	After recovery from acute infection no transmission reported. One report of transmission (see §8.4.2.5)	yes

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

Table 8.7. (continued) **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
HBV infection (hepatitis B virus)	Worldwide Prevalence of anti-HBc reactive > 50 % in Asia, South Pacific, sub-Saharan Africa, Middle East; Prevalence of anti-HBc reactive > 10 % in eastern Europe, Mediterranean, Inuit. People HBsAg-reactive are infected with [4]: Genotype A (which is the reference of the WHO Standard for HBV-testing): North America, northern Europe, South Africa (≈ 3 million people); Genotype B/C: Japan, east Asia, Australia (≈ 240 million people); Genotype D: Russia, India, West Africa, Middle East, Mediterranean (≈ 40 million people); Genotype E: West Africa (≈ 1 million people); Genotype F: South America (≈ 3 million people)	Avoid new infection of naïve recipients. If transplantation is done, anti-viral therapy and HBIG prophylaxis is mandatory plus follow-up. HBV-infected recipients require anti-viral therapy anyway. Check for latest therapy recommendations and development of mutants. Genotype not relevant for risk of infection and therapeutic responses, but may alter serologic results (HBeAg and/or anti-HBe-negative HBV infections). Use donors according to case-based decisions. In emergency situations, organs from viraemic donors have been used with anti-viral therapy and anti-HBs-hyperimmunoglobulin prophylaxis in the recipient only. In HBV-viraemic donors, transmission can occur with any graft. In non-viraemic donors, transmission is only likely to occur with liver transplants	Yes
HCV infection (hepatitis C virus)	Worldwide Prevalence > 3 % in many countries of Africa (Egypt > 15 %), genotype 4b, Asia and local regions of other countries worldwide (Europe, e.g. Italy; America; Australia)	Transplantation of organs to recipients with HCV viraemia possible, in all other cases avoid *de novo* infections by prophylactic treatment by direct-acting anti-viral agents in case of transplantation for dire situations. Check for latest therapy recommendations. Use donors according to case-based decisions	Yes
Hepatitis D virus infection	Relevant in countries with high HBsAg and HDV prevalence	*De novo* infection of naïve recipients may be lethal. HDV needs HBsAg for replication. Use of donors not recommended	?
Hepatitis E virus infection	Insanitary water in developing countries (genotype HEV1 and HEV2), zoonosis in developed countries (consumption of undercooked infected meat – genotypes HEV 3 and HEV4)	Relevance currently unknown. Incidence of chronic HEV infection and its impact on morbidity in transplant recipients continues to be investigated. Awareness must exist so that opportunities for diagnosis and correct management are not missed	Yes
Herpes virus infections (HSV-1 and 2, VZV, HHV 6)	Worldwide	Avoid *de novo* infection of naïve recipients, frequent reactivation in recipients. Anti-viral prophylaxis is recommended if D+/R–. Donors with successful treated herpes encephalitis can be used (see §8.9)	Yes
Kaposi Sarcoma associated herpes virus/human herpes virus 8 (KSHV/HHV8)	globally, prevalence in Mediterranean Basin or Africa very high	Serology generally unavailable prior to transplant. Consider NAT monitoring if donor seropositive, recipient seronegative. Oncogenic potential (Kaposi sarcoma, primary effusion lymphoma or Castleman disease) either as primary infection or reactivation. Consider valganciclovir prophylaxis	Yes
Histoplasmosis (*Histoplasma capsulatum*)	North (Ohio and Mississippi rivers), Central and South America, Indonesia, Africa	Test immigrants from endemic areas (≈ 20 % of people infected, most asymptomatic) by serology, antigen tests or PCR. In endemic areas, no screening of recipients is done and anti-fungal prophylaxis is recommended only if donors are infected, and is used in naïve recipients or lung transplants. Reactivation or dissemination under immuno-suppression in previously infected recipients may occur and may require treatment	Yes

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

Table 8.7. (continued) **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
HIV infection (human immunodeficiency virus I/II)	HIV-1: Estimated adult prevalence (2009): >1-5 % in sub-Saharan Africa, Russia, Ukraine, Estonia, Thailand, Papua-New Guinea, Belize, Surinam, Guyana, some Caribbean regions; HIV-2: especially Western Africa and countries historically linked to this region	Currently donors with HIV disease (or typically HIV seropositive) are not used. Testing should detect HIV-1, HIV-2 and all subtypes. Donors with HIV infection can be used for HIV-positive recipients within an experimental protocol	Yes
HTLV-1/2 infection (human T-leukaemia virus 1/2)	HTLV-1: Romania; southern Japan; Melanesia, Middle East, some Chinese provinces; Caribbean (2-5 %); some US states, parts of South America, Africa HTLV-2: intravenous drug abusers in USA, Europe; South America (Brazil); native Americans; south-east Asia (Vietnam)	Screen at-risk donors (migration), their sexual partners and children (maternal vertical transmission). If infection is confirmed, then organs should not be transplanted into an elective naïve recipient	Yes
Influenza (influenza viruses)	Worldwide: annual prevalence and subtypes change. Latest national recommendations must be regularly checked	Prophylactic treatment of recipients should be considered. Donors at high risk of viraemia must be carefully evaluated. Check national recommendations for latest updates before further decisions. Specific recommendations cannot be given due to rapid changes in epidemiology and the virus itself	Yes
LCMV infection (lymphocytic choriomeningitis virus)	North and South America, Europe, Australia, Japan	Difficult to establish diagnosis; check for contact with rodents. Donors with acute infections should not be used	Yes
Legionellosis (*Legionella* spp.)	Worldwide	Water, air-conditioning, etc.	?
Leishmaniasis (cutaneous and visceral) (*Leishmaniasis* spp.)	All countries with certain sand-fly species: all around the Mediterranean Sea, Middle East, Afghanistan, Asia, southern USA, Central and South America, sub-Saharan Africa	No precise exclusion criteria for organ donation described. Check donors coming from endemic areas since there is delayed breakthrough in visceral (months) and cutaneous (decades) forms. If reactive to serology or antigen test, or suspected, take biopsy from liver, spleen, intestine and skin lesions. Curative chemotherapy of infected persons possible, but outcome is very poor in visceral form (contraindicative)	?
Leptospirosis (*Leptospira* spp.)	Standing water in (sub-)tropical areas	Acute infection affects all organs	?
Malaria (*Plasmodium* spp.)	Any (sub-)tropical country is a risk area (*P. falciparum*: sub-Saharan Africa, south-east Asia, Indian subcontinent, South America, Haiti, Dominican Republic, Oceania; *P. malariae*, *P ovale*: sub-Saharan Africa; *P. vivax*: south-east Asia, Indian subcontinent)	Check travellers and immigrants from endemic countries (within past 5 years) for infection (symptoms: fever, disseminated intravascular coagulation, multi-organ failure; diagnostics: blood drop, PCR if indicated). Most centres reject parasitaemic donors. Successfully treated and recovered donors may be used, with some exceptions, e.g. liver. Consider prophylactic treatment of recipients	Yes
Microsporidiosis (*Microsporidia* spp.)	Contaminated water	Transmitted via contaminated water. Spore with thick wall in intestine. Contagious and disseminates (brain, kidney). No effective therapy known	?
Multi-drug resistant bacteria (e.g. MRSA, VRE, ESBL)	Worldwide: prolonged hospital stays or any stay in nursing homes or exposure to antibiotics	Important risk factor. Check screening on admission to and during stay at ICU. Organs without contamination/infection can be used under prophylactic recipient care; all other cases need an individualised decision	Yes
Non-tuberculous mycobacteria infection (non-tuberculous mycobacteria)	Worldwide		?

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

Table 8.7. (continued) **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Parvovirus B19 infection (human parvovirus B19)	Worldwide		Yes
South American Blasto-mycosis (*Paracoccidioides brasiliensis*)	Soil in (sub-)tropical Central and South America	No precise exclusion criteria for organ donation are described. Trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia is 'cross-effective'	No
Pneumocystis pneumonia (*Pneumocystis jirovecicarinii*)	Worldwide: infection risk in long-term patients in ICU, immunosuppressed or -deficient patients	Partly avoidable problem with specific prophylaxis in recipients. Disseminated infection in donors contraindicated	Yes
Prion disease (prions)	Worldwide	No treatment available. No screening assay. Risk evaluation for CJD/vCJD. Individualised decisions for at-risk donors. Confirmed infection is an absolute contraindication	?
Algemia (*Prototheca* spp.)	Worldwide		Yes
Rabies (Rabies virus)	Animal bites or salivary contact (dogs, bats, other mammals: household and wildlife) Worldwide, though some island territories are low-risk (Japan, Taiwan, UK, Iceland, Australia [where other Lyssavirus exist], New Zealand, Norway, Sweden, Finland). No restriction can be provided for specific animal population in a particular country due to the variability of species infected	Transmission lethal unless previously vaccinated. Only NAT of brain tissue after autopsy is confirmative, but not exclusive. History of animal contact (bites) and any kind of current neurologic disorder is suspicious. Long intervals can occur between bites/animal contact and onset of symptoms (months to years). Donors with recent exposure should not be accepted	Yes
Salmonellosis (*Salmonella* non-typhoid spp.)	Food and poor sanitary conditions, warm/(sub-)tropical countries		?
Scedosporium apiospermum infection (*Scedosporium apiospermum*)	Worldwide in immuno-compromised people		Yes
Bilharziosis (*Schistosoma* spp.)	Contaminated water (Africa, Middle East, Japan, China, Caribbean, South America)	Praziquantel is used for treatment in non-transplant conditions. If acute infection is suspected (liver, intestine, urinary tract), urine or faeces should be tested for eggs	Yes [203]
Strongyloidiasis (*Strongyloides* spp.)	Warm areas with poor sanitary conditions: south-east Asia, sub-Saharan Africa, Central America, Brazil, southern USA, tropical Australia, Spain	Check faeces for larvae (or tracheal secretions if dissemination can be assumed) in donors from (or having travelled to) endemic areas with the known limited sensitivity. Serology is the most useful screening assay. Auto-infection via faeces from the intestines of asymptomatic carriers occurs. Suspect infection if symptoms of gastro-intestinal infection with urticaria, eosinophilia and gram-negative meningitis or pulmonary complications exist. Consider empiric ivermectin in recipients of unscreened, at-risk donors. Immuno-suppressed patients have a hyper-infective status, which requires pre-emptive treatment by, e.g. ivermectin. Otherwise lethal	Yes
Cysticercosis (*Taenia solium*)	Worldwide. Frequent in underdeveloped countries or in poor sanitary conditions (Asia, Africa, Latin America)	No precise exclusion criteria for organ donation are described. Typical CT/MRI lesions of neurocysticercosis. Inspection of meat and avoidance of raw meat consumption is the best prevention. Contagious only if tapeworm eggs are in the intestine	Yes

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

Table 8.7. (continued) **Geographically restricted, rare or critical infectious diseases**

Disease (pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmission reported*
Tick-borne encephalitis by various viral species	Worldwide. Seasonally and locally endemic (e.g. European and far-Eastern types of encephalitis occur from April to November, below 1 400 m altitude)	Check worldwide: any tick bites, seasonal association with neurologic disorders. Viraemic donors should not be used	Yes [204]
Toxoplasmosis (*Toxoplasma gondii*)	Worldwide (animal contact)	Risk for naïve recipients of muscle tissue (e.g. heart and/or VCAs). Specific prophylaxis mandatory in any recipient	Yes
Trematode species infection *Paragonimus*: lung *Clonorchis*: liver *Fasciola*: liver *Schistosoma*: liver	Middle East, Africa, South America, Caribbean islands, east Asia, or anywhere in waste or water or meat	A risk if skin lesions, travel history and water contact in prevalent countries are all present. In donors from endemic areas or at risk after travelling: check faeces, urine, tracheal secretions, blood (in case of eosinophilia) for eggs. Parasites can be treated by specific medication	Yes
Syphilis (*Treponema pallidum*)	Worldwide	Treatment by antibiotics successful	Yes
Sleeping sickness (*Trypanosoma brucei* spp.)	Sub-Saharan Africa, different sub-species	African Sleeping Sickness: different sub-species cause variants with progressive symptoms. Lethal	?
Chagas disease (*Trypanosoma cruzi*)	Central and South America (and the Mexican and Latin American immigrant populations of USA)	Check donors from endemic areas (serology, echo-cardiography, CT of brain for chronic infection, buffy coat from blood in acute infection). No donation from donors with acute infection. The heart and intestine should not be used from donors with chronic infection, while other organs may be used. Recipients having previous contact with the parasite should receive therapy if parasitaemia re-occurs, e.g. benznidazole. Recipients of organs from Chagas-infected donors should be monitored closely for parasitaemia (PCR is the preferred method) and treated as soon as it is detected	Yes [205]
Tuberculosis (*Mycobacterium tuberculosis*)	Worldwide (Asia, Africa, Central and South America, Europe), poor sanitary and/or economic conditions, extra-pulmonal manifestations (south-east Asia, Middle East)	Therapy in recipients is difficult. Donors with active/disseminated tuberculosis should not be used. It is advisable to initiate pre-transplant prophylaxis (e.g. INH/B6) in recipients for latent TB or transmission risk	Yes
Varicella (*Varicella–zoster virus*)	Worldwide	Naïve adults can still become infected by this childhood disease. Anti-viral prophylaxis may reduce the risk of zoster in seropositive recipients (anti-CMV therapy/prophylaxis also active against VZV)	Yes
WNV infection (West Nile virus)	Epidemic breakouts during late summer (Africa, Asia, Middle East, Europe, USA), other Arbo-virus worldwide	Transmission of acute infection often lethal. Screening helpful in regions with reported infections or epidemics within previous 2 weeks	Yes
Zika virus infection (Zika virus)	Outbreaks of primary infection are possible in regions with presence of competent vectors, permissive climate and where there is intense movement of people	The Zika virus (RNA-virus, *Flaviviridae* family) is transmitted mostly by *Aedes aegypti* mosquitoes. Mild illness (e.g. fever, rash, arthralgia or conjunctivitis) with more than 80 % asymptomatic infections may be observed after an incubation period of up to a week with symptoms resolving after one week. Viraemia may be detected by NAT	?

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

8.11. Vigilance methods and tracking

Extensive communication, in both directions between the OPO and the transplant centres, before, during and after transplantation, is crucial [1, 3]. If a recipient develops any unexpected signs and/or symptoms, including unexplained fever, leucocytosis, altered mental status or other signs of hidden infection [2], or if donor-derived disease is suspected, screening of all other graft recipients should be carried out to detect a donor-to-recipient infection

and facilitate early initiation of therapy [1]. Any documented infection early post-transplant should also warrant careful review of donor cultures and consideration of the donor as the potential source. Some donor-transmitted infections may become apparent up to several months after the transplant, and suspicion of imputability requires a high index of suspicion (e.g. HHV-8).

It is mandatory for the health authority of each member state to establish a national vigilance system for monitoring serious adverse reactions and events (see Chapter 15). Free and rapid exchange of data between the vigilance systems of all member states must occur in order to facilitate safe international organ exchange.

Especially in assumed or confirmed infections, the exchange of proper and correct information must be done without delay to ensure that proper diagnostics, preventive and therapeutic interventions (if indicated) are put in place for other recipients.

8.12. Preventive strategies in organ recipients

Preventive strategies that can minimise the risk of donor-derived diseases among potential recipients include:

a. For some infectious diseases, recipient vaccination may reduce the risk of disease transmission by a graft. Therefore, patients at risk of end-stage organ failure should complete their vaccination programme as early as possible. This should include vaccination against hepatitis A, hepatitis B, diphtheria, tetanus, pertussis, *S. pneumonia* and influenza as well as prior exposure to immuno-suppression measles, mumps, rubella and varicella [28]. Their clinical response to vaccination, and antibody status thereafter, should be monitored and, if required, vaccination should be repeated. It is important to check the complete vaccination history of a recipient prior to transplantation [206].

b. Recipient vaccination should be checked or extended to the relevant infections prevalent if travel or contact with persons from foreign countries exists or is planned [207].

c. Prophylactic vaccination may not be effective for some end-stage organ diseases [206].

d. Treatments with antibiotic-, anti-viral- and/or anti-parasitic prophylaxes during transplantation vary from centre to centre for CMV, *Toxoplasmosis*, HSV, HVZ and *Pneumocystis jiroveci* (*carinii*) etc. These protocols should be updated to mitigate against expected transmis-

Table 8.8. **General considerations for infections and vaccines**

In general	Geographic distribution, considerable risks	Remarks	Transmission reported*
Respiratory tract infection	Worldwide	Problem for lung transplantation	Yes
Urinary tract infection, pyelonephritis	Worldwide in countries with poor sanitary and economic conditions (a problem for living donations)	Results in sepsis if overlooked; generally only a risk for recipients of kidney transplants	Yes
Vaccinations during past 4-6 weeks of the donor by live vaccines	Consider live vaccine in: • Influenza (inhaled = live) • Varicella • Rotavirus • Measles • Mumps • Rubella • BCG • Smallpox • *V. cholera* (oral = live) • Yellow fever • *Salmonella typhi* (oral = live) • Polio (oral = live)	Live vaccines are equivalent to transmission of acute viral infection: individual risk assessment of potential recipient for 4 weeks after vaccination of the donor. For some vaccines, limitations exist only for specific organs: • Inhaled influenza vaccine – lung, face • Rotavirus – intestine • Cholera – intestine • Salmonella – intestine	Yes
Vaccinations during past 4-6 weeks of the donor by inactivated vaccines or passive immunisation	Consider inactivated vaccine in: • Influenza (injectable = inactivated) • *V. cholera* (injectable = inactivated) • *Salmonella typhi* (injectable = inactivated) • Polio (injectable = inactivated)	Other vaccines or passive immunisation of donors may not harm the recipient, but may confound diagnostic	No

* Transmission reported by solid-organ transplantation: Yes = reported, No = not reported.

sible infections. After transplantation, close and regular follow-up of recipients helps to rule out infections. This includes screening for latent viruses. Chemoprophylaxis with (val) ganciclovir may mitigate the complications of EBV infection (PTLD) in paediatric D+/R– recipients [208]. Such strategies should be evaluated for improved effectiveness.

e. An antibody response to an infection acquired through the transplanted organ may not develop [107]. It is recommended to rely on NAT or other direct pathogen-detecting assays (e.g. HBsAg) to screen organ recipients for transmitted infections [1]. Because late manifestation of latent infections, e.g. CMV, may occur in recipients, long-term follow-up should include targeted screening for such risks.

f. Pan-genotypic hepatitis C treatment by new DAAs allows treatment before transplantation or after transplantation with the risk associated to interaction with immuno-suppressive drugs (see Appendix 12).

8.13. References

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Related material

- Appendix 12. Hepatitis C – direct-acting antiviral drugs and interaction with immunosuppressive drugs or genotype HCV-DAA and interaction with immunosuppressive drugs

Chapter 9. Risk of transmission of neoplastic diseases

9.1. Introduction

Malignant neoplasms can be transmitted to immuno-suppressed recipients when organs from donors with known or unknown malignancies are transplanted [1-5]. However, with careful donor selection the magnitude of that risk is small, with approximately 0.05 % of organ recipients developing a donor-transmitted cancer [6-9]. The increasing use of older donors, in whom malignancy is more likely, might further increase the risk of transmission of occult cancers. The risk of transmission needs to be considered in the context of the important, life-enhancing and life-saving benefits afforded by organ transplantation. Nevertheless, due to the potentially serious consequences for the individuals affected and for donation and transplantation in general, it is mandatory to select potential donors carefully with the intention of minimising the risk of transmission of neoplastic diseases.

The increasing number of patients on waiting lists, along with the shortage of organs available for transplantation, has encouraged reconsideration of the criteria for acceptance of organs from donors with a past or current history of malignancy [10-12], acknowledging the key role of the medical teams in performing a risk–benefit assessment for each particular case [13]. Proper characterisation of the donor and the organs is essential and is also a legal requirement for EU member states [13], and should include information on any previous history and on the incidental finding of any malignancy in the donor.

Transplant clinicians are regularly confronted with difficult decisions regarding the use of organs from donors who are known to have, or have had, cancer. Donor co-ordinators and transplant teams need guidelines for the management of such complex situations, although ultimately each case will have to be analysed individually. This chapter provides professionals with recommendations for the screening of potential donors with regard to malignancies, and for the selection of organs from donors with a past or present history of malignancy.

This chapter also provides professional guidance on identifying, reporting and assessing cases of potential and actual malignancy transmission. Meticulous assessment to determine the imputability or certainty of donor tumour transmission, rapid notification to appropriate agencies to alert others involved in the care of other potentially affected recipients, and careful management of the transplant recipient not only constitute responsible medical care but also provide the information upon which an evidence-based surveillance system can be built and applied.

Preventive measures recommended in all donor cases are discussed in section 9.2. Section 9.3 provides general recommendations for the assessment of the risk of malignancy transmission. Individual tumour types are further analysed in sections 9.4 to 9.7. Vigilance and surveillance regarding the detection and management of potentially transmitted tumours are discussed in section 9.8.

9.2. General recommendations on detecting and assessing donor malignancy

9.2.1. Clinical history of the donor and physical examination

During donor evaluation, the complete clinical history of the donor should be reviewed. If possible, the donor's general practitioner and family members should be contacted to provide detailed information (see Chapter 6). The following basic points should be taken into consideration, though it may not always be possible to get exhaustive information on all of these during the process:

a. Lifestyle habits (e.g. smoking behaviour);

b. Recent conspicuous features related to neoplastic diseases, such as:
   i. unintentional weight loss;
   ii. special attention for potential hepatocellular carcinoma should be paid in HCV- and/or HBV-positive donors (even without cirrhosis), in donors with an alcoholic or non-alcoholic fatty liver disease, genetic haemochromatosis and those with cirrhosis;
   iii. history of menstrual irregularities after pregnancies and/or miscarriages in women of child-bearing age may be clinical features of choriocarcinoma.

c. History of malignancy: records of any previously diagnosed neoplasms (or tumours resected without documentation of the definite diagnosis) should be checked, with information obtained on:
   i. date of first diagnosis;
   ii. detailed histological report (tumour type, stage, grade);
   iii. data about previous imaging (staging, metastases);
   iv. treatment received (surgery, chemotherapy and/or radiotherapy) including dates;
   v. follow-up conducted including imaging, last follow-up (dates, results, complete remission and/or tumour recurrence at any time);
   vi. in cases of long-term survivors of cancers, special attention should be paid to possible second malignancies (e.g. metachronous new colon cancer 10 years after primary colon cancer, new cancers after aggressive cancer therapies like radiotherapy-induced pleuramesothelioma); see section 9.2.7.

d. Intracranial tumours or metastases should always be excluded in donors diagnosed with intracranial haemorrhage, especially if there is no evidence of arterial hypertension or arterio-venous malformations. In case of doubt, a pre- or intra-operative brain biopsy may be performed (see §9.2.5 and §9.2.6).

A careful physical examination of the donor should be conducted, paying particular attention to the skin, looking for potential neoplasms and especially scars of previous surgical procedures. Any suspicious finding requires clarification: e.g. any previous surgery should be checked for type and indication; any new suspicious naevus should be excised and sent for histopathological examination (before procurement if possible, but otherwise during procurement).

9.2.2. Laboratory determinations, tumour markers

Standard laboratory tests should be conducted in all potential donors with the objective of detecting specific diseases (including haematological malignancies) that may contraindicate organ donation.

Routine screening of tumour markers is not recommended, since false positive determinations may lead to unnecessary discarding of suitable donors and organs. If requested as part of an individual centre's protocol, positive tumour markers should always be interpreted with other clinical findings and should never be the only factor leading to discarding an organ. If there is a confirmed malignancy in the donor history and previous tumour marker results are available, appropriate tumour markers should be tested to evaluate the current situation. These results should be compared with those from the time of first diagnosis and of follow-up examinations performed.

In women of child-bearing age with a history of menstrual irregularities or miscarriages or unexplained intracranial bleeding, levels of human chorionic gonadotropin beta (βHCG) may be determined to detect a choriocarcinoma.

9.2.3. Radiological tests and imaging studies

All radiological studies performed as part of the patient's hospital treatment should be reviewed along with the complete medical history and physical examination. Up-to-date studies at the time of donation should include, at minimum, chest X-ray and abdominal ultrasound (see Chapter 6).

Further radiological tests (e.g. CT scans) may be required for thorough donor evaluation, especially in patients with suspected malignancy or in donors in whom it is thought that appropriate intra-

operative examination of the thoraco-abdominal cavities cannot be adequately carried out.

In patients with a history of neoplastic disease and a certain possibility for tumour recurrence, whole-body CT scans of thorax, abdomen and pelvis should be carried out where possible to evaluate the current disease status and to ensure the highest possible safety for organ recipients [14]. Any suspicious finding has to be further evaluated for its significance. Close communication with the radiologists is essential to assess the grade of suspicion for metastases or recurrent tumour. If there are explicit signs for active malignancy, organ donation might be stopped without further examinations. If the findings cannot clearly be determined as malignant radiologically, a histopathological examination should be performed during organ procurement. In any case, the organ donation process should not be abandoned hastily due to unspecific findings. Rational clarification should always be sought in a reasonable timeframe, keeping in mind that the donor family but also the hospital personnel are in an exceptional situation. Each case has to be evaluated and discussed very carefully with a resulting joint decision. If the organ donation process is continued, the results have to be communicated to the accepting transplant centres.

9.2.4. Donor and organ examination during procurement

During organ procurement, surgeons should examine all intrathoracic and intra-abdominal organs (including the whole intestine and genitals), regardless of whether these organs are being considered for transplantation or not, in order to detect possible hidden tumours or pathological lymphadenopathy (see Chapter 11). Any suspicious lesion should be investigated immediately by frozen section, preferably by an experienced pathologist (see Figure 9.1 and Table 9.1) [14]. As recommended in section 6.2.4, this can be done within a regional network of pathologists provided in an acceptable range of transportation time.

Particular care should be taken when examining the kidneys, considering the relatively high number of tumours that have been found in kidneys following procurement. Here, removal of Gerota's fascia and of the peri-renal fat is essential to ensure detailed inspection of the kidneys before the kidneys leave the donor hospital. In cases where the peri-renal fat is remarkably adherent to the capsule, it should only be removed as far as necessary for inspection at the donor hospital to avoid serious damage. The recipient surgeon should be informed and should inspect the kidney immediately upon arrival. Other recipient centres are to be informed urgently in case of suspicious findings.

Obviously, none of these examinations rules out small metastases or micro-metastases.

9.2.5. Histopathological examination

When a mass in any organ or a lymphadenopathy suspected of malignancy is found during the recovery process, a histopathological examination must be performed using a cytological smear and/or frozen section before any organ is transplanted (see Figure 9.1 and Table 9.1).

The mass should be resected *in toto* (not only parts of it) to investigate potential malignancies properly, if possible without sacrificing a graft otherwise suitable for transplantation. The pathologist should be informed about all donor data and the macroscopy surrounding the suspicious mass (see Chapter 6). It is preferable to send the whole tumour mass with a surrounding safety edge (e.g. Ro-resection in space-occupying lesions in a kidney) to the pathologist. Together with the investigating pathologist, it should be clarified which medium can be used for transport of the sample sent in for histopathologic examination (based on the assumed transport time).

Wherever possible, full histological characterisation of an intracranial space-occupying lesion should be performed before any organ is transplanted. Accurate neuroradiological diagnosis is possible for many brain tumours, but there is the potential that the tumour may be of a different/higher grade than first thought. Post-donation autopsy may confirm the diagnosis and characterise the tumour exactly, but not in a timescale to inform use of organs with a shorter ischaemic time tolerance such as the heart and lungs. Where no histological diagnosis exists, organs from a donor with an intracranial space-occupying lesion should only be used in recipients whose probable waiting-list mortality justifies the extra risk, and only after fully informed consent has been given. If there is a possibility that the space-occupying lesion is a metastasis then it is usually unsafe to use any organ.

When a donor malignancy (primary tumour or metastasis) is identified shortly after organ procurement, e.g. during the implantation procedure, all recipient centres involved must be alerted immediately. In cases where organs have already been transplanted and histology reveals a malignancy (e.g. incidental cancer in a lung lobe discarded due to size reduction), a full donor autopsy should be requested whenever possible to obtain detailed information about tumour origin and dissemination. This will not be necessary

in cases of small primary renal cell carcinoma (RCC) found in one kidney.

Eccher *et al.* [14] describe their experience with 400 donors evaluated by the donor malignancy screening protocol used in Verona, Italy. This detailed two-step protocol (ALERT 1: pre-operative evaluation, ALERT 2: intra-operative evaluation; both including histopathology if needed) led to identification of 73 malignancies, of which 41 were excluded early due to unacceptable transmission risk and 32 were confirmed by histopathology during ALERT 1 or ALERT 2 (12 prostate cancers, 7 RCC, 13 others). Of these malignancies, 15 precluded donation due to unacceptable transmission risk, whereas 17 donors with acceptable malignancies proceeded to donation and transplantation. Three small donor malignancies were missed by the protocol (8 mm hepatocellular carcinoma, 3 mm and 5 mm breast cancer). They were diagnosed during donor autopsy after procurement, which was routinely performed in Verona until 2012.

If no precise histological diagnosis of a suspicious mass can be obtained, the donor should be excluded unless the recipient is sufficiently sick and unlikely to get another offer, in which case the risk–benefit analysis may favour transplantation. It must be emphasised that such cases of accepting risk would be exceptional, and should only be undertaken with the fully informed consent of the recipient or their family.

If a donor tumour is diagnosed after organs have already been transplanted, the recipients must be informed and should be involved in the decision whether removal of the graft and/or re-transplantation may be appropriate. Initial results of frozen section must be interpreted with care (due to the technical limitations of the method) because final results might be different after paraffin embedding and special staining. See also Table 9.1.

Whenever only preliminary donor autopsy or biopsy results are available and final results are pending, all professionals involved should be advised on the importance of timely notification of the final results. Since autopsy findings are usually reported some time after the transplantation event, urgent requests for results may be helpful in these cases. Prompt communication is essential for the benefit of the recipients [15].

9.2.6. Changes in the cancer staging system and classification of brain tumours

Starting from 2017, many countries worldwide are updating the classification of tumour staging according to the TNM staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), updating from the 7th edition to the 8th edition [16].

Figure 9.1. **Workflow: actions for detection/assessment of malignancy in potential organ donors**

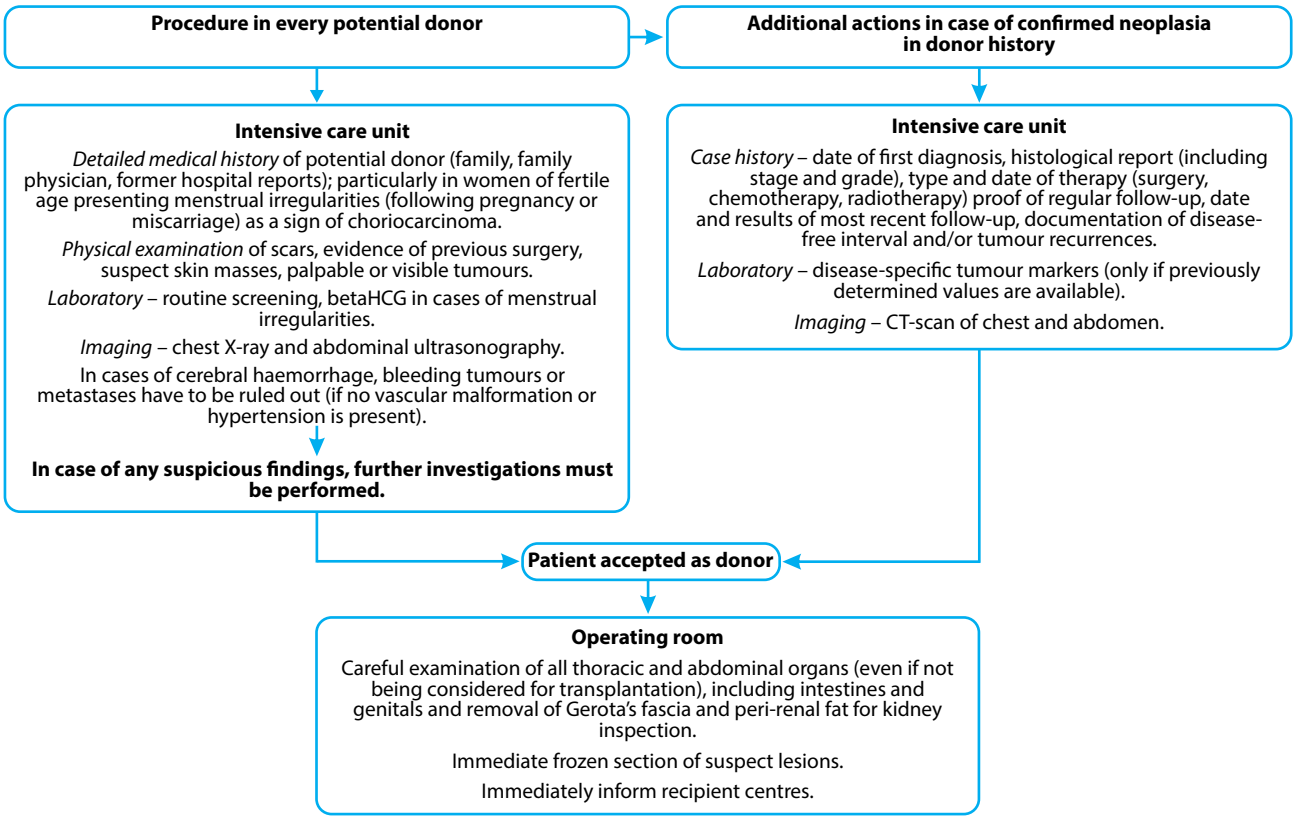

Table 9.1. **Confirmed diagnosis of donor malignancy**

When	How	What to do?
Before donor assessment	Malignancy diagnosed in the patient's medical history	If donors are accepted despite malignant neoplasia: • detailed histological reports, staging and imaging studies as well as all information and actual diagnostic findings are to be documented on the donor information form; • transplant centres may take decision to accept the organs; • oncologist advice can be sought; • obtain informed consent from the recipient/their family prior to transplantation; • carry out careful follow-up, bearing in mind the possibility of transmission; • report any possible transmission to the Health Authority in charge of SARE.
During donor assessment/ procurement and before transplantation	Neoplasia incidentally found during clinical donor assessment or surgical inspection	Immediately perform frozen section for preliminary diagnosis; subsequent work-up to be done for definite diagnosis; • immediately alert all recipient centres; • transplant centres may take decision to accept the organs; • oncologist advice can be sought; • obtain informed consent from the recipient prior to transplantation; • carry out careful follow-up, bearing in mind the possibility of transmission: • report any possible transmission to the Health Authority in charge of SARE.
After transplantation of at least one organ	a) Frozen section misinterpreted as benign, final diagnosis malignant (e.g. initial interpretation oncocytoma, definitive interpretation renal cell carcinoma) or b) neoplasia incidentally found during pre-transplant preparation of the organ in the recipient centre (other organs already transplanted) or c) donor autopsy results available after procurement and transplantation of organs indicate neoplasia or d) diagnosis in recipient at any time after transplantation, e.g. • histological finding of renal cell carcinoma; • suspicious mass in X-ray, ultrasound or CT scan; • symptomatic malignancy.	• immediately alert organ procurement organisation and national Health Authority in charge of SARE; • Health Authority will alert all recipients and tissue establishments involved; • in situation b), especially in cases of detected metastases, consider donor autopsy to identify origin and extent of the primary tumour (not necessary in case of solitary, completely resected small renal cell carcinoma pT1a) • joint decision of physician and recipient about further action (removal, therapy) on the basis of a risk–benefit analysis; • carry out strict follow-up.

Around the same time, the World Health Organization (WHO) revised its classification of brain tumours [17]. This major revision (see Table 9.4) uses not only histologic criteria but also incorporates 'integrated' diagnoses that include both histologic and molecular features (e.g. glioblastoma, IDH mutant). The new system continues to stratify tumours by grade, with grade I representing those with the best prognosis and grade IV representing those with the most aggressive behaviour.

Therefore, in potential organ donors who are long-term survivors (e.g. > 10 years after tumour diagnosis and treatment) a different staging and classification system might have been in place at the time of first tumour diagnosis. Careful consideration should be given to the nomenclature used for staging and grading historically and currently.

Consider changes in the terminology of tumour staging and grading over recent decades and reassess the initial histopathological staging and grading in light of the most recent knowledge.

9.2.7. Risk of second malignancy or complication in long-term survivors of previous malignancies

Frequently, in long-term survivors of aggressively treated malignancies, the risk for other *de novo* 'second' malignancies [18] (e.g. new metachronous colon carcinoma about 10 years after colon cancer; see §9.4.6) and secondary damage of organs caused

by the initial treatment increases, e.g. > 10 years after primary diagnosis and curative treatment with radiation or chemotherapy [19, 20]. This increased risk may include malignancies of other origin than the primary tumour, e.g. pleural mesothelioma after thoracic radiotherapy for breast cancer or a higher risk of breast cancer in females treated with mantle radiotherapy for lymphoma.

In potential donors with long-term survival after an aggressively and successfully treated malignancy, diagnostic work-up should include consideration of the increased risk of developing a second malignancy.

9.3. General considerations to minimise the transmission of neoplasms

9.3.1. Transmission risk and registry data

Although neither the exact frequency of donors with malignancy nor the risk of malignancy transmission through organ transplantation is accurately known, there is some information based on the data available in the registries mentioned below. Additional data, from the many published case reports regarding all kinds of malignancy transmission, can serve as supporting information but cannot contribute to an accurate risk estimation.

When reviewing registry reports, a certain care is required as some historic reports cluster different tumour entities in one group (e.g. skin tumours, brain tumours) instead of describing definite diagnosis and staging information for individual donor tumours, detail which is mostly not available.

9.3.1.1. *The United Network for Organ Sharing Registry (United States)*

The first United Network for Organ Sharing (UNOS) report (1994-96) [21] documented a 1.7 % incidence of donors with a history of cancer. Of these 257 donors, 85 % had a history of skin/brain/genitourinary cancers, but no precise histological diagnosis or stage was specified, and benign meningiomas and non-melanoma skin tumours might be included. The remaining 15 % had other types of cancer, mostly with a recurrence-free interval of > 5 or even > 10 years before donation. No transmission was reported.

A more recent report (2000-05) [22] analysed 1 069 donors with a history of cancer and showed transmission of two donor tumours: one glioblastoma (active at the time of donation) was transmitted to three recipients and one malignant melanoma (resected 32 years before donation) was transmitted in one of six recipients. All affected recipients died of the transmitted tumours.

Among donors with central nervous system (CNS) neoplasms (1992-99) [23], UNOS reported no tumour transmission from 397 donors with CNS tumours (either confirmed in the history or listed as cause of death) from whom 1 220 organs had been transplanted (mean follow-up 36 months).

Another report (1994-2001) [24] described 11 donor-transmitted non-CNS malignancies into 15 (0.017 %) of 108 062 recipients transplanted during this period. The tumours transmitted were: one melanoma (four recipients), one small-cell neuroendocrine tumour (two recipients), one adenocarcinoma, one pancreatic cancer, one undifferentiated squamous cell carcinoma, two lung cancers, one renal tumour reported as oncocytoma, one papillary tumour of unknown origin, one breast cancer and one prostate cancer (from a donor with prostate adenocarcinoma with lymph node metastases found on postprocurement autopsy). They were diagnosed in the recipients between 3 and 40 months after transplantation (mean 14.2 months).

9.3.1.2. *Organ Procurement and Transplantation Network/Disease Transmission Advisory Committee (United States)*

Ison and Nalesnik [5] reported 28 confirmed donor-transmitted malignancies (seven renal cell carcinomas, four lung carcinomas, two melanomas, one liver cancer, three pancreatic cancers, two ovarian cancers, two neuro-endocrine malignancies, six lymphomas and one glioblastoma) from 2005 to 2009. Nine recipients died of the transmitted tumours.

Green *et al.* [25] reported Disease Transmission Advisory Committee (DTAC) data for the year 2013 and showed five additional donor malignancies transmitted into eight recipients (three melanoma, two adenocarcinoma, three other malignancies) with two tumour-related deaths.

In 2011 Nalesnik *et al.* [11] suggested a new classification for assessing the clinical risk of donor malignancies (see §9.3.3).

9.3.1.3. *The Israel Penn International Transplant Tumor Registry*

The Israel Penn International Transplant Tumor Registry (IPITTR) [26] (historical data from 1965 to 2003) reported higher frequencies of malignancy transmission than other registries mentioned in this section. The discrepancy is probably explained by the fact that, due to the voluntary reporting to IPITTR, only a selected cohort and a small number of patients are included in this registry and they are

more likely to be reported if they suffered a transmission event. IPITTR does not cover the outcome of all recipients transplanted from donors with malignancies in the analysed time period. Donor malignancies would have escaped any documentation if none of the respective recipients suffered from transmission or if their follow-up data were incomplete.

Therefore the following data are generally considered to overestimate the malignancy transmission risk. According to IPITTR data until 2001, of 68 recipients of organs from donors with RCC, tumour transmission was reported in 43. Of 30 recipients of grafts from donors with melanomas, tumour transmission occurred in 23 and, of the 14 recipients of grafts from organ donors with choriocarcinoma, there were 13 cases of tumour transmission. Over this same time period, other tumours were also transmitted, including lung, colon, breast, prostate and Kaposi's sarcoma as well as nine transmissions of 53 CNS tumours. No transmission of thyroid, head and neck, hepato-biliary or testicular cancer or lymphoma/leukaemia has been reported. Further extracted data, such as tumour transmission into cardiothoracic recipients [27, 28] or transplantation of kidneys with small renal cancers [29], have been published.

9.3.1.4. *United Kingdom Transplant Registry*

From a 10-year period (2001-10) with a total of 14 986 donors, Desai *et al.* [7] reported 15 transmissions (0.06 % of all recipients) of 13 occult donor malignancies (six RCC, four lung cancer, one lymphoma, one neuro-endocrine carcinoma, one colon carcinoma) with three subsequent recipient deaths.

Another study [30] analysed 202 donors (1.1 % of all donors) from 1990 to 2008 with a history of cancer, including 61 donors with cancers classified as Unacceptable or High transmission risk according to international recommendations (25 glioblastomas, six medulloblastomas, 10 breast cancers, five lymphomas, four sarcomas, three melanomas, eight other malignancies). No transmission was reported in 133 recipients of organs from these 61 donors.

Watson *et al.* [31] found no transmission from 177 donors with primary CNS malignancies in the years 1985-2001. Of these tumours, 33 were high-grade malignancies (24 WHO grade IV gliomas, nine medulloblastomas).

In 2014 the Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) set out recommendations for the transplantation of organs from deceased donors with cancer or a history of cancer [12].

9.3.1.5. *The Organización Nacional de Trasplantes Registry (Spain)*

From 1990 to 2006, 117 donors with malignancies were reported (5.8 per thousand donors), all with tumours diagnosed after organ procurement [6]. Of these donors, five (0.29 per thousand donors) transmitted their malignancy into 10 recipients (0.06 % of all recipients in this period): one soft tissue sarcoma (three recipients), one germinal cell cancer (three recipients), one undifferentiated carcinoma (two recipients) and two RCC. These latter two cases corresponded to two kidney recipients who were transplanted and later presented with a renal adenocarcinoma and a papillary carcinoma, respectively. In both cases the diagnosis was made through a biopsy after transplantation.

In 1996 the Organización Nacional de Trasplantes (ONT) issued recommendations about the use of organs from donors with malignancy. These recommendations inspired the first Council of Europe recommendations on risk levels for donor malignancy transmission.

9.3.1.6. *The Centro Nazionale Trapianti Registry (Italy)*

Since 2001, the Centro Nazionale Trapianti (CNT) has had a new strategy for evaluating the safety and acceptability of donors [32]. This strategy analyses donors with infections and tumours and has established some donor risk levels. Analysis of the years 2001-2002 showed a frequency of 2.9 % of potential donors with tumours. Approximately half of these were rejected as donors before procurement, in a quarter the tumour was detected between organ recovery and transplantation and, in the remainder, a neoplasm was detected following transplantation. New data showed an improvement in diagnostic capabilities before and during organ procurement. Between 2006 and 2008, no neoplasms were transmitted following this risk-estimation approach [33].

Taioli *et al.* [34] analysed the outcome of 108 recipients who received organs from 59 donors with suspected or confirmed malignancy from 2002 to 2004, mostly non-CNS tumours. There was no evidence of tumour transmission after an average of 27.6 months.

Equivalent results were obtained in a subsequent analysis including 131 donors with malignancy from 2002 to 2005 (mostly prostate and RCC) by Zucchini *et al.* [35] and for 28 donors from 2003 to 2010 in southern Italy [36].

In the period 2006-2016, 23 885 recipients received organs from a total of 12 568 donors, of whom 678 donors (5.4 %) had a history of neoplastic

disease, though none of the respective recipients developed a donor-transmitted neoplasm during the follow-up. Six of the 23 885 recipients (0.02 %) developed a donor-related neoplasia (reliable correlation). The corresponding three organ donors had been judged free of neoplasia at the time of organ donation. The transmitted tumours were: Non-Hodgkin-Lymphoma (recipients of liver and both kidneys, all affected, one year after transplantation, all died); metastases of a highly aggressive unknown primary tumour (recipients of liver and both kidneys, all affected, three months after transplantation, all died); and RCC in one kidney (removed 10 days after transplantation) while the other kidney of the same donor developed an RCC 3 years after transplantation [37].

9.3.1.7. *MALORY – MALignancy in Organ donors and Recipient SafetY (Germany)*

The MALORY study analysed data from a six-year period, 2006-11, of 248 organ donors with 254 malignancies (702 organs transplanted into 648 recipients) [9]. Follow-up information was collected in 2012 from 91 % (589) of the recipients. There was no confirmed tumour transmission from donors whose malignancies were known before organ acceptance and transplantation (median recipient follow-up 576 days). The most frequent non-CNS malignancies were RCC (n = 35), breast cancer (n = 15), colorectal carcinoma (n = 11), prostate carcinoma (n = 12) and thyroid carcinoma (n = 9). They presented in different stages, with different grades and ranged from 'minimal risk' to 'unacceptable risk' according to international recommendations. The most frequent CNS malignancies were glioblastoma WHO IV (n = 16) and anaplastic astrocytoma WHO III (n = 12). During the follow-up, 127 recipients (19.6 %) died of tumour-unrelated causes and 135 recipients (23 %) were lost to follow-up (no follow-up data available after January 2011).

Nevertheless, tumour transmissions did occur in the cohort: seven donors without any suspected malignant disease transmitted their occult carcinoma (three RCCs, two neuro-endocrine carcinomas, one breast cancer, one colorectal cancer) into 13 recipients. As of October 2015, seven of these recipients had died as a result of the transmitted tumour (four liver, two kidney, one lung recipient). Three kidney recipients (neuro-endocrine and breast cancer) were disease-free after metastatic disease treated by transplant nephrectomy, withdrawal of immunosuppression and chemotherapy. The three kidney recipients from donors with undetected RCC have never shown any clinical symptoms of the malignancy (all three kidney recipients had undergone transplant nephrectomy for either thrombosis or rejection post-transplant; pathological examination revealed incidental RCC).

The follow-up period is too short and the number of patients lost to follow-up is too high for final conclusions about transmission risk.

9.3.1.8. *Danish Registry Data*

Birkeland and Storm [38] linked all organ donors in a single transplant centre over a 27-year period to the Danish tumour registry. They identified 13 malignancies among 626 donors (2 %), of which eight were detected after the organs had been transplanted (1.3 %). Of those eight donors, only one transmitted the malignancy to the recipient, a melanoma (stage unknown at recovery) (0.2 %).

Tumour transmission through organ transplantation does occur. The number of organs accepted from donors with a previous or current history of malignancy seems to be increasing, but the frequency of documented tumour transmission is low. Under-reporting of transmission cases due to previous lack of mandatory reporting cannot be ruled out. Within the EU legal framework [13], and generally with mandatory reporting to national Health Authorities of SARs (including suspected/confirmed cases of malignancy transmission), it should be possible in future to assess more precisely the frequency of malignancy transmission through organ transplants.

9.3.2. Assessment of transmission risk

In cases where donor malignancy is diagnosed prior to or during organ procurement, a number of issues should be considered (see Table 9.2). In particular, it should be noted that:

a. Tumours that are newly diagnosed at procurement have to be evaluated very carefully. Organ donation is unlikely to proceed because very few types of active malignancy will be considered an acceptable risk. Testing for exact histological entity, stage and grade of the tumour is absolutely necessary prior to acceptance and must be performed according to the latest international criteria: AJCC Cancer Staging Manual, 8th edition [16] and the 2016 WHO Classification of Tumors of the Central Nervous System [17].

b. In cases of a treated malignancy in the patient's medical history, complete remission of 5-10 years (depending on tumour type, stage and grade) typically should have been achieved before the person is accepted for organ donation, although some exceptions exist. Careful assessment of the prognosis is recommended, taking into account that the AJCC/UICC TNM staging system and the WHO classification of

brain tumours have recently been updated. The new systems have been in place from 2017, and therefore the staging and grading of tumours diagnosed before 2017 might differ slightly from current practice.

c. Patients with metastatic tumours (lymph node or distant metastases) should not be accepted as organ donors. Exceptions might be made in selected cases of tumours diagnosed >5 years before procurement with an initial pN1 staging, full treatment and unsuspicious, recurrence-free follow-up with presumed cure.

d. Lack of surgical intervention, absent or incomplete follow-up or palliative therapy of malignancies in the patient's medical history are contraindications for organ donation (except for low-grade prostate cancer under active surveillance and certain brain tumours).

e. A donor with a previous malignancy must be evaluated carefully, both for the previous malignancy and for the increased risk of a *de novo* malignancy. For example, a donor with a previous colon adenocarcinoma (> 10 years) is at increased risk of developing a new colonic adenocarcinoma [39]. Therefore it is important to determine in the donor work-up the results and timing of any surveillance colonoscopies.

f. For a second opinion, advice from specialists in the respective oncological field and/or from experienced pathologists may be sought to further assess the individual transmission risk.

g. Potential recipients of organs from donors with a history of cancer should be fully informed before consent for transplantation is obtained by the transplant centre. The extent of this informed consent should be based on a risk–benefit analysis and should enable the recipient to generate a realistic perception of the situation, but without provoking undue concern in cases of very low transmission risk.

Table 9.3 shows the current transmission risk categorisations published by DTAC/USA [11], SaBTO/UK [12] and CNT/Italy [41]. The Council of Europe classification proposes a risk classification that consciously omits any numerical estimation because of the limited evidence currently available. Details of the risk classification of specific tumours will be found in section 9.3.3 and the subsections of 9.4 that follow.

The clinicians in charge of accepting and transplanting a graft have the overall responsibility for its use in a particular recipient, regardless of the estimated risks according to the classifications in Table 9.3.

OPTN/UNOS [11] classifies the risk of disease transmission for donors with a history of treated non-CNS malignancy (≥ 5 years prior) on the basis of probability that the tumour was cured:

- Low risk for transmission if probability of cure > 99 %;
- Intermediate risk for transmission if probability of cure 90-99 %;
- High risk for transmission if probability of cure < 90 %.

9.3.3. Circulating tumour cells

Circulating tumour cells (CTCs) have been detected in the blood of many cancer patients – e.g. breast [42], colorectal [43], prostate [44] – including early-stage cancers. Their existence has clinical impact on recurrence and survival in metastatic cancers. However, their relevance for the course of disease or the development of metastases in early stages is still under investigation. Different studies have found CTCs in 20 % [45] and 42 % [46] of patients with glioblastoma. To be clinically relevant and cause metastases, CTCs need additional properties such as the ability to implant into favourable sites, protection from host-specific and non-specific responses (decreased in transplant patients) and the

Table 9.2. **Items to consider for a potential organ donor with active or historical neoplasia**

Donor-related	Active tumour	What is the specific type of tumour? What is the extent of tumour, i.e. tumour stage? What is the risk of tumour transmission based on current available evidence?
	Historical tumour	All of the above, and also: How long ago did the tumour occur? What is the tumour-free interval? Is this tumour associated with late recurrence? What is the expected 5-year disease-free survival? Did the donor receive curative treatment for the tumour?
Recipient-related	What is the desire of the potential recipient? Is there a clear understanding of the risks involved? What type of post-transplant screening would be appropriate in this circumstance? For how long? What treatment options are available if tumour is transferred? What are the alternatives for this patient if transplantation is deferred because of concerns about tumour transmission?	

Source: modified after Nalesnik and Ison [40].

abilities to induce a blood supply and initiate growth. Accordingly, the fact that brain tumours rarely metastasise might be explained by the limited capacity of glioblastoma cells to exist outside the brain.

The probability of detecting CTCs in any kind of cancer correlates with the size of the sampling volume: in the case of large sample volumes (e.g. enrichment of cells by leukapheresis with 25 L of blood processed), CTCs might be detected with a high sensitivity. If only 10 mL of blood is tested in the setting of organ donation it is possible to obtain a false negative result due to the unrepresentative nature of the specimen [47, 48]. In addition to these technical difficulties and the limited experience in assessing the results, testing for CTC is expensive and time consuming, and the reliable detection of CTC is dependent on the availability of an experienced laboratory. Therefore, searching for CTC in organ donors is currently not appropriate, though it might become a valuable method in the future.

9.4. Solid organ tumours

Acceptance of donors with particular malignancies varies among European countries as well as worldwide. Published recommendations [11, 12, 41, 49] classify the different tumour entities according to their estimated transmission risk. This is based on the available literature, national data, expert opinions and data on tumour behaviour in non-transplant patients. In general, it is supposed that donors with tumours that are presumed to have been cured – after full treatment, adequate strict follow-up and without suspicion of disease recurrence or metastases – can be accepted for selected recipients, with an awareness of a remaining transmission risk. Probability of cure and the risk of metastases differ among the various tumours depending on their histotype, stage, grade and treatment, and these have to be taken into account. For example, an oesophageal cancer pT1N0M0 will be assessed differently after a recurrence-free survival of 2 years *versus* 25 years. Thus, the below-mentioned risk criteria may decrease for presumably cured donor cancers, but current literature does not provide sufficient data for definitive statements. There is no international consensus on a required time of recurrence-free follow-up, and national recommendations may vary from > 5 or > 10 years to never for the same tumour type and stage.

An individual risk–benefit assessment must be performed for every potential recipient. The permissive environment for growth of transmitted tumours in an immuno-suppressed recipient should also be taken into account.

Informed consent should be obtained from the recipient or their legal representative.

Every recipient who receives an organ from a donor with a history of malignancy should be offered additional testing, monitoring and treatment as appropriate, in addition to routine follow-up care (UNOS/OPTN policy 15.5.A) [50].

This Guide provides recommendations to assist in assessing different neoplasms. To apply these recommendations in clinical practice, donor evaluation should be as complete as possible in accordance with Chapter 6, also section 9.2, Table 9.1 and Table 9.2. In cases of doubt, the relevant national and individual strategy should be discussed with national experts.

The following alphabetical listing of neoplasms covers the most common cancers in terms of incidence and mortality in Europe [51], as well as other frequently reported donor malignancies. Additionally, for neoplasms that are not mentioned in any literature on organ donation but that are increasingly referred to in requests regarding the acceptance of potential organ donors, considerations about transmission risk and acceptability are included.

9.4.1. Basal cell carcinoma

See section 9.4.12.

9.4.2. Biliary cancer

See section 9.4.14.

9.4.3. Breast cancer

Since breast cancer has high potential for late and aggressive recurrence and metastasis, even after many years of complete remission, patients with this cancer should only be accepted as organ donors for very selected recipients and with the highest caution.

Friedman *et al.* reported two cases of breast cancer transmission in kidney recipients at 4 and 12 months after transplantation [52]. One recipient died, and the other was disease-free for 36 months after withdrawal of immune-suppression and anti-oestrogen therapy. Buell *et al.* referred to transmissions of breast cancer, reported to the voluntary IPITTR. These were only noted in cases of invasive breast cancer, not associated with *in situ* carcinomas [53], but the number of cases was not reported. Another case of transmission of an occult ductal breast adenocarcinoma was reported by Kauffman *et al.* [24]. The kidney recipient rejected graft and tumour after cessation of immune-suppression and was relisted for transplant after a recurrence-free survival of 4 years. Transmission of an occult meta-

static donor breast cancer into four recipients has been reported by Moench *et al.* [9], first diagnosed in the lung recipient 2 years after transplantation. The lung and the liver recipient as well as one kidney recipient died of the transmitted tumour. The other kidney recipient showed complete remission of the transmitted metastatic disease after transplant nephrectomy, withdrawal of immune-suppression and chemotherapy.

One recent case report describes donor breast cancer transmission confined to the keratolimbal allograft [54].

As in malignant melanoma, tumour cell dormancy is a well recognised phenomenon with breast cancer. Tumour cells spread to distant sites quite early during cancer progression. They can stay dormant and clinically undetectable after resection of the primary tumour for many years. Metastasis in breast cancer usually manifests asynchronously with the primary tumour and shows variable time to become clinically detectable [55, 56]. Therefore, an extended cancer-free period before accepting a donor with breast cancer is recommended, reliably performed follow-up should be ascertained and current donor examination for metastases including imaging should be very accurate, even after a long disease-free survival.

Receptor expression of oestrogen/progesterone (E/P) and HER2/neu should be checked for in the initial histological report. E+/P+ is associated with a favourable prognosis, but expression of HER2/neu+ results in a poorer outcome in the general oncological setting.

For recommendations regarding *in situ* breast cancer, go to section 9.4.4.

Breast cancer diagnosed during donor procurement

Newly diagnosed invasive breast cancer is an unacceptable risk for organ donation.

Breast cancer in the donor history

Organs from donors with invasive breast cancer might be accepted in selected cases after full treatment, complete remission and stringent follow-up for > 5 years, depending on the initial stage and E/P and HER2/neu receptor expression, always bearing in mind the risk of transmission due to possible late metastases.

Breast cancer stage 1 (AJCC, 8th edition) [16] with curative surgery and cancer-free period > 5 years seems to be associated with low to intermediate risk for transmission. All other invasive breast cancer stages are considered high-risk for transmission, independent of the presumed recurrence-free survival and treatment.

Table 9.3. **International recommendations for the assessment of transmission risk of donor malignancies**

CNT/Italy 2015	DTAC/USA 2011	SaBTO/UK 2014	Council of Europe 2018
Standard risk	No significant risk	—	—
Non-standard – negligible risk	Minimal risk (< 0.1 %)	Minimal risk (< 0.1 %)	***Minimal risk*** Donor acceptable for all organs and all recipients
Non-standard – acceptable risk	Low risk (0.1-1 %)	Low risk (0.1-2 %)	***Low to intermediate risk*** Donor acceptable, justified by the specific health situation of the recipient or the severity of their clinical condition, based on a risk–benefit analysis
	Intermediate risk (1-10 %)	Intermediate risk (2.2 % with upper 95 % CI of 6.4 %). Only high-grade CNS malignancies	
	High risk (> 10 %)	High risk (> 10 %)	***High risk*** Acceptance may be discussed in exceptional cases and for some life-saving transplantation procedures in the absence of any other therapeutic options on a case-by-case basis, after careful and reasonable risk–benefit assessment and informed consent of the patient
Non-standard – unacceptable risk	—	Absolute contraindication	***Unacceptable risk*** Absolute contraindication due to active malignancy and/or metastatic disease
—	Unknown risk (not equivalent to absolute contraindication)	—	—

9.4.4. Carcinoma *in situ* and pancreatic intra-epithelial neoplasia

Carcinoma *in situ* is a non-invasive epithelial tumour that has not crossed the basal lamina. Therefore, it has no potential for metastases, but can transform into an invasive tumour after some time.

In situ carcinoma of the cervix is also known as cervical intra-epithelial neoplasia (CIN) grade III. Less severe forms such as mild or moderate cervical dysplasia are referred to as CIN grades I and II, respectively. Cytologic preparations use the terms low-grade squamous intra-epithelial lesion to correspond to CIN I and high-grade squamous intra-epithelial lesion to correspond to CIN II or III.

Tumour transmission risk seems to be negligible for all forms of dysplasia and *in situ* carcinoma of the uterine cervix and many other sites, with no transmissions being reported.

Historical recommendations contraindicated transplants from potential donors with very aggressive malignancies, such as melanoma or lung cancer, for any stage of the disease, even in cases of *in situ* tumours [57, 58]. Also, high-grade *in situ* breast cancer is thought to be more aggressive than breast cancer *in situ* without high-risk features [53] because it entails the possibility of undetected micro-invasive carcinoma. Since carcinoma *in situ* is a very early, non-invasive tumour stage [59], patients with these diagnoses might be acceptable as organ donors with increased caution.

In cases of urothelial carcinoma *in situ*, which might be multifocal, it has to be kept in mind that urothelial tissue is transplanted with renal grafts and the transmission risk might be higher than for non-renal grafts.

Pancreatic intra-epithelial neoplasia (PanIN), grades 1-3, represents a non-invasive precursor lesion to pancreatic adenocarcinoma with cellular atypia, but without risk for metastases. PanIN do not form a mass, and are frequently associated with chronic pancreatitis. In the context of organ donation, PanIN will be found in three circumstances. First, they may occur in a donor who has previously had an abnormal lesion biopsied. These are often at the edge of frankly malignant tumours, so full histological examination of the lesion will be necessary. Second, they may be detected during organ procurement, where only PanIN that were part of a palpable abnormality would be noted. Third, PanIN may be detected incidentally in the histopathological examination of a pancreas that has not been transplanted. The result will be available after transplantation of other organs from the same donor, but these should not carry any risk for the recipient since PanIN in the absence of invasive cancer has no risk for metastases. Transplantation of the pancreas with PanIN itself, in contrast to other organs from the donor, would not be recommended, although no data exist on this subject.

Carcinoma *in situ* and PanIN diagnosed during donor procurement

Many *in situ* carcinomas – e.g. uterine cervix, colon, breast (only low-grade), non-melanoma skin, vocal cord – and confirmed PanIN in the absence of invasive cancer may be considered minimal risk. Transplantation of the pancreas itself in the case of PanIN is not recommended.

Regarding the non-muscle-invasive urinary bladder cancers, *in situ* urothelial cancer (pTis) and intra-epithelial papillary urothelial carcinoma (pTa/G1-2) – see AJCC, 8th edition [16] – are considered minimal risk for non-renal transplants. Renal transplants from these donors should be considered as a higher risk for transmission due to the often multifocal character of transitional cell cancers and the higher risk of cancer in the renal pelvis.

High-grade *in situ* breast cancer, *in situ* lung cancer and *in situ* melanoma/lentigo maligna are considered low to intermediate risk for transmission.

Carcinoma *in situ* and PanIN in the donor history

Many *in situ* carcinomas – e.g. uterine cervix, colon, breast (only low-grade), non-melanoma skin, vocal cord – and confirmed PanIN may be considered minimal risk. Transplantation of the pancreas from donors with a history of PanIN is considered questionable.

Non-muscle-invasive *in situ* urothelial cancer of the urinary bladder (pTis) and intra-epithelial, non-invasive papillary urothelial carcinoma of the urinary bladder (pTa/G1-2) – see AJCC, 8th edition [16] – are considered minimal risk for non-renal transplants if proper follow-up has been conducted. Renal transplants from these donors could have a higher risk for transmission due to the often multifocal character of transitional cancers and the higher risk of cancer in the renal pelvis.

High-grade *in situ* breast cancer, *in situ* lung cancer and *in situ* melanoma/lentigo maligna are considered low to intermediate risk for transmission.

9.4.5. Choriocarcinoma

Choriocarcinoma is a highly aggressive, malignant neoplasm originating from trophoblastic tissue after hydatidiform mole, miscarriage, ectopic or intra-uterine pregnancy. It has been described as having a high (93 %) transmission rate and a high (64 %) recipient mortality rate [53]. Occasional cases of unrecognised donor choriocarcinoma resulting in multiple transmissions continue to be reported [60]. In cases where choriocarcinoma is suspected (e.g. menstrual irregularities, cerebral haemorrhage in a woman without risk factors), assays for βHCG in the urine or blood (e.g. in cases of renal impairment of the donor) should be carried out, since βHCG levels are increased in females with choriocarcinoma. Due to the rare occurrence of this tumour, no extensive

donor data for a modified risk classification are to be expected in the future.

Choriocarcinoma diagnosed during donor procurement

Due to the high transmission and mortality rates, it is considered an unacceptable risk for organ donation in any stage of disease.

Choriocarcinoma in the donor history

Due to the reported high transmission and mortality rates, it is considered to be associated with a high or unacceptable risk for transmission through organ donation, depending on the recurrence-free period prior to donor death.

9.4.6. Colorectal cancer

There are two case reports describing metastatic transmission of occult colorectal carcinoma of the donor into liver recipients [61, 62]. In one case, liver metastases of donor origin were diagnosed 18 months after transplantation. Re-transplantation was not considered because of the patient's reduced health condition. The recipient died a few months later. In the second report, colorectal metastases were detected in the allograft 13 months after transplant. Following transplantectomy and re-transplant, the patient remained tumour-free with 4-year follow-up. Kidney, cornea and heart valve recipients from the same donor did not develop tumour post-transplant. In both case reports, donors were in the seventh decade of age.

Clearly, these rare but potentially devastating cases should remind procurement surgeons to carefully examine all intra-abdominal and intra-thoracic structures for suspicious lesions, particularly in older donors.

In donors with a past history of colorectal cancer, the higher chance of a new colorectal cancer – a metachronous tumour, incidence of around 3 % at 10 years [39, 63] – should be borne in mind when examining the abdominal contents during organ recovery.

Buell *et al.* [53] describe a 19 % transmission risk for organs from donors with a history of colon cancer but IPITTR has included only very small numbers of donors with colon cancer in its analysis [3]. On the other hand, several cases of organs being transplanted from donors with a past history of colorectal cancer are reported by the above-mentioned registries [5, 9, 22, 34, 36, 38] without subsequent disease transmission (see §9.3.1).

Colorectal cancer diagnosed during donor procurement

Acceptance of pT1-tumours – see AJCC, 8th edition [16] – has been discussed but seems to have a certain risk of lymph node and distant metastases in the donor. Therefore donors with pT1 tumours should only be accepted for organ donation with the utmost caution, and a high transmission risk must be assumed. Patients with higher stages of newly diagnosed, active colorectal cancer should not be accepted for organ donation (unacceptable risk).

Colorectal cancer in donor history

The presence of pT1/pT2 colorectal carcinoma (infiltration of submucosa/muscularis propria) in the donor without lymph node or distant metastases is assumed to have a low transmission risk after adequate treatment and disease-free survival of > 5 years. Risk increases with stage, and probability of presumed cure has to be taken into account.

In the past there has been discussion whether donors with early stages of colorectal cancer (pT1, infiltration of submucosa) might be acceptable, even in cases of a newly diagnosed, unresected tumour. Recent clinical findings show significant influence of submucosal infiltration depth (sm1-3), lymphovascular invasion (Lo-1), tumour budding and microsatellite instability on the risk of lymph node and distant metastases in pT1 tumours [64-66]. This may give reason to be careful in acceptance of a donor with recently diagnosed pT1 colorectal cancer. In these cases, thorough diagnostics should be provided but will not be available in time when a tumour is detected during organ procurement.

For recommendations regarding *in situ* colorectal cancer, go to section 9.4.4.

9.4.7. Gastric cancer

See section 9.4.14.

9.4.8. Gastrointestinal stromal tumour

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours and account for 5 % of all sarcomas. They are mostly detected as very small lesions in the walls of the stomach and/or small intestine, but can also be found in colon or rectum.

The risk of progression and metastases is correlated to four main prognostic factors [67]: tumour localisation, mitotic count (tumour cell proliferation), tumour size and tumour rupture before or during surgery.

Gastric or duodenal GIST < 2 cm, with mitotic index < 5 % have a low risk of metastases. Excision and follow-up are accepted as the only treatment. These GIST do not necessarily contraindicate organ donation. Rectal or jejunal GIST with a size of ≥ 2 cm

or mitotic index ≥ 5 % are associated with higher risk of metastases.

Fiaschetti *et al.* [36] reported a single donor with confirmed gastric GIST during the years 2003-2010 without evidence for transmission in the recipients. Novelli *et al.* [68] recently summarised five cases of GIST diagnosed in a single centre during donor procurement between 2011 and 2016 (three stomach, one ileum, one colon). After the suspicion of GIST in the frozen section, all five have finally been confirmed as low-grade (due to very few or no mitosis) GIST in permanent section and immunohistochemistry. Three organs (two kidneys from donor 1 and the liver from donor 2) have been transplanted without any sign of tumour transmission after 18 and 46 months.

Frozen sectioning can often help to identify GISTs with a very low potential risk of transmission. However, mitotic count evaluation as well as the search for presence of c-kit or DOG1 are performed on permanent sections and are typically not available as a frozen section assessment.

GIST diagnosed during donor procurement

Small (< 2 cm) GIST of the stomach or duodenum may be acceptable for organ donation with a low-to-intermediate risk for transmission. Mitotic index should be determined, though results are only likely to be available after transplantation of the organs. GIST from other primary sites, of larger size or high mitotic count, are associated with an increased risk of metastases and a high risk of transmission.

GIST in the donor history

Small (< 2 cm) GIST of the stomach or duodenum and mitotic count < 5 % may be acceptable for organ donation with a low-to-intermediate or even minimal risk of transmission, depending on therapy, follow-up time and recurrence-free survival. GIST from other primary sites, of larger size or high mitotic count, are associated with an increased risk of metastases and a high risk of transmission. No detailed information or recommendations are available from the literature.

9.4.9. Liver cancer

See section 9.4.14.

9.4.10. Lung cancer

Several registries [5, 7, 24, 53] and case reports [69, 70] have described transmission of an occult donor lung cancer (some of which include small-cell carcinoma), mostly resulting in the death of the recipient. This is indicative of the relevance and very aggressive behaviour of transmitted lung cancers in organ recipients. The transplant clinician should be especially aware of this possibility in the case of a donor with a heavy smoking history.

Jaillard *et al.* [71] report a case of small-cell lung cancer detected in the donor 7 months after living kidney donation. Transmission was confirmed in the asymptomatic recipient, who underwent transplant nephrectomy and three cycles of chemotherapy. Complete metabolic response could be demonstrated by FDG PET/CT 12 months thereafter but long-term outcome has not yet been reported.

A recent systematic review [72] of tumour transmission in the case of renal transplantation showed nine cases of lung cancer with a median onset time of 13 months post-transplant and with metastatic disease at presentation in seven of nine patients. Among patients with donor-transmitted cancers, those with lung cancer (or melanoma) had the worst prognosis. See also section 9.4.13.

For recommendations regarding *in situ* lung cancer go to section 9.4.4.

Lung cancer diagnosed during donor procurement

Any histotype of newly-diagnosed lung cancer is an unacceptable risk for organ donation.

Lung cancer in the donor history

Treated lung cancer is considered to be associated with a high transmission risk. Risk may decrease after curative therapy, with recurrence-free time and with increasing probability of cure.

9.4.11. Malignant melanoma

For malignant melanoma, Buell *et al.* of the IPITTR registry have shown a 74 % transmission rate and a 60 % recipient mortality rate [53]. Transmission events continue to be reported in case reports and in recent registry data [5, 22, 25, 38, 73, 74]. Most cases of reported donor-transmitted melanoma were cases where tumour diagnosis was missed in the donor [53, 75].

The data of Buell *et al.* [53], compiled from transmissions voluntarily reported to the IPITTR registry, conflict with those reported by Kauffman *et al.* [22] in the 2007 UNOS review: in 140 registered transplants with grafts from donors diagnosed with melanoma, only one transmission was reported (via a single lung). The donor had a melanoma resection 32 years before lung procurement and no transmission was reported from the other five recipients of grafts from the same donor. The analysed group of confirmed donor melanomas without transmission may contain a mixture of melanoma stages, including cases of *lentigo maligna*/*in situ* melanoma. This might explain the low transmission rate in this analysis. The report does not preclude the existence of risks, but it concludes that improved data collection, with a

description of the different stages of the donor melanomas, may help to clarify the issue. *Lentigo maligna* as an *in situ* melanoma must be distinguished from invasive melanoma for each individual case in order to determine whether this early stage should be generally considered separately from invasive melanoma.

Alsara and Rafi [76] and Sepsakos *et al.* [77] recently reported the same donor-transmitted melanoma after ocular limbal stem cell transplantation from a donor with metastatic melanoma in the history. Non-ocular malignancy had not been a contraindication for ocular tissue procurement in the USA in the past, except for leukemia and lymphoma. After this case, the Eye Bank Association of America updated the donor criteria to exclude donors with *any* history of melanoma or other solid metastatic tumours from vascular ocular tissue donation (scleral tissue and keratolimbal allografts). Donors with known metastatic melanoma are excluded from any ocular tissue donation [78, 79]. The European Eye Bank Minimal Medical Standards also differentiate vascular from avascular tissue donation and have restrictions on donors with a history of malignancy for vascularised tissue donation [80].

Currently, in most published reports of donors with a known history of melanoma, the precise data about staging, therapy and follow-up are missing [22, 38, 53]. It has to be kept in mind that in non-transplanted patients malignant melanoma often recurs, even after many years of disease-free survival.

Evidence increasingly indicates that single malignant melanoma cells spread to distant sites quite early during cancer progression. They can stay dormant and clinically undetectable after resection of the primary tumour for up to decades. To keep them dormant, a complex and fluctuating interaction between cells and environment is assumed. A change of this environment, e.g. transplantation of an organ with dormant melanoma micrometastases into a new and immunosuppressed host, can lead to metastatic growth in the recipient [81-83].

Late recurrences have been reported also in non-transplanted patients with small melanomas < 1 mm in thickness [84], so this aspect should be evaluated very carefully in the potential donor. Some yet unpublished cases, in which organs have been transplanted from donors with melanoma (mostly superficial spreading melanoma SSM) stage pT1a No Mo, resected (Ro), with recurrence-free survival > 5 years, are currently under evaluation.

Non-cutaneous, uveal melanoma tends to micrometastasise very early (before enucleation), and often to the liver [85, 86] where it may stay clinically undetected for years.

Because of the above-mentioned obstacles, the utmost caution is recommended when considering donors with a history of melanoma [87], unless the tumour can definitely be confirmed as *lentigo maligna* or *in situ* tumour and curative therapy has been adequate [59]. In all other cases of melanoma, the recommendation is to obtain all data about staging (including depth of invasion and ulceration), therapy, type of follow-up or recurrence-free time precisely, and then evaluate the metastasis risks with a dermato-oncologist before including the case for donation.

For recommendations regarding *in situ* melanoma refer to section 9.4.4.

Malignant melanoma diagnosed during donor procurement

Due to the very aggressive behaviour of this tumour, it is considered an unacceptable risk for organ donation.

Malignant melanoma in the donor history

Due to the lack of exhaustive data, transplanting organs from donors with treated malignant melanoma must still be considered to be associated with a high transmission risk.

If precise donor data about staging, therapy, follow-up and recurrence-free survival are available, and evaluation by the dermato-oncologist concludes there is a low probability of recurrence and metastasis, organ donation might be considered for selected recipients.

Taking this consideration into account, recommendations from SaBTO [12] state that a superficial spreading type of melanoma with tumour thickness < 1.5 mm after curative surgery and cancer-free period of > 5 years is associated with a low transmission risk, although these recommendations are based on a small number of cases.

9.4.12. Non-melanoma skin cancer

Basal cell carcinoma and squamous cell carcinoma of the skin usually do not metastasise and their existence in the donor history or diagnosed at procurement should therefore confer only minimal risk of transmission to the recipient. No reports exist of transmission of these tumours via organ transplantation.

In contrast, Kaposi's sarcoma, Merkel cell carcinoma and skin sarcomas are very aggressive skin tumours. Patients with these diagnoses, whether at procurement or in their history, are not acceptable as organ donors.

For recommendations regarding non-melanoma *in situ* skin cancer, refer to section 9.4.4.

Non-melanoma skin cancer diagnosed during donor procurement
Basal cell and squamous cell carcinoma of the skin are considered minimal risk due to very rare metastases.
Kaposi's sarcoma, Merkel cell carcinoma and skin sarcoma are considered an unacceptable risk.

Non-melanoma skin cancer in the donor history
Basal cell and squamous cell carcinoma of the skin are considered minimal risk due to very rare metastases.
Kaposi's sarcoma, Merkel cell carcinoma and skin sarcoma are considered an unacceptable risk.

9.4.13. Neuro-endocrine neoplasms

This section refers to high-grade neuro-endocrine carcinoma (NEC), low-grade neuro-endocrine tumours (NET), phaeochromocytoma (PCC) and paraganglioma (PGL).

NEC and NET most commonly arise in intestinal, lung or pancreatic tissue, but can be detected anywhere.

NEC transmission reports exist. In all cases, the tumour was undetected in the donor [70, 88-92]. All these tumours were high-grade (small-cell) neuro-endocrine carcinoma, manifested a few months after transplantation and showed aggressive behaviour that frequently led to death. A retrospective analysis shows that undetected systemic donor NEC have a high potential for being transmitted into recipients. Therefore, in cases of confirmed NEC transmission, all recipients of organs from the same donor should be considered for immediate retransplantation or transplant nephrectomy, respectively.

No data exist on the risk of transmission of well-differentiated NET (e.g. carcinoid tumours) following transplant.

Because of the impossibility of definitely excluding micrometastases during organ procurement, newly detected high-grade NEC should be a contraindication for organ donation.

PCC and PGL are catecholamine-secreting tumours of the adrenal medulla and extra-adrenal regions, respectively. Approximately 10 % of PCC and 15-35 % of PGL behave in a malignant fashion. At present, however, the only accepted criterion for malignancy is the presence of metastases. Late metastases have been reported up to 20 years after initial tumour resection [93].

In the absence of lymph node or distant metastases (lungs, bone, liver) at the time of the diagnosis, the main criteria to define a risk of malignant behaviour are: male gender, extra-adrenal location, greater tumour weight (average 383 g for malignant v. 73 g for benign), confluent tumour necrosis, vascular invasion and extensive local invasion [94]. Thompson [95] developed a system for assessing malignancy of PCC, the PASS score (Phaeochromocytomas of the Adrenal gland Scaled Score), which analyses and scores vascular invasion, mitotic index (>3), diffuse growth, diffuse necrosis, local invasion and nuclear atypia. Although all these features are possibly correlated with a potential malignant behaviour, the high inter- and intra-observer variations limit the clinical use of this score.

It is extremely difficult to predict the biological behaviour of these tumours when first detected during organ procurement. Criteria such as size and weight of the tumour mass, presence of necrosis, high mitotic rate and infiltrative margins can help to identify the risk profile for transmission, but the mitotic index in particular will not be assessable by frozen section.

Because of the uncertainty about the malignant potential of these neoplasms, all cases of PCC/PGL should be followed up on a long-term basis, even after complete surgical resection of the tumours. Regular biochemical screening and blood pressure monitoring are essential for identifying recurrence or metastasis. Elevated metanephrine levels in urine or plasma in a potential organ donor with a history of PCC/PGL require further evaluation to exclude metastasis.

PCCs and PGLs are rarer in the paediatric population than in the adults, but the chance of malignancy is higher among children with these tumours, with a reported incidence of 47 % [96].

One single case report describes a kidney transplant from a donor with a PCC found intra-operatively. Due to the suspected non-malignant behaviour of the tumour, kidney transplantation was performed and the recipient of the ipsilateral kidney was well 2 years thereafter [97]. The contralateral kidney recipient died of tumour-unrelated causes shortly after transplantation.

A case of transmission of PGL has been reported [98].

Careful risk–benefit consideration is necessary in individual cases of PCC and PGL.

Neuro-endocrine tumours diagnosed during donor procurement
Due to their potential for undetected metastasis, high-grade neuro-endocrine carcinomas are an unacceptable risk for organ donation.
Insufficient information exists to guide practice for neuro-endocrine tumours, carcinoid tumours, phaeochromocytomas and paragangliomas. In the case of critically ill recipients, these tumours might be acceptable after a careful individual risk–benefit analysis.

Neuro-endocrine tumours in the donor history

No data are available from the literature. Due to this and their potential for undetected metastasis, treated high-grade neuro-endocrine neoplasms in the donor history are classified as high risk for organ donation.

In the case of a previous history (> 5 years) of neuro-endocrine tumours without any kind of disease recurrence or progression, it is possible to evaluate a risk profile especially for life-threatened recipients, but insufficient information exists to guide practice for carcinoid tumours, phaeochromocytomas and paragangliomas.

9.4.14. Oesophageal, gastric, pancreatic, liver and biliary cancers

For the majority of these tumours, only scarce data are available. There are two reported liver transplants from donors with confirmed oesophageal carcinoma without transmission [34], but no information about initial stage and recurrence-free survival of the donor is provided. No transmission of oesophageal cancer has been described in the published literature so far. This might be a reporting bias and should not lead clinicians to freely accept organs from donors with such aggressive tumours.

Regarding gastric cancer, there is one case report [99], in which pre-donation evaluation of a living liver donor revealed early gastric signet cell cancer (pT1NoMo, sm1). The designated recipient was the 9-month-old child of the living donor and there was no other living or deceased donor available; meanwhile the child's health situation was deteriorating rapidly. One month after gastrectomy of the donor, liver donation and transplantation were performed. Donor and recipient were well and without malignant disease one year thereafter. This example illustrates an extraordinary situation and should not justify such procedures as a good and routine practice.

One case report shows the transmission of an undetected pancreatic adenocarcinoma through kidney transplant [100]. The tumour was diagnosed after the kidney had been transplanted (in the adrenal tissue that was removed during bench preparation). The recipient developed pulmonary lymphangiomatosis carcinomatosa 9 months after transplantation and died 6 months later. Another transmission of pancreas carcinoma was detected 12 months after transplant in a liver recipient [24] who underwent retransplantation and was alive at the time of the report. Three further recipients have suffered from transmitted pancreatic cancer [5].

One recipient has been reported with transmitted hepatocellular carcinoma [5].

Yamacake *et al.* [101] reported the transmission of a metastatic intestinal adenocarcinoma, undetected in the donor, into both kidney recipients. This indicates the existing risk of tumour transmission through organs which are not considered to be the primary target of metastases.

One renal transplant patient in the series reported by Georgieva *et al.* [102] developed a donor-derived cancer that was found 4 months after transplant and suspected to be of biliary origin. Two other recipients of the contralateral kidney and the liver from the same donor, who had an unremarkable medical history, also developed metastatic adenocarcinoma, whereas no tumour was found in the heart or pancreatic islet recipients. No other reports of suspected or proven transmission of biliary cancer are available in the literature. For recommendations regarding *in situ* cancers go to section 9.4.4.

Oesophageal, gastric, pancreatic, liver and biliary cancers diagnosed during donor procurement

These tumours are classified as unacceptable risk.

Oesophageal, gastric, pancreatic, liver and biliary cancers in the donor history

Treated tumours of these kinds in the donor history are classified as high risk due to their aggressive behaviour. Risk may decrease for early stages after curative therapy, with recurrence-free time > 5 years and with increasing probability of cure, especially in cases of long-term survivors.

9.4.15. Oropharyngeal cancer

A pyriform sinus carcinoma which manifested in the kidney recipient as liver metastases has been reported by Murray *et al.* in 1965 [1]. No further reports of transmission are available from the literature. There is a report of 11 organs transplanted from donors with a history of tongue/throat cancer, without transmission. The initial tumour stage was not reported but all donors had a recurrence-free survival of > 5 years [22]. However, the aggressiveness of these tumours should be kept in mind.

Oropharyngeal cancer diagnosed during donor procurement

The presence of oropharyngeal cancer is considered an unacceptable risk for organ donation.

Oropharyngeal cancer in the donor history

Treated oropharyngeal cancer is considered high-risk for organ donation. Depending on initial stage, grade, therapy and time of recurrence-free survival (> 5 years), the risk category might decrease individually.

9.4.16. Ovarian cancer

There is a published case report [103] about transmission of ovarian cancer into two kidney re-

cipients, with fulminant metastatic disease leading to recipient death.

One example of a potential donor with a past history of well-differentiated serous ovarian carcinoma was reported by Nickkholgh *et al.* [104]. The tumour had been treated surgically and there was no evidence of disease for a 10-year period. At the time of organ procurement, a pelvic recurrence of the tumour was identified and the organs were not used. This highlights the need for meticulous inspection in the setting of a positive cancer history.

Beyond these reports, there are no further data available in the literature.

Ovarian cancer diagnosed during donor procurement

Ovarian cancer is considered an unacceptable risk for organ donation.

Ovarian cancer in the donor history

Treated ovarian cancer is considered high-risk for organ donation. Depending on initial stage, grade, therapy and time of recurrence-free survival (> 5 years), the risk category might decrease individually.

9.4.17. Pancreatic cancer

See section 9.4.14.

9.4.18. Pancreatic intra-epithelial neoplasia

See section 9.4.4.

9.4.19. Paraganglioma

See section 9.4.13.

9.4.20. Phaeochromocytoma

See section 9.4.13.

9.4.21. Prostate cancer

Given the increased incidence of prostate cancer with advanced age and the increasing age profile of donors, it is certain that organs from donors with undiagnosed prostate cancer are currently being utilised.

Sanchez-Chapado *et al.* [105] evaluated prostate cancer in a consecutive series of prostate glands collected at *post mortem* examination from 162 Spanish males who died from trauma. They reported prostate cancer in 23.8 % of individuals aged 50-59 years, 31.7 % aged 60-69 years and 33.3 % aged 70-79 years.

Yin *et al.* found incidental prostate adenocarcinomas in 12 % (41/340) of presumed healthy organ donors over a 13-year period [106] with a similar frequency (23.4 %/50-59 years, 34.7 %/60-69 years, 45.5 % 70-81 years).

The validity of repetitive PSA testing in combination with digital rectal examination has been questioned. The European Randomized Study of Screening for Prostate Cancer (ERSPC) found a 21 % reduction in mortality after 13-year median follow-up, with biennial to quadrennial PSA screening using a 3 ng/mL cut-off for further investigation, as compared to minimal PSA testing [107]. In contrast, data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial showed no survival advantage with 4-6 annual PSA tests with a cut-off of 4 ng/mL at 15 years compared to controls [108]. However, in this study, a significant number of control patients also underwent annual screening, suggesting that more frequent screening might not offer additional benefit [109].

In Italy, digital rectal examination (DRE) of the donor is mandatory, with these provisions:

- in cases of negative DRE with PSA <10 ng/mL histological examination of the prostate is not required;
- in cases of negative DRE but with PSA values > 10 ng/mL, the histological evaluation is preferred but not mandatory;
- in cases of positive DRE, histological examination is mandatory.

There is also broad consensus that single PSA testing is not of high prognostic value [110]. Moreover, there is no agreement as to what PSA levels should be considered suspicious or even normal.

Pabisiak *et al.* [111] reported that the application of PSA screening to the Polish donor population resulted in a 10 % disqualification rate for male donors when a cut-off of > 10 ng/mL was used. They performed follow-up analysis by routine pathologic evaluation of prostates from all male donors over a 4-year period and were unable to find any correlation between elevated (> 4 ng/mL) PSA and either prostate carcinoma or high-grade prostatic intra-epithelial neoplasia. During this study, 12 kidneys and three livers from donors with prostate cancers that were histologically confirmed and confined to the prostate were transplanted with no evidence of disease transmission during 9-52 month follow-up.

For confirmed prostate cancer, the Gleason score and the corresponding grading group according to the ISUP WHO 2014 system [112] in conjunction with staging are the strongest predictor for clinical recurrence and overall survival of prostate cancer. For practical purposes, prostate cancers are generally

classified in Gleason's score groups, each with significant differences in outcome (higher scores/groups result in poorer outcomes). The following overview is describing the recurrence risk in non-transplant patients with prostate cancer:

- group I Gleason 3+3
- group II Gleason 3+4
- group III Gleason 4+3
- group IV Gleason 4+4
- group V Gleason 4+5, 5+4, 5+5

Group I tumours are associated with low risk of biochemical recurrence, groups II and III with intermediate risk and group IV and V with high risk. The presence and the amount of Gleason patterns 4 and 5 are the strongest histological predictors of prostate cancer aggressiveness and local or distant relapse [16].

In the non-transplant setting, carefully selected, very low-risk patients with localised small prostate carcinomas T1/2 and Gleason score 3 + 3 may be followed with an 'active surveillance' approach [113], meaning that they will not undergo surgery but are surveyed at short intervals for further disease progression. This strategy has had no long-term results yet and has not been evaluated in the context of organ donation. However, it may be interpreted according to the staging of the malignancy, which is done during procurement. Pabisiak *et al.* [111] concluded from their study that donors with tumours confined to the prostate and with Gleason scores of 7 or less could be considered as standard-risk donors.

In 2010, the Emilia-Romagna Region and the Italian CNT published the results of a 4-year experience with statements by expert pathologists ('second opinions') in donors with suspected prostate cancer, evaluating the entire gland with frozen sections [114]. According to the initial risk classification effective from 2008 to 2014, donors were classified for transmission risk in three categories: no prostate cancer or intra-prostatic tumour with a Gleason score ≤ 6 – *standard risk* (2015 classification [41]: *Non-standard – negligible risk*); intra-prostatic tumour with a Gleason score 7 – *non-standard risk* (2015: *Non-standard – acceptable risk*); or pT3a/b extra-prostatic cancer or lymph nodes and/or distant metastases – *unacceptable risk* (2015: *Unacceptable risk*).

Overall, 94 % of the donors were classified as standard-risk, a category which had been 63 % before implementation of this protocol. A significant increase in the number of transplanted organs was achieved by expanding the criteria for standard-risk donors. No tumour transmission had been reported by CNT when this Guide was ready for publication.

OPTN/DTAC reported five autopsy-proven cases of donor prostate adenocarcinoma without evidence of transmission [5]. A recent review by Doerfler *et al.* [115] documented 120 organ transplants from donors with confirmed prostate cancer with no evidence of disease transmission.

Additionally, a meta-analysis of the literature on kidney transplantation from donors with prostate cancer by Dholakia *et al.* [116] states that the risk of transmitting prostate cancer is lower than the risk of remaining on the waiting list. Acceptance of these donors requires proper donor characterisation and selection.

A single case report of transmission of prostate adenocarcinoma occurred in the context of heart transplantation from a donor who was subsequently found to have prostate adenocarcinoma metastatic to lymph node and adrenal gland at the time of donation [117]. This case is referred to in various registry reports [3, 24, 27].

Prostate cancer diagnosed during donor procurement

If Gleason score is available, e.g. prostate diagnostics have been initiated a few days before organ procurement, then small intra-prostatic, low-grade (Gleason score ≤ 6) tumours are considered minimal-risk; intra-prostatic tumours with Gleason score 7 are considered low-to-intermediate risk; and intra-prostatic (pT2c) tumours with Gleason score > 7 are considered high-risk.

Histological examination of the entire prostate with a valid grading of the tumour is time-consuming and the results might not always be available before an organ is transplanted.

Donors with extra-prostatic tumour extension should be unequivocally excluded from the donation process as an unacceptable risk.

Prostate cancer in the donor history

The acceptable time intervals for complete remission of prostate cancer are strongly correlated with stage and Gleason grade of the tumour.

Donors with a history of curatively treated prostate cancer ≤ pT2 (tumour confined to prostate) and Gleason 3 + 3, as well as donors with very small prostate cancers and Gleason 3 + 3 under 'active surveillance', can be accepted for organ donation as minimal transmission risk at any time after diagnosis with the prerequisite of a frequently performed and non-suspicious follow-up.

Prostate cancer < pT2 (confined to the prostate) and Gleason grade < 7 after curative treatment and cancer-free period > 5 years is considered minimal-risk.

Higher stages/grades and/or shorter cancer-free periods require an individual risk assessment. A history of extra-prostatic tumour extension poses a high risk for transmission.

In any case, current PSA values should be obtained to compare to former ones and to assess the actual situation.

9.4.22. Renal cell carcinoma

The literature on RCC and transplantation covers four general topics:

- inadvertent transplantation of kidneys that contain RCC not recognised at the time of operation,
- resection of a small RCC at time of procurement with subsequent transplantation of the kidney,
- transplantation of contralateral non-tumorous kidneys or other organs from donors with solitary renal cancers and
- donors with a history of RCC.

In 1995, Penn [4] described 17 recipients with transmission of malignant kidney tumours undetected at time of procurement. Of these, 10 recipients (eight RCC, two urothelial carcinomas) underwent transplant nephrectomy and were recurrence-free at an average of 59 months thereafter. Seven other recipients (two RCC, three anaplastic carcinoma, two urothelial carcinoma) first presented with metastatic disease and died from their tumours after an average of 12 (range 3-47) months post-transplant.

Llamas *et al.* [118] reported the transmission of sarcomatoid (poorly differentiated) RCC in two kidney recipients after transplant without any evidence of tumour in the organs at the time of transplantation.

OPTN/DTAC [5] showed seven recipients with confirmed transmissions from 64 donors with RCCs. Desai *et al.* [7] described six transmitted RCCs incidentally detected in protocol biopsies or biopsies to assess graft dysfunction. The recipients of other organs of those donors were tumour-free.

In a recent systematic review of donor cancer transmission by renal transplantation, Xiao *et al.* [72] found 20 examples of RCC transmission. In each case the presence of tumour was not known by the surgeons at the time of transplantation.

In contrast to the above scenario, a number of reports demonstrate successful outcomes when small (< 4 cm), solitary and well-differentiated (Fuhrman grade I-II) RCCs are resected at time of procurement followed by transplantation of the treated kidney [4, 7, 9, 11, 49]. Nephron-sparing surgery is an established curative approach for the oncological treatment of RCCs ≤ 5 cm in the non-transplant population [119] with cancer-specific survival rates comparable to radical nephrectomy [120].

Following a review of the literature in 2011, the UNOS DTAC [11] concluded that solitary well-differentiated RCCs less than 1 cm and completely resected prior to transplant were associated with a minimal residual risk of transmission, while those of 1-2.5 cm carried a low risk and those of 2.5-7 cm an intermediate risk of transmission. Larger tumours, or those of Stage II or higher, were considered high-risk.

In 2014, a systematic review by Yu *et al.* [121] found 20 examples of kidneys transplanted after resection of well-differentiated (and one Fuhrman grade III) RCC at the time of procurement. Tumour sizes ranged from 0.5 to 4 cm in size with follow-up times up to 200 months. No tumour transmission occurred. An additional 70 examples of kidneys transplanted from donors who had been previously surgically treated (without chemotherapy or radiotherapy, implying limited disease) for RCC were included with follow-up up to 135 months. Of these, one possible tumour recurrence was reported [122] 9 years after transplantation as a 1 cm lesion remote from the initial resection site, thus likely representing a *de novo* rather than a transmitted tumour. The recipient refused diagnostics and treatment, and the final nature of the lesion remained indeterminate. All other kidney recipients showed no tumour transmission after mean follow-up periods of 14-135 months. Additionally, Musquera *et al.* [123] reported the transplantation of eight kidneys after Ro-resection of RCC with a mean size of 1.5 cm (0.3-4.3) and Fuhrman grade I. The recipient follow-up after median 32 months (1-57) was without tumour recurrence.

The necessity of complete resection of RCC before transplanting the affected kidneys was previously shown by Penn [4], who reported two donor RCCs that were either not excised or incompletely excised at procurement and transmitted to the recipients.

Resection of small RCCs with subsequent renal transplantation has also been reported in the setting of live kidney donation. Lugo-Baruqui *et al.* [124] reported four such transplants, Ogawa *et al.* [125] reported a series of 10 transplants and Lim *et al.* [126] reported two kidney transplants with no evidence of tumour transmission in any case. However, ethical considerations have been raised regarding the performance of donor nephrectomy in such circumstances [127], and the American Society of Clinical Oncology guidelines recommend offering partial nephrectomy as treatment for patients with small renal cancers that are amenable to this approach [128].

There are scattered reports of the use of contralateral kidneys or other organs from donors with solitary RCC. Serralta *et al.* [129] reported four donors with RCC, all detected at time of transplant but after the respective livers had been transplanted. No tumour transmissions were seen after a mean follow-up of 58.5 months. Carver [130] refers to a liver

and a contralateral kidney transplant from a donor with solitary RCC, without evidence of a tumour transmission after 4 years of follow-up. In contrast, Sack [131] reported the transmission of a donor RCC detected in the kidney during the ongoing transplantation of the heart recipient, who died of metastatic renal cancer 12 months after the transplant.

Similarly, in 2001, Barrou [132] referred to a contralateral kidney-and-heart transplant from a donor with a 17 mm Fuhrman I-II tubulo-papillary adenoma (which would be classified as carcinoma according to current standards). It was detected in the kidney after the other organs of the donor had already been transplanted because the perinephric fat was not removed for inspection during organ procurement. The contralateral kidney recipient underwent a transplant nephrectomy 4 months later due to tumour infiltration of the kidney, while the heart recipient died 7 months after transplantation due to metastatic renal cancer. Of interest, the post-transplant tumour was described as undifferentiated, raising the possibility that it may have been unrelated to the original small, well-differentiated tumour. Furthermore, the tumour grew in an infiltrative pattern, which is unusual for RCC. Buell *et al.* [27] reported two donor RCCs that were metastatic at the time of procurement (detected after transplantation of organs) that were transmitted in lung and heart/lung recipients who both died of metastatic disease. Organs from three further donors with RCCs detected during procurement and confined to the kidney were transplanted without transmission, with a follow-up of 30, 36 and 70 months.

Yu *et al.* [121] reviewed reports of 21 contralateral healthy kidneys from donors with RCC. Except for the transmission case of Barrou *et al.* [132] described above, there were no reported transmissions from those kidneys.

The ONT Registry did not detect any tumour transmission among 56 recipients transplanted with grafts from 47 donors registered with RCC (15 kidneys, 29 livers, seven hearts and five lungs). Prophylactic removal of the graft was performed in nine of these kidneys, two livers and one heart. After 3 years of follow-up, tumour transmission had not appeared in any of the cases. As mentioned in section 9.3.1, in two of the cases a kidney with an occult tumour had been transplanted. Here, the incidental diagnosis was made by biopsy after transplant and was followed by transplant nephrectomy; no symptomatic malignancy was observed.

The MALORY initiative [9] described a 6-year experience with the transplantation of organs from 35 donors with RCC (three in donor history, 20 found at organ procurement, 12 diagnosed before implantation). From these donors 28 livers, 18 kidneys, 13 hearts and 13 lungs were transplanted, though the affected kidneys were not accepted. No tumour transmission was reported after 2 years. In parallel, three further donors had an occult RCC at the time of transplantation. These RCCs were diagnosed incidentally after transplant nephrectomy for tumour-unrelated causes 6-46 days after transplantation. The recipients did not show any symptomatic malignancy.

Assessment of renal masses at time of procurement should include frozen section analysis since in some cases benign conditions (e.g. oncocytoma, adrenal rest, angiomyolipoma) can mimic RCC. In addition to providing a diagnosis, the frozen section report in the case of RCC should comment upon the size of the resected lesion, estimate of Fuhrman grade and adequacy of resection margin.

According to the 2016 WHO classification of genito-urinary tumours, papillary renal neoplasms < 1.5 cm in size must be considered benign by definition [133] unless the analysing pathologist finds evidence for malignant behaviour. Borderline cases should be discussed thoroughly.

RCCs can be multifocal and have a bilateral incidence in 5 % of cases [134]. Careful examination and the use of ultrasound analysis are desirable for the identification of this tumour in both kidneys after removal, especially in cases of papillary RCC.

In 2012, the International Society of Urological Pathology (ISUP) introduced a new grading system for RCCs [135], based on the assessment of the nucleolar grade (grades 1-4). This has been shown to provide outcome predictions superior to Fuhrman grading for both clear cell and papillary RCCs [136, 137]. Nucleolar grade can be considered similar to Fuhrman grade.

RCC diagnosed during donor procurement

To provide valid histological staging, complete tumour resection (Ro) is required for acceptance of all organs; additionally, tumour-free margins are a prerequisite for transplant of the affected kidney. The contralateral kidney should always be examined for synchronous RCC (5 % of patients).

- RCC < 1 cm (stage T1a AJCC 8th edn) and nucleolar grade I/II (Fuhrman grade I/II) can be considered minimal-risk for transmission;
- RCC 1-4 cm (stage T1a AJCC 8th edn) and nucleolar grade I/II (Fuhrman grade I/II) are considered low-risk;
- RCC > 4-7 cm (stage T1b AJCC 8th edn) and nucleolar grade I/II (Fuhrman grade I/II) are considered intermediate-risk;
- RCC > 7 cm (stage T2 AJCC 8th edn) and nucleolar grade I/II (Fuhrman grade I/II) are considered high-risk;
- RCC with extension beyond the kidney (stages T3/T4 AJCC 8th edn) is considered a contraindication to transplant;

- All RCC with nucleolar grade III/IV (Fuhrman grade III/IV) are considered high-risk for transmission;
- Contralateral kidneys and other organs that are uninvolved in carcinoma are considered to represent minimal risk for transplantation when the RCC in the involved kidney is 4 cm or less and Fuhrman or nucleolar grade I-II.

In all cases, follow-up surveillance is desirable.

RCC in the donor history

The transmission risk of treated RCC depends on the histological type of tumour [133] and its recurrence-free follow-up period. In general, in the first 5 years after initial diagnosis, risk categories correspond to those stated above (RCC diagnosed during donor procurement) if there is no suspicion of tumour recurrence in the donor. After this time, the risk of advanced stages may decrease.

9.4.23. Sarcoma

Despite a bewildering variety of sarcomas, guidance in most cases (with a few exceptions, e.g. GIST, see §9.4.8) is based on the fact that these tumours as a group tend to behave aggressively, with a propensity to recur and spread. Sporadic case reports document extended survival following early transplantectomy [27, 138, 139], but the usual outcome after transmission is fatal [6, 140, 141]. For this reason, sarcoma or a history of sarcoma is at present considered a contraindication to organ or tissue donation.

Sarcoma diagnosed during procurement

Due to the very aggressive behaviour of sarcoma, they are considered an unacceptable risk for organ donation at any stage of disease.

Sarcoma in donor history

Because of the very aggressive behaviour of sarcoma, they are mostly considered an unacceptable risk for organ donation. After curative treatment and a recurrence-free survival of > 5 years, sarcoma are still assumed to be associated with a high risk for transmission.

9.4.24. Squamous cell carcinoma of the skin

See section 9.4.12.

9.4.25. Thyroid cancer

An explosion of knowledge of the molecular genetics of well-differentiated thyroid cancer is under way at present, with specific mutations linked to prognosis in some cases [142]. However, this information is still fragmentary and is typically unavailable in the setting of transplantation. The below-mentioned recommendations [11, 12] have therefore been based to date on the aggregate behaviours in histology (follicular v. papillary) and tumour size/stage.

No transmission cases of donor thyroid cancer through organ transplant have been reported.

Thyroid cancer diagnosed during donor procurement

Solitary papillary thyroid carcinoma < 0.5 cm is considered minimal risk and 0.5-2 cm is considered low to intermediate risk. Minimally invasive follicular carcinoma < 1 cm is considered minimal risk and 1-2 cm is considered low to intermediate risk.

Newly diagnosed medullary and anaplastic thyroid cancers are an unacceptable risk for organ donation.

Thyroid cancer in the donor history

Treated, small, differentiated thyroid cancers (such as papillary and follicular) are acceptable, analogous to the above recommendations for newly diagnosed thyroid cancers. Certainly, curative therapy and sufficient follow-up with presumed cure should be assured.

No recommendations exist for medullary and anaplastic thyroid cancer but, because of their aggressive clinical behaviour, they should be accepted for organ donation, if at all, only with the highest caution and after a long-term recurrence-free follow-up.

9.4.26. Urothelial carcinoma

Reports of transmission of urothelial carcinoma are uncommon and such tumours usually arise from the renal pelvis/ureter accompanying the allograft kidney.

Huurman *et al.* [143] documented ureteric obstruction as the first symptom in their recipient and a separate patient reported by Ferreira *et al.* [144] developed gross haematuria 3 months after transplant as the first indication of tumour. In this latter case, the patient died with metastatic disease and a liver recipient from the same donor required retransplantation for a metastatic donor urothelial cancer that arose in the allograft separately reported by Backes *et al.* [145].

One of two patients reported by Hevia *et al.* [146] was found to have a high-grade urothelial carcinoma of the renal pelvis with fat infiltration on routine sonography 14 months post-transplant. The patient underwent allograft nephrectomy and was free of tumour at 14 months follow-up.

Penn [4] reported metastatic transmission of two undetected donor transitional cell carcinomas into two kidney recipients who died of the tumour.

Mannami *et al.* [147] reported the transplantation of eight 'restored' donor kidneys with confirmed transitional cell carcinoma of stages pTa (three), pT1 (one), pT2 (three), pT3 (one). Tumours were resected back-table before implantation and negative margins were confirmed in permanent section. One recipient (pT3) developed local recurrence after 15 months (tumour resection performed) and died of presumed

primary lung cancer (with liver metastases), but metastatic urothelial cancer could not be ruled out. However, this procedure was subsequently criticised on both ethical and technical grounds [148].

Mitsuhata *et al.* [149] from the same group described the transplantation of three 'restored' kidneys with urothelial carcinoma, pT1/G1 (one), pT2/G2+3 (two), without tumour recurrence in the recipients after 62-109 months.

Urothelial cancer guidelines and prognosis scores distinguish non-muscle-invasive cancer (pTa, pTis, pT1) from muscle-invasive stages (> pT2), which is unique for this type of cancer.

In Italy, the recommendations for the suitability of organ donors consider newly diagnosed single low-grade and low-stage (G1-2, pTa/pT1) papillary urothelial cancers as well as high-grade *in situ* urothelial carcinoma (pTis) as negligible risk for transmission (corresponding to minimal risk in the Council of Europe recommendations). Conversely, multiple tumours (including pT1), high-grade, muscle-invasive urothelial cancer of the bladder, the ureters and the renal pelvis infiltrating kidney parenchyma are considered as an unacceptable risk for organ donation in Italy.

In general, the highly aggressive behaviour and potential multicentricity of these tumours has to be respected in any risk–benefit assessment.

For recommendations regarding *in situ* urothelial cancer go to section 9.4.4.

Urothelial cancer diagnosed during donor procurement

No literature exists regarding newly diagnosed urothelial cancer and organ donation. Therefore, the highest caution is recommended, and the advice of a urologist may be sought in assessing the individual donor tumour transmission risk. National recommendations should be followed since they vary in accepting these tumours.

Urothelial cancer in the donor history

Strict follow-up must have been provided after primary diagnosis because these tumours may be multicentric and tend to recur, with a need for repeated cystoscopy and TUR-B, and for restaging.

Kidney transplantation will be associated with increased risk, but this has not been classified in the literature yet.

After a disease-free interval > 5 years, the transmission risk of invasive urothelial cancer will depend on the probability of cure and has to be assessed individually before accepting a potential organ donor. No specific recommendations are available from the literature.

9.4.27. Uterus and uterine cervix cancer

With the exception of cervical dysplasia/carcinoma *in situ*, which is not associated with tumour transmission [38], no data are available from the literature regarding transmission of uterine and cervical cancer.

For recommendations regarding *in situ* cervix cancer go to section 9.4.4.

Uterus or uterine cervix cancer diagnosed during donor procurement

The presence of invasive uterus or cervix cancers is considered an unacceptable risk for organ donation.

Uterus or uterine cervix cancer in the donor history

After a disease-free interval > 5 years, the transmission risk of invasive uterus and cervix cancers will depend on the probability of cure, and has to be assessed individually before accepting the potential donor; no specific recommendations are available from the literature.

9.5. Haematopoietic malignancies

9.5.1. Leukaemia, lymphoma, plasmacytoma and monoclonal gammopathies of undetermined significance

There are case reports about inadvertent transmissions of lymphomas [150-153]. In a recent systematic review of donor-transmitted cancer in renal transplant recipients, Xiao *et al.* [72] found 15 examples of lymphoma transmission with a median presentation of 4 months after transplant. One of the 15 had metastatic disease at presentation and later died of the disease.

Rarely, unsuspected donor T-cell lymphoblastic lymphoma has manifested as acute lymphoblastic leukaemia (ALL) in the recipient [154] and, conversely, donor leukaemia has presented as a solid tumour (promyelocytic sarcoma) in an organ recipient [155]. Haematopoietic diseases should be handled with the greatest caution in the organ donation process and donors presenting with them should typically not be accepted due to the systemic spread of such diseases.

One patient with a high-grade lymphoma and successful stem-cell transplantation 4 years before organ donation was accepted as a liver donor in Germany. The liver recipient was without signs of malignancy 3 years after transplantation [9].

Currently, no further data are available on organ donors after human stem-cell transplantation in short- and long-term survival cases without relapse. In patients who are in remission and being treated with advanced protocols (without stem-cell transplantation), transmission of malignant clones cannot be excluded.

Sosin *et al.* [156] reported a donor-related peritoneal plasmacytoma 3 years after transplantation in the liver recipient, showing chimeric donor and re-

cipient origin. No further literature exists regarding plasmacytoma in organ donors.

Leukaemia, lymphoma and plasmacytoma diagnosed during donor procurement

These cancers are classified as an unacceptable risk for organ donation.

Leukaemia, lymphoma and plasmacytoma in the donor history

Active (acute or chronic) leukaemia, lymphoma and plasmacytoma are an unacceptable risk for organ donation. Treated acute leukaemia and lymphoma after a definite disease-free interval of 5-10 years may be considered for organ donation with an assumed high risk for transmission.

9.5.1.1. *Monoclonal gammopathies*

Monoclonal gammopathies of undetermined significance (MGUS) should be considered in the growing population of aged donors. In particular, the risk of progression to multiple myeloma or related disorders (1 %/year) should be evaluated. An initial threshold value of 15 g/L of serum monoclonal protein is a significant predictor of malignant progression. In this context, electrophoretic analysis is helpful in suspected cases [41], which should be discussed with a haematologist and possibly be investigated further with a bone marrow biopsy.

9.5.2. Myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN) [157, 158] are a group of chronic malignant diseases caused by dysregulated multipotent haematopoietic stem cells, mostly diagnosed beyond the age of 50 although around 20 % of cases are in patients below the age of 40.

In the following three MPN diseases, the clonogenic stem cells produce increased numbers of blood cells in the peripheral blood, which can cause (e.g. thrombo-embolic or haemorrhagic) complications:

- polycythaemia vera (PV) – all cell lines can be increased (mainly erythrocytes, but also leukocytes and platelets);
- essential thrombocythaemia (ET) – increased platelets;
- chronic myeloid leukaemia (CML) – increased leukocytes (functioning granulocytes) and platelets.

In the fourth disease of the group, the clonogenic stem cells cause a fibrosis of the bone marrow with consecutively decreased blood cells:

- primary myelofibrosis (PMF) – initially leuko-/thrombocytosis and immature blood cells in the peripheral blood, then anaemia, later pancytopaenia.

All of these diseases frequently present with spleno-/hepatomegaly. They can transform into an acute myeloid leukaemia (blast crisis) or myelofibrosis, which leads to the death of the patient. The symptomatic therapy is primarily intended to control disease symptoms and to avoid thrombo-embolic complications [159]. The only curative therapy is allogenic stem-cell transplantation (mainly for PMF but rarely also for selected patients with polycythaemia vera and essential thrombocythaemia).

MPNs are treated symptomatically and generally have a good prognosis. But it should be kept in mind that these are chronic diseases which are normally not curatively treated and therefore they bear a risk for transmission by organ transplantation. Literature has not addressed this topic yet, so there is no evidence available for a valid estimation of the transmission risk. Clonogenic stem cells are mainly located in the bone marrow, but they also circulate in the blood and can accumulate in spleen and liver (and might be transmitted by liver donation). It is possible that the stem cells may adhere to vessel walls even after perfusion of the organs during procurement and may therefore be released in the recipient's blood during reperfusion. Due to the lack of reports and evidence, the transmission risk cannot be assessed and it is not known how a transmitted MPN would behave in an immuno-suppressed recipient.

Myeloproliferative neoplasms diagnosed during donor procurement

Due to the current lack of literature on MPN and organ donation, the transmission risk cannot be assessed. Organs from these patients should only be accepted with the highest caution and only after consultation with an experienced haemato-oncologist. Results of the bone-marrow biopsy should be carefully evaluated.

A patient admitted with unspecific but suspect symptoms like extensive thrombo-/erythro-/leukocytosis should be tested for specific oncogenes in blood and bone marrow (CD34+ cells, BCR-ABL, JAK-2, V617F-mutation, MPL-mutation, Calretikulin-mutation) to distinguish an MPN from a simply reactive situation. Since this will take 2-3 working days, it might not be suitable in the context of organ donation.

Myeloproliferative neoplasms in the donor history

Due to the systemic and chronic character of these diseases and the lack of evidence on their behaviour in the setting of organ transplantation (and in the immuno-suppressed recipient), their transmission risk cannot currently be assessed. Organs from these patients should only be accepted with the highest caution.

The following laboratory tests might be obtained to assess the actual situation of the pre-diagnosed MPN: complete and differential blood count, liver enzymes including LDH. Bone marrow biopsy can help to rule out blasts at the time of donation.

Patients with spleno-/hepatomegaly need particular attention. An experienced haematologist should always be asked for an assessment.

It might be reasonable to accept an organ donor with a pre-diagnosed MPN for selected recipients, especially in cases of confirmed MPN without need for treatment or in cases where the diagnosis has been confirmed years ago and good therapy results were obtained. PMF seems to be more risky due to a higher proportion of circulating blasts and might bear an even higher risk for transmission.

9.6. Primary tumours of the central nervous system

Primary tumours of the CNS represent up to 1.5 % of the causes of death in organ donors [31, 160].

Extraneural metastases from CNS neoplasms are rare but have been described, the most common sites being the lungs, pleura, cervical lymph nodes, bone, liver and intra-thoracic and intra-abdominal lymph nodes [161, 162].

Extraneural dissemination of CNS neoplasms implies that tumour cells have accessed the blood vessels once they have infiltrated the tissues outside the leptomeninges. Several factors have been typically related to the risk of extraneural dissemination of CNS neoplasms [163]:

a. specific histological types and grade of malignancy;
b. peripheral intracranial location;
c. previous history of craniotomy or stereotactic surgery;
d. ventriculo-systemic or ventriculo-peritoneal shunts;
e. previous history of chemotherapy or radiotherapy;
f. duration of the disease and survival after surgical treatment.

There are, however, examples of spontaneous dissemination to the cranial and cervical lymph nodes, and even distant metastases [164]. It is estimated that 10 % of these tumour metastases occur without prior surgical intervention and even within 3-6 months of tumour diagnoses [164].

With respect to the histological type, the neuro-ectodermal tumours that metastasise with greatest frequency outside the cranial cavity are glioblastoma and medulloblastoma. However, this phenomenon has also been described for several types of glioma other than glioblastoma (i.e. various grades of astrocytoma, ependymoma and oligodendroglioma) as well as benign and malignant meningioma and germ cell tumours. In a series of 116 cases of extracranial metastases of CNS neoplasms, the most common primary tumour was glioblastoma (41.4 %), followed by medulloblastoma (26.7 %), ependymoma (16.4 %), lower-grade astrocytoma (10.3 %) and oligodendroglioma (5.3 %) [162].

9.6.1. Classification of central nervous system tumours

The World Health Organization (WHO) provides a comprehensive classification of CNS neoplasia (see Table 9.4), based on the specific cell type involved. Revised in 2016, the WHO classification provides a grading system (I to IV) for each type of tumour, depending on its biological behaviour and, hence, dictates the choice of therapy and predicts prognosis [17, 165]. The recent classification also includes genotypic information which correlates with tumour behaviour; however, most case reports of intracranial tumours and transplantation relate to the previous classification without genotypic information. One major change affects a common tumour of potential organ donors: the term *glioblastoma multiforme* is no longer used, and this tumour is now simply described as *glioblastoma*, but information on different genotypes is also given. The transmission risk of different genotypes on organ donation is not yet specified. This will be a subject for future evaluation.

To date, the two most important factors in assessing CNS tumour transmission risk via organ transplant are:

1. the histologically determined WHO grade of a CNS tumour,
2. any performed interventions (surgery, shunting, chemo- and radiotherapy).

A higher grade of tumour (> WHO grade III) and more interventions will lead to increased transmission risk. The specific tumour diagnosis adds important detail and will be used as supporting information.

The main characteristics of the WHO grades of CNS tumours are as follows.

- WHO grade I applies to lesions with low proliferative potential and the possibility of cure following surgical resection alone.
- Neoplasms designated WHO grade II are generally infiltrative in nature and, despite low-level proliferative activity, often recur and progress to higher grades of malignancy, e.g. low-grade diffuse astrocytomas can transform to anaplastic astrocytoma and glioblastoma. Similar transformation occurs over time in oligodendroglioma.

- WHO grade III is generally reserved for lesions with histological evidence of malignancy, including nuclear atypia and brisk mitotic activity. In most settings, patients with WHO grade III tumours receive adjuvant radiation and/or chemotherapy.
- WHO grade IV is assigned to cytologically-malignant, mitotically-active, necrosis-prone

Table 9.4. **Grading of selected central nervous system tumours (WHO 2016 classification)**

Diffuse astrocytic and oligodendroglial tumours	**I**	**II**	**III**	**IV**
Diffuse astrocytoma, IDH-mutant		•		
Anaplastic astrocytoma, IDH-mutant			•	
Glioblastoma, IDH-wildtype				•
Glioblastoma, IDH-mutant				•
Diffuse midline glioma, H3K27 M-mutant				•
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted		•		
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted			•	

Other astrocytic tumours	**I**	**II**	**III**	**IV**
Pilocytic astrocytoma	•			
Subependymal giant cell astrocytoma	•			
Pleomorphic xanthoastrocytoma		•		
Anaplastic pleomorphic xanthoastrocytoma			•	

Ependymal tumours	**I**	**II**	**III**	**IV**
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Ependymoma, *RELA* fusion-positive		•	•	
Anaplastic ependymoma			•	

Other gliomas	**I**	**II**	**III**	**IV**
Angiocentric glioma	•			
Chordoid glioma of third ventricle		•		

Choroid plexus tumours	**I**	**II**	**III**	**IV**
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	

Pineal tumours	**I**	**II**	**III**	**IV**
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	

Meningiomas	**I**	**II**	**III**	**IV**
Meningioma	•			
Atypical meningioma		•		
Anaplastic (malignant) meningioma			•	

Embryonal tumours	**I**	**II**	**III**	**IV**
Medulloblastoma (all subtypes)				•
Embryonal tumour with multi-layered rosettes, C19MC-altered				•
Medulloepithelioma				•
CNS embryonal tumour, not otherwise specified				•
Atypical teratoid/rhabdoid tumour				•
CNS embryonal tumour with rhabdoid features				•

Neuronal and mixed neuronal-glial tumours	**I**	**II**	**III**	**IV**
Dysembryoplastic neuroepithelial tumour	•			
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	•			
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		

Tumours of the cranial and paraspinal nerves	**I**	**II**	**III**	**IV**
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•			
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•

Mesenchymal, non-meningothelial tumours	**I**	**II**	**III**	**IV**
Solitary fibrous tumour/haemangiopericytoma	•	•	•	
Haemangioblastoma	•			

Tumours of the sellar region	**I**	**II**	**III**	**IV**
Craniopharyngioma	•			
Granular cell tumour	•			
Pituicytoma	•			
Spindle cell oncocytoma	•			

Source: adapted from: [184]. Louis DN, Perry A, Reifenberger G *et al*. The 2016 WHO Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica* 2016;131(6):803-20.

Note: To compare with previous WHO classification, from 2007, see Appendix 13.

neoplasms typically associated with rapid pre- and post-operative disease evolution and a fatal outcome. Widespread infiltration of surrounding tissue and a propensity for cranio-spinal dissemination characterise some WHO grade IV neoplasms such as medulloblastoma but is rare in others, including glioblastoma.

9.6.2. Registry data on central nervous system tumours

Several clinical cases of transmission of CNS neoplasms through organ transplantation have been reported in the literature [5, 27, 166-180]. Most of the reported cases are related to high-grade CNS tumours, usually in association with other risk factors for extracranial metastases, and hence for transmission from donor to recipient. However, cases of transmission have been reported in which no other risk factors, except for the high grade of the tumour, were involved [181].

Follow-up registries containing information on organs transplanted from donors with a CNS malignancy have shown a low risk of disease transmission, placing the above-mentioned cases in perspective. In 1999 the Australian and New Zealand Organ Donation Registry published details of a series of 46 donors with a primary CNS tumour, of which 28 were classified as malignant including four gliomas, four glioblastomas, 10 astrocytomas, five medulloblastomas, one high grade meningioma and four histologically unspecified tumours. Seven donors had undergone a craniotomy, of whom three had ventriculoperitoneal shunts; three others had ventriculoperitoneal shunts without craniotomy. None of the 96 recipients of organs from these donors developed a transmitted tumour [182].

The Czech Republic has reported no cases of transmission among 89 patients receiving organs (79 kidneys, five livers, four hearts and one lung) from 41 donors with CNS malignancies (13 meningiomas, nine glioblastoma, three astrocytomas, two medulloblastomas, one craniopharingioma, one acoustic neuroma, two pituitary adenomas, one lymphoma and eight histologically unspecified tumours) [183].

Similarly, in 2002, the UNOS registry published details of a series of 397 donors with a history of a primary CNS tumour who donated organs to 1 220 recipients, including 574 kidneys, 293 livers, 192 hearts, 76 lungs, 60 kidney-pancreas, 16 pancreas, six heart-lungs and three intestinal transplants [23]. CNS tumour type was not routinely reported to the UNOS registry before 1999, so the histological type of most tumours was not known. However, two donors were reported to have a medulloblastoma and 17 had a glioblastoma. These 19 donors with known high-grade tumours supplied a total of 56 transplanted organs: 26 kidneys, two kidney-pancreata, 15 livers, 10 hearts and three lungs. After an average follow-up of 36 months, no tumour transmission had been detected among the recipients.

In a later publication, based on a review of donors from the years 2000 to 2005 with a previous history of malignancy (as reported to the UNOS registry), 642 recipients had received transplanted organs from donors with a previous history of CNS malignancy, including 175 transplants from donors with a history of glioblastoma [22]. Three recipients (kidney, liver, lung) died following the transmission of a glioblastoma from the same donor, a donor noted to have an enlarged hilar lymph node at organ retrieval which was later shown to contain metastatic glioblastoma [22, 173].

In line with the low rate of transmission reported from the above-mentioned registries, a series of 448 recipients (495 organs) transplanted between 1985 and 2001 with organs from 177 donors with CNS tumours was reviewed in the UK [31]. The types of CNS tumour were (with various grades according to the 2007 WHO classification): astrocytoma (astrocytoma unspecified, pilocytic, gemistocytic, fibrillary), gliomatosis cerebri, glioblastoma, giant cell glioblastoma, oligodendroglioma, ependymoma, malignant glioma not otherwise specified, mixed malignant glioma meningioma, medulloblastoma, Ewing's sarcoma, primitive neuro-ectodermal tumour, pineoblastoma, malignant neoplasm (without any specific, identified morphology), dermoid cyst with malignant transformation and haemangioblastoma. There was a wide range in the time-span of tumour diagnoses in donors prior to their deaths: 119 donors were diagnosed in the last 30 days before death, 23 donors between 31 days and 1 year before death, 16 between 1 and 3 years before, and 19 over 3 years prior to their death. Organs transplanted from these donors included 279 kidneys, one double kidney, 72 livers, one combined liver-kidney, 12 heart-lungs, 13 double lungs, 51 hearts, 10 single lungs, eight combined pancreas-kidney and one isolated pancreas. None of the 448 recipients developed a donor-transmitted malignancy within the minimum follow-up of 5 years.

Based on this experience and a review of the available literature, SaBTO in the UK estimated the risk of extraneural spread of all histological types of CNS malignancies (metastases and lymphoma excluded) as being 1.5 % (upper-95 % confidence interval limit). For WHO grade IV tumours the risk was es-

timated as 2.2 %, with a 6.4 % upper-95 % confidence limit [12, 185]. The risk of extraneural metastases related to the presence of ventricular shunts was estimated to be 1 %, and doubts were raised about the risk related to prior surgery, chemotherapy and/or radiotherapy. This committee recommended providing these estimates when advising recipients undergoing transplantation with organs from donors with CNS malignancies, along with information on the survival benefits compared to remaining on the waiting list.

The registry reports above need to be considered with a degree of circumspection since it is likely that most donors with high-grade tumours from whom organs had been used would not have had ventriculo-peritoneal or ventriculo-atrial shunts, and might not have had extensive resections. Data on the treatment of the donors prior to donation are lacking in most reports.

In contrast to those studies reporting a low transmission risk, the IPITTR published data suggesting that the risk of transmission of primary CNS tumours is high [28]. The IPITTR assessed a number of risk factors for transmission of primary CNS malignancies: high-grade tumour, presence of ventriculo-peritoneal or ventriculo-atrial shunts, prior craniotomy, systemic chemotherapy and radiation therapy. Based on voluntary reporting of data to this registry, a series of 62 recipients were transplanted between 1970 and 2002 with organs from 36 donors diagnosed with primary CNS neoplasms (16 astrocytomas, 15 gliomas or glioblastomas, three medulloblastomas and two cerebellar tumours). Of the 36 donors, 24 received some form of cancer therapy before organ donation, including ventriculo-peritoneal or ventriculo-atrial shunts (12), craniotomy (six), radiation therapy (four) and chemotherapy (two), and 62 organs were transplanted from the 36 donors, including 35 kidneys, 12 hearts, 10 livers, two pancreata and three lungs.

Based on the data in its registry, the IPITTR estimated a 7 % transmission rate of CNS tumours in the absence of the aforementioned risk factors, 36 % if at least one was present, and 43 % if two were present. A high-grade (WHO III or IV) malignancy alone was associated with a 43 % transmission rate.

The high estimated risk of CNS malignancy transmission described by the IPITTR, in contrast with other registries, has to be interpreted with caution. Since cases of cancer in recipients are reported to the IPITTR on a voluntary basis, it is subject to reporting bias; cases of non-transmission will not be reported and the registry does not record the numbers of patients at risk from which the reported cases occur [186].

In 2011, based on information available at the time of their report, the DTAC Malignancy Subcommittee in the USA assigned WHO III-IV CNS tumours to the high-risk category of transmission (> 10 %), along with any CNS tumour (regardless of grade) that had other risk factors for disease transmission [11]. However, the DTAC Malignancy Subcommittee noted, as based on its supporting documentation, that some WHO grade IV tumours might present only an intermediate risk of transmission and that this issue needed to be addressed in a comprehensive, evidence-based fashion. Their quantitative approach to risk estimates suggests that future revisions may take more recent data into account and in some cases revise risk estimates downward. Corresponding data have been published by SaBTO [12], where WHO grade IV tumours have been categorised in the intermediate risk group according to the national data.

9.6.3. Classification of risk for central nervous system tumours

Drawing on the available information and the variable estimates of disease transmission derived from the previously described registries, there is a widely accepted qualitative classification of CNS malignancies, based on the risk of tumour transmission, as shown below.

- WHO grade I and II tumours – minimal risk of tumour transmission.
- WHO grade III tumours – previous classifications have categorised these neoplasms as high-risk. Recent analyses indicate that this may overestimate the risk, and SaBTO/UK assesses them as a low risk for tumour transmission. Until this is supported by larger evidence in the literature, these neoplasms should be accepted as low to intermediate risk if no risk factors are present (resection, ventriculo-peritoneal or ventriculo-atrial shunt, chemo-/radiotherapy). The risk is increased to high risk in the presence of any risk factors.
- WHO grade IV tumours – former classifications have categorised these neoplasms as an unacceptable risk. Recent analyses indicate that this may overestimate the risk, since several transplants without transmission have been reported. SaBTO/UK assesses them as an intermediate risk of tumour transmission. Until this is supported by larger evidence in the literature, these neoplasms should only be accepted with some caution on a case-by-case basis as intermediate to high risk. The risk is increased particularly in the presence of ventriculo-

peritoneal or ventriculo-atrial shunts, as well as previous resection or chemo-/radiotherapy.
- Primary cerebral lymphoma – unacceptable risk of tumour transmission.

Beyond WHO grading, the risk factors outlined above should be taken as additional elements for assessing the risk of extracranial spread of a primary cerebral tumour. This assessment should include exact documentation of all interventions (resection/shunting, chemo- and radiotherapy). At organ procurement, it is recommended that a thorough laparotomy and thoracotomy is performed, as well as inspection of cervical lymph nodes, the scalp over any resection site, and any shunt that may be present to exclude extracranial growth.

9.7. Review of specific tumours of the central nervous system

9.7.1. Neuro-ectodermic tumours

9.7.1.1. *Medulloblastoma*

Medulloblastoma (WHO grade IV) is the most common primitive neuro-ectodermal tumour and represents 6 % of all intracranial gliomas and 44 % of gliomas in children. Normally, they originate in the fourth ventricle, cerebellar vermis or hemispheres. Medulloblastomas that occur during childhood are the ones that most frequently metastasise outside the cerebrospinal axis. Extraneural metastases have been observed in 7 % of cases and some authors suggest that this prevalence could be even higher. In one old series of 77 children with medulloblastomas, eight (10 %) developed metastases; there was no difference in incidence whether they had previously had a ventriculo-peritoneal shunt (3 of 40) or not (5 of 37) [187]. All patients with metastatic disease had undergone complete or subtotal resection and cranial irradiation.

In another series, 1 % of 1 011 patients with CNS tumours developed extraneural metastases, of which six were children with medulloblastomas [188]. In a third series, 3.6 % of children with medulloblastoma developed extraneural metastases [189]. A more recent series reports 14 (4.8 %) of 292 patients with medulloblastoma who developed extracranial metastases [190]. All four series report bone, bone marrow and cervical lymphatic glands as common sites for metastatic medulloblastoma, with intra-abdominal and intra-thoracic metastases less common.

Neoplastic transmission from organ donors with medulloblastomas to recipients has been described. Lefrançois *et al.* [167] documented tumour transmission from a donor with a medulloblastoma to three recipients (heart, renal and kidney-pancreas) 5 months after the transplant. The donor had a ventriculo-atrial shunt and had undergone surgery, radiotherapy and chemotherapy. The IPITTR has registered seven organ recipients from three donors with medulloblastomas, all with a prior ventriculo-peritoneal shunt [28]. Three of the seven recipients presented with tumour transmission within 5-7 months of the transplant. Of these three recipients, two died of metastatic disease and the third had diffuse metastatic disease at the time of reporting. Based on this experience, the IPITTR contraindicates the use of organs from donors with these types of neoplasms because of the high risk of transmission to recipients. Currently, patients with medulloblastoma are accepted as organ donors in exceptional cases. Valid data for a reasonable risk estimation are pending.

So-called neuro-ectodermal tumours should be considered like medulloblastomas.

Childhood medulloblastomas are the CNS primitive tumours that metastasise most frequently outside the CNS. The risk may be increased if prior ventriculo-peritoneal or ventricular-atrial shunts, tumour resection or cranial chemo-/radiotherapy have been performed.

Organs from potential donors with medulloblastomas (WHO grade IV) are considered intermediate to high risk for tumour transmission, depending on different international recommendations, which will be adjusted with increasing evidence. They should be used exclusively for transplants where the recipient's risk of dying while on the waiting list is greater than the risk of tumour transmission.

9.7.1.2. *Gliomas*

Gliomas comprise astrocytomas, oligodendrogliomas and ependymomas. The incidence of extracranial glioma dissemination is calculated to be 0.4-2.3 %, mostly from glioblastoma and predominantly to the lung, pleura, lymph nodes, bone and liver [161]. One confounding factor in interpreting published data on the behaviour of gliomas is the security of the histological diagnosis. In one large national study where histology was reviewed, only 59 % of 258 patients believed to have an ependymoma were confirmed to have one, with other tumours ranging from meningiomas (n = 2) to glioblastomas (n = 34, 13 %) being misdiagnosed [191].

9.7.1.2.1. Astrocytomas

Astrocytomas are divided into:

a. low-grade disease astrocytomas [pilocytic astrocytoma (WHO grade I) and diffuse astrocytoma (WHO grade II)], representing 55 % and 20 % of all intracranial gliomas respectively,

b. malignant astrocytomas [anaplastic astrocytoma (WHO grade III) and glioblastoma (WHO grade IV)].

Pilocytic astrocytoma (WHO grade I) and low-grade astrocytomas (WHO grade II)

Low-grade astrocytomas are normally found in children and young adults. They rarely metastasise through the cerebrospinal axis and may not necessarily locally invade the leptomeninges, although such invasion is a frequent attribute. Metastases occur with greater frequency if tumour growth reaches the ventricular ependyma or if there is progression to anaplastic (malignant) glioma. Pollack *et al.* [192] reviewed 76 patients with low-grade astrocytomas of which one presented with a multicentric pilocytic astrocytoma, underwent resection and placement of a ventriculo-peritoneal shunt and developed peritoneal metastases and ascites two months later. Arulrajah *et al.* described a child with a pilomyxoid astrocytoma of the cervical cord with leptomeningeal metastases who developed peritoneal metastases 2 years after resection and placement of a ventriculo-peritoneal shunt [193]. Schroder *et al.* [194] described a female who had had a pilocytic astrocytoma of the spinal cord treated in infancy with surgery and radiotherapy, which presented 26 years later as metastases from a primitive neuro-ectodermal tumour into which it had transformed.

Up to 30 % of low-grade astrocytomas may be associated with histological grades of greater malignancy. These tumours have a tendency to relapse and frequently present as a higher grade of tumour.

Potential donors with pilocytic astrocytoma (WHO grade I) may be considered for organ donation with minimal risk of transmission.

Extraneural metastases from low-grade astrocytomas (WHO grade II) are rare, and have been associated with resection and ventriculo-peritoneal shunts. In the absence of these risk factors, the donor may be considered minimal-risk. Risk may increase with the extent of performed interventions.

A complete histological examination of the tumour should be performed so that areas of transformation into a more aggressive malignancy can be ruled out. Since astrocytomas have a tendency to relapse with a histologically higher grade of malignancy, new histological examinations to regrade the tumour should be performed where relapse occurs.

If the tumour co-exists with histological areas of greater malignancy or is very invasive locally, it should be considered high-grade and will be associated with an increased risk of transmission.

Anaplastic astrocytomas (WHO grade III) and glioblastoma (WHO grade IV)

At least 80 % of malignant gliomas are glioblastoma, representing the most biologically aggressive type of primary CNS tumour in adults. They can be located in any part of the brain, but normally affect the cerebral hemispheres. Anaplastic astrocytomas appear more frequently in adults aged in their thirties and forties, while glioblastoma more often presents in adults aged in their fifties and sixties. The majority of anaplastic astrocytomas are sporadic, but they can be associated with diseases such as type 1 and 2 neurofibromatosis, Li-Fraumeni syndrome and Turcot syndrome. Although direct dissemination rarely occurs through the *dura mater* without prior surgical intervention, transgression of the *dura mater* can occur with greater ease when ventriculo-peritoneal shunts or radiotherapy have been performed.

Dissemination of a glioblastoma through the cerebrospinal fluid is not uncommon, and generally occurs because of invasion or rupture within the ventricular cavity. Extracranial metastases of anaplastic astrocytomas and glioblastoma have been observed in the absence of prior surgery [162, 170], although they occur with greater frequency following surgery or ventriculo-peritoneal drainage [195]. When extraneural metastases do occur from anaplastic astrocytomas and glioblastoma, they are most commonly found in bone (especially vertebrae), liver, lungs and cervical lymph nodes [196].

Transmission of neoplastic diseases from donors with glioblastoma has been documented in individual reports [5, 22, 168-170, 172-174]. The reported cases occurred where donors had undergone surgery or received some form of cancer therapy. Recipients affected were kidney, liver and lung transplant patients. Glioblastoma transmission to heart recipients has not been reported [27, 197].

Fecteau *et al.* [198] described the case of a patient with peritoneal metastases 9 months after a ventriculo-peritoneal shunt, which was discovered during an organ-recovery procedure and prevented transplantation from taking place.

The IPITTR has described a series of 25 organ transplants from 16 donors with astrocytomas, during the period 1970-2002, in which 14 of those organs had risk factors for tumour transmission: four WHO grade III/IV astrocytomas, five prior craniotomies, four prior radiotherapy and four prior chemotherapy [28]. There was one case of tumour transmission 20 months after transplantation, in which the donor presented a single risk factor (astrocytoma WHO grade III/IV). Of 26 organ transplants from 15 donors with gliomas or glioblastomas, eight were associated

with high WHO grade III/IV glioblastomas and 18 with other gliomas. Of these, 15 had some risk factors (10 prior craniotomies and nine had high WHO grade III/IV gliomas), and eight tumour transmissions occurred 2-15 months after transplantation. It has been suggested that 70 % of glioblastomas exhibit elevated levels of certain growth factors (Akt and mTOR). This would favour the development of extraneural metastases and suggests the possible utility of mTOR inhibitors as immuno-suppressant drugs for organ recipients in such donor cases [174].

Spontaneous extraneural metastases of anaplastic astrocytomas and glioblastoma are rare, but such metastases have been observed, and seem to occur more frequently when associated with prior surgical treatment and/or ventriculo-peritoneal drainage, or chemo-/radiotherapy.

Potential donors with anaplastic astrocytomas (WHO grade III) can be accepted as organ donors. Transmission risk is considered low to intermediate for tumours without any risk factors.

Potential donors with glioblastoma (WHO grade IV) are considered intermediate to high risk for transmission, depending on different national recommendations, which are expected to be adjusted with increasing evidence.

The transmission risk is increased (high risk) in all cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.1.2.2. Oligodendrogliomas

Oligodendrogliomas represent 5 % of primary brain tumours [199]. There are two main types: low-grade oligodendrogliomas (WHO grade II) and anaplastic oligodendrogliomas (WHO grade III). Recent advances in molecular genetics, incorporated into the WHO-2016 revised classification of CNS tumours, have made the diagnosis of oligodendroglioma dependent on the demonstration of IDH mutations and co-deletion of chromosomes 1p and 19q. They are more sensitive to chemotherapy than the equivalent grade of astrocytoma [200].

Low-grade oligodendrogliomas (WHO grade II) are the most frequent form. They typically appear in adults aged in their twenties and thirties. They grow slowly and diffusely infiltrate the white matter, cortex and even the leptomeninges. They are extensively vascularised and often calcified tumours. Low-grade oligodendrogliomas present, in rare cases, as a spontaneous cerebral haemorrhage. Low-grade oligodendrogliomas often progress over time to become anaplastic oligodendrogliomas (WHO grade III).

Anaplastic oligodendrogliomas are very aggressive tumours that behave like glioblastoma. Extracranial metastases of anaplastic oligodendrogliomas have been observed after multiple craniotomies [201], with typical sites being scalp, lymph nodes, bone and bone marrow [202]. To date, no cases of oligodendroglioma transmission to organ recipients have been published.

Low-grade oligodendrogliomas (WHO grade II) represent a minimal risk of tumour transmission.

Anaplastic oligodendrogliomas (WHO grade III) without any risk factors are considered low to intermediate risk.

Donors with anaplastic oligodendrogliomas (WHO grade III) who have previously undergone interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy, are associated with an increased risk (high risk) of tumour transmission.

9.7.1.2.3. *Mixed gliomas*

These gliomas are WHO grade II/III and have the anatomopathologic characteristics of oligodendrogliomas and astrocytomas [136]. Genotypic analysis (IDH mutation and 1p/19q codeletion status) combined with phenotype should in future be able to assign such tumours as either oligodenrogliomas or astrocytomas.

The transmission risk of mixed gliomas is equivalent to other gliomas and is classified according to the respective WHO grade of the tumour (see above, quick reference box in §9.6.3).

9.7.1.2.4. *Ependymomas*

Ependymomas derive from the ependymal cells that line the ventricles and central canal of the spinal cord. They represent 6 % of all intracranial gliomas and are the third most common brain tumour in children. In fact, 50-70 % of ependymomas are infratentorial, are located in the IVth ventricle, and manifest in the first two decades of life. Supratentorial ependymomas can appear at any age and grow in the ventricular cavities or invade the nervous system parenchyma, especially in the parieto-occipital region. They are glial, highly vascularised, infiltrating tumours that generally settle in the rear ventricular cavity and rarely metastasise outside the CNS. However, extraneural metastases of the intracranial and spinal ependymoma have been observed, although the majority were recurrent neoplasms in which the extraneural dissemination followed tumour invasion of the adjacent soft tissues or resulted from seeding from surgery [203-205].

In a series of 81 ependymomas, Newton *et al.* [206] reported five cases (6.2 %) with extracranial dissemination. Two of these tumours were histologically anaplastic and three were benign. Three of the patients had undergone previous resection and one a biopsy, but in the fifth patient, extraneural metastases were present at initial diagnosis. There was no correlation between development of extraneural metastases and

prior radiotherapy or chemotherapy. Tumours metastasised into the lungs, thoracic lymphatic nodes, pleura, peritoneum and liver. Both patients with peritoneal metastases had had ventriculo-peritoneal shunts. Extraneural metastases did not correlate with histologic grade or degree of surgical resection. Another case of extracranial spread (bone metastases) of an anaplastic ependymoma present at initial tumour diagnosis has been described [207], but most reports have followed multiple surgical resections, radiotherapy and chemotherapy [208-212].

To date, no case of transmission of ependymomas to an organ recipient has been reported.

Extraneural ependymoma metastases occur, and the cases observed correspond to recurrent neoplasms or those treated with radiotherapy and/or chemotherapy.

The transmission risk of organs from donors with ependymomas is considered to depend upon the histological WHO grade of the tumour, so a low-grade (WHO I or II) ependymoma represents minimal risk of transmission, whereas an anaplastic ependymoma (WHO III) will be associated with low to intermediate risk.

The transmission risk is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.1.3. *Choroid plexus tumours*

Choroid plexus tumours represent less than 1 % of all neuro-epithelial tumours [199]. They are more often supratentorial in children, but in adults they are more frequent in the IVth ventricle and in the cerebello-pontine angle. Those located in the cerebello-pontine angle are more often benign.

Choroid plexus papillomas are the most frequent tumours and are histologically benign.

Choroid plexus carcinomas are aggressive, malignant tumours (WHO grade III) that can metastasise outside the CNS [213].

To date, no cases of transmission of choroid plexus tumours to organ recipients have been reported, but that may reflect the rarity of the tumour.

Organs from potential donors with plexus choroid papillomas may be considered minimal risk for transmission.

Organs from potential donors with plexus choroid carcinomas (WHO grade III) without any risk factors are considered low to intermediate risk.

The transmission risk of choroid carcinomas is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.1.4. *Pineocytomas and pineoblastomas*

Parenchymal tumours of the pineal gland are rare; they include pineocytomas (WHO grade I), pineoblastomas (WHO grade IV) and pineal parenchymal tumours of indeterminate differentiation (WHO grade II or III). Pineocytomas are derived from relatively mature, pineal parenchyma cells. Little is known about the behaviour of these tumours since some remain well-delimited without exhibiting any aggressive behaviour, while others metastasise through the cerebrospinal fluid and behave like pineoblastomas.

Pineoblastomas are rare tumours that correspond to a more primitive form of pineocytoma. These tumours are highly malignant and, biologically, they behave similarly to medulloblastomas, showing a clear tendency to disseminate in the cerebral-spinal cord. Extraneural metastases have been reported, including bone metastases and tumour spread in association with a ventriculo-peritoneal shunt [214-217].

There has been a single report of transmission of a pineoblastoma to a multivisceral transplant recipient. The donor was a 14-month-old infant who presented in a coma with severe brain injury and was thought to be a victim of shaking; autopsy demonstrated a pineal tumour with meningeal spread, but no other visible spread [176].

Organs from potential donors with pineocytomas (WHO grade I) may be considered minimal risk for transmission.

Organs from potential donors with pineoblastomas (WHO grade IV) are considered intermediate to high risk, depending on the different international recommendations, which will be adjusted with increasing evidence.

Parenchymal tumours of indeterminate differentiation (WHO grade II or III) without any risk factors should be accepted according to WHO grade III if differentiation cannot definitely be assigned.

The transmission risk is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2. Other intracranial primitive tumours

9.7.2.1. *Benign meningiomas, atypical meningiomas, anaplastic or malignant meningiomas*

Meningiomas represent 20 % of all intracranial tumours and can manifest at any age. Typically they occur in adults, and more frequently in women. Less than 10 % are multiple meningiomas that can appear sporadically or be associated with type 2 neurofibromatosis.

Meningiomas are usually benign. Although invasion of the adjacent tissues is frequent, dissemination outside the affected organ is less so. However, although the majority of tumours that originate in the meninges are benign, occasionally they behave

in an invasive manner with a prognosis significantly worse than histologically benign meningiomas. Approximately 5 % of meningiomas are atypical and 2 % are malignant.

Anaplastic or malignant meningiomas are aggressive meningeal tumours that are frequently associated with multiple recurrences and extracranial metastases. Younis *et al.* [218] presented a series of 18 patients with aggressive meningeal tumours, of which 12 were malignant (anaplastic) meningiomas (WHO III) and six atypical meningiomas (WHO II). Three (16 %) developed extracranial metastases (two malignant meningiomas and one atypical meningioma). In these three cases, pulmonary and bone metastases were the most frequent. All three patients had undergone total surgical excision, radiotherapy and chemotherapy, and metastases developed 26, 96 and 108 months after initial diagnosis. Other authors have reported cases of extraneural metastases, with local scalp recurrence, as well as metastases to lung, liver and bone [219-224]. One study suggested that meningiomas expressing high levels of CD90 were atypical and more likely to metastasise [222].

The transmission of a malignant meningioma (originally diagnosed as a grade II astrocytoma) through a kidney transplant with peritoneal invasion and liver metastases was described by Bosmans *et al.* [171]. The tumour regressed following transplant nephrectomy and interferon alpha treatment.

Extraneural metastases by histologically benign meningiomas are very rare. Organs from potential donors with these types of tumour have a minimal risk of transmission.

Anaplastic or malignant meningiomas (WHO grade III) are more aggressive meningeal tumours that can occasionally be associated with extraneural metastases. Organs from potential donors with these tumours are considered low to intermediate risk if no risk factors are present.

The transmission risk of anaplastic or malignant meningiomas is increased (high risk) in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2.2. *Malignant mesenchymal tumours: non-meningeal intracranial sarcomas, meningeal sarcomas and haemangiopericytomas*

Intracranial sarcomas represent 1 % of all tumours of the CNS. The most anaplastic forms of sarcomas metastasise through the cerebrospinal fluid. However, extraneural metastases are rare, probably due to the fact that the rapid development of these tumours does not provide sufficient time for the extraneural metastases to develop. Metastases of polymorphic sarcoma have been observed in the leptomeninges, liver, lungs and bone marrow; in one of these cases there was a massive local recurrence of a primitive tumour in conjunction with invasion of the muscle and fascia and, in another case, the dissemination was preceded by an exploratory craniotomy. Cerame *et al.* [225] described the existence of extracranial metastases in gliosarcomas.

Meningeal sarcomas and anaplastic haemangiopericytomas are locally aggressive meningeal tumours that are frequently associated with extraneural metastases and multiple recurrences. Younis *et al.* [218] described four cases of haemangiopericytoma and three meningeal sarcomas in a review of aggressive meningeal tumours. Three of these seven cases developed extracranial metastases; two haemangiopericytomas metastasised within 96 and 102 months while the meningeal sarcoma had metastasised in multiple organs within 3 months of the initial diagnosis. Kaneko *et al.* [226] reviewed 20 cases of haemangiopericytoma with extraneural metastases, commonly to bone, liver, lung and lymph nodes. Late pancreatic and bone occurrence of extracranial metastases, 22 years after apparently curative craniectomy, has also been described [227].

No cases of transmission of haemangiopericytoma from organ donor to recipient have been reported in the literature so far but this should not give a false sense of security.

Organs from potential donors with sarcomas of the CNS (WHO grade IV) and haemangiopericytomas (WHO grade IV) are considered intermediate to high risk for tumour transmission, depending on the different international recommendations, which will be adjusted with increasing evidence.

Organs from potential donors with anaplastic haemangiopericytomas (WHO grade III) without any risk factors are considered low to intermediate risk for tumour transmission.

Organs from potential donors with haemangiopericytomas (WHO grade II) without any risk factors represent a minimal risk for tumour transmission.

The transmission risk for donors with sarcomas of the CNS and any kind of haemangiopericytoma is further increased in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2.3. *Haemangioblastomas*

Haemangioblastomas are benign tumours of the blood vessels that occur with greatest frequency in the cerebellum. Dissemination of haemangioblastoma is rare, although Hoffman *et al.* [228] observed two spontaneous cases of extraneural metastases.

In 20 % of cases, haemangioblastomas appear to be associated with other tumours as part of Von Hippel–Lindau syndrome, which is also associated with a high incidence of RCC.

Due to the usually benign behaviour of haemangioblastomas, organs from potential donors with this diagnosis may be considered minimal risk for tumour transmission, provided that coincidental neoplasms and the existence of Von Hippel–Lindau syndrome are ruled out.

Any recommendation for a particular tumour must be considered in the context of any coincidental neoplasms. In the case of Von Hippel–Lindau syndrome, particular attention must be paid to possible coincidental neoplasms.

9.7.2.4. *Germ cell tumours*

Tumours of the pineal region are rare. Approximately half are germ cell tumours, which include germinomas, mature teratomas, immature teratomas, teratocarcinomas, choriocarcinomas and embryonal carcinomas; many are of mixed cell type with different elements of germ cell tumour. Intracranial germinomas most frequently occur in the pineal gland. They are histologically malignant, infiltrating tumours that usually disseminate through the third ventricle. Non-germinomatous germ cell tumours may be associated with increased levels of human choriogonadotropin (HCG), alpha fetoprotein and placental (AFP) alkaline phosphatase in serum and cerebrospinal fluid. Extra-gland metastases have been observed following craniotomies, cranial-spinal radiotherapy or ventriculo-peritoneal diversion [228].

Extragonadal choriocarcinoma is a type of teratoma that also occurs in the pineal region. They are highly malignant tumours with a tendency to invade adjacent structures. Extracranial metastases have been reported in the lungs [229].

Organs from potential donors with mature teratomas represent a minimal risk of tumour transmission.

Organs from donors with other germinal cellular tumours should be considered intermediate to high risk for tumour transmission, depending on the different international recommendations, which will be adjusted with increasing evidence.

The transmission risk is further increased in cases with previous interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy.

9.7.2.5. *Chordomas*

Chordomas arise from remnants of the embryonic notochord and are slow-growing, locally invasive tumours that can lead to extracranial metastases.

Organs from potential donors with chordomas should probably be considered high-risk for tumour transmission, but there are no recommendations available in the current literature.

9.7.2.6. *Primary cerebral lymphomas*

Primary intracranial lymphomas appear with greater frequency in immuno-suppressed patients, such as those diagnosed with AIDS. Their prognosis is bad and they progress to extracranial dissemination.

There is a reported transmission of a primary intracranial Non-Hodgkin's Lymphoma into both kidney recipients [15]. It was detected in the donor autopsy but not reported to the transplant centres because no distant metastases were found. Both recipients underwent transplant nephrectomy and withdrawal of immune-suppression after the incidental diagnosis of transmitted lymphoma. One recipient had only localised graft disease and was free of recurrence after 10 months. The other recipient, who was found to have diffuse infiltration of the kidney-surrounding tissue, received radiotherapy and, due to lymphoblastic ascites, additional poly-chemotherapy. He was in complete remission but died of pneumonia and pericarditis a few weeks later without signs of recurrent disease in autopsy.

Organs from donors with primary cerebral lymphomas have an unacceptable risk for tumour transmission and should not be considered for transplantation.

9.8. Suspicion of tumour transmission in an organ recipient

9.8.1. General considerations

Tumours in organ recipients can originate either from recipient cells – *de novo* tumours, including post-transplant lympho-proliferative disorders, in immuno-suppressed patients – or from donor cells. For the safety of other recipients of the same donor, it is important to distinguish between donor-transmitted tumours, which are already present in the donor (detected or undetected) and transmitted to the recipient with the transplanted organ, and donor-derived tumours, which can develop from donor cells at any time after transplantation but were not present in the donor at the time of organ procurement (e.g. RCC in graft kidney 8 years after transplantation). In some cases this distinction might be arbitrary (e.g. RCC arising 2-4 years after transplant). Attention should be paid in cases of a lymphoma in a recipient after transplantation. Categorised simply as lymphoma, it can cover a lymphoid tumour (e.g. associated with Epstein–Barr virus) arising in the recipient *de novo* as well as a donor-transmitted lymphoma. Clarification should be attempted for the above-mentioned reasons.

Several events in the post-transplant period can raise the concern of a potentially transmitted donor

tumour (see Table 9.1). These may include donor malignancies diagnosed after transplantation, either by final pathologic examination or donor autopsy, signs or symptoms suspicious of malignancy transmission in the recipient, suspected malignancy transmission in another recipient(s) from the same donor but also a tumour diagnosis in a living donor shortly after donation.

Some scenarios [230] that would raise reasonable suspicion of a possible donor-transmitted tumour include:

a. cancer (other than post-transplant lymphoproliferative disorders (PTLD)) arising within the first 2 years after transplant,
b. cancer arising in the allograft organ in a patient with no history of carcinoma in the corresponding native organ,
c. metastatic carcinoma arising in an allograft recipient, particularly when a primary site cannot be identified,
d. metastatic carcinoma of allograft type (e.g. RCC in a renal transplant recipient) in a recipient with no known history of that type of cancer,
e. CNS neoplasm occurring outside the CNS, particularly in a transplant patient with no known CNS involvement,
f. sex-specific cancer (e.g. choriocarcinoma) arising in a transplant patient of the opposite sex,
g. age-discordant cancer (e.g. paediatric cancer arising in an adult transplant recipient, or vice versa),
h. cancer in which there is specific suspicion of donor origin (e.g. use of organs from a donor with a known history of cancer).

Clinical symptoms and signs of malignancy transmission are heterogeneous, depending upon the type of tumour and organ transplanted. Usually, the transmitted malignancy is identifiable in the transplanted organ with or without extra-graft metastases, reflecting a tumour borne by the allograft. Exceptionally, the graft does not show evidence of malignant infiltration, which suggests that isolated tumour cells might be transmitted through the organ.

Recipients who received organs from donors with a confirmed malignancy should be strictly followed up to detect a possible transmission as early as possible.

Jaillard *et al.* [71] describe a case of small cell lung carcinoma diagnosed in a living kidney donor 7 months after donation. Transmission was confirmed in the clinically asymptomatic kidney recipient by FDG PET/CT (fluorodeoxyglucose positron emission tomography/ computed tomography).

A number of clinical trials and epidemiologic studies have found the use of mTor inhibitor-based immuno-suppressant regimens in the recipient to be associated with reduced incidence of mainly *de novo* non-melanoma skin-cancers [231-233], while the effects on other cancers are less well defined [234-236]. The presumed long-term benefit on hepatocellular carcinoma recurrence after liver transplantation could not be confirmed in the large international prospective randomized SiLVER trial [237]. To date it remains subject to further investigations whether recipients who received organs from donors with a confirmed malignancy may benefit from these immunosuppressants.

It should be borne in mind that occult donor malignancies may also cause tumour transmissions. Therefore, where a recipient shows signs or symptoms of a malignant tumour after transplantation, tumour transmission should always be considered. Temporal sequence should be reasonable according to the tumour type. Most transmitted tumours appear within the first 14 months after transplantation. Therefore, it is unlikely, but not impossible, that an aggressive tumour diagnosed in the recipient 5 years after transplantation is donor-transmitted.

In cases of suspected recurrence of the recipient's primary disease (e.g. hepatocellular carcinoma), one should be aware that these liver findings might also be metastases of a donor tumour [238]. Jumping to the wrong conclusion should be avoided and, in cases with ambiguous histology, the possibility of a donor-transmitted tumour should be specifically raised with the pathologist.

A correct assessment of a case involves analysis of the literature in order to understand whether the same tumour type has been transmitted before. Registry reports and case reports provide information regarding the type of transmission and the methodology followed for the assessment of imputability.

A review of the literature (the Notify library) is maintained by the Centro Nazionale Trapianti in association with OCATT/ONT and WHO and is accessible at www.notifylibrary.org.

9.8.2. Steps to take in cases of suspected malignancy transmission

Transmission of a malignant tumour is considered a serious adverse reaction (SAR) in the recipient, and requires reporting of suspected transmission events to the assigned national Health Authority, consecutive investigation and review of the cases.

These actions are mandatory in EU states according to Directive 2010/53/EU [13] (see Chapter 15).

In cases of suspected malignancy transmission from donor to recipient:

a. The Health Authority in charge of co-ordinating vigilance has to be informed immediately, before further investigation or confirmation, to allow initiation of the appropriate precautionary actions to prevent harm to other recipients of organs from the same donor (see Chapter 15).

b. The respective recipient centres of organs from the same donor as well as tissue organisations and the organ procurement organisation will be alerted by the Health Authority in charge of co-ordinating vigilance, and the examination and a review process for this case will be started (e.g. *ad hoc* or standing expert committee). In the absence of such a Health Authority, an alternative procedure should be established to alert the recipient centres concerned.

c. Histologic examination of the recipient tumour and genetic comparison of tumour tissue and recipient sex chromosomes or DNA would be desirable to prove or exclude transmission of a donor malignancy. National law should be checked (e.g. consent required) prior to performing any DNA analysis in human tissue.

Close communication between centres and co-ordinating agencies/authorities (according to the administrative organisation of each setting) is necessary for alerting other teams regarding a potential risk that should be carefully monitored, but also for determining the level of transmission in a lineage of recipients.

9.8.3. Tumour histology and genetic testing of donor and recipient

When a neoplasm is detected, histology can provide the histotype of the tumour. Immunohistochemistry can help to identify a possible histogenesis, and molecular analysis can give information regarding donor or recipient origin. For example, multiple metastases in a recipient, detected 9 months after liver transplantation for hepatocellular carcinoma, have been identified as malignant melanoma by histology and immuno-histochemistry. Molecular-based microsatellite analysis helped to confirm donor origin [74]. Similarly, the identification of a lung carcinoma in the donor during or immediately after transplantation needs a detailed investigation of the tumour (histological type and grade, immuno-histochemical profile) and a careful follow-up of the recipients. In the case of a tumour in one or more recipients transplanted with organs from this donor, the morphological/immunohistochemical comparison of the tumour in the donor and the tumour arising in the recipients can strongly imply donor origin if they are equivalent, even in the absence of molecular studies.

Currently, different molecular cytogenetic methods are available for determining if a donor is the origin of a recipient tumour. They all work by comparing tumour biopsy material with regular allograft material (containing donor DNA) against a sample of tumour-free recipient DNA [90]. In cases of a positive match between donor and tumour material (or mismatch between recipient and tumour material respectively), the donor origin is confirmed. Molecular cytogenetic methods include but are not limited to:

- Fluorescence *in situ* hybridisation (FISH): In cases of sex-mismatched recipients, this method indicates the presence of the XX or XY chromosome pair in a small biopsy of the malignant tissue. Routinely processed paraffin-embedded tissue can be used.
- Microsatellite allelic analysis: This analysis permits distinctions between individuals based on the genetic polymorphisms of repetitive DNA sequences. Routinely processed paraffin-embedded tissue can be used.
- Comparative genomic hybridisation (CGH): This method allows simultaneous comparison of all chromosomes in the genome, and can also be performed on routinely processed tissue.

9.8.4. Steps to take in cases of confirmed tumour transmission

When tumour transmission has been confirmed, physicians must discuss and decide on the options for intervention together with the recipient. There are no definite recommendations on how to act, but obviously the decision must take into account the tumour type, spread of the disease, condition of the recipient and kind of organ transplanted. Organ removal, with a return to dialysis, re-substitution of insulin and withdrawal of immuno-suppression (in combination with immuno-modulants if appropriate) to promote rejection of residual tumour cells, is only suitable for kidney or pancreas recipients. Re-transplantation can be considered for all other recipients when tumour-free survival of the recipient is likely, albeit knowing that this might not elimi-

nate the transmitted tumour. In addition, systemic spread of the transmitted tumour should be treated by chemotherapy or appropriate targeted therapy according to the tumour type.

All other recipients of grafts from the same donor, as well as the organ procurement organisation, allocation agencies and tissue establishments involved, have to be informed immediately so that they can initiate diagnostics and consider the possibility of prophylactic transplant removal, re-transplantation or other intervention. Whether or not other grafts from the same donor that are currently not affected by the tumour should be removed requires careful assessment and will depend on the kind of malignancy and the clinical condition of the recipient. After lowering or completely withdrawing immuno-suppression, it takes time until the immune system recovers and can potentially reject allogenic tumour cells, as has been reported [9, 52, 73, 171, 239]. Additional chemotherapy should be considered.

9.8.5. Perspectives for data reporting and recording

National expert committees should be put in place to review the reported suspected transmission cases [5]. In the countries of the European Union, a final report of each case has to be prepared after a defined period of 3 months [13] (see Chapter 15). Since this is a very short period for malignancy follow-up, long-term surveillance of the respective recipients at risk is preferred for at least 5 years.

To attain the requirements of quality assurance and to ensure maximum recipient safety in the future, reliable data must be collected for a reasonable risk estimation of tumour transmission. Obligatory transplant tumour registries should be established in every country or allocation network (e.g. Eurotransplant). International consensus should be sought on the data to be documented, with a view to eventually facilitating interlinked registries.

9.9. Conclusions

A history of malignancy or, in some cases, an active malignant disease in the potential donor should not automatically be a veto to organ donation. The estimated risk of tumour transmission has to be balanced against the benefit of the transplant for the designated recipients. The available literature consists of retrospective series with limited background information and many case reports. Taken as a whole, the reported transmission rates are low (though high for some aggressive and advanced tumours) and the overall results seem to be encouraging, although this may reflect a high degree of selection. Nevertheless, to allow a more evidence-based decision process, it will be necessary to collect detailed international data including reliable reporting of transmission events. A comprehensive traceability system with details of management of adverse events is essential.

Prerequisites for the individual acceptance of such organs should be a review of the detailed history of the donor malignancy and its management, and the informed consent of the organ recipients. The frequently urgent nature of organ transplantation often precludes the possibility of obtaining all of the desired information and the physician must weigh available clinical data and published experience along with the medical condition and desires of the patient in arriving at the best possible decision. Although a certain transmission risk will remain in many cases, selected patients on the waiting lists will benefit from these organs in times of organ shortage.

9.10. References

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Related material

• Appendix 13. World Health Organization 2007 classification and grading of central nervous system neoplasms

Chapter 10. Risks related to the use of organs from donors with other conditions and diseases

10.1. Introduction

Besides infections (see Chapter 8) and malignancies (see Chapter 9), some pre-existing conditions and diseases in the donor can compromise organ function or can be transmitted by the organ to a transplant recipient. After donor evaluation and characterisation, a risk–benefit assessment for a particular recipient can be performed. This chapter provides general recommendations on the approach to follow when assessing donors with poisoning or donors diagnosed with different inherited diseases and other disorders. Reviewing the endless list of rare diseases in a single chapter is an impossible task. More than 3 500 rare diseases are described currently and a rapid change in genetic knowledge will change the information about rare diseases. Therefore it is recommended to consult specific up-to-date portals such as Orphanet (www.orpha.net). This portal includes a brief section about organ donation in the emergency guidelines adapted for some but not all of the rare diseases currently. Nonetheless, helpful contacts for experts and basic information can be found here. An example of a form for recording such information is provided in Appendix 14.

10.2. Poisoning

There are more than 3 000 deaths by poisoning or intoxication per year reported in the United Kingdom. There is a large variation between countries in the rates and circumstances, but most poisoning cases arrive at the hospital still alive, and they represent a group of patients in whom organ donation should be considered [1]. Published data are not sufficient to determine whether these deaths occur under circumstances that would easily allow diagnosis of brain death and monitoring of the subsequent recovery of organs. Further legal limitations may come up because toxin uptake may occur by accident, through suicide or wilfully by a third party. Established best practice is collaboration with legal investigating authorities (police, prosecution and forensics) in order to fulfil legal requirements while awaiting detoxification in order to perform proper brain-death diagnostics.

The number of cases varies among registries where poisoning is the direct cause of brain death. The rate of such cases is low, but this rate is increasing in the US: deaths due to drug intoxication were 6 % higher in 2014 than in the previous year [2], and in 2016 they were 13 % higher than in 2013 [3]. Evolution to brain death mainly results from anoxia or brain oedema. Anoxic brain damage can occur as a result of a cardiac arrest due to myocardial ischaemia or fatal arrhythmias (e.g. cocaine) or a respiratory depression (e.g. barbiturates, opioids). Brain oedema might derive from an acute liver failure (e.g. paracetamol), hyponatremia (e.g. ecstasy) or unknown mechanisms (e.g. methanol). Haemorrhagic and ischaemic brain lesions are less frequent causes of brain death in intoxicated patients.

Opioids, carbon monoxide (CO), analgesics and anti-depressants are the leading causes of fatal poisoning. There is a great variety of reports on successful transplantation using multiple organs from brain-dead donors having suffered from various kinds of poisoning. However, there is no systematic overview and it can be expected that only positive outcomes are being reported. Hantson summarised case reports, expert opinions and other knowledge in this field exhaustively in 1999 [4]. In addition, there is one consensus document from the International Society for Heart and Lung Transplantation regarding drug toxicities and the use of cardiac allografts [5]. The overall conclusions of these documents are:

a. Patients who die due to (or with) intoxications by drugs or other substances should be considered as potential organ donors. In general terms, donor poisoning is not a contraindication to organ donation. Organs should be

Table 10.1. **Reported cases of toxins and poisons leading to successful organ transplantation following brain death and considerations for assessment of the donor**

Substance	Heart	Lung	Liver	Pancreas	Kidney	Remarks
barbiturates	yes, careful assessment	yes	yes	yes	yes	
benzodiazepines	yes	yes	yes	yes	yes	
tricyclic antidepressants	yes, careful assessment	yes	yes	yes	yes	
neuroleptica	yes, careful assessment	yes, careful assessment	yes, careful assessment	yes, careful assessment	yes, careful assessment	Exclude multi-organ failure; wait for recovery from neuroleptic syndrome.
cocaine	yes, careful assessment	yes,	yes	yes	yes	Exclude multi-organ failure or sepsis; check for chronic abuse; check for elevated risk of HCV, HIV transmission; check for abuse of other substances. Methadone can accumulate in the liver in long-term users.
ecstasy	yes	yes	yes	yes	yes	
opioids	yes	yes, careful assessment	yes	yes	yes	
methadone	yes	yes	yes	yes	yes	
ethanol	yes	yes	yes	yes	yes	Chronic abuse: liver/pancreas damage.
methanol	yes, careful assessment	yes	yes	yes, careful assessment	risk of rhabdomyolysis	Correct acidosis, wait until o.o mg/L.
ethylene glycol	yes, careful assessment	yes	yes	yes	risk for oxalate	Correct acidosis.
calcium inhibitors	yes, careful assessment	yes	yes	yes	risk of acute kidney injury	
venlafaxine	yes	yes	yes	yes	yes	Wait for recovery from serotonin syndrome.
acetylsalicyl acid	yes	yes	yes	yes	yes	
paracetamol	yes	yes	acute liver failure	yes	yes, careful assessment	
insulin	yes	yes	yes	yes	yes	
cyanide	yes	yes	yes	yes	yes	
colchicine	yes, careful assessment	ARDS: unsuitable	yes, careful assessment	yes, careful assessment	yes, careful assessment	multi-organ failure
brodifacoum (rodenticide)	yes	yes	yes	yes	yes	
pesticide	yes, careful assessment	ARDS: unsuitable	yes, careful assessment	yes, careful assessment	yes, careful assessment	multi-organ failure
malathion			yes		yes	
carbon monoxide	yes, careful assessment	yes	yes	yes	yes	

yes = donation of organ possible after proper assessment taking into account data from the literature.

yes, careful assessment = in these donors, the poisoning might compromise the organ function irreversibly; otherwise the risk factors are listed in the table which may limit donation of a graft

blank = currently no data available – donation can be considered after proper assessment

ARDS = acute respiratory distress syndrome

considered for transplantation following the routine biological and morphological assessment of the graft. Unless irreversible organ damage is confirmed, poisoning is not an absolute exclusion criterion for organ transplant.

b. Discussion with experts in toxicology or pharmacology is helpful or necessary to evaluate the suitability of different organs for transplant. As these professionals may not be experts in the field of transplantation, case-by-case decisions have to be made collaboratively, taking into account the risk of organ dysfunction and the specific situation of a patient on the transplant waiting list.

c. A list of websites and telephone numbers with 24-h services for intoxication advice should be made available to donor co-ordinators locally.

d. The diagnosis of brain death may be complicated in cases where a given drug or poison has a direct or temporary influence on brain cells and their functioning (see Chapter 3). In addition, some sedative drugs used during intensive care management can also interfere with brain activity. Proper determination of brain death is still possible in poisoned patients when the injury responsible for irreversible brain damage has been identified (e.g. hypoxic brain damage in the case of opiate intoxication). Primary hypothermia due to secondary complications after poisoning must be corrected before brain-death testing. Ancillary tests to prove the cessation of cerebral perfusion (e.g. transcranial Doppler sonography, cerebral angiography, cerebral perfusion scintigraphy or cerebral CT-angiography) can be required. The reason is that some poisons interfere with the interpretation of certain electrophysiological tests (e.g. barbiturates can affect electro-encephalogram results).

Usually, in patients admitted to an intensive care unit, most (or all) of the toxin can be eliminated before brain-death diagnosis has been initiated. Metabolites or delayed action should also be considered, including their specific dosage or pharmacokinetics. If complete detoxification cannot be confirmed or the toxin is still able to influence central nervous system cell function, then interference with electro-physiological measurements could be a major issue, whereas confirmed cessation of cerebral perfusion is a measurement independent of such interactions.

e. The risk of toxin transmission to a recipient can be further limited by continued detoxification during evaluation of organ function in the deceased donor.

f. In this context, information about the period of ingestion of drugs (either in chronic use or as single event) is valuable, in order to identify co-existing behavioural risk factors concerning the acquisition of a potentially transmissible infection (e.g. chronic intravenous drug abuse is associated with a higher probability for recent hepatitis C infection; for this, see Chapter 8).

10.2.1. Basic considerations for donor and organ characterisation

Generally, organ donation is considered possible if there is no evidence of functional or structural damage of the organs in question. The organs of donors with poisoning that leads to brain death need to be evaluated according to case history and information about the specific toxin involved. The following points should be considered for such potential donors:

- Identification of agent(s) causing the poisoning; multi-agent poisoning should not be overlooked.
- Acute poisoning should be differentiated from chronic poisoning or substance abuse with an acute overdose.
- The type and effectiveness of elimination therapy should be taken into account. Observation of the patient's medical status during this elimination period helps to exclude irreversible organ damage or risk of toxin transmission. Possible redistribution from fatty tissue and the extra-vascular space following clearance from the blood should not be overlooked. Experts in toxicology can provide data about tissue concentrations and elimination methods and times.
- Irreversible damage of specific organs should be excluded, and the extent of organ recovery after poisoning should be evaluated.
- Toxins not completely eliminated from specific organs may be transmitted to the recipient during transplantation with consequent adverse effects (e.g. solvents) or without any serious consequence (e.g. some narcotics). After a proper assessment of the preconditions for brain death certification, which includes adequate detoxification, this risk can be assumed to be negligible.
- Appropriate recipients should be selected on the basis of acceptable risk levels.

- For the certification of death by neurologic criteria, intoxication by sedative or narcotic medications/substances must be ruled out and the cessation of cerebral circulation must be confirmed.
- In some poisoning cases, it may be impossible to identify the toxic agent because of inappropriate samples, rapid toxin elimination before sampling could take place or measurement techniques not being available (e.g. blood or urine testing may be inconclusive for short-acting recreational designer drugs). In such cases, even though the process is time-consuming (days) or not available, as far as possible the most common toxic agents should be ruled out by chromatography screening. If any suspicions remain, organs should only be used at an increased risk level.
- Intoxication is not a natural cause of death. Therefore, any donation procedure should ensure that interference with criminal investigations is ruled out by proper prospective collaboration with the authorities performing forensic investigations.
- In cases of chronic substance abuse, consideration should be given to the risks discussed in Chapters 8 and 9.
- In cases where poisons were inhaled, acute or chronic lung injury must be properly assessed. Lungs without damage should be considered for transplantation.
- Organ viability must be checked against other existing pathologies and co-morbidities, especially after resuscitation events, extracorporeal membrane oxygenation or hypoxia arising from the poisoning [2-9].

10.2.2. Poisoning agents

The following is a non-exhaustive list of toxic agents potentially causing brain death, and being the underlying cause of death of potential organ donors. The prevalence of toxic agents may vary between countries and over time [2].

a. *Amanita phalloides*

Liver donation is obviously not considered, as the liver is the direct target organ of poisoning by *Amanita phalloides* and other mushrooms. Acute renal failure is a frequent complication due to dehydration, but not directly due to the toxin. Other organs may be also considered for donation after normal routine biological and morphological assessment of the graft.

b. *Antidepressants/tricyclic antidepressants (TCA, e.g. amitryptiline)*

Fatalities after acute TCA overdose are becoming less frequent since the introduction of newer generation antidepressants, i.e. selective serotonin reuptake inhibitors (SSRI). Death is mainly caused by fatal cardiac arrhythmias, shock or status epilepticus.

Hearts for donation should be evaluated critically, particularly in patients with abnormal electrocardiographic findings or high serum concentrations of TCA (> 2 000 ng/mL). Liver, kidney or lung donation remains possible, based on the results of routine laboratory tests. The recommendation is to determine the concentration of TCA in the recipient, although there is no definite evidence in the literature of a significant risk of transmission to organ recipients.

c. *Chemical solvents*

Solvents require an individualised decision. Most solvents lead to cardiac arrest due to arrhythmias, and there is an endless range of such solvents. Adherence of solvents to lipids or their hydrophilic effects and the possibility of destruction of tissues and secondary lesions (e.g. accumulation of a substance in hepatic tissue, rupture of intestine leading to peritonitis) should be considered.

d. *Cocaine*

This narcotic causes early atherosclerotic lesions, and also dilated cardiomyopathy in cases of chronic abuse. Atherosclerotic lesions are most likely to occur in the coronary arteries at an early stage. Therefore, special attention should be paid to atherosclerosis in potential heart donations after chronic cocaine use, and a coronary angiography should be considered. However, multivariate analysis revealed no difference in mortality or development of coronary artery disease at 1 and 5 years between transplant recipients who received an organ from donors with a history of cocaine use when compared with donors having no history of cocaine use [10, 11]. A number of successful heart, lung, liver and kidney transplants have been reported, especially after acute poisoning associated with massive brain injury (e.g. haemorrhage). In cases where cocaine has been inhaled, acute or chronic lung injury must be properly assessed. Lungs without damage should be considered for transplant.

Cocaine abuse may be associated with an increased risk of viral infections in their window

period (e.g. hepatitis C after intranasal cocaine sniffing). The metabolite coca-ethylene is formed after simultaneous consumption of cocaine and ethanol, and is more cardiotoxic than isolated cocaine.

e. Cyanide

Cyanides are rapidly absorbed through the skin and can lead to irreversible inhibition of mitochondrial cytochrome oxidase. The toxicity of cyanides may be reversed rapidly by specific therapy (hydroxo-cobalamin). Following cardiac arrest, a few cases of successful heart transplantation after cyanide intoxication have been reported after resuscitation with hydroxocobalamin. Successful transplantations of all organs following cyanide intoxication in the donor are possible, provided that effective antidote therapy has been used and no more cyanide is detected in blood.

f. Ethylene glycol (see also j. below for methanol)

Ethylene glycol is metabolised in the body by alcohol dehydrogenase into oxalic, glycolic and glyoxylic acids, leading to metabolic acidosis. Patients can be treated with ethanol or 4-methylpyrazole to inhibit the alcohol dehydrogenase, and sometimes with dialysis. Although the kidneys (the target organ for ethylene glycol) may be damaged due to tubular necrosis, transplant may be considered after recovery from this complication. Heart, lung or liver donation may also be considered. Ethylene glycol poisoning may occur in combination with methanol.

g. Ecstasy (3,4-methylenedioxymethamphetamine)

This drug may cause brain death due to secondary complications after excessive use, as well as first time or single use. Successful organ transplants (heart, lung, kidney, pancreas, liver) of ecstasy-poisoned donors have been reported without detectable transmission of the agent to the recipient [4]. However, ecstasy can cause fulminant liver failure in some cases, with the urgent need for liver transplantation of the poisoned patient due to unknown or possibly an immune cause. In the heart evaluation, ischaemia or myocardial necrosis should be ruled out, since these complications have been described in patients intoxicated by 3,4-methylenedioxymethamphetamine in relation to coronary spasm and arrhythmias.

h. Ethanol

All organs may be used, except for those confirmed with organ damage related to chronic abuse.

i. Insulin

There is no contraindication to organ donation, but normalised electrolyte and glucose metabolism is preferred [2]. Monitoring of glucose and electrolytes is standard practice.

j. Methanol (see also f. above for ethylene glycol)

Intoxication is not uncommon in countries where people produce their own alcoholic spirits without strict governmental controls. Cases have been reported where branded spirits and drinks have been diluted with methanol, causing intoxication. Methanol is rapidly absorbed by the gastro-intestinal tract and is metabolised by alcohol dehydrogenase into formic acid, leading to metabolic acidosis. Patients can be treated with ethanol and 4-methylpyrazole to inhibit the alcohol dehydrogenase, and sometimes with dialysis.

Although the kidneys may be damaged as a consequence of shock and multi-organ failure (the kidney is not a target organ for methanol poisoning), there are a number of reports of the successful transplantation of all organs after fatal methanol intoxication, dependent on the serum methanol concentration remaining at organ procurement. Liver, heart, lung, kidney and, in some cases, pancreas transplant might be possible if methanol remnants are absent from the serum and if metabolic acidosis is fully corrected.

k. Opiates and methadone

Except for the risk of temporary respiratory problems before terminal failure of the brain stem, no obstacles concerning organ donation exist. Caution is required because of the increased risk of acquired infections in the context of intravenous drug abuse or methadone substitution.

With methadone, and particularly in patients on maintenance therapy for a long period with high dose, heart donation should be considered carefully. There is also a theoretical risk of accumulation of methadone in numerous tissues. The risk is minimal in patients with a single methadone overdose.

l. Organophosphate pesticides

Pesticides require careful evaluation of the donor due to the risk of tissue accumulation and cardiac arrhythmias. It is important to identify the substance and to ensure that maximum terminal elimination half-life has been exceeded before organ recovery (e.g. parathion > 140 h) [6].

m. *Paracetamol*
In cases of acute liver failure due to paracetamol poisoning, irreversible liver injury may exist. However, in cases of brain death, all other organs may be recovered for transplantation.

n. *Rodenticides (dicoumarin) and other anti-coagulants*
Coagulation disorders should be considered due to ongoing vitamin K deficiencies until the recovery of the liver. The liver itself continues to function normally. Transplantation reports are lacking.

o. *Selective serotonin re-uptake inhibitors*
Fatalities following SSRI overdose appear less frequent than with TCA. Death is usually the consequence of brain failure (seizures) or sometimes of multiple organ failure in the event of a serotonin syndrome with high degree of hyperthermia. Organ removal should be possible, provided that the function of the organs is preserved. Cardiotoxicity is exceptional, but should be evaluated by routine testing (electrocardiogram, echocardiography and troponin).

p. *Other drugs or poisons*
In the event of intoxication or poisoning by unusual drugs or substances, a careful examination of the case has to be made jointly by the intensive care physician, the donor co-ordinator, a clinical toxicologist and the transplant team. This careful analysis and recording of the case could help decision making in future cases.

Reported cases of toxicity and poisonings leading to successful organ transplantation following brain death are summarised in Table 10.1 [1, 7-9].

10.2.3. Unusual conditions causing poisoning

The following unusual conditions or environmental hazards require consideration of the effect of multiple agents and or events:

a. *Burning and smoke inhalation*
In the worst cases, burn victims may have a combination of poisoning (smoke inhalation, carbon monoxide and cyanide). Proper treatment does not preclude organ donation in cases of certified brain death.
Smoke is a mixture of CO, particulate matter and other gases, which may include cyanide. Detailed information is required about the circumstances of smoke inhalation. If cyanide and CO poisoning are treated properly, smoke inhalation should not prevent organ donation (see individual toxins). Bronchoscopy for bronchial examination and cleaning is recommended. Lung transplantation has also in some cases been performed [12].

b. *Carbon monoxide*
The literature dealing with CO poisoning mentions several cases of successful transplantation of heart, lung, kidney and liver obtained from CO-poisoned donors [13-14]. All organs procured from donors with carbon monoxide poisoning and burn survived during follow-up. As the brain and the heart appear particularly sensitive to hypoxia, a careful examination of cardiac function is mandatory before accepting heart donation. As a minimum, the following criteria have to be respected: no cardiac arrest or a very short period of cardiac arrest, rapid successful resuscitation and normal echocardiography.

c. *Drowning*
Drowning and asphyxia are associated as one cascade: cardiac arrest and asphyxia after drowing are not per se a contraindication to organ procurement. When the possible donor has been stabilised at the intensive care unit the requirements for correct certification of death must be fulfilled. In donor and organ-specific selection, the complications associated with asphyxia have to be evaluated. Recent studies suggest that the results of lung transplantation with grafts procured from donors whose cause of death is asphyxia or drowning are equivalent to cases of other causes of death [15-16]. The only issue here is careful evaluation of the organs, including the question of pulmonal airway exposure to fresh water or salt water and the contamination of the different pathogens in it, as well as exclusion of tissue damage.

10.3. Inherited or congenital diseases

Many lethal incidents occur in patients without genetic disorders or inherited disease, and in such cases organ donation must be considered. If one of such conditions exists, careful donor evaluation becomes mandatory. For example, genetic disorders may cause various enzyme deficiencies which are linked to different metabolic pathways in the liver. Some of these genetic disorders with enzyme defects can be fatal since no alternative pathway exists for the metabolism except for this particular one linked to the liver tissue, while in other ones alternative

pathways may exist. Based on this, exclusion or inclusion criteria exist for liver donation. Regarding such issues, detailed lists of inherited kidney and liver diseases are available in recent reviews and they are helpful in defining organ-specific selection criteria [17-18]. Other gene defects may result in connective tissue disorders, haematopoietic disorders or predisposition for malignancies, or they may cause other terminal organ damage.

The basic considerations and strategies outlined below will contribute to assessing organ donors diagnosed with inherited diseases. They may also be applied when assessing donors with non-inherited and other congenital diseases.

10.3.1. Basic considerations

Experience with the transplantation of organs recovered from donors with genetic disorders is limited. To date, a registry of donations associated with rare diseases has not been established, although in about 1 % of all donation cases this is an issue and, in each case, an individual decision pathway has to be followed. The definition of a rare disease is variable from one country to another but in Europe the definition is a prevalence of 1/2 000. The diagnosis process may be long and not compatible with an emergency situation, including extensive clinical screening, family exam and finally, specific genetic tests. Those are increasingly used to characterise the (often private) causative mutation(s).

The European database Orphanet (www.orpha.net) provides regular updates of information about rare diseases. The section on emergency guidelines briefly mentions organ donation for each particular rare disease, but there is also a growing summary of guidelines for an endless list of rare diseases. International case references can also be found at https://rarediseases.org/organizations/rare-diseases-clinical-research-network/ or https://ghr.nlm.nih.gov/condition.

Certain genetic diseases are more common in some regions in Europe. Experience in organ recovery exists for familiar amyloid polyneuropathy (FAP), autosomal dominant polycystic kidney disease (ADPKD) and haemochromatosis. In some cases, common knowledge should enable a decision to be made about using a graft in a particular recipient or not; for example, transplant of a liver from a donor with a congenital coagulation disorder related to a Factor V Leiden mutation, or a Protein S or C deficiency, will require anti-coagulation therapy in the graft recipient.

Sometimes it is impossible to detect latent genetic disorders or metabolic deficiencies, for example late-onset ornithine transcarbamylase (OTC) deficiency. Transplant of an organ from a donor with an undetected genetic disorder risks impaired organ function or failure in the recipient with potentially severe consequences, and may require re-transplantation. In some heterozygous defects, the disease may only manifest in the recipient, for example Protein S deficiency [19]. Genetic disorders [20-23] should be considered when assessing donors with known thrombocytopaenia, haemochromatosis, mitochondrial deficiency and/or mental disorders not related to infection, poisoning or malignancy. Some authors highlight the need to consider determination of plasma ammonia as part of the routine evaluation of all brain-dead donors. The isolated finding of hyperammonaemia in a brain-dead person suggests a disorder of the urea cycle such as OTC deficiency [23]. Although this deficiency is a contraindication for liver donation, this restriction does not extend to other organs such as kidneys, as these organs are not affected by the disease [20].

In contrast to deceased donors for patients with selected, inherited, homozygote metabolic disorders requiring liver transplant, it is possible to use a living segmental-liver graft from a related heterozygote donor [21].

Whenever an inherited or congenital disease is suspected in a potential donor, the following steps should be followed to clarify the suitability of each organ or tissue for transplantation:

1. Establish the diagnosis by collecting all available data and by consulting the experts responsible for the care of the donor. This may require specific sampling for examination by specialised centres (national reference centres).
2. Each organ or tissue under consideration for procurement must be checked for its functionality and level of damage. Impaired or damaged organs should not be transplanted. In some cases, a different metabolic pathway exists that might resolve the problem; for example, in glycogenosis type 5 (McArdle disease), an enzyme defect affects all cells (especially muscle cells), but this defect is successfully mitigated in liver cells due to an enzyme coded on a different gene performing the metabolism.
3. The risk that organs from donors with inherited diseases will transmit a genetic defect to recipients needs to be carefully considered. This assessment needs to be weighed against the possibility of post-transplant therapy in the recipient, and its associated risks, or the emergency needs of a recipient.

All transplant teams involved must be aware that this assessment procedure is time-consuming and requires an interdisciplinary approach.

For helpful links to further information about diseases, contacting experts and emergency guidelines, see:

- www.orpha.net
- https://rarediseases.org
- https://ghr.nlm.nih.gov/condition

10.3.2. Examples of inherited disorders in cases of organ donation

a. Enzyme abnormalities and familiar amyloid polyneuropathy

A remarkable example of genetic disorders affecting the question of graft use is FAP [22]. In Portugal, Spain and Sweden, specific populations suffer from this disease at an exceptionally high prevalence. For some patients, liver transplant may be the only therapeutic option. FAP is characterised by the ongoing destruction of nerves (and other tissues), with an onset of sensory-motor polyneuropathy in the lower limbs. Due to a point mutation of the transthyretin or prealbumin gene, endoneurinal amyloid deposits occur that are responsible for irreversible damage by amyloid aggregates between the ages of 30 and 50 years, unless a functioning enzyme pathway is introduced through a liver transplant. The otherwise healthy livers of FAP patients can then be used in non-FAP patients (or even divided between two recipients) waiting for liver transplant in a so-called domino liver transplantation procedure [23-25]. However, FAP is, without exception, ultimately transmitted to these domino transplant recipients and clinically manifests after a variable time period. Risk–benefit assessment in recipients should take into account that FAP could occur after a variable delay of 5-10 years in the recipient (e.g. in recipients with indication for liver transplantation for hepatic carcinoma).

On the other hand, serious adverse outcomes are described in case of hyperoxaluria, acute intermittend porphyria, apolipoprotein A1 amyloidosis, lysozyme amyloidosis and acute intermittent porphyria.

b. Autosomal dominant polycystic kidney disease

ADPKD is not a contraindication to organ donation; even polycystic liver and kidneys can be considered for transplant [26]. In the case of associated complications in other organs, for example polycystic liver disease, it is advisable to assess graft quality at recovery and to transplant suitably selected recipients. Some gene carriers are at higher risk of developing subarachnoid bleeding after rupture of a cerebral aneurysm. ADPKD may serve as an example for flexible interpretation of the disorder and its effect on donor-selection criteria. In a donor who has a family history of ADPKD, normal kidney function and only minor morphologic changes, a rapid deterioration of kidney function is not likely and transplant is possible [20]. In contrast, in a young donor (e.g. < 30 years) with normal kidney function but having an enlarged kidney typical of ADPKD, deterioration of kidney function and other complications are likely to occur over an unpredictable timeframe, thereby warranting a reluctance to use the kidneys.

There is no reported case of liver failure in patients with ADPKD. Some authors suggest that the selective use of polycystic donor livers containing small cysts with preserved liver function is safe. Cardiovascular abnormalities are the most important non-cystic manifestations of ADPKD. A careful clinical evaluation of cardiac function by routine testing is mandatory before heart donation for transplantation is considered.

c. Congenital coagulation disorders

Factor V Leiden mutation. Affected patients with recurrent thrombosis need anticoagulation therapy, thereby exposing them to the risk of intracerebral bleeding. Organ donation is possible although, in the case of liver transplants, the defect will be transmitted and recipients will require anti-coagulation therapy, with a consequent high to unacceptable risk to the recipient's life.

Haemophilia. The type of haemophilia must be determined, which will indicate the location of the gene defect. If it is attributable to one organ, for example liver, the other organs can be used without elevated risk. However, transplantation of an affected organ transmits all complications associated with the type of haemophilia to the recipient. Some authors suggest that haemophilia donors should not be precluded from organ donation. However, high levels of factor VIII inhibitor in the donor before organ procurement represent an absolute contraindication to liver donation [27].

d. Trisomy

There are several types of trisomy. If organ function per se is not affected, it can be used as a graft.

e. Connective tissue defects (e.g. Marfan syndrome)

Although organ functioning at the cellular level is good, transplant practitioners are reluctant to use organs or tissues (e.g. heart, heart valves, arteries) due to destruction of the vascular walls. Experts should be consulted before a final decision is made. There is a risk of transmitting the defect, but there are no data on

whether or not vascular walls would undergo further destruction after transplantation.

f. *Phacomatosis and neurofibromatosis*

Four major types are described in these inherited conditions that are genetically and clinically different. In the case of neurofibromatosis type 1 (Morbus Recklinghausen), organ donation is possible if the increased risk (5 %) for development of other malignancies is properly considered (e.g. optic glioma, astrocytoma, phaeochromcytoma, GIST). Neurofibromatosis type 2 is related to bilateral Schwannoma (WHO°1) of the cranial nerve 8. Irradiation could increase the thrombotic risk in organs. Tuberous sclerosis (Bourneville's disease) should be excluded.

Donors with von Hippel–Lindau syndrome could be considered (preferably for the heart donation) when inappropriate risks associated to RCC and other malignancies are excluded when using organs according to guidance in Chapter 9.

g. *Further examples*

Table 10.2 provides a non-exhaustive overview of inherited, congenital or otherwise acquired diseases where organ donation has been realised with success, and other cases where transplantation of single organs did not have a successful outcome [27-33].

10.4. Autoimmune defects and autoimmune reactions

It is well known that autoimmune diseases can be transmitted by haematopoietic cell transplantation from the donor to an unaffected recipient. But only exceptionally has the occurrence of *de novo* autoimmunity in solid organ transplantation been described as donor-derived. Typically, these autoimmune diseases occur in the context of liver transplantation from a donor with documented autoimmunity (e.g. immune haemolytic anaemia and autoimmune thrombocytopaenia) [33]. Thereby the aetiology of post-transplant autoimmunity can be explained by graft-versus-host response in most cases and only exceptionally by direct transfer of antibodies from the donor during transplantation [34]. Fortunately in most cases no side-effects will be observed since immuno-suppression is also part of the therapy of autoimmune diseases. An example of such rare complication is immune-mediated haemolysis caused by transfer of passenger lymphocytes from the donor to the recipient due to minor ABO blood group donor–recipient mismatch or previous immunisation of the donor against other erythrocyte antigens which are found on the erythrocytes of the recipient [35].

Organs from donors with autoimmune diseases can be transplanted when relevant organ damage has been excluded. This must be considered for each organ separately. Transient complications of post-transplant autoimmunity are rare, but awareness about this issue, early identification and appropriate treatment are important in patients at risk. This requires a critical risk–benefit assessment. Table 10.3 shows a non-exhaustive list of autoimmune and systemic diseases.

Since immunological response to infections may cause cross-reactivity to antigens in the body with autoimmune reactions, the risks of such infections should be considered in the case of autoimmune diseases known in the donor. Helpful information can be obtained from the emergency guidelines provided by www.orpha.net or by application of the algorithm provided in Table 6.2 (see Chapter 6, §6.3).

To summarise the advice on transplants involving autoimmune diseases:

- In the case of autoimmune diseases in the donor, monitoring of the recipient is recommended.
- Organs from donors with autoimmune diseases can be used for transplantation after exclusion of end-stage organ damage and infections associated with the treatment with immune-suppressive drugs for autoimmune disorders.
- The potential risks of effects of donor-derived passenger lymphocyte activity in the recipients do not preclude organ donation itself.
- In the case of donors with erythrocyte antibodies, prospective monitoring of the recipients contributes to early detection and appropriate treatment of mediated haemolysis.

10.5. Allergies

Passive transfer of type I hypersensitivity reaction from donor to recipient has been reported with liver, lung, intestinal, kidney and heart transplantation [35, 38-43]. Recipients suffered allergic reactions to peanuts or nuts after having received an organ from donors who died as a result of an anaphylactic reaction to those ingredients or from donors with well-known allergic reactions to them in their medical history. There was a systemic response in the liver recipient and 'respiratory distress' in lung recipients.

Table 10.2. **Examples of successful/unsuccessful donation in cases of inherited, congenital or acquired disease**

Disease	Organs	Comment
Rendu–Osler–Weber syndrome	Kidney	Successful transplantation is reported. [28]
HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)	Kidney	Successful transplantation is reported. [29]
IgA-nephropathy	Kidney	Depending on the degree of kidney damage the graft may be used, since immune-suppressive therapy may be therapy of original disease. [30]
	Other organs	Can be used for transplantation.
Moyamoya disease	Heart, kidney, liver, lung	After exclusion of defects in other organs due to vascular defects, transplantation is possible. [31]
Gilbert syndrome	Liver	Gene defect causes unconjugated hyperbilirubinaemia. Impaired long-term outcome not observed. [32]
Bleeding disorders	Liver	In cases with isolated factor XII, VII, XI deficency in short term, no adverse events are observed (haemophilia A should be excluded). [33]
	Other organs	Can be used for transplantation.
Thrombotic disorders	Liver	In the case of a donor with unknown protein C, protein S or Factor V Leiden mutation deficiency, serious thrombotic events are observed if the graft is used. In the case of a donor with known protein C, protein S or Factor V Leiden mutation deficiency, recipients must be selected carefully. They should be able and willing to receive adequate anti-coagulation therapy after transplantation, though still with increased risk of thrombotic events [19].
	Other organs	Can be used for transplantation.
Hereditary haemochromatosis	Liver	In the case of heterozygote recipient receiving a graft from heterozygote or homozygote donor, disease is manifested which requires treatment of iron overload; no data available on long-term success.
Ornithine transcarbamylase (OTC) deficiency	Liver	Fatal outcome in deceased donation.
	Other organs	Can be used for transplantation.
Alpha-1-antitrypsin deficiency	Liver	Very likely to develop cirrhosis or fibrosis with intermediate time interval; re-transplantation necessary; no long-term follow-up.

Table 10.3. **Autoimmune and systemic disease and factors to be considered for donor- or organ-specific evaluation and selection**

Autoimmune and systemic disease	Donor (global)	Organ-specific				
		H	Lu	Liv	K	Pa
Primary biliary cirrhosis (PBC)	Consider carcinoma of the bile ducts and/or complications due to inflammatory bowel disease	Ev	Ev	N	Ev	Ev
Endomyocardial fibrosis	Yes	N	Ev	Ev	Ev	Ev
Idiopathic lung fibrosis	Yes with evaluation	Ev	N	Ev	Ev	Ev
Auto-immune hepatitis	Yes with evaluation	Ev	Ev	N	Ev	Ev
Lupus erythematosus cutaneous	Yes	Y	Y	Y	Y	Y
Systemic lupus erythematosus	Yes (50 % of renal disease) [36]	Ev	Y	Y	Ev	Y
Heubner–Herter disease or coeliac disease	Yes	Y	Y	Y	Y	Y
Pemphigus	Yes after evaluation (cortisone, malignancy)	Y	Y	Y	Y	Y
Purpura rheumatica	Yes	Ev	Ev	Ev	Ev	N
Sclerodermia	Depends on degree of systemic involvement	Ev	Ev	Y	Ev	Y
Severe antiphospholipid syndrome	Exclude if severe (evaluate in mild case)	Ev	Ev	Ev	Ev	Ev
Crest syndrome	Yes	Y	Ev	Y	Y	Y
Goodpasture syndrome	Yes	Y	N	Y	N	N
Gougerot–Sjögren syndrome	Exclude lymphoma	Y	Ev	Y	Y	Y
Familial Mediterranean fever	Check amyloidosis (M694V mutations in FMF) [37]	Y	Ev	Y	Ev	Ev

H = heart; Lu = lung; Liv = liver; K = kidney; Pa = pancreas. Y=yes. Ev=evaluation and discussion with expert. N=no.

This can be explained either by degranulation of donor food-specific IgE-loaded mast cells bound to liver or lung tissue after allergen exposure, or to passive transfer of IgE retained in the liver sinusoids and bound to mast cells later on with the same effect (both persisting for months). In addition, there may be transfer of specific IgE-producing B cells, allergen-specific Th2 lymphocytes, stem-cells or dendritic cells inducing IgE production together with the graft, causing allergic reactions in the recipient (with long-term persistence).

The exact mechanism causing this transfer of anaphylactic reactions cannot yet be explained; neither is it known why this happens in some but not all recipients, nor why it is more or less often observed in grafts hosting more 'immune-reactive donor cells' (e.g. lung, liver, intestine) than others (heart, kidney, pancreas). Until further evidence exists, it is imperative that autoimmune disorder allergies (mainly to food allergens) are considered as part of the donor health assessment. Since a residual risk of transferring an anaphylactic reaction to the recipient exists, this information should be passed on to the recipient centre, especially in the case of liver, lung and probably intestinal transplantation.

Due to post-transplant immuno-suppression, recipients may acquire *de novo* allergies which are related to the graft and to the kind of immunosuppression received, such as tacrolimus or cyclosporine, but not to the issue of passive transfer from donor to recipient via donor lymphocytes or mast cells contained in the graft.

Most importantly:

In the case of known anaphylactic reactions in the donor history, this information must be included in the donor characterisation (section on autoimmune issues).

Lung, liver and probably intestinal transplant recipients should be taught to avoid such allergen exposure (especially to food allergies in a donor with known anaphylactic reactions).

10.6. Neurodegenerative diseases, demyelinating diseases

Neurodegenerative and demyelinating diseases are caused by multiple different agents (e.g. ageing, genetics, autoimmune reactions, infections, exposure to environmental agents or unknown factors). Multiple co-factors further complicate the individual progression of these diseases.

When genetic defects or metabolic disorders cause such diseases, then transmission risks are not associated with a particular organ, unless the defect also causes damage to this organ. Further information about organ involvement can be extracted from www.orpha.net and/or consultation of national experts listed there. When autoimmune defects cause such neurodegenerative and demyelinating diseases, then the rare event of transfer of autoimmune reactivity cannot be definitively excluded.

Current data suggest that patients with amyotrophic lateral sclerosis (ALS) are eligible organ donors [44]. However, multiple lines of evidence suggest that many neurodegenerative diseases, including ALS, might progress due to transcellular propagation of protein aggregation among neurons. ALS patient grafts may serve as the sole life-saving materials available, making moot any discussion of ALS transmission risk.

In potential organ donors with a neurodegenerative or demyelinating disease, it is essential to ensure that the disease:

- is not caused by an infection (e.g. prion disease in relation to variant Creutzfeld–Jakob disease, HIV-related neurocognitive impairment) that excludes organ donation (see Chapter 8);
- is not associated with infectious complications related to specific treatment of the disease (e.g. progressive multifocal leuko-encephalopathy, caused by JC virus after treatment by natalizumab in multiple sclerosis) or the further course of disease that excludes organ donation (see Chapter 8);
- is properly diagnosed.

10.7. Conclusions

Multiple disorders or conditions exist that may be perceived as contraindications to organ donation due to potential additional risks to organ recipients. This chapter is not exhaustive in listing and providing recommendations about the use of organs from donors with a variety of diseases and conditions. Before dismissing any potential donors, however, it is necessary to assess each case individually and, when literature or reference websites cannot provide all information needed, experts in the field should be contacted.

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Related material

- Appendix 14. Reporting form for rare diseases and intoxication (France, English-language version)

Chapter 11. Organ procurement, preservation and transportation

11.1. Introduction

The organ shortage is increasing every year, and organ transplantation is more important than ever. In many cases it is the best and/or only effective treatment for end-stage organ failure. There are a number of key components in high-quality organ procurement, preservation and transport that enable specialist teams to procure donated organs and to preserve and transport them safely for transplantation. Opportunities for transplantation are lost at all stages of the pathway from offering to implantation. In most cases, there are clearly valid clinical reasons for this loss of opportunity – for example, brain-death testing that cannot be done because the potential donor remains unstable, or an organ that may be unsuitable, such as a fatty liver that would not function if transplanted. In other cases, the reasons are less clear. The organ procurement team is responsible for obtaining those organs suitable for transplantation for which consent has been given and for which a suitable recipient has been identified. This requires clear, written organ-procurement protocols, covering where appropriate donation after brain death (DBD) and donation after circulatory death (DCD). Formerly, these types were classified as heart-beating donation (HBD) and non-heart-beating donation (NHBD) [1].

A good understanding of organ cooling with perfusion solutions and cold storage, to slow down biological deterioration of removed organs, and its use in practice are both essential to ensure that there is enough time to organise such a complex logistic procedure. However, the low temperature also has some destructive effects on cell biology, so optimal conditions are required. There are many ongoing studies of how to optimise this process, with or without the use of machine perfusion.

11.1.1. History of organ preservation

In the early 1900s, there was already significant knowledge about how to keep organs functioning outside the body. From that time, physiologists investigated the principle of perfusion with the use of pumps [2]. After several years, the initial use of blood in machine perfusion was replaced with synthetic perfusate solutions, and low temperatures were used to reduce cell metabolism [3-5]. In 1963, the additional benefit of whole-organ cooling by perfusion of deceased donor kidneys was described, showing that longer ischaemia times could be tolerated by the organ if it was sufficiently cooled [6].

Collins *et al.* were the first to design a preservation solution that tried to mimic the intracellular electrolyte balance of the mammalian cells. The solutions that followed were considered the new standard and they improved the preservation of organs significantly to survive 24 h [7].

11.1.2. Physiology of organ cooling

During and after organ retrieval, and even directly after reperfusion, organs will sustain damage on several levels (e.g. tissue/cell changes, molecular changes, ischaemia/reperfusion injury) [8]. On one hand, it is believed that organs need to be cooled down to preserve them until implantation, but on the other hand, because of the cooling, they will get injured by oxidative stress and cytokine production/inflammation. Although solutions improve preservation, we should be aware that they only slow down ischaemic and hypoxic damage. However, they are necessary to reduce cellular metabolism.

In metabolically active cells, adenosine triphosphate (ATP) levels are maintained constantly; at 4 °C, some metabolism continues. With regard to the cells, several metabolic pathways are affected: inhibition of the Na^+/K^+ ATPase pathway causes cell oedema, rapid depletion in ATP reserves and a corresponding increase in adenosine diphosphate levels, and this depletion of ATP leads to the degradation of adenosine causing accumulation of hypoxanthine and xanthine oxidase. Cell membrane depolarisation also occurs very early in the cascade, leading to a breakdown of ion homeostasis, and an interplay of other intracellular and membrane-associated events that eventually culminate in cell death by either apoptosis or necrosis [9-10]. Although there is no hard cut-off point for the period that organs can suffer from cold ischaemia without being harmed, the generally accepted times are 24 h for a kidney, 12 h for a liver, 8 h for a lung and preferably under 6 h for a heart. Obviously, cold ischaemia times should be as short as possible and machine perfusion, if needed, can be a bridge to implantation.

11.2. Facilities, personnel and equipment for organ procurements

Deceased donation is a complex process involving a range of necessary actions that can break down if not managed appropriately. That is why competent professionals with the necessary skills and experience must be appointed to act in accordance with written agreed procedures. Their performance should be continuously monitored and evaluated, to identify where improvement or learning may be gained.

11.2.1. Donor co-ordinator

The presence of a donor co-ordinator at the donor hospital has been identified as the most important step to support organ donation [11-12]. Some patients will die following an unexpected cardiac arrest, and may be suitable as uncontrolled DCD donors (Maastricht categories I and II) (see Chapter 12, Table 12.1) [13]. Alternatively, a decision may be taken that further active treatment is futile and/or inappropriate. Life-sustaining treatment is then withdrawn and such patients may be potential controlled DCD donors (Maastricht category III). For various reasons, countries may procure organs from Maastricht category II donors rather than III, or vice versa. It has to be noted that many countries in Europe do not have a DCD programme or do not accept organs from DCD donors. However, it is vital that particular attention is given to donor management (see Chapter 5), organ procurement and preservation of expanded criteria donors, as summarised in the Critical Pathway for Organ Donation at the 3rd WHO Global Consultation on organ donation and transplantation, held in Madrid in March 2010 [14].

DBD can only be performed when a patient is declared brain-dead, which is based on strict neurological criteria (see Chapter 3). DBD can be further divided into 'standard criteria' and 'extended criteria' donation. However, the exact definition varies, it naturally differs per organ and the literature does not give a uniform description. For example, donors who meet the standard criteria for kidney donation after brain death are aged 59 or younger. The expanded criteria for kidney donation after brain death include donors older than 60 and also donors aged between 50 and 59 who satisfy two or three of the following conditions: cerebrovascular accident as the cause of death, a serum creatinine concentration of more than 1.5 mg per decilitre (133 µmol/L) and a history of hypertension. In recent years, as a result of organ donor shortage, an increase has been observed in the use of expanded-criteria DBD donors, whose organs are considered of inferior quality compared to standard-criteria donors, resulting in worse patient and graft survival [15].

The donor co-ordinator's duties could include co-ordinating action to optimise all conditions for deceased organ donation within the hospital, assessing the suitability of the potential donor, obtaining consent or authorisation, obtaining all necessary available clinical, social or behavioural information for characterisation, liaising with relevant organisations for allocation, liaising with the surgical teams for organ retrieval and liaising with the potential recipient surgical team for transplantation. The donor co-ordinator might also arrange theatre availability for procurement, provide follow-up for donor families and supply data, statistical capture

and support for the evaluation of the procurement programme.

There should be an agreed line of communication between the donor co-ordinator and the transplant co-ordinator to ensure that effective retrieval, allocation and transport arrangements are put in place. This requires good co-ordination to manage the timing of the abdominal and cardiothoracic procurement teams. This will minimise the risks of adversely affecting the viability of the organs. It will also limit disturbance within the donor hospital and respect the bereaved family. Finally, it will give sufficient time for the organs to be allocated and for potential recipients to be contacted and to arrive in the transplant centres.

11.2.2. Donor hospital

The donor hospital should provide the operating theatre with appropriate facilities and personnel as agreed. Suitable equipment and personnel should also be agreed for transporting the donor from the emergency room or intensive care unit to the operating theatre in order to avoid circulatory instability of the donor [16]. Some countries may authorise or license only specific hospitals for organ procurement (e.g. in EU member states, as specified in Directive 2010/53/EU).

11.2.3. Procurement teams

It is recommended that, where possible, fully staffed on-call procurement teams are available 24/7. Unfortunately, obtaining (often regional) funding for these teams is extremely difficult. Ideally, teams will at least include a certified surgeon for organ procurement, an assisting surgeon, a co-ordinator who monitors the donation process and a technician to support organ perfusion and preservation. Some teams will also include an anaesthesiologist or pulmonologist. There are usually separate teams for the thoracic and abdominal organs, because the recipient centre often sends out its own surgical team for hearts and lungs. The composition of the team will vary between transplant centres, organ procurement organisations and donor hospitals, but should be the size necessary for optimal donor management and training. Agreed protocols can clarify the composition of the procurement team and their roles in the process. It is essential to perform the entire procedure in a standardised manner, in order to minimise organ damage and to reduce the potential for discarding valuable donor organs. Therefore, the organ procurement team must be properly trained for its retrieval task, including the use of novel technologies for perfusion and preservation where necessary. In some Council of Europe member states, adequate training and certification for organ retrieval surgery have become normal practice, leading to a decrease in surgical injuries [17].

11.3. Multi-organ procurement procedures

Each procurement team/transplant centre must have clear written protocols for both DCD and DBD retrieval. When separate cardiothoracic and abdominal teams attend a donor, the respective surgeons must agree details of the procedure before starting to recover the organs. This enables discussion of any potential uncommon procedure or modifications to normal procedures that might affect other donated organs, e.g. the use of hypothermic or normothermic regional perfusion as the *in situ* preservation strategy after procurement (see Chapter 12). Also, the donor surgeon responsible for procurement should check the brain-death criteria, in case of DBD, and check the declaration of (circulatory/cardiac) death after DCD.

As early as 1987, Thomas Starzl described techniques for procurement of multiple organs [18]. In 2009, Reich *et al.* recommended guidelines for procurement of organs from DCD donors [19-20] (see also Chapter 2).

The procedure usually begins with a laparotomy. If the chest is opened, a thorough inspection of the thoracic organs should be undertaken to exclude malignancy and any other pathology that might mean the organs cannot be used for transplant. In the case of lung procurement, a bronchoscopy by the procurement team is usually performed as a final quality control of the organ. A rapid cannulation of both the aorta and vena cava is performed in order to start organ preservation by cooling as soon as possible. This procedure is used in DCD donors, and also in DBD donors who are haemodynamically unstable. A less hasty, more considered approach to multi-organ retrieval, with inspection and precluding of vascular structures, is typically performed in stable DBD donors. In donors with excellent liver function, *in situ* splitting of the liver can be considered. However, the quality and integrity of other organs should never be compromised when undertaking such a procedure. In cases of deterioration in the donor's condition, *ex situ* splitting of the liver may be preferred. Also, during the inspection of the thorax and abdomen the surgeon should inspect for potential malignancies; if these are suspected, biopsies/frozen sections should be taken. The procurement should not be stopped,

but the recipient centre makes a final decision on whether to accept an organ, once the results from the biopsy are available (see Chapter 6).

For the retrieval of thoracic organs, their inspection and dissection can begin after opening the sternum, and the thoracic and abdominal teams can simultaneously begin *in situ* perfusion of the organs after cross-clamping of the aorta or circulatory arrest. Topical cooling of the organs can be performed while awaiting the end of perfusion. Before cannulation for *in situ* perfusion of the organs is done, procurement teams request heparinisation of the donor (e.g. 300 IE/kg) or alternative anticoagulation when heparin is contraindicated.

Thoracic and abdominal organs may be recovered simultaneously. It is the decision of the procurement surgeons whether extensive *in situ* preparation of the organs with separate removal is performed, or whether all organs are removed *en bloc*, with further preparation of the organs (if necessary) outside the body.

The abdominal surgeons should recover the iliac and in some cases, other vessels, to be sent with liver, pancreas and intestinal grafts. These 'vessel toolkits' contain the arteries and veins needed for reconstruction of the vascular inflow and outflow between graft and recipient vessels. Tissue material (e.g. spleen and lymph nodes) for supplemental HLA-typing and cross-matching should also be collected. Proper labelling of this material is mandatory for traceability and assignment to the matching organ(s). When vessels are not used with the organ at transplantation, then their use for other purposes should adhere to the rules of tissue donation of vessels if suitable; please refer to the *Guide to the quality and safety of tissues and cells for human application*.

The heart is the most sensitive organ to ischaemia (with maximal accepted ischaemic times below 6 h) and should be the first organ to be removed. The intestines (where recovered) should be second, followed by the liver, pancreas (can be recovered *en bloc* with the liver and separated *ex situ*) and then the kidneys. The lungs, if recovered, are often procured at the same time as the liver, but after the heart.

The procurement team is responsible for appropriate closure of the thorax and abdomen, thereby restoring the appearance of the body according to local practice. Relatives must be supported to make arrangements for the care of the body after the procedure.

Any abnormality or injury (whether accidental or pre-existing) must be reported and information about any delays should be appropriately communicated and acted upon. The surgical team responsible for organ retrieval should assess the quality of the organs and their viability for transplant. In cases of doubt, this information should be communicated to the recipient centre and, where appropriate, to the centre responsible for allocation to consider re-offering or re-allocating the organ to another potential recipient in another transplant centre if necessary.

In the case of unexpected anatomical findings, the recipient team should be informed immediately and additional examinations (e.g. biopsies) should be performed. As soon as such results are available, the recipient team must receive these, thereby allowing them to make a final decision about the offer.

11.4. Organ preservation

When they have been procured, organs should be flushed with suitable and sufficient preservation fluid while keeping them cool in order to slow down their metabolism. A number of preservation solutions are available, some of which are outlined in section 11.4.2 [10]. Not all solutions are approved for use in all organs, and they are likely to be different for thoracic and abdominal perfusion. The perfusion solution must be recognised nationally and agreed with the recipient team. The procurement team should always ensure that a sufficient amount of preservation solution is available at the beginning of the procedure. The solutions should be specified in the standard operating procedures and comply with existing national regulations. Regulations about flush volume and preservation should be followed, according to the instructions of the manufacturer and/or national standard operating procedures. These should include procedures for DBD and DCD *in situ* perfusion and back-table perfusion. Contamination of the preservation fluid must be avoided.

11.4.1. Novel techniques for organ perfusion and preservation

Since the organ shortage (of both deceased and live donors) is increasing all over the world, transplant professionals are reconsidering their options. In living donation, more expanded-criteria donors are being accepted, e.g. donors with hypertension, obesity, vascular multiplicity or advanced age [21-22]. In deceased donation, DCD donors and (especially) expanded-criteria donors are increasingly being accepted for donation. To optimise organs, new techniques are being investigated to aim for better early graft function.

In general, organs from DCD donors are considered to be of less quality, because of the longer

warm ischaemia time. This certainly holds true for liver transplantation [23-24]. However, in kidney transplantation, recent literature suggests only minor differences between DCD and DBD organs, and probably results may even be slightly better in, for example, DCD lung transplantation [25-26].

Since the 1970s, after the introduction of organ preservation fluids for cold perfusion, their use has been considered as the gold standard for hypothermic machine perfusion [27-28]. Several different preservation fluids have been used since then [29].

11.4.2. Preservation solutions

Since the beginning of organ procurement and transplantation there has been a lot of development in different types of preservation solutions and their mechanisms. Table 11.1 is a non-exhaustive list of the main solutions created over the years and the principles they are based upon.

11.4.3. Machine perfusion

In recent years, some studies have shown that machine perfusion might have more benefits compared to cold storage alone [40]. Others have stated that there is little evidence for improved long-term outcomes by machine perfusion [41].

These conflicting results have led to several new research ideas combining the use of supplemental oxygenation with different preservation techniques and machine perfusion. The idea behind the additional value of oxygen delivery is that it may support the mitochondrial synthesis of ATP, thereby delaying the injury that occurs during ischaemia. There are several methods for providing this so-called supplemental oxygen during hypothermic preservation, and they include:

- oxygenated perfusate or perflurocarbon emulsion,
- hyperbaric oxygenation by the delivery of oxygen under increased atmospheric pressure,
- retrograde persufflation of gaseous oxygen bubbled through the renal vasculature [28], one technique being hypothermic oxygenated perfusion.

A recent systematic review has compared results of the following procedures that use either supplemental oxygen during hypothermic preservation or non-oxygenated preservation techniques [42]:

a. Normothermic regional perfusion: *in situ* perfusion of the thoracic and/or abdominal organs in the DCD donor before and at the time of organ retrieval (see Chapter 12);
b. Hypothermic regional perfusion (see Chapter 12);
c. Machine preservation, including during transport of the organ to the transplant centre:
  i. hypothermic machine preservation,
  ii. hypothermic machine preservation with delivery of oxygen,
  iii. normothermic oxygenated machine preservation;
d. *Ex vivo* perfusion: either
  i. end-ischaemic machine perfusion, or
  ii. machine preservation, including during transport of the organ to the transplant centre, (normothermic or hypothermic) on the bench.

Worldwide, there are several groups that are currently collecting evidence on and performing trials for machine preservation in heart and lungs

Table 11.1. **Overview of commonly used preservation solutions**

Solution	Basis
Collins Solution	a combination of high potassium ion content and osmotic barrier supported by glucose [30]
Citrate Solutions (Marshall/Ross)	electrolytic composition characterised by high potassium, sodium and magnesium content; citrate added to replace phosphate and as buffer agent to maintain intracellular pH [31]
University of Wisconsin (UW) Solution	prevention of oedema (raffinose, lactobionate), supplementation with precursor of ATP (adenosine), antioxidant defence (allopurinol, reduced glutathione) [32-33]
Bretschneider's (Custodiol) Solution (HTK)	strong buffer (histidine), osmotic barrier (mannitol), low-permeable amino acids (tryptophan and alpha-ketoglutaric acid), which help to stabilise cell membranes [34-35]
Celsior Solution	adopted many of the principles of UW Solution and the strong buffer from Bretschneider's HTK. Good tissue cooling, excellent properties in prevention of cell swelling, free radical scavenging and energy depletion [36]
Kyoto University Solution	a recently developed solution, with two-fold higher survival rate after 30 h of canine lung preservation compared to UW Solution and superior to Celsior solution in pancreas cold storage and islet isolation; a novel candidate for the procurement and preservation of multiple organs [37]
IGL-1 Solution	the composition of the medium is identical to simplified UW Solution and characterised by an 'extracellular' type, high-sodium/low-potassium ratio [38-39]

[43-48], kidneys (COPE-trial) and livers (HOPE and dHOPE trials; ClinicalTrials.gov Identifiers: NCT03124641 and NCT02584283). The existing published literature does not allow any more definitive statements than that these trials are going on and we have to wait for new evidence before introducing new techniques and procedures into guidelines. Within the next few years it will become clearer whether organ preservation and utilisation can be optimised by using normothermic and/or hypothermic modalities to improve patient and graft survival.

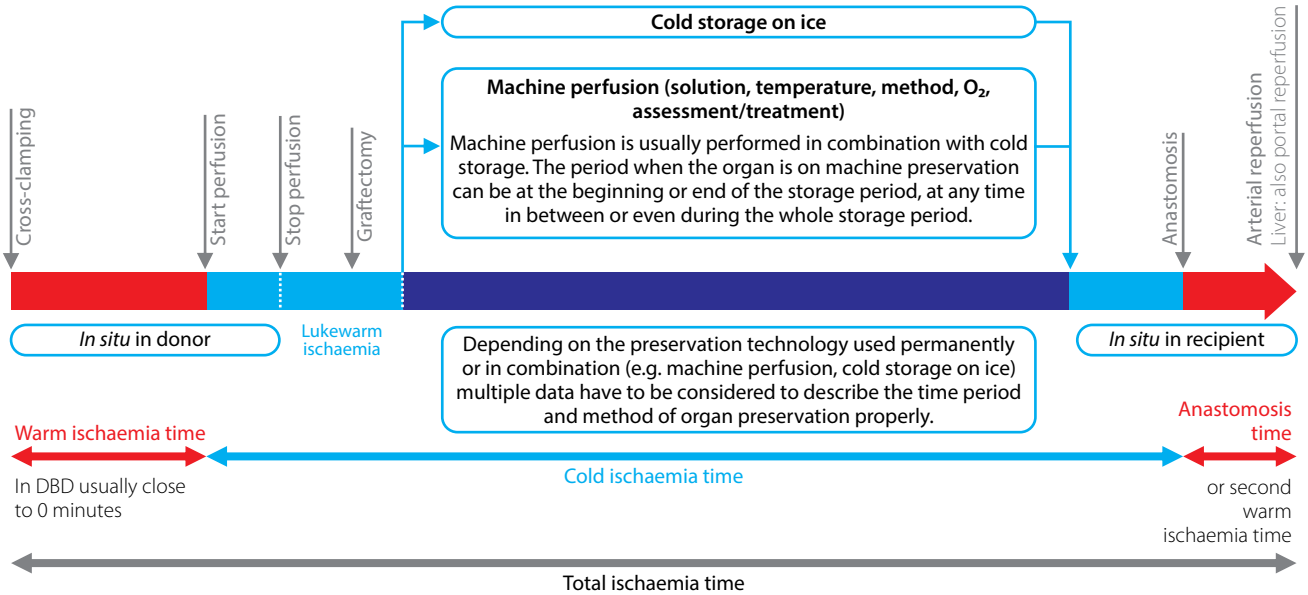
11.4.4. Ischaemia times

This chapter does not recommend optimal cold ischaemia times. Much will depend on the specific organ, age and co-morbidities of the large vessels in the donor and the method of preservation. There is also the danger that specified times will limit the use of an organ that could successfully be used for transplantation.

Between the cross-clamping of a graft in a donor and its reperfusion in the recipient, multiple events occur which may influence the quality of the organ (see Figure 11.1). For example, cold ischaemia induces endothelin gene upregulation [49]. However, recent literature shows that there is no actual messenger RNA upregulation during cold ischaemia [50-51]. Also, during reperfusion, the release of free radicals plays an important role in organ retrieval and function [52]. For the transit from the donor hospital to the transplantation centre, the organ is either stored static in cold solution or it is put on a preservation machine and flushed by different kinds of solutions (e.g. UW, Soltran) [53-54] and technologies with different aims, e.g. expanding the transport time without harm or evaluating graft quality *ex vivo*. Therefore, a uniform definition of total ischaemia time cannot be applied without mentioning all specific details, as outlined in Figure 11.1. Different time points in donor warm ischaemia in DCD are discussed in detail in Chapter 12 (see particularly Figure 12.2 and Figure 12.6).

Nevertheless, it is recommended that all organs be transplanted as quickly as possible; it is generally agreed that shorter preservation times correlate with better subsequent organ functioning [55-58].

Figure 11.1. **Ischaemia times: events and intervals during procurement and implantation of a graft**



Total ischaemia time: time interval from cross-clamping until arterial reperfusion. This includes the **cold ischaemia time**, which covers only the interval between the start of perfusions and the start of anastomosis. Adding this time to the **warm ischaemia time** in the donor and anastomosis time in the recipient gives the **total ischaemia time**. Note that between the ending of organ perfusion and the next stage (proper storage of the graft in cold storage or machine perfusion) the graft is exposed to an uncontrolled period of '**lukewarm ischaemia**'.

General Note: it is advised to document specific time points (e.g. cross-clamp, start of perfusion, graft-ectomy, start of machine perfusion etc.) rather than to document only the duration of each period.

For definition of warm ischaemia time in DCD, refer to Figure 12.2 and Figure 12.6.

11.5. Packaging and transportation of organs

11.5.1. Organ packaging for cold storage

The procurement team should provide all necessary blood tubes, containers and transport coolers. The organ(s) should be stored in the same solution used for perfusion. Triple sterile packing is preferred. The organ(s) are stored directly in perfusion fluid in the innermost container with the exclusion of air, with a second solution (cooled to 4 °C in the case of cold storage) in the middle container, again with the exclusion of air. Both containers are then inserted into a third container without fluid or air (as air expands at altitude, its inclusion can cause rupture of the containers if organs are transported by aircraft). The package is placed in an insulated organ transport box (or outermost container) to achieve good thermoregulation, with sufficient cooling elements or crushed ice in case of cold storage. Deviation from triple packing may be appropriate if the packing system used is certified and validated by the responsible authorities.

The packaging material should be inert, impermeable and sterile. All packaging materials should be validated for their intended use, with particular attention to the maintenance of temperature within the desired range and for the specified time. The outer container should be thermally insulated and made of a material robust enough to prevent leakage of contents and to withstand shocks, atmospheric pressure changes and other possible conditions during the course of transportation. In the case of cold storage, it must ensure that the organ is kept within a temperature range of 1-6 °C. The innermost container should contain sufficient fluid to prevent direct contact between the organ and cooling elements or crushed ice (produced from uncontaminated water).

Transplant-organ containers should be labelled externally with all the necessary identification details, while preserving the anonymity of the donor.

Labelling should include, as a minimum, the following:

a. anonymised donor identification,
b. contents of the package, including the type of organ/tissue and, where appropriate, whether it is the right or left organ,
c. address of destination, including details of the person to be notified upon arrival,
d. address of the shipping institution and details of the person to be notified in the event of unexpected complications,
e. recommended transport conditions, including instructions for keeping the container at an appropriate temperature and position, as well as 'handle with care' and 'Human Organ for Transplantation' marks.

Before release for transportation, it is mandatory to check the contents of the package and to ensure that all relevant information and documentation is provided, along with the appropriate labelling, as well as any additional donor-relevant attachments (e.g. spleen or lymph nodes for tissue-typing and cross-matching, sera and plasma samples and the 'vessel toolkit', where applicable). There are vessels and potentially other donor material that will be essential when the organ is to be transplanted. These vessels and other material should be clearly identified on the package label. The outer organ transport box should be properly sealed.

The surgeons and co-ordinators responsible for the organ retrieval and transplantation should be notified of the progress and results of all procedures pertinent to the organ procurement operation. In cases of delay or unexpected findings, the recipient centres should be informed.

Detailed organ documentation should include:

a. donor identification number,
b. time and date of declaration of death of the donor,
c. blood group of donor,
d. place of donation,
e. time and date of donation,
f. time of perfusion or organ preservation,
g. anonymous medical details of the donor and retrieval process,
h. detailed descriptions of the organ anatomy and a full report of any damage,
i. type and volume of preservation fluid and start of cold ischaemia time (and for DCD: time from circulatory arrest until cold perfusion in warm ischaemic time),
j. members of the retrieval team.

11.5.2. Organ transport

Worldwide, there are several different preferences and options in organ transport [59-60]. Organs are mostly transported via land, but can also be flown to the receiving hospital. For transport between hospitals, shipping containers should conform to local, national and international regulations. Transit times should be minimised and cold storage (where appropriate) must be maintained throughout transit. The means and route of transportation should be prop-

erly documented to enable the donor co-ordinator to trace the organ at any time. The receiving facility should verify that the indicated storage temperature and appropriate conditions of the shipped organ have been maintained during transit.

11.5.3. Traceability of organs

All Council of Europe member states must ensure that all organs retrieved, allocated and transplanted can be traced from the donor to the recipient and vice versa in order to safeguard the health of clinical personnel and organ recipients [61]. Organ procurement and allocation organisations must also

Table 11.2. **Tool for the evaluation and audit of organ procurement**

Audit and monitoring of procurement	
Activity	**Time to be recorded (hh:mm)**
Procurement team notified	
Procurement team arrives in donor hospital	
Donor arrives in theatre	
Cardiothoracic surgical starts (knife to skin)	
Abdominal surgical starts (knife to skin)	
Aortic cross clamp (if DBD)	
Removal of each organ • heart • lungs • liver • pancreas • small bowel • kidneys	
Time each organ is placed under ice in transport box • heart • lungs • liver • pancreas • small bowel • kidneys	
Donor operation ends (completion of skin closure and body reconstruction)	
Treatment withdrawn (if DCD)	
Systolic blood pressure < 50 mm Hg (if DCD)	
Oxygen saturation < 80 % (if DCD)	
Asystole (if DCD)	

Procurement team personnel	
Name	**Role in Procurement** ***(e.g. lead cardiothoracic/abdominal surgeon, theatre practitioner, donor hospital personnel, etc.)***
1.	
2.	
3.	
4.	
etc.	

Record of organ damage	
Details of damage (to be recorded by procurement and implanting surgeon) and when (e.g. below)	**Severity (e.g. below)**
• Prior to recovery • Surgical injury • Poor perfusion • During transport • During back table preparation at recipient centre • During implantation at recipient centre	• Mild (organ useable) • Moderate (useable with repair) • Severe (organ untransplantable)

Record of non-use of organ	
Organ(s)	**Reason for non-use**
	Declined without attempt at recovery due to: • Unsuitable donor • Poor quality graft • Other (specify) Declined following surgical exploration due to: • Poor quality graft • Graft damaged during recovery • Poor perfusion Unable to allocate organ due to: • No suitable recipient • Prolonged ischaemia • Other (specify) Failure to retrieve due to: • Unable to send recovery team • Donor becomes unstable before procurement

Outcome measures	
Primary non-function	**Primary dysfunction**
• Liver and heart (no evidence that the organ ever functioned leading to death or re-transplantation) • Kidney (no evidence that the organ ever functioned leading to need for dialysis)	• Liver (peak AST/ALT 2000 IU/l) • Kidney (need for temporary post-operative dialysis within the first seven days) • Cardiothoracic (need for device support)

Source: prepared by NHS Blood and Transplant for their National Organ Retrieval Programme in the UK.

ensure that all transplanted material can be traced back to the donor and forward to recipients.

It is vital to inform relevant medical personnel in contact with the donor and transplant recipients about any problems that may arise during retrieval and after transplantation, especially where there are health risks due to potential adverse events. Recipient centres must be able to demonstrate adequate arrangements for traceability between donor and recipients, for feedback (see §11.5.4) and for quality assurance (see Chapter 16), to ensure that any serious adverse reactions/events can be reported, monitored and acted on as appropriate (see Chapter 15). Careful follow-up and documentation of transplant outcomes is a prerequisite for the entire transplant process, for both clinical and scientific purposes. Therefore, in order to facilitate analyses of the results of transplantation procedures, it is mandatory to retain all relevant data related to the donor, the graft and the recipient outcome. The collection and analyses of these data on a regular basis will assist in evaluating the effectiveness and quality of transplant programmes, as well as identifying measures to be adopted for improvement.

11.5.4. Feedback

Following organ retrieval, a letter of thanks should be sent to the donor hospital, as well as to the relatives of the deceased donors (if requested) giving feedback on the transplantation of the organ(s). Throughout, confidentiality of donor and recipients must be maintained in line with national regulations. In addition, it is important that the transplant centre give feedback, about the quality and anatomy of the organ(s) received and inspected, to the retrieval team. Any injuries or missed abnormalities should be included, to enhance quality and competence. In several member states, such quality circles are now available for other member states to adopt [62]. Appendix 15 shows an example of such an (electronic) quality form.

11.5.5. Evaluation and monitoring

It is recommended that all procurement programmes be fully audited and evaluated. This provides a useful tool for service improvement and training. An evaluation tool prepared by NHS Blood and Transplant for their National Organ Retrieval Programme in the UK is included in Table 11.2.

11.6. Conclusion

Organ preservation, procurement and transport are key parts of the transplantation pathway. It is therefore vital that countries have an organ procurement, preservation and transport programme that ensures that the safest, highest-quality organs are offered for transplant, and that organs are retrieved in a timely and co-ordinated fashion by experienced personnel whose objective is to optimise all organs retrieved for transplantation.

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Chapter 12. Donation after circulatory death

12.1. Introduction

The majority of transplants from deceased organ donors use organs recovered from patients whose death has been declared on the basis of the irreversible cessation of neurological functions, i.e. donation after brain death (DBD). However, the shortage of organs for transplantation, along with technical developments leading to improved post-transplant outcomes, has resulted in renewed interest in donation from persons whose death has been determined by circulatory criteria, i.e. donation after circulatory death (DCD) or donation after the circulatory determination of death.

The first attempt to classify DCD donors dates back to 1995, when the first International Workshop on what was then called 'non-heart-beating donation' took place in Maastricht (the Netherlands) [1]. DCD donors were classified in four categories, depending on the circumstances of the cardiac arrest preceding death. The Maastricht classification was updated at a dedicated conference held in Paris (France) in February 2013 (Table 12.1) and now includes the following categories [2]:

a. Category I: Donation from persons who have suffered a cardiac arrest and in whom cardiopulmonary resuscitation (CPR) has not been attempted for various reasons. This is nowadays only compatible with tissue donation.

b. Category II: Donation from persons who have been declared dead following an unexpected cardiac arrest and in whom CPR has been exhausted and deemed unsuccessful by the attending team. This type of donation includes two subcategories:

i. Category IIa: The cardiac arrest has occurred out of hospital. The moment of loss of consciousness, or that of loss of pulse, has been documented and the duration of the cardiac arrest can be estimated. Emergency services have attempted to resuscitate the patient, but according to international standards (American Heart Association, European Resuscitation Council and International Liaison Committee on Resuscitation), cardiac arrest has been deemed irreversible.

ii. Category IIb: The cardiac arrest has occurred in a hospitalised patient (e.g. emergency room, hospital ward), with otherwise similar settings to category IIa. Organ donation is often unlikely due to the patient's advanced age and/or co-morbidities.

c. Category III: Donation from patients in whom cardiac arrest has occurred following the planned withdrawal of life-sustaining therapy (WLST) because this is no longer in the best interests of the critically ill patient.

d. Category IV: Donation from patients who meet brain-death criteria and have suffered a cardiac arrest. In the original Maastricht classification, this category referred to unrecovered cardiac arrests derived from the haemodynamic instability inherent to the brain-death condition, which still allowed activating a DCD procedure. This is a rare type of donation, because adequate intensive care treatment is usually able to

prevent such events (see Chapter 5). However, category IV also refers to donation after a cardiac arrest following a planned but aborted donor management to accommodate the possibility of organ donation when the DBD process cannot be developed (e.g. when the family wishes to be with the donor at the time of the cessation of the heartbeat, in countries where DBD is culturally difficult to accept).

Categories II and III are the commonest types of DCD. Because in Category II the cardiac arrest causing the death of the individual occurs in a non-monitored setting, this chapter uses the term 'uncontrolled DCD' (uDCD) to refer to donation from persons declared dead following unsuccessful CPR. Similarly, since in Category III the cardiac arrest occurs in controlled and monitored circumstances, the term 'controlled DCD' (cDCD) is used to refer to donation from persons declared dead following the planned WLST.

Table 12.1. **Maastricht classification for DCD donors, as modified in Paris (February 2013)**

Maastricht Category and type of DCD	Observations
I: Found dead (uncontrolled) I a out of hospital I b in hospital	Sudden unexpected cardiac arrest, with no attempt at resuscitation by a medical team.
II: Witnessed cardiac arrest (uncontrolled) II a out of hospital II b in hospital	Sudden unexpected irreversible cardiac arrest, with unsuccessful attempt at resuscitation by a medical team.
III: Withdrawal of life-sustaining therapy* (controlled DCD)	Planned, expected cardiac arrest, following the withdrawal of life-sustaining therapy.
IV: Cardiac arrest while brain dead (uncontrolled or controlled)	Sudden or planned cardiac arrest after brain death diagnosis process, but before organ recovery.

* This category mainly refers to the decision to withdraw life-sustaining therapies. Legislation in some countries allows euthanasia (medically-assisted cardiac arrest), and subsequent organ donation is then described as an additional category.

cDCD and uDCD donors can also be classified as possible, potential, eligible, actual and utilised DCD donors, depending on the stage of the process of donation, as specified in Chapter 2, section 2.3.

DCD remains an activity restricted to a limited number of countries [3]. This is due to legal and ethical obstacles in some countries. In other settings, DCD has not evolved due to the lack of technical expertise or organisational capability. There are also differences in the practice of DCD between countries [4]. In Australia, Belgium, Canada, Ireland, Latvia, the Netherlands, Norway, Switzerland, the United Kingdom and the United States, DCD donors are predominantly or exclusively cDCD donors. In Austria, Israel, France, Italy, Poland, Portugal, Russia, the Netherlands and Spain, uDCD programmes have been developed. In France and Spain, which historically focused only on uDCD, cDCD has emerged with strength in recent years [5-6]. At present, the two types of DCD co-exist in both countries. The fact that countries have focused on one specific type of DCD may be related to different legislations, ethical concerns, end-of-life practices (with WLST based on futility being a limited practice in some settings) and organisational approaches to the treatment of out-of-hospital cardiac arrest.

In Belgium and the Netherlands, cDCD is also possible after euthanasia. Euthanasia needs to take place in a hospital and a thorough evaluation of the motives for euthanasia has to take place according to national protocols [7-8]. Countries engaging in these activities need to discuss various legal and logistical issues, such as where is the patient admitted, who is the doctor responsible, and how and by whom is death determined, among others.

DCD should be grounded on a robust regulatory framework. Legislation enabling this activity should be issued. National protocols or guidelines should be available and a continuous evaluation of activities and results should be undertaken by health authorities. This chapter provides an overview of the process of uDCD and cDCD, highlighting factors for success at each step of the different processes, provided that this activity is possible within a given jurisdiction.

12.2. Uncontrolled donation after circulatory death

Uncontrolled DCD refers to donation from persons whose death has occurred following an unexpected cardiac arrest and who have not been successfully resuscitated.

Although this type of donation can substantially increase the potential donor pool, uDCD is practised in only a few countries which have been able to overcome the different legal, ethical and logistical obstacles related to this type of donation [9]. France and Spain have the largest experience with uDCD.

Good long-term kidney graft survival has been reported from uDCD procedures, although an increased incidence of delayed graft function (DGF) and early graft failure have been described compared with ideal DBD kidneys [10-24]. These results can

however be improved by the use of specific *in situ* preservation strategies, such as normothermic regional perfusion (NRP) [23]. Although the use of NRP has also led to promising results in liver transplantation from uDCD donors, these results are still mixed and not consistently similar to the results of livers from DBD donors, mainly due to a higher incidence of primary graft dysfunction, graft non-function and biliary complications [25-32]. uDCD liver transplantation has also been associated with severe haemodynamic and coagulation abnormalities requiring a proactive recipient-management strategy to avoid catastrophic consequences [33]. There is still limited experience in uDCD lung transplantation; however, the reported results are encouraging [34-37].

Category IIa uDCD donors can hence yield good-quality organs provided strict selection criteria are applied. uDCD donors may be healthy individuals with a normal lifestyle until sudden death. They also have a low risk of nosocomial infections because they have not been previously admitted into an intensive care unit (ICU). Importantly, uDCD donors have not been exposed to the systemic organ injury caused by brain death (see Chapter 5). Counterbalancing these positive considerations, organs from uDCD donors are subject to the deleterious effect of warm ischaemia. There is also the risk of being unable to obtain detailed medical data within the short time frame provided by uDCD procedures. The process of donation in this setting should be designed to minimise the duration of warm ischaemia and its impact on organ viability, but also to ensure the highest possible safety of the donated organs.

The process of uDCD, particularly of category IIa, is represented in Figure 12.1 and the key steps are summarised in the rest of section 12.2 below [9]. Technically, the IIb process is identical to the IIa, except for the absence of an out-of-hospital stage and the step of donor transfer. The complementary Figure 12.2 outlines the limits of warm ischaemia time (WIT) and cold ischaemia time (CIT).

12.2.1. Identification and referral of potential donors

Potential uDCD donors are persons with a documented cardiac arrest in whom advanced CPR has been exhausted in accordance with international standards and deemed unsuccessful by the attending team – this will also include novel advanced CPR techniques if these are components of specific local CPR protocols [38-40]. Potential donors should be medically suitable on the basis of similar criteria to those applied in DBD. In addition, some specific selection criteria need to be met (see Table 12.2) and there are limits to the interval between cardiac arrest and the initiation of *in situ* preservation strategies, traditionally referred to as duration of total WIT (see Figure 12.2).

Table 12.2. **Standard selection criteria for uDCD donors**

Advanced CPR started within a maximum of 15 min of the witnessed loss of consciousness or cardiac arrest (some programmes accept a maximum of 30 min for kidney donation).
Age between 18 and 60 years (some programmes accept donation from donors outside this age range).
Cause of death known (or suspected). Potential donors who die in circumstances that may interfere with judicial investigations should still be considered.
No exsanguinating lesions from chest or abdominal wounds.
Normal external appearance (e.g. persons with signs of high-risk practices such as parenteral drug addiction should not be selected as potential donors).
Time between cardiac arrest and start of *in situ* preservation should be less than 150 min.

CPR: Cardio-pulmonary resuscitation

When an individual suddenly or unexpectedly suffers a cardiac arrest on the street or at home, the sequence of events – after alerting the emergency services – should be as follows:

a. Cardiac arrest is assessed, and advanced CPR measures are initiated with the sole objective of saving the patient's life.

b. The time of cardiac arrest is recorded according to the reports of witnesses.

c. If at least 30 min after the initiation of advanced CPR measures, attempts to recover a heartbeat fail according to the current American Heart Association, European Resuscitation Council and International Liaison Committee on Resuscitation guidelines and national/regional legislation, the resuscitation attempts can be considered unsuccessful and the individual can then be assessed as a potential uDCD donor based on the general and specific selection criteria for uDCD detailed in Table 12.2.

d. In some countries (e.g. Spain and France), patients whose out-of-hospital cardiac arrest was followed by an unsuccessful attempt at resuscitation can be transferred to the hospital with the purpose of enabling organ donation. In both countries, with physician-led emergency medical services, if advanced CPR has been considered unsuccessful in the out-of-hospital setting and the patient does not meet criteria for an extracorporeal life support (ECLS) protocol (where available), then the potential of uDCD can be considered. The patient is then

kept under mechanical ventilation and external cardiac compression, but with no drug administration, since advanced CPR for resuscitative purposes has been exhausted. The team in charge of advanced CPR contacts the receiving hospital informing of the potential donor transfer and activating the uDCD procedure. The hospital is informed of the estimated time of arrival. The hospital staff gets ready to receive the potential donor. Simultaneously, the surgical team starts to prepare for the initiation of *in situ* preservation measures.

e. In other programmes (e.g. in the Netherlands), with paramedics-led emergency medical services, the possibility of uDCD in the setting of an irreversible cardiac arrest is considered exclusively when such irreversibility has been determined in the in-hospital setting, limiting the activations to patients with a cardiac arrest who are transferred to the hospital with a therapeutic purpose. However, the sequence of events described above does not vary substantially.

12.2.2. Donor transfer

The transfer to hospital of a person with an irreversible cardiac arrest for the purpose of considering organ donation (possible in France and Spain) should be carried out by an out-of-hospital emergency team. Transfer of the potential uDCD donor is performed in an intensive care mobile unit maintaining the lines, but with no drug administration (no vasoactive drugs, no adrenaline, no anti-arrhythmics). As soon as the irreversibility of the cardiac arrest under current international resuscitation guidelines has been declared and ECLS is not indicated where protocols are implemented, any kind of life support is considered futile. Cardiac compression and mechanical ventilation are maintained for the sole purpose of ensuring organ viability, until definitive organ-preservation measures can be initiated in the hospital.

Cardiac compression – performed either manually or with mechanical devices – is allowed in existing programmes. Although there is no evidence that organ viability is improved with the use of mechanical devices, the quality of the cardiac compression has been shown to be better than with manual chest compression [37].

Figure 12.1. **The key steps in the process of uncontrolled donation after circulatory death**

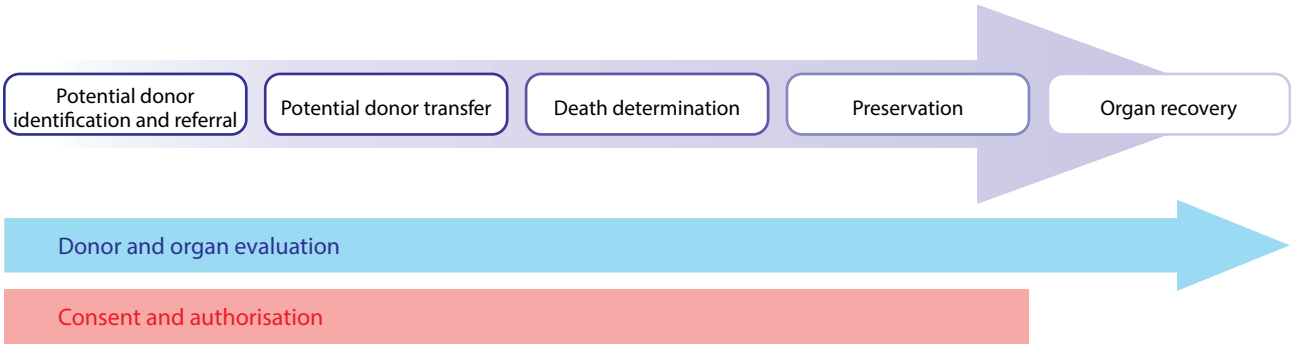
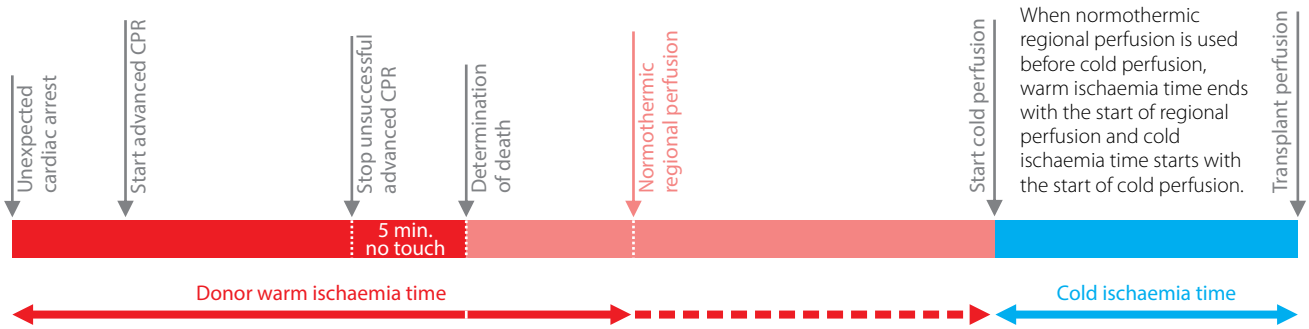


Figure 12.2. **Process of uncontrolled donation after circulatory death, specifying limits of warm and cold ischaemia time**



CPR: cardio-pulmonary resuscitation

If needed, the out-of-hospital emergency service may require the support of the police or other agencies during donor transfer for swift transportation.

Complete information about the quality of these manoeuvres for preservation purposes is desirable. If possible, values of end-tidal CO_2, pH at the beginning and during transfer, lactic acid, etc., must be recorded. This will be helpful for the transplant team when they later assess the quality of the preservation measures and of the organs to be used for transplantion purposes.

12.2.3. Determination of death

Existing programmes of uDCD base the determination of death on the prerequisites of an exhausted advanced CPR as per international standards (including at least 30 min of advanced CPR) and cessation of spontaneous circulation (absence of electrical activity by ECG or absence of pulse) for a minimum observation period that varies from country to country, but is most commonly established at 5 minutes. These criteria for the determination of death differ from the standards developed in countries focused on cDCD, where the permanent cessation of circulation ('will not return') is used as a surrogate for the irreversible cessation of circulation ('cannot return') for the diagnosis of death [41-44]. The difference is that, in uDCD, CPR has been applied and is unsuccessful, whereas in cDCD there is a cessation of supportive therapy. These different approaches to the determination of death have been discussed internationally [45-48].

Death by circulatory criteria should be determined and certified by professional(s) independent of donation and transplantation teams. In practice, this is usually done by the team taking over the CPR manoeuvres for patients transferred from the out-of-hospital setting. Hence, even if CPR has been considered unsuccessful in the street, death is determined in the hospital.

12.2.4. *In situ* preservation and organ recovery

Once death has been determined and certified, existing programmes vary in the approaches they follow. In some countries, cardiac compression and mechanical ventilation are restored to ensure organ preservation until the donor is transferred to the operating room, where *in situ* preservation manoeuvres are established. In other countries, resumption of cardiac compression and mechanical ventilation is avoided [9]. If cardiac compression and mechanical ventilation are restarted after death is determined, it is also recommended that a bolus of sodium heparin 500 IU/kg be administered before *in situ* preservation strategies are initiated. Other anticoagulant strategies are currently being explored but there are no data to support their benefit.

12.2.4.1. *Abdominal preservation procedure*

There are two different strategies for the *in situ* preservation of abdominal organs in uDCD: hypothermic regional perfusion (HRP) or normothermic regional perfusion (NRP); and *in situ* cooling. The two procedures are described below.

12.2.4.1.1. Hypothermic or normothermic regional perfusion

This entails the following processes (see Figure 12.3):

a. Cannulating the femoral vein and artery of one leg for the connection to an extracorporeal circulation system, which includes a membrane oxygenator and temperature exchanger.

b. Introducing an endo-aortic balloon into the descending aorta, via the contralateral femoral artery, to restrict preservation to the abdominal cavity.

c. Simultaneously introducing the prime solution and premedication in the extracorporeal circulation pump. This should be finished before cannulation is completed.

d. Inflating the endo-aortic balloon before establishing HRP or NRP, once the correct position of this catheter has been checked radiologically.

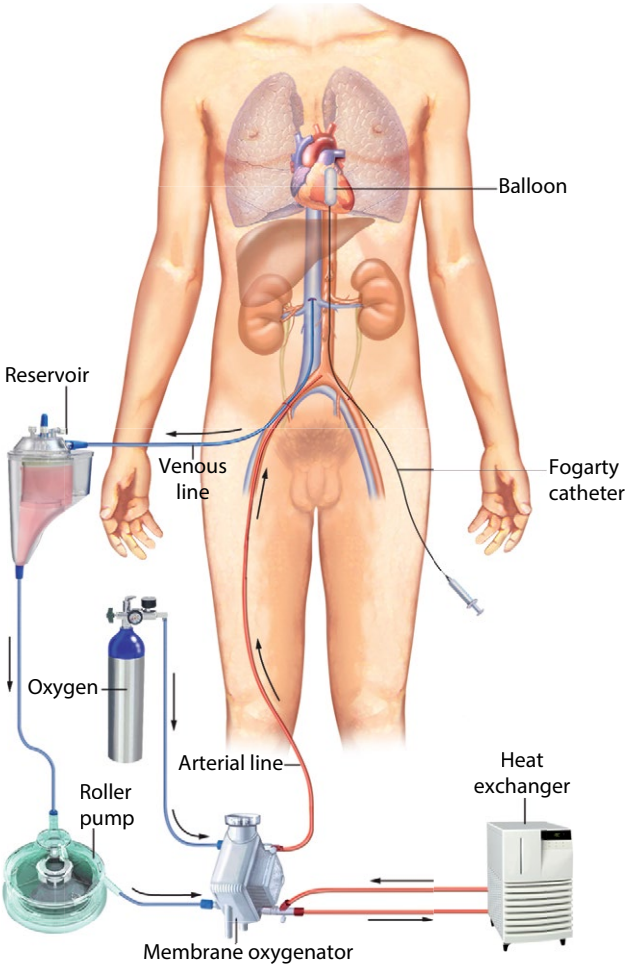
e. The maximum duration of HRP or NRP in uDCD procedures has been established empirically at 240 min in most of the existing programmes. If liver donation is planned, NRP rather than HRP should be established. If lung donation is planned, HRP is preferred, to avoid warming the thoracic cavity. Dual temperature – HRP for thoracic organs and NRP for abdominal organs – is feasible, allowing more organs to be recovered, but there is limited information on the results of lung and liver transplants using this strategy [36]. The available evidence suggests that kidneys can be recovered using both HRP or NRP.

f. *In situ* preservation manoeuvres based on HRP or NRP should be discontinued in the following situations:

i. When the necessary consent and authorisation requirements for organ recovery have not been obtained.

ii. If after 240 min of HRP or NRP, the necessary requisites for organ recovery (e.g. consent and authorisation) have not been fulfilled.

Figure 12.3. **Regional perfusion circuit and heat exchanger with Fogarty catheter placed in correct position to establish hypothermic or normothermic regional perfusion**



12.2.4.1.2. *In situ* cooling preservation with the double-balloon triple-lumen catheter technique

This method uses a double-balloon catheter that is placed in the aorta, with one of the balloons inflated above the diaphragm, and the other balloon inflated at the aortic bifurcation (see Figure 12.4). The renal vascular tree is exsanguinated and then perfused with a high-flow preservation solution at 4 °C. In this way, kidneys can be obtained for transplantation within 2 h. This method does not allow recovery of liver for transplantation with acceptable results, but it is compatible with lung donation.

Once preserved through any of the methods described above, kidneys and/or liver are recovered using the usual surgical techniques. From this moment on, there is no difference from organ recovery in the brain-death setting (see Chapter 11). However, cold ischaemia time should be minimised as much as possible.

Kidney transplants from uDCD donors have yielded good results with the previously described *in situ* preservation strategies. However, cumulative experiences in France and Spain now indicate that NRP (and HRP) leads to better kidney-transplant outcomes compared with *in situ* cooling of kidneys. In France, the analysis of 499 kidney transplants from uDCD donors during 2007-2014 identified that the use of NRP was associated with a significant reduction in the incidence of primary non-function (including DGF with early graft loss), and was a predictive factor of poor function (eGFR < 30 mL/min) or graft failure at one year [24]. Similar results have been derived from the analysis of 511 kidneys from uDCD donors in Spain during 2012-2015 [23]. Compared with NRP, *in situ* cooling was associated with a significantly higher probability of graft loss during the first year after transplantation in an independent manner (HR 9.1; 95 %CI 3.9-21.3; p < 0.001). No differences were observed between HRP and NRP. Based on these results, all centres in France and most centres in Spain now use NRP (or HRP) as the preferred kidney *in situ* preservation strategy in uDCD.

In liver transplantation from uDCD donors, promising results have been obtained with the use of NRP, although still inferior to those obtained with DBD livers [25-26, 28-32].

12.2.4.2. *Lung preservation procedure*

Lung recovery and transplantation has been successfully developed in experienced uDCD programmes. There is a specific method to preserve the lungs of uDCD donors, based on topic cooling developed in Spain [34-35]. Currently, dual preservation (cooling up above the diaphragm and normothermia below the diaphragm) is possible, although experience is still preliminary [36]. Further work is needed to develop the optimal conditions to enable the concomitant recovery of abdominal and thoracic organs.

Lungs are preserved as follows:

a. A 300 mL volume of venous blood is collected into a heparinised bag via the vein cannula, prior to starting the pump.

b. A bronchoscopy is performed and ventilation is stopped when the potential donor is placed on the extracorporeal circuit and the endo-aortic balloon is inflated.

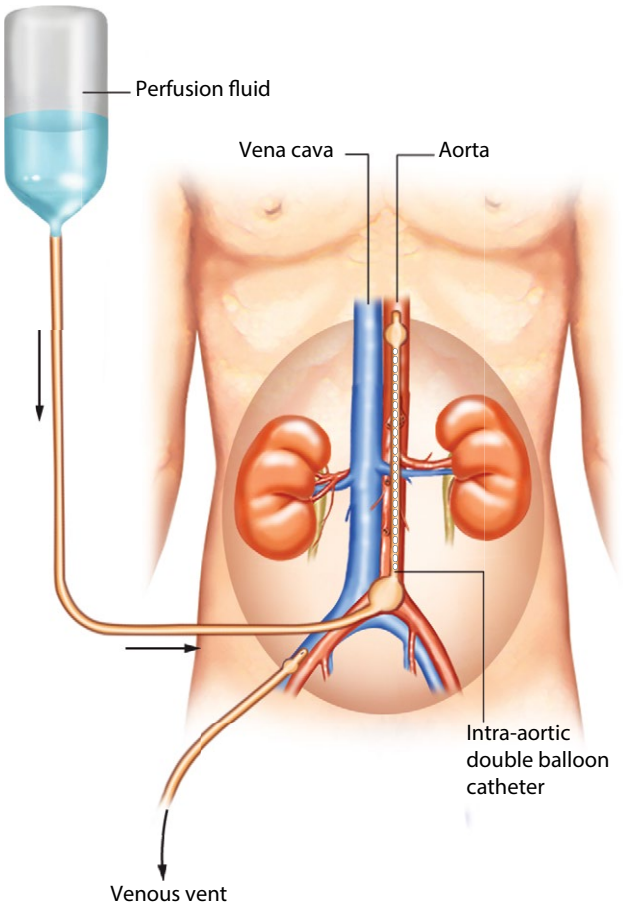
c. Two anterior pleural drainage tubes are introduced (2nd intercostal space, midclavicular line) and instilled with preservation solution at 4 °C, until the pleural cavities are completely filled and the lungs collapse (5-6 L per hemithorax).

Two additional tubes may be placed at the 5th intercostal space, mid-axillary line, to allow the perfusion solution to recirculate through the heat exchanger to maintain a lower preservation temperature of the lungs. A maximum time of 3 h is allowed before initiating lung recovery.

d. Thoracic temperature must be monitored through an oesophageal probe.

Usually, this method allows temperature to remain stable between 10 °C and 15 °C, which is excellent to preserve lungs until recovery.

Figure 12.4. ***In situ* cooling preservation of kidneys with the double-balloon triple-lumen catheter technique**



Once lungs are preserved and consent/authorisation has been obtained, the recovery procedure follows as described below:

a. The pleural cavities are drained and ventilation is restarted with FiO_2 1 and positive end-expiratory pressure (PEEP) + 5 cmH_2O. The pulmonary artery is cannulated so that the lungs can be flushed until the effluent from an incision in the left atrium is clear.

b. The lungs are then perfused with the venous blood withdrawn previously from the donor via the pulmonary artery. At this point, blood samples are taken from each pulmonary vein (from the left auricle) for blood-gas determination (pvO_2) while ventilating with FiO_2 1 and PEEP +5 cmH_2O. Each lung is assessed separately, testing the blood samples from each vein. The intrathoracic temperature is determined using a disposable oesophageal probe for temperature correction of the pvO_2/FiO_2 ratio.

c. The lungs are considered suitable for transplant if adequate oxygenation can be observed. This is defined as a difference of pO_2 greater than 350 mmHg between pulmonary artery (paO_2) and pulmonary vein (pvO_2).

d. The recovery of lungs is performed as in the brain-death setting, with a similar surgical technique, through a medial sternotomy.

12.2.5. Consent and authorisation process

The process for consent to organ recovery (and preservation where appropriate) in uDCD must be adapted to the legislation and practice applicable in a given jurisdiction, including the type of consent system in place (see Chapter 4) [9].

In France and Spain, with an opt-out system, consent is focused on checking any expressed opposition towards donation during lifetime. In both countries, interviews with relatives are employed and existing registries (donor and advanced directives) must be consulted. However, donation is facilitated by the existing legal framework. In uDCD, consent may be obtained at different time points along the process: as soon as the irreversibility of the cardiac arrest is established by the emergency service, or when *in situ* preservation measures have started. Organ recovery must never proceed before consent is obtained.

In countries with an opt-in system, as in the Netherlands, the practice is to assess if the person has expressed a wish about organ donation. A national registry must be consulted to assess the person's wishes. In uDCD, the registry may be consulted as soon as the emergency service announces that a potential donor is being transferred to the hospital. In case of any registered opposition, the organ donation process is not pursued. If no opposition to donation is identified, *in situ* preservation measures after death can commence, even if the family has not been consulted yet. If positive consent is identified, organ recovery can be continued after the family has been informed. If the patient's wishes are unknown, the family will be asked to give permission. Organ re-

covery is not continued if the family opposes it or if the family interview cannot be held within the first 2 h following the initiation of preservation measures.

12.2.5.1. *Family interview*

Communication with the family is particularly challenging in uDCD. While death based on circulatory criteria is easier to understand than brain death, the unexpected nature of the cardiac arrest makes the circumstances distressing for the relatives and professionals.

Families are confronted with the communication of the completely unexpected death of their loved one, and then they are approached with the option of donation. The principle of transparency in communication is paramount during the entire process. But the information has to be provided progressively and in a manner adapted to the emotional and other needs of the family [49].

The family interview is dealt with as an intervention in a moment of crisis and seeks to resolve the problems induced by stressful circumstances. For the person in crisis, the essential issue is that they feel incapable of dealing with the situation. Well-administered support can help manage these feelings and help the person to make a decision. It has to be accepted that, at this moment, incapacity due to pain and lack of information are the greatest difficulties to overcome. Through 'active listening' and 'an offer of help', the interviewer seeks to generate a relationship with space for an exchange of information and for thinking about the idea of organ donation, helping the family to make an informed decision.

The family must be accompanied and supported from the moment they reach the hospital. If the family is present at the moment of death, as in the case of a sudden death at home, the out-of-hospital emergency service must evaluate the possibility of informing the family there and then about the possibility of organ donation. This is not always possible, because often there is no relative near the potential donor or the situation does not allow presentation of complex information. The donor co-ordinator must offer the family a quiet and isolated environment to give them privacy and comfort. The whole information process must be transparent, and any questions the family has about the death of their relative must be answered.

Once consent has been given, a follow-up period is established in which the needs of the donor's family can be periodically attended to.

For further information on the family interview, see Chapter 4.

12.2.5.2. *Judicial authorisation*

uDCD donors are frequently within the scope of a judge's investigation or under forensic medical investigation if death has occurred in the context of a traffic or occupational accident or if the cause of the cardiac arrest is unclear. Insurance policies need to be attended to and a crime incident has to be ruled out. Given the time constraints of the uDCD process, a procedure should be established for judicial/coroner authorisation in order to proceed with *in situ* preservation manoeuvres and organ recovery in this setting.

12.2.6. Continuous evaluation

Evaluation and validation of uDCD donors is done according to general inclusion criteria for organ donation, along with the specific selection criteria for each organ (see Chapter 6 and Chapter 7). Additionally, criteria specific to uDCD must be taken into account, as summarised in Table 12.2.

As in DBD, donor and organ evaluation are based on a review of the past and present medical history and risk behaviours of the potential uDCD donor, as well as a physical examination and complementary tests. Available medical records and charts must be carefully reviewed. A dedicated and guided interview with the relatives should always take place for assessment of the donor's suitability.

Donor evaluation can be facilitated by the out-of-hospital emergency service in several ways. Usually, blood samples are taken once death has been determined. It should be noted that potential uDCD donors are frequently haemodiluted when cardiac arrest occurs outside the hospital environment and has been followed by the transfer to hospital. To ensure that non-haemodiluted samples are available for donor evaluation, e.g. serology, some programmes have incorporated into the out-of-hospital emergency service protocol the recovery of blood samples once the uDCD procedure is activated. These early samples are also of value when potential donors have exsanguinating lesions, preserving the option of lung donation.

12.2.7. Organ-specific evaluation criteria

12.2.7.1. *Kidney evaluation criteria*

A history of chronic renal disease is an exclusion criterion for kidney donation (for more information on organ-specific contraindications, see Chapter 7). Biochemical determinations upon arrival into the hospital – mainly values of serum creatinine, urea and LDH – help in the decision on kidney donation. *Ex situ* hypothermic non-oxygenated pulsatile pres-

ervation of kidneys is today used in many uDCD programmes. The machine parameters are not absolute rules for utilisation of the kidney but, in general, a resistance index below 0.4 mmHg/mL/min/100g kidney tissue and a flow above 70 mL/min may indicate that a kidney is suitable for transplantation. This measurement must be considered together with other kidney selection criteria, including biochemical, anatomical and histological assessments.

12.2.7.2. *Liver evaluation criteria*

The liver is very sensitive to ischaemia, and is the most difficult organ to obtain for transplant in uDCD. NRP not only contributes to ischaemic preconditioning of organs, but also allows assessment of the evolution of liver enzymes – alanine transaminase (ALT) and aspartate transaminase (AST) – as a marker of organ injury. The initial Spanish experience suggested that during NRP a pump flow greater than 1.7 L/min combined with ALT/AST levels below three times the upper normal values at the beginning of NRP, and less than four times the upper normal value at the end of NRP, were indicators that the liver could be recovered and successfully transplanted [28].

There are some *ex situ* devices for liver preservation, but today there is not enough evidence to establish markers or monitoring values to help decisions regarding liver viability in uDCD. Validation should be based on general and specific selection parameters, as well as on macroscopic evaluation of the organ and histology.

12.2.7.3. *Lung evaluation criteria*

For lung validation, the orotracheal tube must be clear of blood and purulent secretions at admission and there must be no suspicion of bronchial aspiration. Chest X-ray must be clear, with no mass or infiltrates. Validation of lungs from uDCD donors based on gas exchange has been summarised in section 12.2.4.2. There are devices available to preserve lungs *ex situ*, assessing their capability of oxygenation and preserving organs through a longer cold ischaemia period. An appropriate gas exchange should be confirmed.

There is no experience with the transplantation of other organs in the uDCD setting. Special consideration must be given to the contribution of uDCD programmes to tissue donation.

12.3. Controlled donation after circulatory death

In the case of cDCD, cardiac arrest occurs following a planned WLST after it has been determined and documented that further intensive care medicine therapy is no longer in the best interests of a critically ill patient in accordance with the patient's personal preferences and values [50]. Unlike uDCD, in cDCD the cardiac arrest is anticipated and expected, which allows the donation procedure to be planned. cDCD can therefore take place in any hospital that has facilities for surgery. However, in cDCD the patient is still alive while the donation process is being organised. Clear and robust policies supported by professional bodies and by legislation are required to ensure that best practices in end-of-life and palliative care can continue to be provided at a time when interventions to minimise WIT are also being considered. Healthcare staff can be particularly uncomfortable in this scenario where end-of-life care and donor care in effect overlap. The challenge in the practice of cDCD is not only to identify patients suitable as potential donors, but also to support and maintain the trust of grieving families and society at large, and to decide how best to minimise the consequences of warm ischaemia in a fashion that is professionally, ethically and legally acceptable.

In countries practising cDCD, these donors have become an increasingly important source of organs for transplantation (see Chapter 1, Figure 1.1). The potential for cDCD varies between countries, with the biggest determinant being the frequency of decisions in favour of WLST in critically ill patients. The Ethicus study highlighted the variability in end-of-life care practices across Europe, with WLST being decided nearly three times more frequently in northern European countries such as the United Kingdom and the Netherlands than in southern European countries such as Italy and Spain [51]. It also found that the incidence of brain death was nearly four times more frequent in these southern countries than in the northern European countries. However, end-of-life care practices have been changing since the Ethicus study was conducted, with the practice of WLST becoming increasingly frequent in some southern countries, such as France and Spain [52]. It is not just the frequency of WLST that makes a difference to donation practices, but also the timing of that decision after ICU admission. It is accepted that DBD is the preferred deceased organ donation pathway because more organs are utilised, including more cardiothoracic organs than from cDCD donors. Early WLST means that some patients with catastrophic brain injuries will not deteriorate to brain death, precluding the potential for DBD. A recent study considered that up to 30 % of actual cDCD donors had the potential to progress to brain death and DBD if the WLST had been delayed by a further

36 hours [53]. This also highlights how changes to end-of-life care practices, within an appropriate legal and ethical framework, have the potential to improve organ donation.

cDCD has hence become an increasingly important source of organs for transplantation in countries like Australia, France, Canada, Belgium, the Netherlands, Spain, the United Kingdom and the United States. For example, between 2011 and 2016 the number of DCD donors increased from 405 to 603 in the United Kingdom, and from 117 to 495 in Spain. In the Netherlands, 50 % of deceased donor procedures are from cDCD donors (www.transplant-observatory.org).

A key issue is whether grafts procured from cDCD donors are equivalent in quality to grafts procured from DBD donors, due to combination of WIT and CIT in the donor. DGF is more common in transplanted kidneys recovered from cDCD donors, but the long-term outcome in terms of survival and kidney function is similar to that of kidneys recovered from DBD donors [54-56]. Moreover, a recent United Kingdom registry study made evident that results of kidneys from cDCD donors with expanded criteria were broadly similar to those obtained with expanded-criteria kidneys from DBD donors [58]. The frequency of DGF in kidney transplantation from cDCD donors can be decreased by reducing the duration of cold ischaemia [57] and potentially through the use of NRP for *in situ* preservation [23-24].

The outcomes of liver transplantation from cDCD donors are also considered acceptable, with a 3-year patient survival rate of 63 % compared to 72 % for recipients of livers from DBD donors. However, between 10 % and 15 % of the grafts are lost within the first year post-transplant (patient death or re-listing for transplantation, United Kingdom NHSBT data). In fact, large registry data have identified DCD as an independent risk factor for graft loss in liver transplantation [58-60]. The incidence of primary graft failure is increased from 6 % to 12 % in recipients of a liver from a cDCD donor. However, the primary concern with cDCD liver utilisation is a significantly higher incidence of biliary complications, particularly ischaemic type biliary lesions (ITBL) which are associated with longer WIT [61-65]. Many of these patients require re-transplantation. Long-term follow-up of cDCD liver transplantations in Belgium and the Netherlands has shown similar results. However, the diminished graft survival seems to level out after about 10 years, and although cDCD livers have a higher risk of retransplantation, patient survival is equal to DBD liver transplantation [66]. This is likely due to strict donor and recipient selection criteria for DCD livers and weighting other risk factors to reduce these complications and optimise outcome. The use of *in situ* NRP [23-24, 67] or *ex situ* hypothermic [68] or normothermic machine perfusion [69] of the liver have shown very promising results in mitigating the ischaemia-reperfusion injury, and short-term outcomes seem to reach similar results as from DBD livers [70].

Although DCD is an independent risk factor for decreased outcome after pancreas transplantation [71], results can be excellent if other risk factors are kept low. Results from a short-term comparative study on pancreas transplantation from cDCD and DBD donors in the United Kingdom reported similar one-year pancreas and recipient survival rates for transplants from cDCD and DBD donors, with pancreas graft survival being significantly better in the cDCD cohort if performed as a simultaneous pancreas–kidney transplant [72]. Similar promising results have been published with data derived from the OPTN/UNOS Registry [73]. A recent meta-analysis has also shown comparable graft and patient survival for cDCD and DBD pancreas grafts [74].

Figure 12.5. **The key steps in the process of controlled donation after circulatory death**

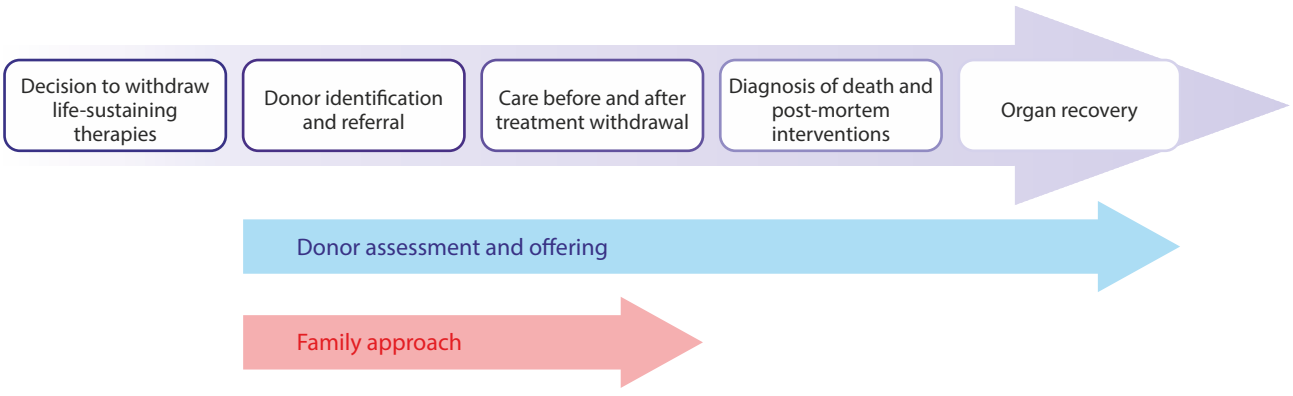
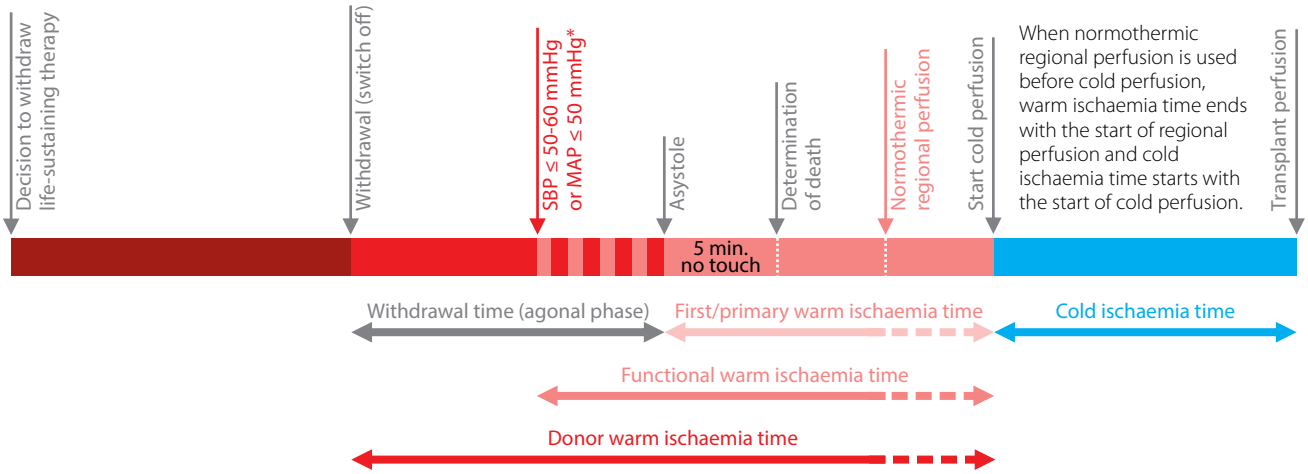


Figure 12.6. **Process of controlled donation after circulatory death, specifying limits of warm and cold ischaemia time**



* There is no general consensus for a cut-off value for the start of functional warm ischaemia time, although this is mostly in the range of the values shown for systolic blood pressure (SBP) or mean arterial blood pressure (MAP).

Cold ischaemia time: for details see Figure 11.1.

Theoretically there may be advantages to transplanting lungs recovered from cDCD donors, since they have not been exposed to the cardiopulmonary effects that the autonomic storm causes during brain stem coning before brain death (see Chapter 5). The lungs also appear to be more tolerant of warm ischaemia than other organs as long as they are kept inflated with oxygen [75]. The consequences of warm and cold ischaemia may be further reduced by the use of *ex situ* lung perfusion techniques. Indeed, initial results from the United States suggest that survival is better for recipients of cDCD lungs than for recipients of DBD lungs, with 2-year survival rates of 87 % and 69 %, respectively [76]. However, it is recognised that variations in donor and recipient selection criteria and surgical techniques may make comparison of outcomes difficult.

More recently, hearts recovered from cDCD donors have been successfully transplanted in Australia [77] and the United Kingdom [78]. The results of cDCD donor heart transplantation using either direct procurement and perfusion (DPP) or thoraco-abdominal NRP (TA-NRP) appear to be at least equivalent to those with DBD hearts in short and mid-term follow-up, with a current world experience of 34 cDCD donor hearts transplanted in the United Kingdom, 14 in Australia and 5 paediatric hearts in Colorado (United States). The long-term results of this encouraging initiative are eagerly anticipated.

The process of cDCD is summarised in its key steps in Figure 12.5 [79]; the steps from decision on WLST to transplant reperfusion are shown in Figure 12.6.

12.3.1. Withdrawal of life-sustaining therapies

The decision to withdraw treatment should always be made in accordance with national guidance on end-of-life care. All such documents recognise the fundamental principle that a decision to withdraw treatment must always be made in the best interests of the patient and independent of any subsequent consideration of organ donation. No member of a donor co-ordination team may be involved in this decision-making. For example, in the United Kingdom it is good practice for two senior doctors to independently verify and document in the medical notes that further active treatment is no longer in the patient's best interests whenever a decision on WLST is being made, but particularly when cDCD is a possibility [80]. National end-of-life care guidance that recognises organ donation [81] as a routine part of end-of-life care is helpful in reducing the perception of any conflict of interest, even though none may exist. It also makes it clear to medical practitioners that they are obliged to follow national procedures for identifying potential organ donors and referring them to the donor co-ordinator.

Individual hospitals should develop guidelines for treatment withdrawal based on the national guidance. Although the need to develop and comply with such protocols applies to all end-of-life care decisions, it is particularly important that units practising cDCD make the process consistent and transparent. These protocols should not only address the principles of the decision-making process but also give practical guidance on how to manage treatment withdrawal, particularly with regard to airway management and the use of sedatives and analgesics.

While there may be variability in current critical care practice on these issues, the interests of a patient who wishes to be a donor may be better served by end-of-life care management that makes organ donation more likely and, importantly, represents no actual harm to the patient or their relatives [82]. Procurement teams must not advise on how treatment should be withdrawn.

If the family agree, WLST must be delayed until a procurement team is ready and prepared in the operating theatre. Those responsible for organ allocation and recovery should do all they can to minimise delays, recognising the needs of the donor and their family at this time. The location of WLST also needs to be considered. When this occurs in the theatre complex, which is essential for recovery of cDCD hearts, WIT is reduced by avoiding transferring the donor from ICU to theatre after death [82]. However, it is important that this practice does not compromise the delivery of end-of-life care, and units that choose to undertake WLST in theatres should ensure that appropriately trained healthcare professionals continue to provide this care rather than expecting theatre staff, who may be untrained and inexperienced in end-of-life management, to do so. Arrangements should also be in place to ensure access for close family, friends and those meeting the religious or spiritual needs of the patient [83].

cDCD can only take place if cardio-respiratory arrest follows soon after WLST. This time limit is most commonly around 2 h, although this has been extended to 3 h in France and the United Kingdom. Although up to 84-90 % of cDCD donors will have died within 2 h of WLST [84], successful kidney recovery has occurred more than 4 h after WLST in circumstances where the functional warm ischaemic time (FWIT) has been acceptable [85]. Examples of registration forms can be found in appendices 16 and 17. Procurement teams need to work to nationally agreed standards to ensure that organs are not lost unnecessarily and also to maintain the confidence of referring units. The reasons for standing a donation down should always be documented for audit and also informing the referring team.

A clear plan must be in place for the subsequent continuation of end-of-life care of the patient when donation cannot take place, particularly when WLST has taken place outside the ICU.

12.3.2. Identification of potential donors

The potential for cDCD should be considered in any critically ill patient where a decision in favour of WLST has been made (see Chapter 2). Most cDCD donors have suffered severe acute brain injury of aetiologies similar to DBD donors, albeit with a higher frequency of anoxic brain injury among cDCD donors [23-24]. When identifying such patients as potential cDCD donors, it is important to consider whether death by neurological criteria can be certified while cardio-respiratory stability is maintained and the WLST is delayed. If brain death is likely to occur within a short period of time, consideration should be given to maintaining life-support measures beyond futility to enable the determination of death by neurological criteria [86-87]. Although the majority of actual cDCD donors die from acute brain injury, data from Spain and the United Kingdom suggest that 4 % to 15 % of cDCD donors die from other conditions such as end-stage respiratory failure or neuromuscular diseases [23].

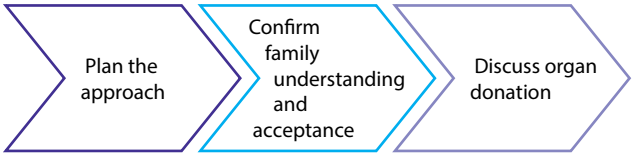
Clear practical guidance for the identification and referral of potential cDCD donors should be developed, specifically addressing who should be referred as a potential donor, when the referral should take place and how the patient should be cared for while initial assessments of donation potential are made. The guidance should ensure that identification and referral can be made without causing clinicians caring for dying patients to feel that there is a potential conflict of interest. Ideally the donor co-ordinator should be notified whenever a decision on WLST is being considered, because this may allow background enquiries to be made and potentially reduce the delay in WLST and any distress this may cause relatives. It also allows the approach to the family to be planned. Examples of how this can be achieved in practice can be found in NHS Blood and Transplant's document on *Timely identification and referral of potential organ donors: a strategy for implementation of best practice* [88].

The development of an accurate and reliable scoring system, capable of predicting whether death after WLST will occur within a time period compatible with cDCD, would reduce the number of donations that are stood down, avoid family distress, increase the efficient use of procurement teams and reduce the burden on critical care services. Individual donor hospitals and transplant centres may choose to use systems like the University of Wisconsin and the UNOS scoring systems [89-90] when deciding to refer or accept individual potential cDCD donors. However, it is currently impossible to reliably identify potential cDCD donors who will die within 2 h after WLST [91]. Consequently, centres may choose to initiate a donation process in every potential donor.

12.3.3. Consent and authorisation

Potential cDCD donors usually lack the capacity for decision-making while being cared for in an ICU or emergency department. On rare occasions, for instance when withdrawing ventilatory support from a competent patient with end-stage neuromuscular disease or respiratory failure, it will be possible to discuss donation with the patient directly. However, on most occasions the patient's relatives will need to be approached for organ donation. National end-of-life care guidance should be explicit in that, if a patient is close to death and their views cannot be determined, medical staff should explore with the relatives whether the patient had expressed any views in life about organ or tissue donation and/or if donation was consistent with his moral values. The approach for cDCD should take place in three stages (see Figure 12.7) [92].

Figure 12.7. **The three discrete stages in approaching the family of a potential controlled donation after circulatory death donor**



Source: NHS Blood and Transplant 2013. Approaching the families of potential organ donors. Best practice guidance [95].

The approach should be planned between the medical and nursing staff caring for the patients and the donor co-ordinator to clarify the clinical situation, identify key family members, define key family issues, seek evidence of prior consent (e.g. checking donor registries), agree the timing and setting of the approach and agree who will be involved. The approach should not be made until the clinical team is satisfied that the family understands and accepts the reasons for treatment withdrawal and the inevitability of death thereafter. To ensure this, the conversation on withdrawing treatment should be decoupled from the approach for organ donation. This also helps reduce any perception that a decision on WLST is linked to a need for donor organs.

However, it may not always be possible to completely separate discussions about treatment withdrawal and donation, particularly if the family raises the issue of donation themselves. The final stage is discussing donation, which should ideally be led by someone experienced in organ donation and who is trained in communication with grieving families, usually the donor co-ordinator. He or she will discuss options, provide knowledge and expertise, recognise modifiable factors, challenge misconceptions, provide support for the family and spend time with the family. The donor co-ordinator will also collect all the information required to assess whether the patient is suitable for donation, and may discuss whether certain *ante mortem* interventions are acceptable to the family [93]. See also Chapter 4.

12.3.4. Care before and after treatment withdrawal

cDCD is only possible if elements of the care that a patient receives both before and after WLST are adjusted. Changes to end-of-life care before the patient dies must continue to be made in the patient's best interests and in accordance with national, legal and professional guidelines. Any such change to routine end-of-life care to facilitate cDCD is in effect an *ante mortem* intervention. Most such changes are applied to reduce both warm and cold ischaemic damage to the organs.

Ante mortem interventions can be justified, both ethically and legally, on the grounds of best interests if they facilitate the wishes of a patient to donate, and if they do not cause harm or distress to that patient or their relatives and/or can be reasonably controlled [82, 94]. In general, the stronger the evidence that an individual intervention improves donation or transplant outcomes and the smaller the risk of that intervention being harmful, then the more acceptable that intervention is. Conversely, interventions with weak evidence of improving outcomes, and with a bigger chance of causing harm, are less likely to be justifiable [95]. The views of the patient's relatives are also relevant in assessing this balance. Each country needs clear legal and/or professional guidance as to which *ante mortem* interventions are considered acceptable and which interventions should be accepted with the specific consent of family after appropriate information has been given. The guidance should be specific about the role of the donor co-ordinator in cDCD. Donor co-ordinators have an important role in donor management and optimisation in DBD, but there is a clear risk of being conflicted if they are involved in the care of a potential cDCD donor. As a result, many policies generally do not allow a donor co-ordinator to be involved in the physical treatment of potential cDCD donors or in the management of WLST.

After the death of the patient further interventions are quickly undertaken before or during the recovery operation, to reduce the ischaemic time or to optimise organs before transplantation. cDCD protocols should acknowledge the potential risks associated

with *post mortem* interventions that may restore cerebral perfusion with oxygenated blood. Most cDCD protocols allow the recovery procedure and organ perfusion with cooled crystalloid or colloid solutions as soon as death has been confirmed (after 5 min of evidence of continuous absence of circulatory and respiratory functions). The recently introduced NRP procedure can reduce the warm ischaemic damage to vulnerable transplantable organs by recirculating the abdominal viscera with oxygenated blood prior to explantation. Protocols applying such interventions describe how reperfusion will be reliably restricted to the relevant organs, and how the cerebral circulation is excluded by the use of vessel clamps or intravascular balloons [69, 93, 96-98]. If the lungs are to be recovered from a cDCD donor, the trachea needs to be re-intubated and the lungs re-inflated after death.

12.3.5. Determination of death

It remains absolutely fundamental to the practice of all types of deceased organ donation that the dead donor rule – the requirement that organ recovery must not result in the death of the patient – must be respected at all times. The point at which death can be declared after loss of circulation and respiration remains widely debated. Yet, for DCD to be successful, the organs need to be recovered as soon as possible after cardio-respiratory arrest to minimise warm ischaemic damage. Cardio-respiratory criteria have been used extensively by doctors to confirm death for a couple of centuries and are well understood by the public. However, the introduction of DCD programmes and reports of auto-resuscitation have highlighted the need for development of scientifically, ethically and professionally acceptable criteria to diagnose death in time-sensitive situations. It is essential that authoritative legal or professional guidance is available and followed in any country or jurisdiction practising DCD.

There appears to be increasing international consensus that death can be confirmed (and therefore organ recovery can begin) after a minimum of 2 min of continuous cardio-respiratory arrest as this means that the possibility for spontaneous resumption of the circulation has passed [99]. In practice, most countries require a minimum duration of 5 min of cardiac arrest before death can be confirmed. If any circulatory or respiratory activity occurs during these 5 min then the timing should be started again at the next point of cardio-respiratory arrest. The absence of circulation must be confirmed by the absence of pulsatile flow on an arterial line or by absence of ventricular contraction on transoesophageal echocardiography, on the rare occasions when this is used. Although a silent ECG is not required to determine death, if only an ECG is used to assess the absence of circulation, then asystole must be observed for 5 min. Many would consider palpation of a pulse as inadequate in this setting. The diagnosis of death must be made by experienced clinicians not involved in the procurement or transplant process.

The time of 5 min is based on the concept of 'permanent' loss of circulation, i.e. circulation will not be restored, rather than the concept of 'irreversibility' which is more variable and dependent on the available technologies [41]. It follows that diagnosing death at 5 min is conditional on there being no intention to resume CPR or to introduce interventions that may potentially restore cerebral circulation after the declaration of death (see Figure 12.8). This does not preclude the use of organ-reperfusion techniques since they are applied after the isolation of the cerebral circulation.

12.3.6. Preservation and organ recovery

12.3.6.1. *Pre-recovery preparations and definitions of warm ischaemia times*

The surgical team should arrive at the donor hospital prior to WLST. Upon arrival, the lead surgeon should check the relevant paperwork with the donor co-ordinator (blood group, relevant past medical history, virology and consent for deceased donation) and confirm the time for WLST. This should allow preparation of the bench and the operative table to enable a swift procedure. A team brief is mandatory, particularly when both thoracic and abdominal teams are present, and allows a common strategy to be agreed to ensure safe organ recovery. The team should be scrubbed in theatre at the time of WLST.

The outcome of transplantation with organs from cDCD donors is significantly influenced by the length of WIT. Following WLST, several time periods have been defined (see Figure 12.6). Note that anastomosis time in the recipient is not included in any of these definitions:

a. Agonal phase (withdrawal time): the time from WLST to circulatory arrest.

b. First/primary WIT (asystolic or acirculatory time): the time from circulatory arrest to the start of *in situ* preservation.

c. Functional warm ischaemia time (FWIT): the time between first episode of significant hypoperfusion (the start of which depends on national guidelines) and the start of *in situ* preservation [41].

d. Donor WIT (DWIT): agonal phase (withdrawal time) + First WIT. Also referred to as Total WIT.

The moment that defines the start of FWIT (significant hypoperfusion) is yet to be universally agreed upon, but in general a sustained fall in systolic blood pressure ≤ 50 or 60 mmHg is accepted in Europe, while a fall in systolic blood pressure < 80 mmHg and/or O_2 saturation < 80 % is accepted in the United States [43, 100]. In addition, in the United States the term WIT refers to the total DWIT, as the time from WLST to *in situ* preservation, whereas in the United Kingdom it refers to the FWIT and in the Netherlands to the First WIT. Because of these varying definitions being used to describe WIT it is essential to verify the exact definition when comparing literature.

The acceptable FWIT varies for different organs and ranges from 30 min for the liver and pancreas to 60 min for kidneys and lungs [101]. There is a lack of evidence supporting these times, and several reports suggest that longer times yield transplantable organs, especially for kidneys [87, 102] and pancreas [103]. In liver transplantation it has been shown that every minute of extra ischaemia (First WIT) decreases graft survival, with a significantly higher chance of biliary complications [104], and care should be taken when First WIT exceeds 25 min [68]. These times are likely to change with the use of NRP.

Following WLST, the donor co-ordinator must communicate the vital signs (saturation, pulse and blood pressure) and inform the procurement team when certain values or time points are met.

12.3.6.2. *Organ recovery procedure for abdominal organs*

During the process of determination of death, preservation and organ recovery, respect for the dying donor must be ensured. At each step, their privacy and dignity must be maintained and the end-of-life wishes of the donor and family must be honoured as far as possible. All personnel involved should make an effort to personalise care within the given time constraints.

Once death has been confirmed after the mandatory no-touch period, and after final confirmation of identity, a rapid midline laparotomy from the sternal notch to pubis is undertaken. The recovery procedure follows the super-rapid technique described by Casavilla [105]. After laparotomy, the caecum, terminal ileum and the rest of the small bowel are reflected cranially to expose the aorto–iliac bifurcation. The peritoneum is incised and the aorta is identified and cannulated. Cold perfusion begins, using any preservation solution with heparin (as protocol prescribed, usually around 300 IE/kg) under pressure (150-200 mmHg). The inferior vena cava should be vented in the abdomen just before or immediately after starting perfusion to avoid congestion of the abdominal organs. Topical cooling is instituted and a median sternotomy is then carried out. The pericardium is incised and the supra-hepatic inferior vena cava vented for improved drainage. Both pleural cavities are opened to enable supra-diaphragmatic topical cooling. The descending aorta can be cross-clamped to reduce the volume of perfusate used. If the liver is to be recovered, the portal vein may also be cannulated and perfused, as described by Casavilla [105]. When the pancreas is also being procured, the venous outflow of the intestinal package should be decompressed. Therefore, either portal perfusion may be omitted or it could be done at the level of the hepato-duodenal ligament, where the portal vein is completely divided to enable pancreas drainage without congestion. A recent systemic review and meta-analysis showed equal results after dual and aortic-only perfusion and therefore could not support the additional time and complexity of using (*in situ*) portal perfusion [106]. The subsequent steps are similar to the DBD procedures.

The liver and pancreas can be removed *en bloc* or separately. *En bloc* removal has the advantage of a shorter explant time for the pancreas and allows for the identification of accessory or replaced right hepatic artery from the superior mesenteric artery during bench dissection. The duodenum is fully kocherised to expose the inferior vena cava. The stomach is stapled above the pylorus and the small bowel is stapled beyond the duodeno-jejunal flexure, having divided the transverse mesocolon. The small bowel mesentery is stapled away from the inferior pancreatic border. The short gastric vessels are divided and the pancreas tail is mobilised, using the spleen as a handle. The liver is mobilised, dividing the diaphragm around it. The superior mesenteric artery is divided at the aortic origin and the supraceliac aorta is transected. The bloc is removed and separated on the bench.

Kidneys can be removed individually or *en bloc*. If they are removed separately, the left renal vein is divided flush with the inferior vena cava, allowing the vena cava to be recovered with the right kidney. The anterior wall of the aorta is divided in the midline and the posterior wall is incised between the lumbar arteries. The kidneys are removed with the peri-nephric fat, which then needs to be bi-valved on the bench to allow inspection of the kidneys and to facilitate placement on machine perfusion (if in-

tended to be used). If removed *en bloc*, the ureters are divided as they cross the iliac arteries and then dissection is carried in the plane behind the inferior vena cava, aorta and ureters in a cranial direction. This approach is preferred for paediatric recovery when kidneys are transplanted in a single recipient.

A modification of the super-rapid technique involves an initial thoracotomy and intrathoracic cava venting prior to aortic cannulation and perfusion.

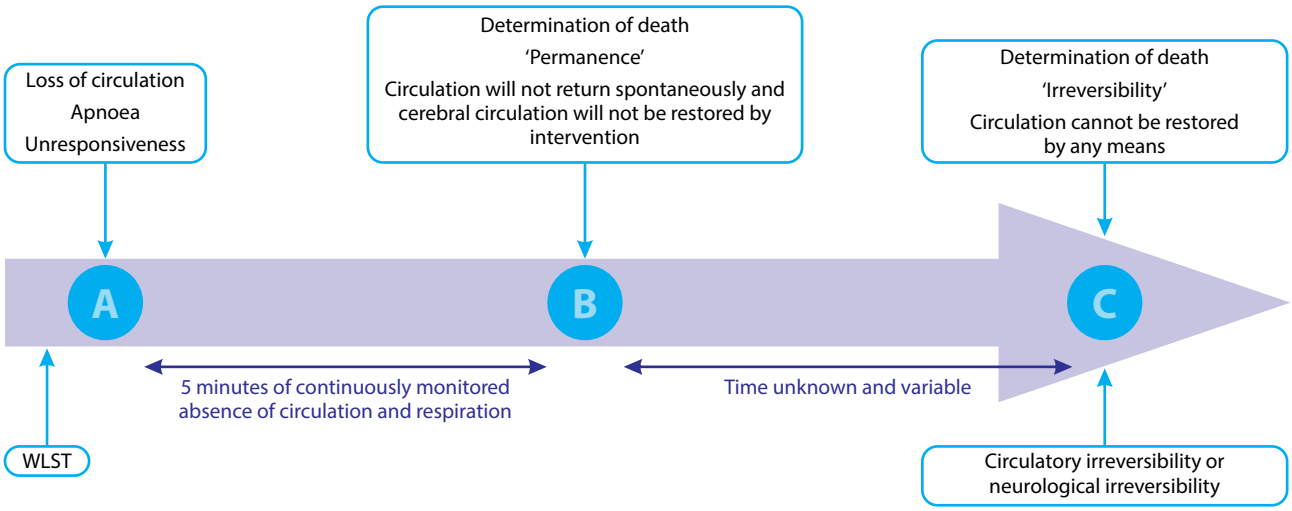
12.3.6.3. *Organ recovery procedure of abdominal organs using normothermic regional perfusion*

Following Spanish experience in uDCD, several countries have explored the feasibility of NRP in cDCD using similar technology (heat exchanger, oxygenator and pump). The process of organ recovery described above is modified to enable a period of 1.5-2 h of NRP.

Certain *ante mortem* interventions are permitted in some, but not all, European countries. In those countries where these interventions are allowed by local legislation, heparin can be administered prior to withdrawal. Alternatively 25 000-50 000 units of heparin should be added to the NRP priming solution. Some countries also allow the *ante mortem* cannulation of femoral vessels in order to facilitate immediate initiation of NRP following the determination of death. For example, *ante mortem* heparinisation and vessel cannulation are allowed in Spanish guidelines if no contraindications are identified (e.g. heparinisation would not be allowed if there was a haemorrhagic lesion) and if specific informed consent is obtained [107]. A similar protocol has been developed in the United States [108]. In France, where *ante mortem* vessel cannulation is not allowed, central lines can be introduced in arterial and venous femoral vessels prior to WLST, after relatives have been informed [5]. This allows invasive arterial pressure monitoring during the agonal phase and, in some cases, facilitates *post mortem* cannulation prior to the start of NRP. Although both *ante mortem* heparination and vessel cannulation are thought by clinicians to yield organs of higher quality in greater numbers for transplantation, there is still no strong evidence of the superiority of using these *ante mortem* interventions.

In cases where *ante mortem* cannulation of femoral vessels is performed for NRP, a specific procedure must be followed as described by Miñambres *et al.* [69, 93, 101]. In summary, once femoral vessels are cannulated surgically or percutaneously (with adequate sedation and analgesia), an aortic occlusion balloon is placed at the contralateral groin to restrict preservation measures to the abdominal cavity during NRP. The position of the balloon must be radiologically confirmed prior to WLST. Two arterial lines, one from the femoral arterial cannula and the second one from the left radial artery, are used for monitoring purposes. After the determination of death, the balloon is inflated and NRP initiated. During NRP, the arterial pressure from the left radial artery should disappear with an adequate blocking of the thoracic aorta while the pressure from the femoral arterial cannula is maintained as a continuous, non-pulsatile pressure. Should arterial pressure from the left radial artery be detected during NRP, this should be immediately stopped. The correct position or filling of the catheter must then be checked and NRP reinitiated after another period of no-touch.

Figure 12.8. **Diagnosis of death in controlled donation after circulatory death**



Point A = Start of cardio-respiratory arrest; Point B = Permanent loss of circulation; Point C = Irreversible loss of circulation; WLST: Withdrawal of life-sustaining therapies.

If *ante mortem* cannulation of femoral vessels is not performed, once death has been confirmed, *post mortem* cannulation can be undertaken and NRP initiated (as performed in France). Most usually (as performed in the United Kingdom), the donor is taken to theatre and a midline incision (xiphoid to pubis) is undertaken. The distal infrarenal aorta is identified and slung using a vascular snugger. The distal aorta is cross-clamped or ligated. The aortic cannula is inserted, checking the proximal position of the tip. The cannula is secured in place with the vascular snugger and connected to the arterial limb of the circuit. The infrarenal inferior vena cava is then dissected and encircled using a vascular snugger. The distal end is clamped or ligated. The venous cannula is inserted into the inferior vena cava. The tip should sit just below the diaphragm to allow clamping of the suprahepatic inferior vena cava without compromising the venous return in the circuit. The venous limb of the circuit is then connected to the cannula. A rapid sternotomy is carried out using either a power saw or Gigli saw. The thoracic aorta is clamped below the level of the left subclavian artery. At this point the NRP circuit can be started.

An alternative approach would be to insert an aortic endo-clamp in the descending thoracic aorta and commence NRP before undertaking the sternotomy. This approach would allow the cardiothoracic team to undertake the sternotomy, mobilise the lung and clamp the descending aorta (if simultaneous lung recovery). Once NRP is established, meticulous haemostasis must be ensured from the abdominal wound edges, sternotomy and retroperitoneal tissues disrupted during aortic and IVC cannulation.

NRP is performed for 1.5-2 h, although the optimal duration remains to be determined. The pump parameters are yet to be fully established but Spanish and United Kingdom experience suggests a pump flow of 2-3 L/minute, temperature 35.5-37.5 °C, O_2 2-4 L/min (or air/O_2 mix as required to maintain paO_2), a pH of 7.35-7.45 (administer bicarbonate as required), a paO_2 > 12 kPa (> 90 mmHg) and a haematocrit > 20 % (> 0.2) [109]. Venous oxygen saturation is a good guide of oxygen delivery and SvO_2 should be around 60-80 %.

During this period, serial blood samples are taken to assess the function of the liver and kidneys. Organ mobilisation and preparation for the cold phase can be undertaken, following the same steps as a DBD recovery.

Once NRP is completed, cold *in situ* perfusion is instituted and organ recovery continues as described above.

12.3.6.4. *Organ recovery procedure of thoracic organs*

12.3.6.4.1. DCD lung procurement

Upon arrival in theatre, the donor should be re-intubated with a cuffed endotracheal tube and a thorough airway toilet performed. Atelectatic lung may be recruited with a single breath (e.g. 25 mmHg pressure for 40 s), ideally using the anaesthetic machine, which is also useful for maintaining CPAP at 5 cmH_2O and delivering continuous O_2. The time of lung inflation should be noted but cyclical ventilation should be delayed until the chest is open and, in case abdominal NRP is used, the aorta clamped. These early manoeuvres lessen the WIT and allow time for the removal of the liver, which is highly sensitive to warm ischaemia.

The chest is rapidly opened and the lungs are examined for collapse, consolidation, mass lesions and pleural adhesions. The lungs should be tested if there is a suspicion of airways disease, and the degree of collapse when the lungs are disconnected from the ventilator noted. The pulmonary artery is then cannulated, and the right ventricle opened to remove clot. Antegrade perfusion should be started, as per the practice of the retrieval team. The left atrium or atrial appendage should be widely opened, washing the clot out of the pulmonary veins. Once antegrade perfusion is completed, the pulmonary veins should be cannulated and retrograde perfusion is undertaken until the effluent from the pulmonary artery is clear. The lungs may be removed either collapsed or ventilated. The lungs are re-examined after removal and then re-inflated for storage.

If lung recovery is planned in a donor where NRP is undertaken [110], the supra-hepatic inferior vena cava is clamped at the cavo-atrial junction. The ascending aorta is clamped, the main pulmonary artery cannulated for cold flush-perfusion and the left atrial appendage is vented widely.

Ventilation is started at half tidal volume with 5 cmH_2O PEEP and FiO_2 0.4, and pulmonary flush with cold preservation solution is commenced. The pleurae are opened widely and lungs inspected and palpated, ensuring adequate delivery of flush and topical cooling with copious volumes of 4 °C saline. While waiting for the pulmonary flush to be delivered, the superior vena cava is ligated and divided just below the azygos take-off and the systemic connections of the heart are disconnected, leaving the inferior vena cava clamped within the pericardium. The division of the main vessels proximal to the clamps ensures that there is no blood loss, to avoid compromising the NRP flow.

Once the cold pulmonary flush is completed, the main pulmonary artery is divided just proximal to its bifurcation. The lungs are allowed to deflate at this stage. The left atrium is divided, leaving behind an adequate cuff for the lungs and the excised heart is removed for later recovery of heart valves. The pericardium above the diaphragm is incised, the inferior pulmonary ligaments are divided and the plane up to and behind the trachea is developed. The trachea is dissected bluntly circumferentially, in the space between the superior vena cava and aorta, and pulled down to gain as much length as possible. The endotracheal tube is withdrawn, a breath with 50 % tidal volume is delivered and the trachea is stapled with the bronchial stapler and divided above the staple line. The lung block is removed and complete haemostasis of the mediastinum should be ensured. Retrograde pulmonary venous flush of the lungs is performed with 1 000 mL of preservation solution on the back-table at the donor site. Abdominal NRP continues for the planned duration as detailed above.

12.3.6.4.2. DCD heart procurement

The DCD heart is regarded as profoundly ischaemic, having suffered an extended normothermic anoxic insult during WLST, asystolic stand-by and confirmation of death. It is believed that the human heart will tolerate 30 minutes or so of normothermic anoxia before irreversible changes occur [111-112]. Prompt replenishment of nutrients is essential to save the organ and this is carried out in two ways, currently:

a. by removing swiftly the cold, heparin, cardioplegia-infused DCD donor heart from the donor chest and placing it onto a blood-based normothermic organ perfusion circuit on which it is both resuscitated and transported to the recipient hospital.

b. by opening swiftly the donor chest, injecting 30 000 units heparin into the right atrium and 20 000 units heparin into the pulmonary artery, cross-clamping the aortic arch vessels and cannulating, centrally establishing thoraco--abdominal NRP (TA-NRP). In this way the heart and all solid organs of interest for transplantation are reperfused and energy stores re-established. The cDCD donor heart resumes sinus rhythm or, if not, this is re-established with DC transcardiac shock of 10 joules. The heart is supported in this way for 20 minutes during which time the lungs are inspected externally and by bronchoscopy, re-intubated with an appropriate endotracheal tube and ventilation is resumed. The heart is then weaned from TA-NRP and assessed by pulmonary artery flotation catheter thermo-dilution flow measurement, by transoesophageal echocardiography and by clinical inspection (maintenance of good tissue perfusion clinically and biochemically) [78]. Once the abdominal team are ready for abdominal organ removal, all solid organs of interest are removed in the way described for heart-beating donors (as is the case for TA-NRP donation).

12.3.6.5. *Organ preservation: in situ cold preservation*

A variety of preservation solutions can be used. There have been no randomised controlled trials of preservation solution in DCD donors, but several solutions have been designed to minimise the detrimental effects of cold ischaemia and reperfusion. Several studies have investigated the differences in performance (organ cooling, DGF) of these solutions in use with different organs [113-117]. The total volume of solution used for multi-organ abdominal recovery should be in accordance with the instructions of the manufacturer and the clinical situation [118-119]. It is important that the initial bags of perfusion solution contain heparin (ca. 300 IE/kg) for the aortic perfusion as well as portal flush if applied (also ca. 300 IE/kg).

In situ lung preservation uses a solution supplemented with 3.6 % THAM 3.3 mL, 0.6 mL CaCl + 2.5 mL prostacyclin/L and which is infused with a minimum of 60 mL/kg body weight.

12.3.6.6. *Organ preservation: in situ normothermic regional perfusion*

The optimal priming solution for NRP has not been fully established. An example combination includes [114]:

- Bicarbonate 8.4 %, 1 mL/kg
- Compound sodium lactate solution – 1000 mL
- Succinylated gelatin – 500 mL
- Heparin – 50 000 U
- Fluconazole – 200 mg
- Meropenem – 500 mg
- Vancomycin – 1 g (without gelofusin)
- Methylprednisolone – 1 g
- Pancuronium – 12 mg.

12.3.6.7. *Organ preservation: ex situ preservation*

Currently, the accepted method for *ex situ* liver and pancreas preservation is static cold storage, using any of the available preservation solutions.

Hypothermic machine preservation is increasingly used in many countries, but the benefit in cDCD kidney transplantation remains uncertain.

A European study suggested a lower DGF rate [120] but no survival benefit at one year [121], but a subsequent three-year extension [122] as well as a United Kingdom-based study [123] showed no difference in outcome between static cold storage and machine preservation. This randomised study was terminated early due to lack of benefit.

Novel approaches are currently being explored, including oxygenated hypothermic machine preservation for the kidney and liver [124] and normothermic machine preservation for the liver [125], kidney [126], lungs and heart. These approaches can be applied during transport (preservation) or at the end of the ischaemic period (end-ischaemic perfusion) with the purpose of reconditioning the organ prior to transplantation. Currently, normothermic preservation of the liver and hypothermic preservation of the kidney (with and without oxygen) are being explored in clinical trials. Several liver end-ischaemic strategies are being explored in clinical trials, including hypothermic oxygenated perfusion (HOPE) [68], dual hypothermic oxygenated perfusion (D-HOPE) [127] and normothermic liver perfusion [128-129]. Similarly, end-ischaemic normothermic kidney perfusion is subject to a multi-centre trial in the United Kingdom [130]. The constituents for the perfusion solutions (cellular or acellular) require further research.

12.3.7. Continuous evaluation

The evaluation of cDCD donors starts with a detailed medical and socio-demographic history that the donor co-ordinator should obtain from all relevant sources (notes, interviews with treating physicians, family, general practitioners, etc.). Factors such as age, duration of hospital and ICU admission, the use of high-dose vasopressors and the absence/presence of infection are highly relevant for the decision on whether to utilise the organs.

Based on these characteristics, the 'ideal' cDCD donor can be defined as a donor of age < 50 years with a weight < 100 kg, a short ICU stay (< 5 days) and a WIT < 20 min [43].

The absolute contraindications to cDCD organ donation are the same as those for DBD (see Chapter 7), e.g. invasive or haematological malignancy, untreated systemic infection, prion disease and HIV disease.

Biochemistry samples must be obtained prior to donation and, if relevant, compared with other samples taken during admission (especially for donors with a history of out-of-hospital cardiac arrest or a history of hanging).

The procurement surgeon must assess the quality of the perfusion and the aspect and anatomy of the organs *in situ* and on the bench. Unlike DBD, where assessment includes a period before circulatory arrest, DCD assessment is much more difficult and is subjective to a surgeon's experience.

The decision to utilise cDCD organs should also take into account the recovery factors, such as duration of WIT (agonal phase, First WIT, FWIT or DWIT).

NRP offers the additional benefit of in-depth *in situ* macroscopic assessment of the organ's appearance, including the appearance of the small bowel and gall-bladder mucosa (both highly sensitive to ischaemic damage). This is corroborated by serial biochemical and blood gas analyses which are undertaken (every 20-30 min) to evaluate function. Given the limited experience, further clarification of the factors that are important is required.

The use of novel preservation and end-ischaemic perfusion strategies offer additional options for functional organ assessment, particularly if undertaken at normothermic temperatures. However, the criteria for organ assessment require further refinement and validation.

12.3.8. Organ-specific evaluation criteria

Once a patient's suitability to donate has been established, additional evaluation criteria come into consideration for specific organs. These may relate to the donor's age, the timings of recovery (such as agonal phase duration, length of the First WIT or length of predicted CIT) and specific pre-existent co-morbidity (such as cardiovascular disease, hypertension, diabetes or liver disease).

12.3.8.1. *Kidney evaluation criteria*

The absolute contraindications for cDCD kidney transplantation are end-stage kidney disease (chronic kidney disease stage 5, eGFR < 15 mL/min), chronic kidney disease stage 4 (eGFR 15-30 mL/min) or acute cortical necrosis on pre-implantation kidney biopsy [43].

Acute kidney injury, even when requiring dialysis, does not exclude donation but is associated with a higher incidence of DGF (see Chapter 7, §7.2.1).

In addition to donor and recovery issues, factors such as hypertension and cardiovascular disease may have an impact on the outcomes of cDCD kidney transplantation. For these donors, a pre-implantation biopsy may be helpful in identifying those organs that will have a poor outcome when transplanted as

a single organ [131-132], allowing dual transplantation to be considered [138].

The use of kidneys with prolonged FWIT in excess of 2 h should be restricted to centres investigating *ex situ* perfusion technologies that may enable further evaluation of viability [132], but the criteria remain to be further defined.

The use of *ex situ* hypothermic machine perfusion has led to the development of viability assessment criteria such as flow on the machine and the level of intracellular enzymes such as glutathione S-transferase, ALT, fatty acid-binding protein [133]. None of the perfusion-pressure dynamic characteristics, the perfusate-effluent biochemical analysis or kidney-transplant biopsy scoring systems – alone or in combination – have sufficient predictive value to justify discard of an organ.

12.3.8.2. *Liver evaluation criteria*

The presence of end-stage liver disease, acute liver failure (viral or drug-related) or non-recovering acute liver injury are additional absolute contraindications for liver donation. The following specific factors should be considered for cDCD liver evaluation:

a. Age – Despite increased utilisation of older cDCD donors, reports suggest that age is associated with an increased risk of complications such as graft loss and ITBL [60, 134]. In fact, next to DCD itself, age is the highest predictor of outcome after liver transplantation [58, 61]. It has been suggested that NRP can help to raise acceptable donor age with good results in cDCD liver transplantation [69].

b. Body mass index – Increased body mass index appears to be associated with higher recipient mortality and a higher risk of graft loss [135-136].

c. FWIT – There is evidence that a time longer than 20 min is associated with poorer outcome, particularly with regard to the development of ITBL [137-138].

d. Agonal time/First WIT – A shorter time (< 10 min) is beneficial for graft function [108, 139], and care should be taken when exceeding 25 min [68] unless consideration is given to using NRP.

e. Cold ischaemia time – A short time (ideally less than 6-8 h) is preferred for cDCD. Longer CIT is associated with increased risk of graft failure, patient mortality and ITBL [138, 140].

Based on these considerations, the United Kingdom guidelines describe the ideal cDCD and the extended criteria cDCD for liver donation, and make recommendations for their use (see Table 12.3) [43].

Table 12.3. **Categorisation of the cDCD liver donor**

	Standard cDCD donor	**Expanded cDCD donor**
Age (years)	< 50	> 50
Weight (kg)	< 100	> 100
ICU stay (days)	< 5	> 5
WIT (min)	≤ 20	20-30
CIT (hours)	≤ 8	> 8-12
Steatosis (%)	≤ 15	> 15
Recommendation	All potential liver donors fulfilling these criteria should be used	These grafts should be used selectively

CIT: cold ischemia time; DCD: donation after circulatory death; ICU: intensive care unit; WIT: warm ischemia time.

Currently, there are no defined criteria for assessing the quality of the graft but, in addition to the factors listed above, macrovesicular steatosis (> 60 %) is probably the best measure of poor quality, especially when combined with a prolonged FWIT and CIT > 12 h, given the high susceptibility to warm and cold ischaemic injuries.

The use of NRP allows a more detailed evaluation of the liver's function and quality. This evaluation involves the macroscopic aspect before and during NRP perfusion, as well as post-cold-perfusion appearance, the level of bile production, an improving lactate on serial measurements and the liver function test evolution. A dramatic increase in the ALT/AST value is probably an indication not to use the liver. Nevertheless, clarification of the liver function test range that would preclude transplantation is needed. The first uDCD criteria in Spain [25, 28] suggested that the initial ALT/AST should be < 3 times the upper limit of normal and that during NRP the ALT/AST should not rise to more than four times the upper limit of normal at the end of the procedure. However this experience in uDCD cannot be directly transferred to cDCD. For example, United Kingdom centres use the trend rather than the above criteria, but a rapid increase in ALT/AST is seen as a contraindication to transplantation.

12.3.8.3. *Pancreas evaluation criteria*

Similarly to cDCD liver grafts, utilisation of the pancreata is more restrictive in cDCD, with a lower donor age and body mass index (< 28 kg/m^2). FWIT is preferably kept as short as possible, although no strong recommendation on an exact limit exists in the literature. Currently the best way to describe pancreas graft quality is by the Pancreas Donor Risk

Index [73], which has been validated in the United Kingdom [141] and Eurotransplant region [142]. However, pancreas evaluation and graft assessment also strongly relies on the quality of perfusion, the degree of fatty infiltration, the texture of the graft and possible surgical injury [143]. Nonetheless, the quality of perfusion and especially the interpretation of the degree of fatty infiltration are highly subjective, and the final decision should be made by the pancreas transplantation surgeon.

Based on the donor criteria, the United Kingdom cDCD guidelines [43] suggest classification and graft utilisation as shown in Table 12.4.

Table 12.4. **Categorisation of the cDCD pancreas donor**

	Standard cDCD donor	**Expanded cDCD donor**
Age (years)	< 45	45-60
BMI (kg/m^2)	< 28	28-30
WIT (min)	≤ 30	> 30
CIT (hours)	≤ 9	> 9
Steatosis	None	Mild-moderate
Recommendation	All potential pancreas donors fulfilling these criteria should be used	These grafts should be used selectively
	All potential liver donors fulfilling these criteria should be used	

BMI: body mass index; CIT: cold ischaemia time; DCD: donation after circulatory death; WIT: warm ischaemia time.

However, grafts that are not used for solid organ transplantation should be considered for islet transplantation, particularly when CIT is < 8 h and body mass index is high. Early outcome after cDCD islet transplantation is encouraging and seems comparable to DBD islet transplantation [144-146].

12.3.8.4. *Lung evaluation criteria*

cDCD lung donation should be considered in donors aged < 65 years old without pre-existent trauma or lung or pleural disease. Most cDCD lungs can be transplanted without separate *ex situ* assessment. *Ex situ* (or *ex vivo*) normothermic perfusion should be considered when oxygenation is impaired (systemic arterial PO_2 < 40 kPA (300 mmHg) on 100 % FiO_2 and 5 cmH_2O PEEP) when a bronchoscopy shows inflammation/soiling of the airway or there is a sustained peak airway pressure of > 30 cmH_2O. Additional indications for using *ex situ* normothermic perfusion include DWIT > 60 min to > 90 min for cDCD donors, difficult-to-recruit atelectasis in the donor, an unsatisfactory deflation test on disconnecting endotracheal tube, unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross oedema, unsatisfactory inspection of the lung after administration of the preservation flush and logistical reasons that will extend donor lung ischaemic time > 10-12 h [43]. *Ex situ* normothermic perfusion assesses the ability of the lung to provide perfusate oxygenation, together with evaluation of the lung compliance, airway resistance and peak airway pressures at a given tidal volume.

12.3.8.5. *Heart evaluation criteria*

The assessment of the cDCD donor heart varies, depending on the recovery approach:

a. DPP: a transthoracic echocardiogram is obtained before WLST to describe ventricular and cardiac valvular function. It is then inspected on the perfusion rig, the manufacturers of which recommend following perfusion fluid lactate levels. It is accepted that a downward trend and a drop between arterial and venous lactates is suggestive of good heart function.

b. TA-NRP: the heart is inspected after return of sinus rhythm within the cDCD donor after weaning off NRP relying on the heart to perfuse the thoracic and abdominal organs. The donor is now a heart-beating donor. The donor heart is assessed clinically and by pulmonary artery catheter (cardiac output and atrial filling pressures), transoesophageal echocardiography and visual inspection. It is also assessed by its ability to support the limited thoraco-abdominal circuit.

12.4. Conclusion

The field of DCD is rapidly evolving, with an increasing number of countries participating in this type of deceased donation that poses particular challenges. Criteria for donor selection are expanding as the results of DCD transplants are becoming more favourable. Current developments in *in situ* and *ex situ* organ-preservation techniques may contribute to a greater use of organs per donor, better quality of organs and improved post-transplant outcomes.

DCD is a much needed addition to DBD when we consider the persisting worldwide shortage of donor organs and the need for countries to progress towards self-sufficiency in transplantation. Moreover, in the overall best interests of the dying patients, there is a need to develop DCD programmes that allow donation in all circumstances of death. However, DCD should not be a substitute for DBD because there still is a higher risk for decreased outcome after DCD

donation, which is likely due to the extra warm ischaemia in the donor.

It is important for countries that are considering DCD programmes to develop a regulatory framework that enables the practice while addressing all of its challenges, such as time constraints, family approach and consent issues, determination of death and allowed *ante mortem* and *post mortem* preservation strategies. Existing programmes should be optimised according to the most recent developments and experiences in the field.

12.5. References

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Related material

- Appendix 16. Donation after circulatory death – reporting form (Belgium, English-language version)
- Appendix 17. Donation after circulatory death – reporting form (Netherlands, English-language version)

Chapter 13. **Living donation**

13.1. Introduction

In 2010, through the Madrid Resolution, countries were urged to pursue self-sufficiency in transplantation, i.e. to satisfy the transplant needs of their patients by using resources from within their own patient population. The key to self-sufficiency is developing donation from deceased donors (DDs) to its maximum therapeutic potential, facilitating donation in as many circumstances of death as possible, maximising the outcomes from each donor and optimising the results of transplantation. Nevertheless, living donation has become a necessary addition for self-sufficiency and is therefore increasingly performed in Europe. Thus, deceased donation and living donation should be regarded as complementary sources of organs for transplant [1].

From an ethical, medical, psychosocial and surgical point of view, it should be emphasised that living donation presents some unique considerations:

a. The living donor (LD) is not a patient – not suffering from an illness – but on the contrary is a healthy person who is selected for donation on the basis of his/her health. It is hard to evaluate the long-term impact on morbidity and mortality of donating an organ during a person's lifetime, because the optimal control group from the general population is difficult to identify and validate [2-3].

b. The surgical procedure is not performed with the aim of removing a malfunctioning, infected or cancerous organ, but an optimally functioning one.

c. Social and healthcare insurance systems have not been conceived with living donation in mind.

Worldwide, 42 % of kidney and 18 % of liver transplant procedures are performed with organs obtained from LDs. Living donation contributes to 35 % of all transplantation activity [4-5]. In addition to liver and kidney transplants, living donation can also facilitate the transplantation of lung, intestine and pancreas segments [6-7]. Living donation rates vary from country to country. In Europe, living kidney donation is increasingly accepted, but there are considerable differences between countries regarding frequency, practices and acceptance of donor–recipient relationships (see Table 13.1). Some countries, such as the Netherlands, Norway, Turkey and the United Kingdom, have a long history of living donation with good results [4-5]. In contrast, in other countries – including Spain, where DD activity has been extraordinarily developed – LD activities have been limited, though they have experienced a dramatic increase over the past 10 years.

Living kidney transplantation has been shown to be the best therapeutic alternative for patients with end-stage renal disease, because of several advantages compared with kidney transplant from DDs [8]:

a. Graft survival of LD kidneys is significantly longer.

b. The incidence of delayed graft function is decreased.

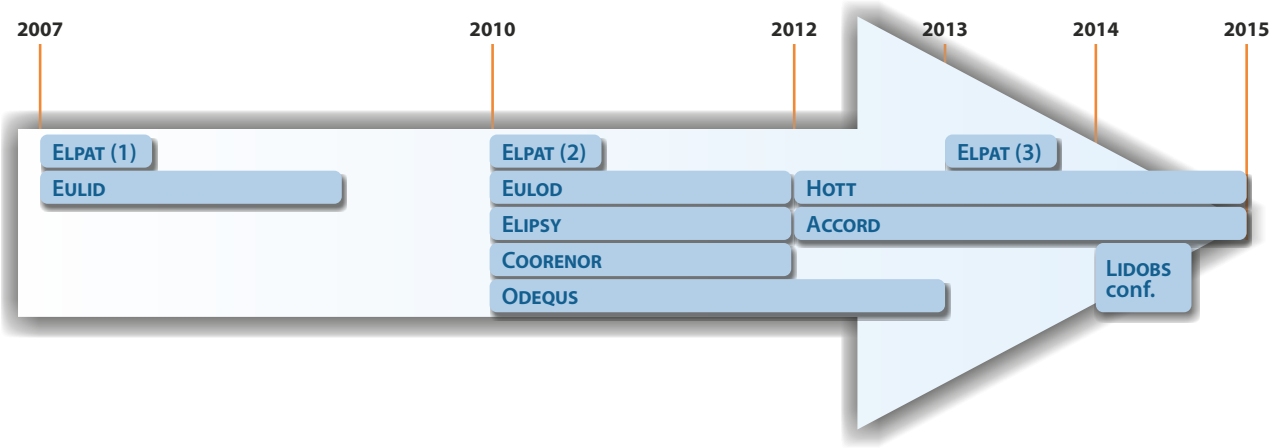
c. Living donation makes pre-emptive kidney transplant (transplantation prior to dialysis)

more feasible, especially for young recipients and children at risk for retarded growth. Also pre-emptive re-transplantation in patients whose graft has failed should be considered before restarting dialysis in order to minimise the further risks associated to immunisation by a graft without function *in situ*.

In addition, by adding to the pool of available organs for transplant, implementation of an effective LD programme may shorten the DD waiting time for those patients with no LD available or who do not wish to receive an LD organ.

Regarding liver transplant, the advantage of using LD livers is most obvious in urgent cases, adult to adult and especially adult to child. Urgent LD liver transplants have particularly been performed in countries with low DD rates, where organ shortage can justify the use of LDs in acute or 'acute on chronic' liver failure. This may specifically be the case of patients with expanded Milan criteria for hepatocellular carcinoma, patients with high mortality and morbidity while on the waiting list and some elec-

Figure 13.1. **Summary of European Union funded projects in living donation**



EULID (2007-2010)
Analysed the current European situation regarding legal, ethical, protection and registration practices related to living organ donation, in order to set standards and recommendations that guarantee the living donor's health and safety.

ELPAT Congresses (2007, 2010 and 2013)
ELPAT Congresses bring continuity and progress in European research and dialogue on Ethical, Legal and Psychosocial Aspects of organ Transplantation of the European Society for Organ Transplantation (ESOT). They aim to integrate and structure this field of science by bringing together European professionals from different disciplines.

EULOD (2010-2012)
Aimed to establish an inventory of living donation practices in Europe, to explore and promote living donation as a way of increasing organ availability, and to produce recommendations that improve the quality and safety of living organ donations in Europe.

ELIPSY (2010-2012)
Aimed to contribute by guaranteeing the good quality of organ living donation for transplant through a living donor long-term psychosocial and quality of life follow-up. The recipient's outcome was correlated with these aspects and a follow-up methodology was created.

COORENOR (2010-2012)
The aim was to establish a co-ordinated network of national programmes in the participating European member states in organ transplantation. It co-ordinated efforts of countries in eastern and western Europe, all having different approaches and programmes to tackle the issues of organ procurement and transplantation.

ODEQUS (2010-2013)
ODEQUS' specific objectives were to identify Quality Criteria (QC) and to develop Quality Indicators (QI) at hospital level, in three types of organ donation: after Brain Death (DBD), after Circulatory Death (DCD) and Living Donation. Those tools are useful in self-assessment and external evaluation of hospitals, and in developing a European auditing model.

LIDOBS Conference (2014)
Exchange of experience and knowledge on Living Donation programmes in order to assure safety, quality and transparency of the procedures and high quality standards. The conference planned and set up a community of experts in Living Donation Programmes named LIDOBS that will continue to expand and increase the knowledge of donation and transplantation procedures.

HOTT project (2012-2015)
Combating trafficking in persons for the purpose of organ removal: an international research project that aims to increase knowledge and information to raise awareness about the crime and to improve the non-legislative response to such a crime.

ACCORD (2012- 2015)
ACCORD intends to improve the potential of Member States in the field of organ donation and transplantation and to contribute to the effective implementation of EU Directive 2010/53/EU and the EU Action Plan on Organ Donation and Transplantation (2009-2015). The work on living donation helps by creating a common methodology for registers of living donors.

Source: Adapted from LIDOBS Conference recommendations [20] Final leaflet.

tive patients [9]. In countries with extensive LD liver transplant experience, such as Japan, USA, Turkey and South Korea, LD livers constitute an important way to decrease mortality by offering immediate transplants to urgent patients. Many of the countries performing liver transplants from LD sources are those where deceased donation has not been substantially developed for a variety of reasons. However, in paediatric liver transplantation, the probability of receiving a size-matched full-size or split graft procured from a DD is very low for a small infant; therefore LD for this group of recipients is a procedure to be well considered in order to avoid death on waiting list even in countries with DD programmes.

The safety and protection of the LD is essential for any LD programme and must be grounded on an appropriate regulatory framework, ethical principles and evidence-based clinical pathways. Living donation must be performed according to best practice and published evidence, following international recommendations from scientific bodies and societies such as the Amsterdam Forum on the Care of the Live Kidney Donor [10], the Vancouver Forum on the Care of the Live Organ Donor: Lung, Liver, Pancreas, and Intestine [11] and the KDIGO Clinical Practice Guidelines on the Evaluation and Care of Living Kidney Donors [12].

Living donation must only be performed in centres authorised by the corresponding Health Authority and following strict ethical standards and regulations to minimise the medical and psychosocial impact of donation and to avoid organ trafficking and human trade, as recognised by the World Health Organization *Guiding Principles on Human Cell, Tissue and Organ Transplantation* [13] and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism [14]. The recently adopted Council of Europe Convention against Trafficking in Human Organs [15] and the Council of Europe Convention on Action against Trafficking in Human Beings [16] need also to be taken into account. The last two legal instruments criminalise the violation of basic principles in living donation, in particular the recovery of organs without valid consent or in exchange for financial gain or comparable advantage. Other standards that complete the international ethical and legal framework for living donation are the Council of Europe Convention on Human Rights and Biomedicine [17] and its Additional Protocol on Transplantation [18], as well as Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation [19].

Living donation is only acceptable when: the donor grants informed, specific and free consent; selection criteria for donors are scrupulously applied and monitored; professional care is ensured; and medical and psychosocial follow-up is well organised. LDs must be informed about the potential medical and psychological risks of donation in the short and long term. Furthermore, the economic, occupational and social consequences of donation must be conveyed in a complete and understandable fashion.

Table 13.1. **Categories of living donation, based on the donor–recipient relationship**

Category	Sub-category	Definition
A – Related	The donor is genetically and/or emotionally related to the recipient	
	A1: genetically related	A genetic relation exists between donor and recipient (e.g. brother/sister, parent/offspring). Therefore a certain immunological compatibility exists too.
	A2: emotionally related	The donor is a genetically unrelated family member (e.g. spouse) of the recipient or a friend (to be considered as a family member).
B – Unrelated	The donor has no genetic or emotional relationship with the recipient. The relation between donor and recipient must be outlined further by a sub-specification. Immunological compatibility exists only by chance.	
	B1: paired exchange or cross-over	By a controlled programme, unrelated donor and recipient pairs exchange grafts beyond any emotional or genetic relation, with the aim of overcoming immunological restrictions.
	B2: non-directed altruistic or anonymous	By a controlled programme, the donor can provide a graft to society which allocates this to a previously unknown recipient by defined rules.
	B3: directed altruistic	By a controlled programme, the donor provides a graft to a recipient of the donor's choice.

Source: adapted from the WHO Global Glossary of terms and definitions on donation and transplantation (www.who.int/transplantation/activities/GlobalGlossaryonDonationTransplantation.pdf?ua=1).

The donor must be considered competent to receive and weigh the information, must act willingly and must be free of any undue influence or coercion. Registration of all LD cases and of the outcome of all

LD procedures must be performed for the purposes of traceability, safety and transparency of the activity.

Several European Union-funded projects (ACCORD, ELIPSY, EULID, EULOD, ODEQUS; see Chapter 1) have been launched to establish consensus and ascertain high-quality practices regarding all aspects of LD handling and LD transplantation, including the establishment of national and supranational LD registries (see Figure 13.1) [19].

13.2. Ethical and legal aspects of living donation

Reflection on the four principles of beneficence (doing good), non-maleficence (avoiding harm), respect for autonomy and respect for justice (promoting fairness) is essential in placing altruism as the fundamental ethical principle of living organ donation [21-22].

Donor consent and autonomy are necessary, but not sufficient, to proceed with organ donation from an LD; donor autonomy should not overrule medical judgment and decision making. To ensure donor autonomy, it is important: to provide extensive specific information; to allow a reflection period; to involve an independent LD advocate, and to exclude minors and persons unable to make decisions from being LDs [23]. The LD advocate is defined as an independent medical, psychosocial and legal counsellor, with neither time constraints nor interests shared with any party, someone who ensures the protection and safety of the LD. Reflecting this type of concern on how to protect donors, the Living Donor Community of Practice of the American Society of Transplantation has recently published a guidance document [24].

It is vital that Health Authorities and professionals responsible for transplant programmes promote deceased donation up to its maximum therapeutic potential. However, considering the large deficit of kidneys for transplantation compared to demand, at present and in the foreseeable future, member states should develop and optimise programmes for kidney donation from LDs based on recognised ethical and professional standards as a way to pursue self-sufficiency in transplantation. Liver donation from LDs should only be considered in the context of there being no alternative with similar efficacy and in the necessary timescale.

To assure the above-mentioned principles, regulations must include:

a. specific regulation of donation by minors and persons unable to provide valid consent;
b. prohibition and criminalisation of trafficking in persons for the purpose of the removal of organs and organ trafficking;
c. authorisation of centres for recovering organs from LDs under the control of Health Authorities;
d. provisions to protect the non-resident LD, which should be linked to a policy of close co-operation between Health Authorities of different countries to implement a programme of referral and post-donation follow-up of non-resident LDs;
e. oversight of the LD process – evaluation, information and approval – according to national regulations, by an independent committee that includes healthcare professionals who are not involved in the organ removal or subsequent transplantation procedure (a specific ethics committee);
f. implementation of a reimbursement model of expenses related to donation to protect donors and their families from discrimination, permanent injury or death.

13.3. Consent and authorisation for living donation

Every stage of donation from the LD, including consent and authorisation, procurement, follow-up, transparency, quality and safety systems, accreditation of transplant units and medical staff qualifications must be controlled by national regulations (see Chapter 15). This section 13.3 gives especial emphasis to issues related to the valid consent of the LD and authorisation of the LD procedure.

13.3.1. Consent to living organ donation

In order to ensure that the donor has given valid consent, the following requirements must be respected:

a. The decision to donate must be voluntary and expressed without any pressure.

b. The donor must be able to revoke consent at any time before the recovery of the organ, with no need for a specific formal procedure.

c. Before consent is given, the potential LD must be informed about the type and risk of surgery by the surgeon who will perform the procedure, and by another doctor who does not directly participate in donor or recipient procedures. Information must extend to potential complications in the short and long term, both medical and psychosocial, including individual risk for the donor. Information must be culturally appropriate to and understandable by the person giving consent.

d. The potential LD must also be informed about possible adverse outcomes in the organ recipient: risk of organ rejection, medical and sur-

gical complications and possibility of organ failure.

e. Valid written informed consent must be given by the donor after he/she has been interviewed, and preferably approved by an independent donor advocate who is not involved in the recipient care.

f. In many countries, after the potential LD has given consent, further approval is required by an Ethics Committee. Such committee has to be independent from the procurement and transplant team. In some countries the participation of the Ethics Committee is only mandatory in cases of unrelated donation. Some countries also require the approval to be confirmed by a court.

13.3.2. Authorisation of the living donation procedure

Beyond consent of the donor, some other aspects need to be considered before any living donation procedure is authorised:

a. Organ donation must be preceded by the necessary medical tests [25] (see tables 13.2 and 13.3), to be assured that the risk to the donor is acceptable.

b. The result of the medical assessment of the health status of the potential donor should be documented by a physician experienced and qualified in organ donation. The written statement must conclude that: 'there are no contraindications to organ donation' while also providing appropriate medical evidence. This should include appropriate documentation, provided by the head of the medical team that will perform organ procurement and implantation, about the purpose and legitimacy of surgery as well as the expected outcome.

c. If the risk to the donor is unacceptable, or there is doubt about the donor's ability to give informed consent, then organ donation must not proceed, regardless of whether the potential donor would consent.

d. In the case of planned transplantation from an LD, the allocation process only occurs in the case of a non-directed altruistic living donation. Nevertheless, any potential organ recipient should remain on the waiting list until the date of transplantation; up to that moment the recipient should be able to receive an organ from a DD. This aspect is important for maintaining the transparency and unity of the system and for providing feedback in the event of unexpected withdrawal of consent or medical disqualification of the LD. However, practice varies, as for example in Norway where, if a possible LD is under evaluation, the recipient is temporarily removed from the waiting list.

e. Each LD must be provided with permanent long-term follow-up, free of charge. If the donor refuses follow-up, donation must be considered carefully in the context of the individual donor. Information about their health status at the time of donation, and in the long term, should be documented in a dedicated registry.

f. The LD must not demand or receive any material benefits from the organ recipient, or from a third party, that could be considered as either coercion or reward. However, living donation should be cost-neutral for the donor, who should receive reimbursement of all expenses related to donation and the immediate recovery period. The LD should not be subject to any prejudice detrimental to employment, insurance coverage or the obtaining of credit, loans or mortgages.

g. Organ procurement from LDs must be performed only at specifically authorised centres and by medical staff who have formal permission and appropriate qualifications.

13.3.3. Authorisation of living donation from non-residents

Authorisation of donation in case of non-resident LDs must be performed according to the legal and medical rules valid for the country where donation takes place. This type of donation cannot proceed unless full adherence to all recommendations specified in sections 13.2 and 13.3 is assured. It should be noted that non-resident LDs may be especially vulnerable. In addition, the donor–recipient relationship and the donor's motivations may be difficult to assess due to language barriers and cultural differences. Therefore those transplants should preferably be limited to first- or second-degree genetic relatives or spouses (or equivalent). In exceptional cases, other relationships may be accepted when they can be unequivocally verified and are in accordance with national legislation.

Also it is recommended that the Health Authority of the donor's country of residence (or the relevant embassy) be informed of the donation to provide information that can help identify victims of exploitation.

The procurement centre must inform the potential donor of the necessity of regular donor

follow-up. Moreover, the procurement centre must make sure that the donor has the necessary means for this follow-up either in his/her country of residence or elsewhere. As stated in the 2016 CD-P-TO Position Paper on the long-term outcome of living kidney donation, if adequate lifelong follow-up cannot be guaranteed, the donor should not be accepted [26]. Information about health status at the time of donation, and in the long term after procurement, must be documented in the registry of LDs in the procurement country or in the country of origin.

13.4. Medical and surgical aspects of living kidney donation

13.4.1. Risks of living kidney donation

The risks of donor nephrectomy can relate directly to the nephrectomy itself or can arise in the mid- to long term.

Perioperative mortality, based on large compiled series of mostly open, conventional LD nephrectomies, has typically been reported at 0.03-0.05 % [8, 27]. The immediate perioperative risks are: bleeding, deep vein thrombosis, pulmonary embolism, wound complications, urinary tract infection, atelectasis and pneumothorax.

Minimally invasive LD nephrectomies – either laparoscopic or retroperitoneoscopic – have, in recent years, been shown to be superior to the open procedure regarding post-operative pain, hospital stay, sick leave and cosmetics. Complication rates have been shown to be equal to or even lower than those of the open procedure [28]. Furthermore, the hand-assisted alternative (laparoscopic or retroperitoneoscopic) may further improve safety [29]. During the first part of the laparoscopic era (1995-2005), an increased rate of fatal cases was reported, possibly related to the learning curve of this procedure. However, with increasing experience with minimally invasive LD nephrectomies during the latter half of that era, donor safety may even have improved, compared to the 0.03-0.05 % mortality rate described in the open LD nephrectomy era. Therefore, in transplant centres with sufficient laparoscopic competence, minimally invasive LD nephrectomy should be the method of choice.

Previous studies have compared kidney donors with the general population. This is an inappropriate comparison since kidney donors are healthy at the time of donation, and the general population includes individuals with pre-existing diseases. During the last decade, several publications have emerged describing adverse outcomes after kidney donation. Meta-analysis found that kidney donation is associated with increased incidence of hypertension as well as proteinuria [30-31]. Females who have donated a kidney are at increased risk of pre-eclampsia in subsequent pregnancies [32]. Most disturbingly, a study from Norway with a median follow-up of 15 years found increased cardiovascular and all-cause mortality [2]. Although two other studies have not corroborated this finding, these studies had a shorter follow-up of around six years. Several studies have found an increase in end-stage renal disease after donation [2-3, 33-36].

It is important that every donor can give valid consent for donation by being appropriately informed of the risks involved for all donors and for them as an individual. Young donors and those from ethnic backgrounds must be considered carefully in the context of their individual lifetime risk of donation and they should be appropriately counselled, using the best evidence that is available. Potential donors of Hispanic and African-American ethnicity are at higher risk, and in these groups strict attention must be paid to the assessment of glomerular filtration rate, blood pressure and glucose tolerance tests.

It is advisable to minimise risk factors and optimise the physical and psychological status of the donor before surgery, including physical activity, nutritional care and psychological support. After donation, the donor must be advised to maintain a healthy lifestyle, control body weight, promote physical activities and follow the recommendations on health promotion according to age and gender.

13.4.2. Medical evaluation and exclusion criteria for living kidney donation

All potential LDs should have a final medical and psychosocial assessment performed by an independent LD advocate who is not involved in the care of a recipient. The aim of the evaluation is to ensure that the potential donor is in good health and has no increased risk (bearing in mind the standard and accepted risks after donation), and that he/she is not under coercion, taking a free and informed decision.

The medical evaluation must be performed by clinicians with experience in living donation. A complete past medical history and physical examination, as well as laboratory and imaging tests, should be performed according to established national and international guidelines. An example is provided in Table 13.2.

Table 13.2. **Basic routine screening of the potential living kidney donor**

Assessment of renal function and urinalysis	**Cardio-respiratory system**
• Estimation/measurement of GFR • Dipstick for protein, blood and glucose • Microscopy, culture and sensitivity • Measurement of protein excretion rate	• Chest X-ray • Electrocardiogram • Stress test • Echocardiography (where indicated)
Immunological screening	**Virology and infection screening***
• Blood group • HLA-typing • Crossmatch	• *Brucella* (where indicated) • *Cytomegalovirus* • Epstein–Barr virus • Hepatitis B and C virus • Hepatitis E virus (where indicated) • HHV8 and HSV (where indicated) • HIV and HTLV 1/2 • *Mycobacterium tuberculosis* (where indicated) • *Plasmodium* (where indicated) • *Schistosoma* (where indicated) • *Strongyloides* (where indicated) • *Treponema pallidum* • *Toxoplasma* • *Trypanosoma cruzi* (where indicated) • Typhoid (where indicated)
Assessment of renal anatomy	**Blood tests**
Appropriate imaging investigations should allow confirmation of the presence of two kidneys of normal size and enable abnormalities of the collecting system and calcification or stone disease in the renal tract to be detected. They must also delineate the anatomy of the renal vasculature.	• Haematological profile • Complete blood count • Haemoglobinopathy (where indicated) • Coagulation screening (PT and APTT) • G6PD deficiency (where indicated) • Biochemical profile • Creatinine, urea and electrolytes • Liver tests • Urate • Fasting plasma glucose • Glucose tolerance test (if fasting plasma glucose is 6-7 mmol/L) • Bone profile • Blood lipids • Thyroid function tests (if indicated) • Pregnancy test (if indicated) • PSA (if indicated)

APTT: activated partial thromboplastin time; G6PD: glucose-6-phosphate dehydrogenase; GFR: glomerular filtration rate; HHV: human herpes virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; HTLV: human T-lymphotropic virus; PSA: prostate-specific antigen; PT: prothrombin time.

* For further details refer to §13.7.1 and §8.3.1.

Medical criteria that could be considered as contraindications for living kidney donation are listed here:

a. Significant chronic disease (cardiovascular, pulmonary, hepatic, neurological or autoimmune).

b. Obesity, even though it is modifiable. Body mass index (BMI) should be computed, based on weight and height measured before donation, and classified based on World Health Organization criteria for the general population or for race-specific categories. The decision to approve donor candidates with obesity and BMI > 30 kg/m² should be individualised on the basis of demographic and health profile in relation to the transplant programme's acceptable risk threshold. [12].

c. Hypertension – although uncomplicated hypertension well-controlled with one drug may be allowed in donors older than 60 years.

d. Diabetes or intolerance to oral glucose test.

e. Disorders requiring anticoagulation, depending on the underlying disease.

f. Chronic viral infection (HIV, HBV, HCV, HTLV) as outlined in section 13.7.1.

g. Active cancer or history of cancer. Cancers with completed treatment and low risk of metastases and/or recurrence can be accepted under certain conditions, e.g. non-melanoma skin cancer as outlined in section 13.6.2.

h. Low glomerular filtration rate in relation to age.

i. Proteinuria (e.g. > 300 mg/day).

j. Haematuria – potential donors with haematuria can be accepted in the absence of relevant urological or kidney disease.

k. Anatomical anomalies (e.g. multiple renal vessels) that do not allow safe surgery.

l. Nephrocalcinosis, bilateral kidney stones or recurrent nephrolithiasis.

13.5. Medical and surgical aspects of living liver donation

13.5.1. Risks of living liver donation

This procedure is still carried out by conventional open technique, but the introduction of modern haemostatic devices should be employed, with obvious potential to increase donor safety.

The safety issue is even more pronounced than with LD nephrectomy, because the perioperative risk is higher, particularly in adult-to-adult LD liver transplantation. Taking into account the clearly sub-

stantial mortality risk (compared with LD nephrectomy), the preoperative assessment of donor risk and motivations is even more essential. Also to be considered are: the level of surgical LD liver resection competence and (modern) equipment, recipient status and alternative DD organ availability. Even in transplant centres with substantial LD liver resection competence, the indication should be carefully considered.

The perioperative mortality rate has been estimated at 0.1-0.4 %, and the surgical complication/morbidity rate has been reported to be 24-40 % [37-39]. Right-sided resections have been considered to involve a higher risk. In the Vancouver Forum on living donation in 2006, where 6 000-7 000 LD hepatic resections were reported, 0.4-0.6 % of patients presented with catastrophic complications (14 deaths, two transplantations and one vegetative state) [11]. As seen through the years, right donor hepatectomy is the operation among donor hepatectomy procedures with highest complication rates and may be related to the larger resection of liver parenchyma. The mortality rates after donor right hepatectomy surgeries (liver graft including segments V, VI, VII and VIII) performed from 1990 to 2000 were reported as around 2 %. Through the years this rate has reduced to 0.4-0.5 % [40]. The increase in LD liver transplantation each day has led to an increase in donor deaths. In the literature on 21 countries where LD liver transplantation was performed, the morbidity and mortality rates for 11 553 liver donors in 148 centres were reported as 24 % and 0.2 %, respectively. In this study 23 donor deaths (0.2 %) were reported, with four reported to be related to donor hepatectomy surgery and four (0.04 %) in connection with re-transplantation to the donor. The other 19 (0.16 %) donors who died were in the early post-operative period (first 60 days after donor surgery) [39].

The incidence of complications after liver donation is difficult to assess due to the lack of uniformity in the data available. There is a large variation, of 0-67 %, in the overall published complication rates from experiences in single centres. In most series, however, overall morbidity rates for LDs remain low. The most common complications in LDs are related to the surgical procedure. Biliary leaks can cause collections adjacent to the resection line, usually resolved with conservative treatment, but sometimes requiring percutaneous drainage. Stenosis of the remaining biliary system is less common, around 1 %. Other surgical complications are bleeding, wound infection, paralytic ileus or pleural effusion. The most common medical complications after donation are fever, pneumonia and urine infection. When analysing complications according to the type of hepatectomy performed, right-lobe liver donation was associated with a higher rate (range 20-60 %, overall approximately 35 %) and more severe complications compared to left-lobe liver donation [39-40].

Table 13.3. **Basic routine screening of the potential living liver donor**

Assessment of liver function	**Cardio-respiratory system**
• ASAT, ALAT, bilirubin, ALP, albumin, GGT • PT, INR	• Chest X-ray • Electrocardiogram • Stress test • Echocardiography
Immunological screening	**Virology and infection screening***
• Blood group • HLA-typing • Cross-match	• *Brucella* (where indicated) • *Cytomegalovirus* • Epstein–Barr virus • Hepatitis B and C virus • Hepatitis E virus (where indicated) • HHV8 and HSV (where indicated) • HIV and HTLV 1/2 • *Mycobacterium tuberculosis* (where indicated) • *Plasmodium* (where indicated) • *Schistosoma* (where indicated) • *Strongyloides* (where indicated) • *Treponema pallidum* • *Toxoplasma* • *Trypanosoma cruzi* (where indicated) • Typhoid (where indicated)
Assessment of liver anatomy	**Blood tests**
Appropriate imaging investigations should allow confirmation of the liver size and enable abnormalities of the biliary ducts. They must also delineate the anatomy of the liver vasculature. • Liver ultrasound with Doppler • CT scan liver • MRI cholangiography	• Haematological profile • Complete blood count • Haemoglobinopathy (where indicated) • Biochemical profile • Creatinine, urea, and electrolytes • Proteinogram • Blood lipids • Thyroid function tests • Alpha-fetoprotein • B-HCG • NSE • CEA • Pregnancy test (if indicated) • PSA (if indicated)

APTT: activated partial thromboplastin time; B-HCG: beta human chorionic gonadotropin; CEA: carcinoembryonic antigen; GGT: gamma-glutamyl transferase; HHV: human herpes virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; HTLV: human T-Lymphotropic virus; NSE: neuron-specific enolase; PSA: prostate-specific antigen; PT: prothrombin time.

* For further details of virology and infection screening, refer to §13.7.1.

It is advisable to minimise risk factors and optimise the physical and psychological status of the donor before surgery, including physical activity, nutritional care and psychological support. After donation, the donor must be advised to maintain a healthy lifestyle, control body weight, promote physical activities and follow the recommendations on health promotion according to age and gender [39-40].

13.5.2. Medical evaluation and exclusion criteria for living liver donation

LD liver transplant is an important strategy to consider in many patients waiting for transplant and has been shown to achieve excellent outcomes in the recipient. It is based on the principle of double equipoise, where donor risk is justified by recipient benefit. Therefore, donor safety is of the utmost importance when considering the procedure. The optimisation of donor-selection criteria, the experience of the surgical team in hepatobiliary and transplant surgery and the establishment of careful post-operative management are essential to achieve low donor morbidity rates.

A summary of the routine screening of potential living liver donors is provided in Table 13.3.

Once a patient is on the liver transplant waiting list, he/she can be offered the possibility of LD liver transplantation in centres where the procedure is performed. Evaluation of possible donors starts when they voluntarily request information about the process. In general, a maximum age of 55 is recommended to start the evaluation. It is also required to have a blood group identical or compatible with that of the recipient and an apparently normal state of health with no associated diseases. If the ethical and legal criteria are fulfilled, the evaluation process may begin. It involves hepatologists, surgeons and psychologists.

An extensive evaluation of the health status of the potential donor is mandatory in order to minimise the impact of a major abdominal surgery procedure. It is very important to rule out the presence of liver, infectious or neoplastic diseases. Also, a psychological assessment must be performed.

The evaluation of the liver itself in an LD has two aspects:

a. to ensure that a graft of adequate size is procured,

b. to ensure that the remaining liver in the donor is not compromised and is able to sustain adequate liver function.

In this regard, a precise analysis of the liver volume and its detailed vascular and biliary anatomy is essential to determine donor suitability. This knowledge, before obtaining the graft, is very important for guaranteeing the success and safety of the surgery, in both the donor and the recipient.

Nowadays, non-invasive imaging techniques, such as angio CT-scan and cholangio-MRI performed by experienced radiologists, are necessary to obtain this information. Their utility is evident because they calculate the total liver volume of the potential donor and the residual amount of hepatic parenchyma after resection. If the liver volume is insufficient, the consequences for the recipient and the donor may be fatal, causing the feared small-for-size syndrome due to liver insufficiency after surgery. Both techniques are equally effective for evaluating the vascular distribution of the liver, but MRI can also effectively evaluate the liver's biliary anatomy, so it is currently the gold standard in evaluation of potential donors. In living donation for small infants, knowledge of the vascular anatomy is essential for the planned surgery, including microsurgical techniques.

In some instances, a complex anatomy of the portal vein or the hepatic artery may contraindicate donation. Variations of the hepatic veins have to be addressed pre-operatively in order to make a surgical plan to prevent congestion of the graft and the remnant liver due to insufficient venous drainage. The bile duct is the structure with the largest number of anatomical variations, although this is not usually a contraindication for donation.

The selection of either right or left lobe hepatectomy/transplantation requires individualising each particular case and choosing the best procedure depending on the particular characteristics of the donor and the recipient.

13.6. Living donor lung transplantation

Along with the regular shortage of organ donors, only 15-20 % of them are suitable for lung donation. As a result the waiting-list mortality for lung transplantation is high, reaching 30-40 %. In order to increase the number of suitable lung donors, mainly for small and critically ill patients, the use of lobar lung living donors was introduced in the 1990s. Living donor lobar lung transplantation (LDLLT) provides a similar survival rate to deceased lung transplantation, even for very ill patients, with acceptable risk for the donor [41-43]. However, in a 2017 article from Japan, among 33 living lung donors without any medical problem 1 year post-transplantation, a significant

deterioration in the quality of life was reported [44]. A psychological evaluation showed a higher anxiety level among the 33 lung donors compared with their anxiety levels pre-transplantation. Especially in cases of recipients' deaths, a more significant decrease in the quality of life and sleep quality was found among the donors.

Surgical techniques of LDLLT typically include recipients' bilateral pneumonectomy and subsequent implantation of a right lower lobe from one donor and a left lower lobe from the second donor. To overcome the issue of size matching, novel techniques have been applied, after careful anatomical and functional measurements. Those techniques are single-lobe transplants, native upper-lobe-sparing transplants and right-left inverted transplants. Three- and five-year survival rates of standard and non-standard living donor lung transplantation have been similar [45].

13.7. Medical evaluation of the living donor with regard to the risk of disease transmission

Disease transmission from donor to recipient can occur in the context of LD. Contrary to the situation with DDs, sufficient time is available in less urgent cases for appropriate donor investigations and possible treatment in advance. Therefore more extensive diagnostic procedures should be attempted for safer risk assessments. In general, the investigations and procedures recommended in DDs should be performed (see chapters 6 to 10), but in contrast the risk–benefit assessment of a possible donor–recipient pair can be done without time constraints.

13.7.1. Risk of transmission of infectious diseases

Addressing the risk of transmission of infectious diseases through living donation adheres to the same principles as applied in DD, as outlined in Chapter 8. In the case of a LD, an infection can be acquired by the LD between screening and organ recovery. Therefore, basic LD screening tests must be performed both at initial counselling and again at the final counselling and/or before the organ is procured. Results must be available before the organ is removed for transplantation. Counselling of the donor and recipient must include the information that infections may be acquired during the period from initial or final screening and counselling up to the day of transplantation. Therefore, transmission risks still exist beyond appropriate screening, and such transmissions have indeed occurred. Education should be given about how the LD can avoid infections like HIV, HCV, HBV or HEV, to further reduce these risks.

Some special considerations might help in reducing the risks of transmission of infectious diseases through an LD:

a. It is advisable to screen LDs with NAT for HIV, HBV and HCV shortly (one week) before organ donation in order to minimise risks due to undisclosed risk behaviours.

b. In the case of vaccinations with live vaccines, transmission of a vaccine-derived pathogen can be avoided by postponing the transplantation by 4 weeks if necessary (see §8.3.4). In LDs, it is advisable to perform HAV and HBV vaccinations before donation in non-immunised donors (see §8.4.2.5 and §8.4.2.6), and also to complete vaccinations as recommended by the local healthcare system.

c. In the case of Epstein–Barr virus D+/R–, protocols for close monitoring of such recipients help to reduce the fatal complications of post-transplant lymphoproliferative disorders by earlier diagnosis. EBV-DNA monitoring and early treatment should be adopted for all D+/R– recipients (see §8.4.2.4).

d. In the case of a donor with HBV infection or HCV infection, the principles outlined in sections §8.4.2.6 and §8.4.2.7 should be applied. In LD with HCV infection and viraemia, after treatment with the new pan-genotypic direct acting antiviral (DAA) drugs and sustained virological response, living donation and transplantation are possible with some precautions. Current studies are investigating this. It is unlikely that an LD with sustained virological response or spontaneous clearance of viraemia will transmit HCV with the graft, but this has not been confirmed yet. In any case, proper follow-up of the donor and recipient (HCV-PCR test) will help to identify the need for intervention. Beyond this level of follow-up, the pathways discussed for DD might be applied in living donors based on case-by-case decisions (see §8.4.2.7).

e. Transmission of Kaposi sarcoma herpes virus (HHV-8) from organ donor to recipient has been documented through seroconversion and by molecular epidemiologic studies (see §8.4.2.10.1). Although the optimal serologic assay technique has not been determined, the combination of whole virion ELISA

(enzyme-linked immunosorbent assay) and lytic immunofluorescence assay should be utilised to improve sensitivity and specificity. Screening donors and recipients for HHV-8 in low-prevalence countries is currently not recommended. However, in high-prevalence countries, screening of LDs is advised, and donors with positive HHV-8 serology should be excluded from organ donation due to the increased risk for the recipient of developing HHV-8 associated diseases. Infected recipients may experience fever, splenomegaly, lymphoid hyperplasia, pancytopenia and occasionally rapid onset cutaneous or visceral Kaposi sarcoma. A very severe clinical picture and high mortality associated with primary HHV-8 infection has recently been observed in a series of liver transplant recipients.

f. Seasonal screening for West Nile Virus (WNV) using NAT should be considered at least in the case of febrile neuro-invasive illness or local epidemics of WNV. For laboratory screening, LDs should be screened by WNV-NAT within 7-14 days of donation. The use of serologic testing offers an additional potential strategy to screen potential LDs for WNV but poses significant limitations in its performance and interpretation. During the mosquito season, prospective LDs should be counselled to use personal protective measures against mosquito bites, such as using insect repellents and avoiding outdoor activities between dusk and dawn. These practices are meant to mitigate the risk of acquiring WNV between diagnostic testing and organ donation.

g. Anti-HTLV-1/2 screening should be performed in all donors, particularly those coming from geographic regions with a high prevalence of HTLV-1/2 infections (see §8.4.2.12). D+/R– combinations are usually not accepted, though evidence-based policies do not exist.

h. As a minimum, acute or chronic persisting bacterial infections or abnormal colonisation of the organ to be transplanted should be cured in LDs. Donors colonised or infected with multi-drug resistant bacteria should have documented eradication of the pathogen before organ donation. This does not apply to simple faecal carriage of multi-drug resistant pathogens.

i. Donors with curative treatment of tuberculosis (TB) can be used in LD with some care and follow-up of the recipient. The risk of latent TB with transmission risks, as outlined in section §8.5.6, should be considered; in living donation, IGRA-Tests of donor and recipient are helpful. LDs with a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) should be offered treatment for latent TB (LTBI) prior to donation or as per local or national guidelines. As completion of this treatment may delay the transplant and adversely impact the recipient, expert opinion is that each situation should be individualised, but the prophylaxis need not be completed before the transplant occurs. There are no data on the optimal duration of possible LTBI therapy in this setting. Information about LD LTBI status and treatment history should be noted in the medical record of the organ recipient. Chemoprophylaxis should be considered for recipients whose donor TB screening test (TST or IGRA) was positive, in cases where the donor did not receive either any or sufficient chemoprophylaxis. Recipient risk for isoniazid (INH) toxicity must be weighed against the risk of donor-derived TB transmission; drug interactions with transplant medications and rifamycins (rifampicin, rifampin, rifabutin, rifapentine) should also be carefully considered after transplant. Clinicians should consider the impact of local TB resistance rates when developing effective chemoprophylaxis protocols, and should refer to local or national guidelines.

j. Disseminated fungal infections (or fungaemia) must be eradicated completely before donation. For localised infections, case-by-case consideration is necessary (see §8.6).

k. Active parasitic disease of the donor is a contraindication for donation. Exceptions may be possible if unacceptable risks for the recipients have been ruled out by transplant infectious disease specialists (see §8.7).

l. *Trypanosoma cruzi*, the parasite responsible for Chagas disease or American trypanosomiasis, has a predilection for muscle, heart and neurological cells. Screening is important for residents of, immigrants from or travellers to endemic areas (Latin and South America, see §8.7.2).

m. Strongyloidiasis typically occurs only in the setting of specific environmental exposures; thus, screening all potential LDs is not indicated. Screening is justified for the following potential organ donors:

i. Persons who were born in or lived in tropical or subtropical countries where sanitation conditions are substandard. This includes candidates

with prior military service in endemic areas. Strongyloidiasis has occurred in most countries, with the exception of Canada, Japan and northern Europe.

ii. Persons with unexplained oeosinophilia and a history of travel to an endemic area.

iii. Those born in the United States who have had significant exposure to soil in Appalachia or the south-eastern United States.

iv. Persons reporting a prior history of *Strongyloides* infection. *Strongyloides* IgG antibody testing is readily available in many reference labs. Test sensitivities vary and false-negative results have occurred, including in early infection and immunocompromised hosts. Indirect immunofluorescence assays have improved sensitivity; however, they are generally only available through research laboratories. There is no standard commercially available confirmatory testing for antibody-positive specimens; false-positive tests are uncommon. Individuals with a history of treatment for *Strongyloides* infection may have persistent antibody; consequently, those donors should undergo further evaluation by an expert in infectious diseases.

n. In many countries where geographic restrictions do not apply, risks for infections should also be considered according to lifestyle, living and sanitary conditions, vertical transmission, etc., as outlined in section 8.10. Surveillance of disease transmission vectors contributes to detection of new transmission risks in LD too.

o. Preventive strategies that can minimise the risk of donor-derived diseases among potential recipients are summarised in section 8.12.

p. Not enough data exist for patients under treatment for HIV infection in Europe for conclusions to be drawn and recommendations to be made about whether they can be considered as potential LD. Transplantation to HIV-infected recipients is possible (see §8.4.2.11).

q. Migrants represent a population at risk for infectious diseases, depending on the prevalence of the particular infection in their country of origin, their vaccination status, the countries visited during their journey and the conditions experienced during the process of migration. Thus, migrants serving as organ donors may have a higher probability of being infected with common or rare pathogens, which they may transmit to the recipient. On the other hand, migrant recipients may experience reactivation of the respective pathogens under immunosuppression. At present, there is a lack of data regarding the frequency and the specific characteristics of infectious diseases among migrant donors or recipients. To address the risk of infectious diseases through transplantation involving migrants, it is advisable to refer to the epidemiological data of health organisations regarding infectious diseases among newly arrived migrants according to the country of origin. Moreover, migrant recipients' immunisation status should be thoroughly evaluated and, if there is uncertainty about their documentation, they should be considered as unvaccinated [46-48].

13.7.2. Risk of transmission of malignancies and other diseases

It is important to adhere to the principles applied in deceased donors as outlined in chapters 9 and 10 regarding malignancies and other diseases, respectively.

Any active malignancy must be ruled out during the work-up of the LD. In the case of pre-existing malignancies, curative treatment must be checked and the cure of the donor disease ensured. Exceptions might be justified, as in the reported living liver donation from a mother to her 9-month-old child in whom the pre-donation evaluation revealed an early gastric signet cell cancer (pT1NoMo, sm1) of the donor. There was no other living or deceased donor available, while the child's health situation was deteriorating rapidly. One month after gastrectomy of the donor, liver donation and transplantation were performed. Donor and recipient were well and without malignant disease 1 year thereafter. This example illustrates an extraordinary situation and should not justify such procedures as an acceptable practice (see 9.4.14).

Regarding donor malignancy transmission risks, see Chapter 9.

The relevance of transmission of inherited or congenital defects has to be assessed individually. In more or less autoimmune-triggered diseases of the recipient causing terminal organ failure, grafts of genetically identical or closely related LDs can be at increased risk of recurrence.

In cases of a planned stem-cell transplantation for curative treatment of the recipient, the LD should be selected in collaboration with stem-cell experts.

13.8. Psychosocial aspects of living donation

13.8.1. Psychological risks and evaluation of living donors

Despite kidney living donation being a safe practice in general, several long-term studies on outcomes suggest that LDs may be at increased risk of end-stage renal disease, cardiovascular mortality and all-cause mortality [2-3, 49-50]. About 25 % of LDs report psychological distress, depression and anxiety disorders, and about 30 % find that their health has worsened since donation [51]. In the 2013 RELIVE study, 9 % of LDs showed an impairment of their physical health-related quality of life and another 9 % of LDs had significantly impaired mental health-related quality of life [52]. Deterioration of the donor–recipient relationship has been observed in up to 14 % of cases (18 % in marital relationships with spousal and non-spousal donors; 17 % in general family relationships) [53]. For these reasons, not only the donation procedure itself, but also the decision to donate after appropriate informed consent, may become a stressful event, coping with which requires not only good medical health but also psychological stability including, but not limited to, resolving ambivalence about donation [54].

For instance, recipients' appraisal of transplantation as a set of stressful events along with a coping style predominantly oriented to emotion and/or based on avoidance has been found to be related to a poorer psychological adjustment and adherence to post-donation medical treatment. Similarly, LDs who remain in a stable low mental state from before donation to a time up to 1 year post-donation are partly characterised by an avoidant coping style, lack of social support and appraisals of the donation process as an unmanageable and/or negative event. Other relevant characteristics of these donors include suffering previous psychological problems and expectations of interpersonal benefit and negative health consequences after donation. Expectations of interpersonal benefit, avoidant coping style and appraisals of unmanageability seem to lead to an LD suffering greater psychological symptoms by increasing the perceptions of stress. The assessment of these variables might help in deciding which LDs might need intensified care pre- and post-donation.

Undergoing LD evaluation may carry its own potential risks, such as negative psychological consequences of being aware of an elevated risk of a future health problem or the negative emotional consequences of being rejected for donation [55]. Currently, the US Department of Health and Human Services Advisory Committee on Transplantation recommends an independent informed consent process for the evaluation of potential LDs.

Previous consensus statements and regulations have consistently underscored the relevance of the psychological and social evaluation of potential LDs [10, 56-57] as well as giving them comprehensive risk–benefit information [58]. Proper education adjusted to case-specific risk factors should be provided for every LD [59].

Other factors that are considered warnings include a history of poor adherence to healthcare recommendations, limited family or social support, problematic donor–recipient relationship, lack of disclosure to others potentially affected by living donation, and unrealistic expectations. However, much less consensus exists on how to consider these psychological issues, because current research is still unclear about their influence on LD outcomes. It seems advisable that all programmes include the assessment of these factors to better inform the LD. Smoking, for instance, is not a clear-cut contraindication for donation. However, it seems reasonable to advise donors of the increased medical risks of not quitting smoking. As will be described below, the same applies to several psychological and social risks.

Other reasons suggested for prospectively assessing long-term psychological and social outcomes in living kidney donors include [51]:

a. To improve the evaluation process and criteria used to approve individuals as donors.
b. To delineate outcomes that donors themselves consider as being important, and thus to accurately anticipate donors' long-term care needs and provide timely interventions for donors.
c. To document outcomes among donors participating in evolving programmes such as kidney paired exchange and anonymous non-directed donation.
d. To identify any additional psychological and social benefits of donation.
e. To further improve the donation experience so future donors, recipients, and families are not deterred from considering living donation.

The recent loosening of requirements in the nature of donor–recipient relationships has led to other parties, such as colleagues, now being considered as potential LDs. The relationships involved here may be more complex than the classic genetic/emotional relationships between donor and recipient, and thus may require a more careful evaluation of motives, expectations, risk–benefit knowledge and coercion [57].

Table 13.4. **Risks and exclusion criteria for living donation detectable during psychosocial evaluation**

A. Absolute contraindications	
Coercion	Besides cases of flagrant coercion, any pressures from family or from the donor–recipient relationship must not impose either an unacceptable medical, psychological or social risk to the donor, nor a shortening of the period between consent and surgery set aside for potential reconsideration of the decision to donate.
Financial gain or comparable advantage	
Active substance abuse or dependence without willingness to receive appropriate treatment	
Mental health disorder or psychological instability compromising the ability to give free and informed consent. Mental health disorder or psychological instability that, according to the clinical judgment of the mental health specialist, may worsen as a consequence of the donation process. Mental health disorders requiring pharmacological treatment for stability incompatible during surgery or at post-donation.	
Cognitive disability preventing free and informed consent	Donors must demonstrate capacity to understand the information included in the informed consent at a level of complexity adapted to each donor.

B. Risk factors	
Extreme and maladaptive personality traits	For instance, conscientiousness and compulsiveness (lowest: poor adherence to healthcare recommendations; highest: rigidity towards receptors' health behaviours); impulsiveness; narcissism; histrionism; emotional dysregulation.
Understanding of donation risks and benefits, and ambivalence	Includes awareness of the possibility of renal failure in the future or being unable to donate to a spouse/partner/significant other. Donors with a strong feeling of making an autonomous decision cope better with the post-operative course. Ambivalence worsens physical and mental outcomes [54], whereas comfort with decision to donate protects the mental health quality of life [52].
Motivations	Verify the absence of potentially iatrogenic motivations or indicate a pre-donation intervention and close monitoring after donation (e.g. delusional or megalomaniac, placing receptor in debt to donor, compensating for past mistakes or restoring position in the family [67], donation as a moral obligation [64], desire for recognition, using donation for publicity).
Expectations	Detect and modify unrealistic or idealised expectations (e.g. improve relationship with recipient [68]; solve psychological problems and familial conflicts [69], interpersonal benefit and shorter time of recovery than can be expected [52]). Detect and modify expectations of low manageability of transplantation demands. Expectations define transplantation success from the patient's point of view [70].
Donor-recipient relationship	In 20 % of all cases, unresolved problems appear (e.g. unilaterally dependent relationships), and half of that 20 % resign from being an LD [71]. In general terms, donation amplifies the quality of the pre-existing relationship both for better and for worse.
Limited family and social support, including health providers	Feeling ignored and perception of low attention after surgery worsens quality of life, whereas strong perceived support is protective [51]. Lack of a partner predicts worse mental health after donation, while generally lower social support contributes to the maintenance of pre-donation lower mental health.
Lack of disclosure to others potentially affected by living donation	Knowledge by family of possible donation is a protective factor for LD outcome. Family conflicts about other potential alternatives to donation (e.g. other donors available) may cause diminished support for donation.
Fear of kidney failure	13 % of living kidney donors report moderate or high fear of renal-related health problems after donation [71-72].
Stress management and current coping resources (optimism, coping strategies and resilience)	History of maladaptive emotional responses to, and management of, stressful life events. Higher optimism leads to expectations of benefit, whereas lower optimism is associated with expectation of negative consequences from donation [52]. An avoidant coping style predicts worse mental health after donation.

In summmary, pre-donation psychological assessment is intended to prevent donation from individuals with significant risk of developing mental health disorders or psychological/social problems, and to avoid worsening their quality of life. Therefore, it should be aimed at: the assessment of competence; knowledge and understanding of donation risks and benefits; psychological functioning, motivations and expectations; the donor–recipient relationship; and social support (see Table 13.4) [57, 60-62].

Pre-donation psychological assessment should be performed through semi-structured interviews

conducted by professional mental health specialists with extensive experience in living and deceased donation, supported by reliable and valid psychometric tests adapted to the cultural characteristics of the donor. Interpretation of the results of these questionnaires should be carried out by a mental health specialist with expertise in these psychometric tools.

Psychological assessment may be even more useful if applied to improving the donation procedure rather than being a tool to identify contraindications [63]. For instance, the detection of expectations of being rejected by family (or of losing a job in subordinate donor–recipient relationships), in the event of declining to be a donor, may lead the transplant team to help the potential donor to refuse without reprisals.

A history of alcohol or drug abuse is not an exclusion criterion for those donors in sustained abstinence or those donors who receive appropriate substance-abuse treatment. In fact, virtually all psychological risk factors are amenable to modification through evidence-based interventions. For instance, poor management of financial stress or feelings of moral obligation to donate are often identified in donors more likely to develop future depression [64]. Indeed, pre-donation interventions on risk factors have been able to increase knowledge about live kidney donation and produce a more favourable attitude towards being a donor, both in patients and in families [65]. Donors who have received a pre-donation intervention on ambivalence have shown better outcomes, both physical and psychological [54]. Potential improvements include: prevention of depression; promotion of health behaviours (which tend to remain unchanged after becoming an LD) and prevention of obesity (which proportionally increases with time after living donation) [66].

13.8.2. Social evaluation

The independent donor advocate is responsible for ensuring that the donor is aware of the consequences of their decision (somatic, mental and psychological as well as personal, familial and professional).

An interview between an independent donor advocate and the LD is required in order to:

- understand how the process of decision making has been performed;
- evaluate family and social environment and social support;
- review employment (contract type, labour implications of their decision) including economic impact of their decision and measures adopted to counteract any adverse situation (see Table 13.4).

In particular the family environment should be explored in order to detect family conflicts, to find out who will be in charge of post-donation care, and how the welfare of the person(s) taking charge has been planned in the event of any complication.

It is advisable that the recipient not be present during the interview in order to ensure that the donor speaks freely, expressing the donor's own concerns and doubts.

As outlined above, it is advisable that a donor advocate assesses the donor's biological risk in order to minimise neoplastic or infectious transmission from donor to recipient. Therefore it is necessary to ask about biological risk behaviours (e.g. sexual promiscuity, drug addiction, travelling to endemic areas of tropical diseases) and to ensure that the relevant serological tests have been performed and that these are negative.

13.9. Living donation registries: regulatory audit

LD registries are needed for transparency of practice, to facilitate evaluation of the consequences of donating an organ and for the generation of evidence. Systematic and appropriately designed data collection makes it possible to obtain sufficient information to define and secure proper follow-up of LDs, to document donor prognoses (safety/morbidity) and to investigate causal relationships between pre-donation risk factors (body mass index, estimated kidney/liver function, mild hypertension, etc.) and future prospects, including cardiovascular events, kidney/liver failure and death. Therefore, all Council of Europe member states must ensure that harmonised national LD registries are developed and maintained according to Resolution CM/Res (2015) 11 [73]. The appendix to this resolution provides appropriate characteristics and general guidelines for the construction of national/international LD registries, and the explanatory memorandum details the parameters (mandatory and optional) for data to be collected.

In the EU, Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation establishes the legal requirement for EU countries to develop a 'register or record of living donors' [19].

International professional standards, such as the 2004 International Forum on the Care of the Live Kidney Donor [10], have also recommended regular lifelong follow-up and monitoring of LDs, and the establishment of dedicated LD registries.

Regular audits and controls of centres authorised for LD procurement/transplantation procedures must be conducted by Health Authorities.

The Lidobs Conference (2014) made possible an exchange of experiences and knowledge of living donation programmes in order to assure the safety, quality and transparency of the procedures and high-quality standards. The conference aimed to set up a community of experts in living donation programmes named Lidobs [20] that would continue to expand and increase knowledge of donation and transplant procedures through a network (http://lidobs.eulivingdonor.eu/).

13.10. ABO blood group incompatible transplantation

ABO-incompatible (ABOi) transplantation has been introduced during the past 30 years worldwide as a strategy to expand the donor pool in LD transplantation – mostly for kidneys. The success of centres performing ABOi transplantation is related to strict adherence to a protocol in an ongoing structured programme. Such protocols take into account all recipient- and donor-related obstacles associated with antibody-incompatible transplantation, including effective desensitisation protocols, subsequent adapted immunosuppression and knowledge of the immune pathogenesis. The key issues in ABOi transplantation are:

a. pre-transplant antibody removal by the use of either plasmapheresis or cascade filtration and unselective or selective immunoadsorption to prevent hyperacute rejection,
b. intravenous immunoglobulin,
c. B-cell depletion by rituximab,
d. patient-tailored maintenance immunosuppression.

Individualised immunosuppression is combined with immunomonitoring for early detection of re-increasing antibody titres, mainly during the first two weeks after transplantation. Thereafter, even when antibodies recur at high levels, they do not seem to harm the kidney transplant, a phenomenon that is called 'accommodation'. Nevertheless, there are cases where protocols for antibody removal fail for unknown reasons.

For the most recent era, since 2000, overall patient and graft survival rates for ABOi and ABO-compatible kidney transplantation are similar. With regard to infectious complications after ABOi transplantation, there are conflicting results with an increased risk, mainly for early severe infections. No increased cancer risk was found [74-78].

13.11. Human leukocyte antigen-incompatible transplantation

There is an increasing population of highly sensitised patients with donor-specific anti-HLA antibodies (DSA) against an available LD. Therefore several desensitisation protocols have been developed, which generally use plasmapheresis with infusions of intravenous immunoglobulin and rituximab, aiming to eliminate or reduce anti-HLA antibody levels so that the flow cytometry cross-match becomes negative in order to enable transplantation. Those recipients experience high rates of antibody-mediated rejection and the higher pre-transplant DSA levels are those associated with antibody-mediated rejection [79-80]. Long-term survival after transplantation across the HLA barrier is impaired [81-82]. However, the 8-year patient survival rate in desensitised LD kidney transplant recipients was strikingly higher than in patients waiting for a compatible deceased donor organ, 80.6 % versus 49.1 % respectively [83].

13.12. Kidney paired exchange

The strategy of kidney paired donation (KPD) was first introduced 30 years ago and initially was applied in developing countries and those relying mainly on living donation. When multiple transplant centres within the same country combine their registries, they can achieve more matches. This has been accomplished in several European countries, as well as in the United States, Canada and Australia. Besides the success of large multi-centre or national KPD registries, single-centre programmes also exist, which are logistically simpler but may lack the benefits of a larger pool size. However, given the facility of matching more pairs within large KPD programmes, co-operation between more countries is evolving [84].

Pairs are entering the exchange programmes because of ABO incompatibility, high recipient sensitisation (in DSA, age and graft size), mismatched pairs and pairs that are borderline-compatible but would benefit from a better HLA match. In addition, combining desensitisation with KPD as a complementary modality increases the chances of finding a compatible donor [85-86]. Furthermore, the use of KPD while disregarding ABO compatibility may facilitate transplantation in highly sensitised recipients. In such cases, the kidney paired exchange can involve a manageable ABOi pair, in order to avoid the HLA barrier.

Finally, the use of altruistic donors to start linear domino chains of transplantations, otherwise known as non-simultaneous extended altruistic donor chains, is another option for expanding the success of kidney paired exchange [87]. Recently it has been proposed to use deceased donor kidneys to help initiate a KPD chain [88].

With regard to the results of KPD, the overall match rates are approximately 50-60 % in a large KPD registry with more than 1 000 pairs. Those recipients that are sensitised and/or are blood type O achieve match rates of about 15 % [85].

13.13. Conclusion

Transplantation of grafts procured from properly performed living donation procedures is complementary to grafts procured from DDs. Legal, ethical, psychosocial and medical requirements have to be considered, since the otherwise healthy LD is exposed to some risks. LD transplantation must be performed according to the best published evidence, following international recommendations from scientific bodies and societies. Registries of LDs and follow-up of LDs are mandatory for the purpose of traceability, safety and transparency of the activity and of the outcome of LD procedures performed in each country. In the treatment of small children with end-stage organ failure (specifically not included), the experts contributing to this chapter agree on considering LD or DD as the preferred option.

13.14. References

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Chapter 14. Donation of vascularised composite allografts

14.1. The concept of transplantation of vascularised composite allografts

The use of vascularised composite allografts (VCAs) is a novel field of transplantation. In many European countries, it is still operating under research protocols. The aim of VCA transplantation is to restore and repair large severe anatomical defects for patients suffering from severe disabilities that cannot be repaired by plastic reconstructive surgery or undergoing life-saving procedures (e.g. abdominal wall reconstruction in intestinal graft recipients) that VCA transplantation can complement.

Following some previous attempts, successful VCA transplants started in 1998 in France with the first transplantation of hands [1], followed by the first face transplantation in 2005 [2]. Nowadays, VCA activity is mainly restricted to the upper extremities and face, using transplantation of grafts procured from deceased donors. Without a mandatory requirement to report all procedures at a supranational level, it is difficult to provide accurate data. Since 2002, the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) has collected information on a voluntary basis [3].

Directive 2010/53/EU [4] defines organs as 'a differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularisation'.

VCAs are considered as organs because they are differentiated parts of the human body, containing different type of tissues such as skin, muscles, bones, tendons and vessels that require surgical connection of blood vessels for allograft function. Once transplanted, they maintain their structure, vascularisation and capacity to develop physiological functions at an autonomous level. They are also subject to the same time constraints as organs due to their vulnerability to ischaemia, the absence of storage options and the absolute need for immunosuppressive therapy in the recipient. In 2011, the US Department of Health and Human Services announced that VCAs fall under the scope of organ legislation [5].

Beyond the upper extremities and face, VCA grafts are transplanted in other parts of the body at a lower frequency (see Table 14.1).

14.2. Special issues in donation of grafts for upper extremity and face transplantation

14.2.1. Donor selection

The majority of grafts are procured from donation after brain death (DBD) and grafts come less frequently from donation after circulatory death (DCD). Because of the limited number of candidates, all

co-ordination teams involved in a VCA programme should be aware of any potential candidate, either already registered on an existing waiting list or otherwise proposed in the context of a clinical research protocol. For each proposed VCA recipient, previously validated by the Health Authority in charge of organ transplantation activities, the VCA surgical team or the protocol investigator should complete a standard technical sheet about each proposed donor containing information on expected donor criteria (mainly morphologic criteria) for the best matching of donor and recipient (see Table 14.2). All other information should also be available, in order to facilitate donor detection and selection.

Table 14.1. **A summary of VCA graft transplantations performed**

Kind of VCA	Remarks
Upper extremity and face transplantation	To our knowledge, 90 patients have undergone upper extremity transplantation worldwide (42.4 % unilateral and 57.6 % bilateral) and 39 patients have undergone total or partial face transplantation [3, 6-7]. Such transplantation requires a multidisciplinary approach for the evaluation and management of complex medical, psychiatric and social issues. The goal of these transplantations is to improve the patients' quality of life. A careful evaluation and selection of the potential candidate is indispensable. The transplantation teams are multidisciplinary. Potential recipients have to be evaluated for reconstructive surgery and at the same time for transplantation. The psychosocial assessment is important, due to past and current severe disabilities [8]. Overexpectations of success by potential recipients must be ruled out because serious complications occur. Upper extremity transplantation needs an intensive and long-lasting rehabilitation programme, which starts usually after the first 24 hours. Patient motivation is indispensable throughout the long and slow rehabilitation period, which can last many months and, sometimes, years. In the follow-up, immunosuppressive therapy is mandatory. Acute and chronic rejection require further interventions. Exhaustive studies of functional outcome are pending, but single cases of successful procedures are reported. At the beginning of the VCA era, the functional recovery of transplanted hands was uncertain, but recovery mechanisms are now better understood; recovery is based on peripheral nerves regeneration and on cerebral cortex re-organisation. Patients' compliance with immunosuppressive treatment and the rehabilitation programme is the key to achieving successful functional recovery.
Abdominal wall	Abdominal wall transplantation (partial or full-thickness) was initiated in 2003. The indication is coverage of the fascia defect (when alternative techniques fail) after a life-saving intestinal and/or multi-visceral transplantation. Up to now, 38 full-thickness vascularised abdominal wall transplantation, 6 partial-thickness vascularised and 17 partial-thickness non-vascularised rectus fascia grafts have been performed [9].
Femoral and knee joint – lower extremity	Like upper-extremity VCAs, functional results of lower extremity transplantation depend on the level of amputation (proximal, mid- and distal femur or tibia), the more distal being associated with faster recovery and fewer complications [10-12]. Currently the results show limited outcomes.
Larynx and trachea	The indications for laryngeal transplantation are either 1. severe traumatic or stenotic injuries causing a loss of laryngeal function or 2. a large benign or low-grade malignant tumour, for which patients have undergone treatment by way of a total laryngectomy. At present, it is impossible to propose laryngeal transplantation to patients with locally advanced laryngeal cancer because immunosuppression is contraindicated. Tracheal replacement with prosthetic or biological substitutes such as allografts or autologous grafts (trachea, oesophagus, bowel, skin, bladder, aortic segment) is complex. The main critical issue is to manage allograft revascularisation [13-15].
Tongue	The putative indication for tongue transplantation, apart from face transplantation, could be cases of head and neck cancer with a functional deficit following total or subtotal loss of tongue tissue and graft-able hypoglossal and lingual nerves, in the absence of other contraindications. The one and only tongue transplantation was performed in 2003 [16].
Uterus	Uterus transplantation is nowadays a treatment for absolute uterine infertility. To date, 13 human uterus transplantation attempts have been reported [17-19]. A Swedish team has performed nine uterine transplantations, all from genetically-related or unrelated living donors [17]. So far, seven healthy babies have been born by *in vitro* fertilisation (IVF). Two grafts were removed within the first months. A preliminary French study shows the feasibility of uterus retrieval within multi-organ donation, without any competition for the pelvic vessels. Even without morphologic changes observed in the myometrium after 24-hour cold storage, the tolerance to cold ischaemia time remains uncertain [20]. Uterus transplantation has a particular status that should next be clarified by each national Health Authority with further experiences. Most grafts have been from living donation, with fewer reports of rejection in cases where donor and recipient are genetically related. The unique transplantation from the deceased donor did not reach the goal of live birth. All the births required IVF procedure surrounded by medically assisted reproduction and gametes regulation.
Penis	Penile transplantation has been performed in four cases [21]. Even if phalloplasty seems to be nowadays the best and efficient therapeutic option, some teams wish to develop such a VCA programme. Transgender individuals have expressed an interest in the procedure [22].

Table 14.2. **Donor selection criteria: information for co-ordination centres**

Donor selection is based on the following criteria:

- Type of donor: DBD or DCD.
- Details of past trauma, maxillo-facial surgery; face cancer is a contraindication for face transplantation.
- Age range; gender; height and weight range; skin tone-phototype, hair pattern, tattoos.
- Blood group; HLA typing, prospective cross-match.
- Anthropometric criteria (main matching criteria):
  - For upper extremities: photographs, level of amputation, upper extremity X-ray (anterior, posterior, lateral views) and measurements (length, circumferences), skin examination (no wounds/injuries), ultrasonography study of arteries (radial, cubital, palmar arches …) and veins (basilic cephalic). Of note, radial catheter insertion has been responsible for graft thrombosis [23]. Preparation of the cosmetic prosthesis.
  - For face: photographs, X-ray (anterior, posterior, lateral views) and measurements (specific to face segments), skin examination (no wounds/injury), computed tomography (with 3-dimensional reconstruction), angiography (to be discussed with the transplant team according to the nephrotoxicity); preparation of the facial mask.

14.2.2. Consent to donation

The process of obtaining next-of-kin consent should obey the legal requirements in place nationally. Currently the general public and relatives of potential donors are not, or may not be, aware of what VCAs are, or that they may be donated. In the USA, where VCA programmes have become standard care, once a matching donor is identified by the organ procurement organisation, a specific and explicit consent for VCA donation has to be obtained and documented through a separate consent process, independent of solid organ donation [24].

For hospitals not familiar with VCA procurement, support should be provided by the VCA centre in order to ensure that consent to VCA donation has been obtained properly and that all necessary questions have been asked. Best practice is that the person performing the VCA donation request is fully familiar with VCA procurement and transplantation, and trained to consider well all the issues that are briefly discussed in §14.2.3.1.

14.2.3. Co-ordination teams

The lack of proactive detection of potential donors for VCA grafts might be associated with a negative perception of this type of transplantation and weak knowledge of the results. This underlines the need for dedicated co-ordinators, trained and confident in such communication during the interview with the relatives.

As a prerequisite, co-ordination teams involved in VCA programmes should be part of such a programme on a voluntary basis, being already involved in DBD/DCD procurement activity. They should be aware of the potential recipients on the waiting list and, for each of them, their donor profile; all of this information should be known by the procurement centres, on the basis of the technical sheet describing the donor selection criteria (see Table 14.1). As soon as a potential VCA donor is identified by the co-ordination team, the Health Authority in charge of organ allocation must be rapidly informed of such potential procurement in order to begin searching for the best match among the potential recipient(s) on the waiting list, in conjunction with the VCA (and solid organ) transplant teams involved. Currently, VCA donors in Europe are mostly detected locally, in accordance with the recorded characteristics of the potential candidate.

The co-ordination teams of VCA centres should provide on-site support and a clearly defined checklist to hospitals not familiar with VCA procurement. The VCA team should fully respect the fact that teams in such hospitals are not familiar with the procedure and will need *ad hoc* training, explanation and appropriate guidance. After the donation procedure is completed, a debrief session by the VCA team for the hospital team is mandatory.

14.2.3.1. *Interview*

Requesting part of a limb or a face is different from requesting a life-saving organ such as a heart, because they are visible, external and highly sensitive body parts where removal may naturally provoke reluctance in the family. At present, co-ordinators begin and secure the interview by presenting the opportunity of solid organ donation before any other approach. The most desired situation would be when, following the co-ordinator's request for a VCA donation, the relatives spontaneously suggest that the potential donor 'wanted to donate every organ' and they show that they are definitely open-minded about VCA donation.

In cases of donation acceptance, co-ordinators should be able to give appropriate information to the relatives on VCA activities, the procurement modalities and post-transplantation outcomes (global aesthetic and functional results). Since osseous and cartilaginous substructure defines the face shape, the recipient's face will look different from the donor's face, unlike hand- or upper extremity transplants. Co-ordinators should stress that face donation will allow the restoration firstly of basic functions such as breathing, swallowing, eating, drinking and speaking, and only secondarily an 'acceptable' appearance. For upper extremity transplantation, because the donor's personal traits will be more visible, the physical matching criteria (limb

size and length, skin and pilosity, gender) are more relevant in donor selection.

The possibility of procuring supplementary material such as haematopoietic stem cells, skin or bone tissue should also be explained. Intended for the immunosuppressive strategy and/or further surgery, they are best procured from the unused parts of the grafts.

The obligation to give back to the relatives the deceased body consistent with the original image is a key point in any successful VCA programme in order to maintain a climate of absolute trust, as much for the next-of-kin's sake as for the sake of the medical community. It is essential to tell the relatives about the policy and practice of *ad integrum* body restitution – restoration of the donor's external appearance and physical integrity using cosmetic prosthesis – and it is important to recall this fact during the interview.

The co-ordinator should inform the donor family that, despite all efforts and the obligation of professional discretion in all circumstances, protection of confidentiality cannot always be respected as it should be. Transplanted patients usually accept requests to be shown in public or scientific meetings, which might unintentionally compromise the donor's anonymity.

14.2.3.2. *Procurement*

The co-ordinator's role in the operating room is essential, to manage the temporal and logistical constraints of simultaneous multi-organ procurement, with management of the different teams (e.g., novice plastic surgeons with experienced organ teams). They should be aware of the planned sequence of VCA/organ retrieval to guarantee a well co-ordinated process and, when required, to accelerate the solid organ procurement. For face procurement, the co-ordination team should be reinforced due to the surgery time.

The co-ordination and procurement teams of VCA centres must provide on-site support and clearly defined checklists to hospitals not familiar with VCA procurement in every step. The VCA team should fully respect the fact that teams in such hospitals are not familiar with the procedure and will need *ad hoc* training, explanation and appropriate guidance prospectively. After the procurement is completed, a debrief session by the VCA team is mandatory.

14.2.3.3. *Specific training*

According to Directive 2010/53/EU [3], specific training programmes should be developed, but to date there are no existing international standards or guidelines. VCA programmes' success mainly depends on surgeons' willingness to regularly interact with the co-ordination centres. The more they are involved and informed about the demand for and progress in VCA, the better they will promote this activity and approach the donors' relatives with confidence.

At present, co-ordination and donation teams not affiliated to a VCA centre are probably not familiar with the details of any kind of VCA. In a VCA centre it is very likely that a dedicated core team is familiar with the kind of VCA performed in that centre. Based on this hypothesis, an education programme will have to be developed, with appropriate guidance from the VCA core team, to enable co-ordination and donation teams to manage a VCA donation procedure without harm to other interests in the healthcare system. Although the core team of the VCA programme may have been preparing the donation–transplantation procedure for a long time in advance, we must be aware that other co-ordination and donation teams may have a severe 'psychological shock' if they are suddenly exposed to this issue for the first time.

14.2.4. VCA procurement

14.2.4.1. *VCA procurement sequence*

As a rule, multi-organ procurement should not be compromised by VCA retrieval. No case of solid-organ transplantation being compromised by VCA retrieval has been reported. Up to now, no standardised protocol for VCA procurement has been established, but experience is well described [23, 25-27]. Two thirds of limb and face procurement started with VCA recovery, followed by the multi-organ procurement simultaneously or immediately after VCA retrieval. Actually, donor haemodynamic stability is the critical factor determining the optimal timing of VCA retrieval. Because of the added complexity of VCA retrieval alongside the multi-organ procurement procedure, a detailed algorithm for each individual case, planning each team's function and intervention order, is required before the day of such events occurs. Positions for face/limb, thoracic and abdominal teams working simultaneously should be described in a schema depicting operating-room arrangements [25-26]. Communication between all procurement teams is essential, before and during surgery, to ensure efficient and safe retrieval with the best viability of all organs.

14.2.4.2. *VCA recovery phase*

14.2.4.2.1. Upper extremities

For upper extremities, the most important criterion in matching donor and recipient is the limb size. This is a straightforward and rapid recovery procedure, with minimal blood loss and minimal risk of destabilising the donor's haemodynamic conditions. Mean duration is 1 hour. Amputation under a tourni-

quet is performed just before solid organ recovery; the graft is perfused on the back table with pre-defined preservation solution. In a few cases, VCA recovery has been performed after vital organ procurement, mostly because this was forced by the donor's haemodynamic instability. When possible, a preservation technique using specific cannulation of proximal vessels (i.e. brachio-cephalic or sub-clavian) while keeping the venous return may improve the upper extremity viability (and is recommended in the case of an unstable donor). Upper extremities are prepared for transplantation and kept in ice pack while the VCA recipient is prepared. The graft is packed in dry and cold labelled bags and transported in an isotherm container. During the body restoration, the custom-made cosmetic prostheses are put in place [3].

14.2.4.2.2. Face

The duration of facial segment recovery is highly variable (4 to 15 hours); this is a function of the recovery sequence (sequential or simultaneous) and the number and type of aesthetic units to be replaced and consequently to be retrieved. The procedure's complexity can induce blood loss in volume and compromise circulatory control. On the basis of the experience of face procurement in DBD, tracheostomy (preferred to tracheal tube) and a mould for the facial mask could be performed pre-operatively in the ICU [25]. Usually, organ recovery starts with heart and lungs, along with liver, pancreas and small intestine. Kidneys and face are then removed. In some cases, donor haematopoietic cells have been simultaneously collected by a bone marrow aspirate from the iliac crest in order to induce a chimerism-tolerance status. Skin from the donor should be retrieved, at best issued from unused parts of the graft, to be further frozen. Donor bone tissue retrieved from an unused part of the graft is sent to the tissue bank. Facial graft is prepared on the back table, washed and packed in dry, cold and labelled bags for transportation in an isotherm container.

14.2.4.2.3. Restoration

Body restoration is a usual and mandatory step in any organ/tissue procurement, but of the utmost importance in any case. Replacement of the extremities or the face should be done using well-designed prostheses and mask, ensuring a perfectly restored external appearance.

14.2.4.2.4. Times

Since most VCA procurements have been performed locally, ischaemia times are around 4 hours [23, 26]. Median cold ischaemia time was around 356 minutes (30-365) in upper extremity transplantation and 132 minutes (20-540) in face transplantation [27]. Although no current clinical studies exist, time minimisation is advocated. As surgical procedures expand to include an increasing number of potential recipients, the effect of the ischaemic time becomes more important [28].

14.3. Conclusion

In summary, the wide spectrum of VCA types, mainly represented by upper extremity and face transplantation, can be referred to European directive 2010/53/EU as organs to be considered further in the context of quality and safety of organs for transplantation. Due to the limited number of VCA transplantations performed up to now, two issues need to be considered:

a. Further data are required to demonstrate the long-term benefits of each single VCA for the recipient as well as their cost for society.

b. Training of healthcare professionals – especially involved in organ donation – is needed on how to manage VCA donations well without harm to other issues of organ and tissue donation.

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Chapter 15. **Biovigilance and surveillance**

15.1. Introduction

Vigilance and surveillance (V&S) is an essential component of a properly functioning healthcare system; it aims to avoid any recurrence of a serious adverse reaction and/or event (SARE) [1-2]. V&S ensures better quality and safety in organs donated and used for transplantation; it also ensures that, when an SARE does occur, timely treatment can be given to mitigate further harm in other recipients from the same donor.

This chapter provides guidance on the implementation of V&S practice for all professionals involved, including organ donation and transplantation teams, members of staff caring for transplant recipients and living donors (LDs), regulators and the Health Authority.[1]

A V&S programme, co-ordinated by the Health Authority, should include:

a. the reporting of any serious adverse reaction (SAR) and/or serious adverse event (SAE),

b. management of cases (which may help to prevent further SAREs or to identify whether an SARE occurred or not),

c. surveillance, that is, follow-up of transplanted recipients' outcomes with active monitoring for adverse events and reactions of the donation and transplantation processes, including grading of severity, imputability (when applicable in case of a reaction) and the likelihood of recurrence and, if so, its impact.

Ideally, all SAREs should be reported by health professionals to the Health Authority in charge of V&S, to ensure that a rapid alert is sent to all transplant centres involved, if necessary, that there is an appropriate investigation and that corrective and preventive actions are adopted in the future, as needed.[2]

However, many complications are expected ones. They are not reported to the vigilance system because they are perceived as part of the usual range of undesirable clinical outcomes (e.g. fever, thrombosis). Some of them can indeed be part of the normal clinical follow-up of the recipients (e.g. events causing graft failure) whereas others might be associated to the donor or the process and should be analysed further. Health Authorities should develop V&S systems to help professionals to identify which events or reactions should be monitored and reported in order to be assessed as SAREs caused by unexpected incidents, with the aim of improving quality and safety in transplantation of organs and tissues.

1 'Health Authority' is the term used in this chapter for the authority responsible for the V&S system. In some member states/countries, V&S tasks and responsibilities are organised differently, being placed under the competent authority or the authority responsible for Substances of Human Origin (SoHO). Missions and responsibilities are defined in each country's legislation.

2 Development of a V&S system applied to organ donation and transplantation for the reporting and management of SAREs is a requirement of Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation in EU countries [3]. Its requirements can be recommended as good practice for all Council of Europe member states.

Two key activities are important in organising a V&S system:

a. The alert system is an early step in the vigilance process and should be developed in order to help professionals to communicate quickly with each other when a potential or real risk for other organ and tissue recipients is identified.

b. The quality management system is an elective process in the background, which focuses on detecting and preventing errors and maintaining a consistent standard of agreed specifications for organs and tissues recovered and transplanted.

15.2. Definitions

15.2.1. Serious adverse event

A serious adverse event (SAE) has been defined as any 'undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity' [3].

In Directive 2010/53/EU, the definition of an SAE includes those incidents often referred to as 'near misses', where an error or fault is detected and corrected without causing harm, but where there was the potential of causing serious harm to a living donor or to an organ recipient. Council of Europe member states should consider carefully how to appropriately address this issue under the domain of biovigilance and quality management.

15.2.2. Serious adverse reaction

A serious adverse reaction (SAR) can be defined as an 'unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity' [3].

An SAR should be differentiated from situations where a risk has been identified and is known by all stakeholders before procurement and transplantation (e.g. a recent antecedent malignancy, hepatitis B or C infection or reactivation of *cytomegalovirus* infection): here the recipient should be followed up for clinical outcomes as part of the surveillance system, but initially this case does not fall into the scope of biovigilance unless unexpected complications occur that might be related to an inappropriate pre-transplant assessment of donor-derived risks. Such conditions are described in chapters 8, 9 and 10. It is recommended that informed consent from the recipient should have been obtained.

In conclusion, an SAR is a biovigilance case where a living donor or a recipient has been seriously harmed (e.g. confirmed transmission of an undetected donor malignancy to an organ recipient), whereas an SAE is a biovigilance case where there is a risk of serious harm to a living donor or recipient, although no harm has occurred yet (e.g. autopsy finding of a donor malignancy after transplantation of the organs, but no signs of transmission in the recipients yet). Therefore, an SAE may or may not cause an SAR. Similarly, an SAR may or may not be related to an SAE. An analogous approach has been adopted by the World Health Organization (WHO) Notify project for V&S of all medical products of human origin, where adverse incidents are also categorised into those that have caused harm and those that involve a risk of harm [4].

15.2.3. Alert

The term 'alert' or 'rapid alert' describes the immediate notification of an SAE or SAR to all recipient centres and other institutions involved in a specific case. When there is a possibility that many other recipients could be affected, this alert may need dissemination at national or international level (see §15.4.3; e.g. one lot of organ perfusion solution is contaminated and this may affect other centres in the same country or other countries). It is therefore mandatory that the centre initially affected rapidly notifies Health Authorities. Spreading all available information allows prompt assessment of need to adjust the individual care of recipients in order to mitigate risk of harm or SAR. Some of these incidents may be identified during routine follow-up of mandatory procedures in the donation-transplant process (e.g. microbiological tests); others may be identified during work-up of an error or an accident occurring during this process.

15.2.4. Adverse event and adverse reaction

In contrast to an SARE, an adverse event (AE) or adverse reaction (AR) is a non-serious incident that relates to deviations from standard procedures or clinical complications that do not require a rapid alert because their impact on recipients is minor. Nevertheless, AEs and ARs have to be communicated in a timely

manner to the recipient centres and other institutions involved because it is not always easy to distinguish between an SAE and AE, or SAR and AR (see §15.4).

15.2.5. Vigilance

Vigilance describes the attention that should be paid to clinical situations and incidents during the course of routine work with the aim of detecting and reporting acute SAREs and AREs and thereby improving patient safety. Specifically trained professionals are crucial for the success of vigilance systems.

15.2.6. Surveillance

The term 'surveillance' denotes the follow-up of organ or tissue recipients or living donors (suffering from, or at risk of, an SARE) to provide indicators and information on stratification of risks [5]. An active surveillance system should also monitor specific, expected, serious reactions or events. Surveillance systems can highlight trends of systematic occurrences and can reveal anticipated SAREs, AEs or ARs. These should be reported to the Health Authority so that analysis of the root cause can be initiated and corrective measures can be implemented.

15.3. Setting up an effective vigilance & surveillance system

15.3.1. General organisation

National healthcare systems must provide appropriate human and technical resources for the establishment and running of an efficient V&S system.

Preferably, one specific Health Authority should be mandated to co-ordinate V&S within a given jurisdiction [3]. This authority would be the link to all parties involved and would be responsible for establishing, maintaining and regulating the system by synchronising all steps in the process.

A V&S system should be developed as a national, centralised and web-based network, integrated with other registries related to organ procurement and transplantation (deceased donor data base, waiting list, co-ordination records of deceased donors, transplant registry, living donor registry, registry of tissue establishments and its activities etc.). Modern network technologies may connect all participants associated with organ and tissue donation and transplantation.

All institutions involved in living and deceased donation and transplantation are responsible for reporting suspected SAREs, before investigation or confirmation, allowing the Health Authority in charge of co-ordinating V&S to take appropriate actions to avoid recurrence and to prevent harm to other patients. Therefore, it is recommended that every institution involved (e.g. donor hospital, organ procurement organisation [OPO], transplant centre, post-transplant care facility, laboratory, pathology unit or establishment) should take the following actions:

a. designate specialist contact persons (often called 'go-to persons') in their institution who are responsible for the notification of SAREs and for support in the investigative work-up (biovigilance correspondent/co-ordinator) [6],
b. facilitate collection of information relevant to the specific case without fear (no-blame culture),
c. co-operate fully and become involved in their individual case work-up,
d. receive a final assessment of each case they were involved in from the Health Authority and provide feedback on all lessons learned to the parties involved.

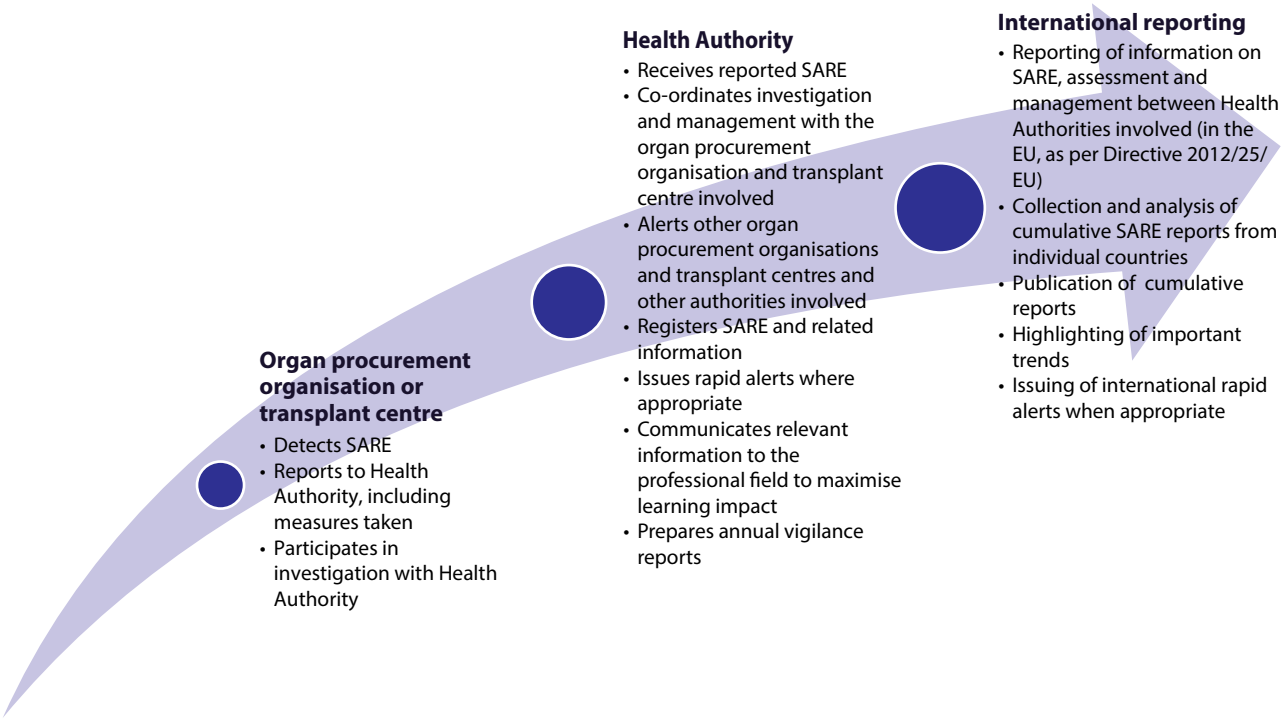
Regarding an ARE, reporting and management should be incorporated in the centre's quality-management system, with one or more operating procedures that describe the processes for acknowledgment of notifications, investigation and follow-up on corrective and preventive actions and reporting. The procedures should enable rapid action to be taken by all affected organisations in order to protect the safety of recipients. This may involve a review of patients who have received organs, tissues and cells from the same donor, and tissue or cell quarantine and recall in the event that the donor involved also donated tissues or cells.

Co-ordination between various systems of vigilance (e.g. tissue and cell vigilance, medical devices vigilance, pharmacovigilance) should be in place both at the local level (centres) and at the Health Authority level (see Figure 15.1).

15.3.2. Organisation of the vigilance system on a national level

The Health Authority ensures that a reporting system is in place for the local health professionals and local biovigilance correspondents/co-ordinators. It is recommended that the Health Authority should:

Figure 15.1. **Reporting flow for serious adverse reactions and events**



SARE: Serious adverse reactions and event.
Source: figure modified from [7].

a. provide OPOs, transplant centres and all other institutions involved in the organ donation and transplantation process with clear instructions on how to report an SARE, preferably using standardised (online) documentation (Appendix 18 provides some examples of standardised forms for the reporting of an SARE),
b. appoint qualified and trained personnel for the assessment and processing of incoming reports (available 24/7),
c. provide national protocols and standardised forms for notifications,
d. appoint qualified and trained personnel to lead and co-ordinate the investigation process and follow-up of actionable points (quality and clinical governance teams),
e. prepare national protocols for case work-up including root-cause analysis, final assessment and dissemination of findings and actions,
f. establish national expert committees to discuss and assess cases, and provide expert advice for special questions or diagnostics in difficult cases,
g. organise telephone conferences and meetings for case work-up,
h. provide and disseminate best-practice guidelines to help professionals to improve practices and avoid the recurrence of biovigilance cases,
i. support close communication between the involved institutions to collect all results relevant for objective assessment (networking),
j. support local health professionals/local biovigilance correspondents in their assessment or in their implementation of corrective measures when and as required,
k. provide ongoing updates and training on V&S for all persons and institutions involved in the process,
l. monitor and improve V&S processes,
m. analyse data and publish an annual report,
n. establish a good, trusting relationship between all parties involved to ensure a constructive process without any blame but assuring all parties involved that they will receive feedback on lessons learned,
o. close the case and prepare the final report (see §15.4.5).

15.3.3. Organisation of the surveillance system

Each Council of Europe member state should have vigilance systems designed to facilitate quick and smooth communication between Health Authorities and health professionals, establishing a vigilance network. This network should collect at least SAREs. A complementary surveillance system is integrated into the vigilance system in order to improve

the quality and safety of the donation and transplantation processes.[3]

Routine monitoring of clinical outcomes (recipient follow-up) is part of the surveillance system. Clinical teams set up registries, with follow-up on graft and recipient post-transplant as well as living donor outcomes, in order to review the results and to identify currently unknown risk factors [5]. This kind of monitoring should be complemented by an active surveillance system looking at cases with SAREs where their frequency could suggest a systematic cause. As an example, vascular complications (e.g. venous or arterial thrombosis of the graft) after kidney transplantation do occur, and they could be considered as expected adverse reactions. Although they are outside the scope of the vigilance system, because this focuses only on undesired and unexpected SARs, they should be evaluated further in order to establish whether a systematic error (e.g. incorrect handling of arteries during procurement or implantation) can be excluded as the cause.

Each team should evaluate their clinical outcomes and their results, based on local experience, and compare them with evidence from literature data, e.g. expected rate of venous or arterial thrombosis after kidney transplantation in a population of patients with end-stage renal disease, adjusted for confounders (see Chapter 17). Applying a quality-management system and risk assessment, local teams become able to identify complications at an early stage. Whenever there is the suspicion that such complications could be associated to an SARE for any reason (e.g. lack of clear protocol on how to handle multiple arteries, organ not stored in the recommended temperature range, inadequate storage system etc.), it is recommended that the Health Authorities are notified. The root-cause analysis has to be performed by the local investigation team in order to determine the reasons for this deviation and to review whether it is necessary to apply any change in the protocol to avoid more cases. This investigation falls within the framework of the vigilance system, which aims to trigger corrective measures and to improve quality of care to patients, but such surveillance should also identify whether good results are achieved by risk-avoiding behaviour of an institution or the application of true best clinical practice (see Chapter 17).

Such cases can then be registered and monitored by healthcare professionals. Quality-monitoring tools have been developed in recent years to facilitate quality assessment regarding the outcomes of grafts used for transplantation. For example the cumulative sum technique (CUSUM) provides charts that are intended to track performance in near real-time at a single institution. This enables users to flag criteria about graft failure and vigilance issues.

The widespread use of active surveillance systems will be a step-by-step process that still requires healthcare professionals to obtain a consensus view on some important points, such as the definitions of serious adverse reactions and events, and a description of their appropriate monitoring. However, willingness to systematically monitor daily practices and enhance awareness of the risk of SAREs or AREs may be a first approach.

15.4. Procedures in organ vigilance

15.4.1. Detection of cases

Effective V&S relies on all healthcare professionals involved, from procurement to transplantation, namely:

a. donor and transplant co-ordinators and staff of OPOs;
b. staff at organ allocation offices;
c. surgical and clinical staff involved in procurement of organs;
d. transplant professionals;
e. all other staff involved in any procurement and transplant activities, e.g. staff from donor hospitals, testing laboratories, pathology departments and tissue establishments (in case of combined tissue/organ donation);
f. staff of other vigilance systems (e.g. tissue and cell vigilance, material/device vigilance, pharmacovigilance, etc.) when issues of concern are detected that might have an impact on the safety of organs for transplantation.

For effective detection of biovigilance cases, all relevant stakeholders must be aware of their responsibilities for identifying errors or unexpected results/outcomes as well as 'near misses' (see §15.2).

Although there is an international consensus on the conditions that qualify adverse events as SAREs [3, 5], a thin line between serious and non-serious events still exists, requiring a case-by-case analysis.

3 To quote Directive 2010/53/EU, 'besides the system for reporting serious adverse events and reactions, the collection of relevant post-transplantation data is needed for more comprehensive evaluation of the quality and safety of organs intended for transplantation' [3]. The same practice is recommended to all Council of Europe member states.

15.4.1.1. *Examples of serious adverse events*

The non-exhaustive list below enumerates conditions reportable as SAEs [5]. It aims to avoid overburdening the organ donation and transplant system with unnecessary reports, while preserving the principles of V&S at a high level:

a. Inappropriate organs were distributed for transplant, even if not used (the event has a potential impact on patient safety or organ quality, even if identified before the transplant). Examples:
   i. Loss of organ, or inappropriately procured or preserved organ is delivered, but the patient is not under anaesthesia; it is an SAE because there was no harm to the intended recipient.
   ii. Inappropriate characterisation of donor or organ.
   iii. Inappropriate transmission of information related to screening of donors for HCV, HBV or HIV infection, or donor ABO group.
   iv. Inappropriate preservation of an organ (e.g. prolonged storage or inadequate temperature).

b. Inappropriate organs were used for transplant. Examples:
   i. Infection or positive serological status discovered in an organ donor (deceased or living) after at least one organ was transplanted (reporting can be limited to those conditions that would have prevented transplant of the organ, or would have re-allocated it, had they been known in advance).
   Example: HCV NAT-reactive in an anti-HCV non-reactive donor identified after the transplantation of at least one organ.
   ii. Malignancy discovered in an organ donor (deceased or living) when at least one organ has been transplanted.
   Examples: Autopsy reveals a glioblastoma multiforme in a donor whose cause of death was spontaneous intracranial bleeding, after organs have been transplanted; or renal cell carcinoma is identified during examination of the procured kidney shortly before implantation.
   iii. Any other potentially transmissible disease discovered in an organ donor (deceased or living) when at least one organ has been transplanted.
   Example: Metabolic disease in the donor undiagnosed at the moment of organ transplantation.

c. Event that could have implications for other patients or donors because of shared practices, services, supplies or donors.

Non-compliance with the operating procedures in place should be documented and investigated as part of the internal quality-management system. On occasion, however, a particular non-compliance may be of such importance that it should be considered as an SAE and reported through the vigilance system.

Some situations are undoubtedly SAEs. Some situations may not have been clearly identified as SAEs at the time of transplantation, such as microbiological results of organ preservation/transport fluid or donor broncho-alveolar lavage. The results are available after transplantation and they are not always easy to interpret; in any case they must be forwarded to the different transplant teams for correct interpretation in the context of their own recipients. Each result should be evaluated case by case by the staff involved together with the Health Authority in order to determine whether it could be classified as an SAE (e.g. fungi, aggressive pathogens etc.) or not, in order to avoid over-alerting: initial unfiltered reporting of all findings to the national Health Authority enables the experts to select the relevant ones for alerting all other professionals involved, but this may also cause confusion and increases the risk of inappropriate handling of serious incidents compared to non-serious ones. For example, the national Health Authority should not screen all microbiological results received as there will never be sufficient information at that point to make such decisions. The work in progress is to work very hard with the microbiology laboratories so that microbiologically relevant organisms are reported, allowing cascading of results by the national Health Authority to all other centres involved. However, as there is no consensus currently, we should be careful not to cause instability and distraction, thus increasing the risk of errors.

The following examples are **not** SAEs. After the transplant, several results are obtained from an organ donor retrospectively, such as

- anti-*cytomegalovirus*-IgG
- anti-Epstein–Barr virus-IgG

– both of which are very often positive, denoting previous exposure to these viruses and usually requiring preventive intervention in recipients (see Chapter 8). These results are not required for organ acceptance and are used to inform recipient management. Therefore they must be communicated to the transplant team for complete donor characterisation but they do not need to be reported to the biovigilance system, unless there is specific reason to do so (e.g. newly detected pan-resistance of the virus against antiviral agents).

15.4.1.2. *Examples of serious adverse reactions*

The non-exhaustive list below enumerates conditions reportable as SARs [5]. Again the challenge for healthcare professionals exists to distinguish between serious and non-serious cases as outlined in section 15.4.1.1. In contrast to an SAE, in an SAR harm to the recipient or living donor must or may have occurred:

a. Immunological reactions that are beyond the inherent known risk of the transplant procedure. Example: Any medical condition due to an unintended ABO-incompatible transplantation.

b. Interruption of a transplant procedure involving unnecessary exposure to the risks associated to it. Example: an inappropriately procured or preserved organ is delivered, where the problem is detected once the potential recipient has been at least subjected to anaesthesia. This would be an SAR because the patient is already exposed to the risk of anaesthesia for major surgery.

c. Unexpected disease in an organ transplant recipient that might be donor-transmitted. Examples: Unexpected infection or serological conversion, unexpected malignant disease transmission, unexpected metabolic disease suspected to have been transmitted through liver transplant.

d. Death of a recipient that might be the consequence of an SAR related to the donor or the donation process.

e. Graft loss that might be related to the donor or the donation process (including a prophylactic graftectomy) once the potential recipient has been at least subjected to anaesthesia.

f. Death of a living donor as a consequence of donation.

g. Serious (surgical and/or non-surgical) complication in a living donor that is related to the donation procedure.

The following examples are **not** SARs. Symptoms such as

- fever,
- bleeding,
- positive cultures

may be found in the post-operative period with very clear recipient-related causes and might be regarded as normal evolution of the transplantation itself. Not all such occurrences need to be communicated, especially when there is no suspicion of donor origin or of a process error as root cause. Nevertheless, they need appropriate monitoring and a case-by-case assessment. Therefore, protocols in place are extremely useful in these circumstances. Independently of the V&S system for tracking SAEs or SARs within the donation and transplantation processes, the healthcare facility should monitor such complications within an internal V&S system in order to identify systematic errors (see §15.3.3).

As adverse transplant outcomes are most likely a result of a combination of multiple risk factors associated with the surgical procedure itself, the recipient's underlying clinical condition, chronic use of immuno-suppression or other donor risk factors, clinicians might not consider the transplanted organs as a possible source of the adverse outcome in a case-by-case analysis. Health Authorities in charge of co-ordinating vigilance, organ procurement and exchange organisations, should encourage procurement and transplant professionals to carefully consider whether adverse outcomes might have been associated with the donation process or with the transplanted organ: then similar incidents might be prevented in the future or actions could be taken to mitigate the (risk of) harm to other recipients from a common donor. Occasionally incidents are identified quite late (days to years) after the implantation of a graft, which requires a good understanding of the pathogenesis and the epidemiology of the given condition causing the incident. If in doubt, it is prudent to obtain a second opinion and to consult with specialists (preferably via the network of the V&S system).

15.4.2. Reporting of cases

Ideally all AREs should be reported, but in many countries this is not mandatory.[4] Nevertheless, professionals should be encouraged to monitor all kinds of suspected AREs (serious and non-serious), so that incidents that are considered serious can be filtered out and reported to the Health Authority in charge of co-ordinating the V&S system. When an active surveillance system is set up, healthcare professionals should monitor the occurrence of some SAREs and the risk factors contributing to this. Standardised reporting forms should be provided by the national Health Authority (see §15.3.2 and Appendix 18) because all notifications must be made in written form after proper initial rapid alert, in order to avoid miscommunication and misunderstandings.

The minimum data set to be reported is an initial report [5, 8] that includes the following:

4 In EU countries, Directive 2010/53/EU requires mandatory reporting only for SAREs.

a. Reporter: identification, function, institution, contact data;

b. Recipient/organ: recipient number/identification (if applicable), type of organ(s)/tissues (identification number), location (e.g. left/right);

c. Donor: donor number, date of donation, donor region/country;

d. SAE/SAR: start date, detection date, description (nature, severity, characteristics, evidence of findings), related phase of the process and origin of the event (organ defect, equipment failure, human error, other); in the case of an SAE, original test results, corrective measures taken in order to avoid recurrence, course and outcome.

It is also recommended that healthcare professionals submit interim reports when relevant new data come up and final reports when work-up has been finalised, with a recommendation for further surveillance of recipients if indicated.

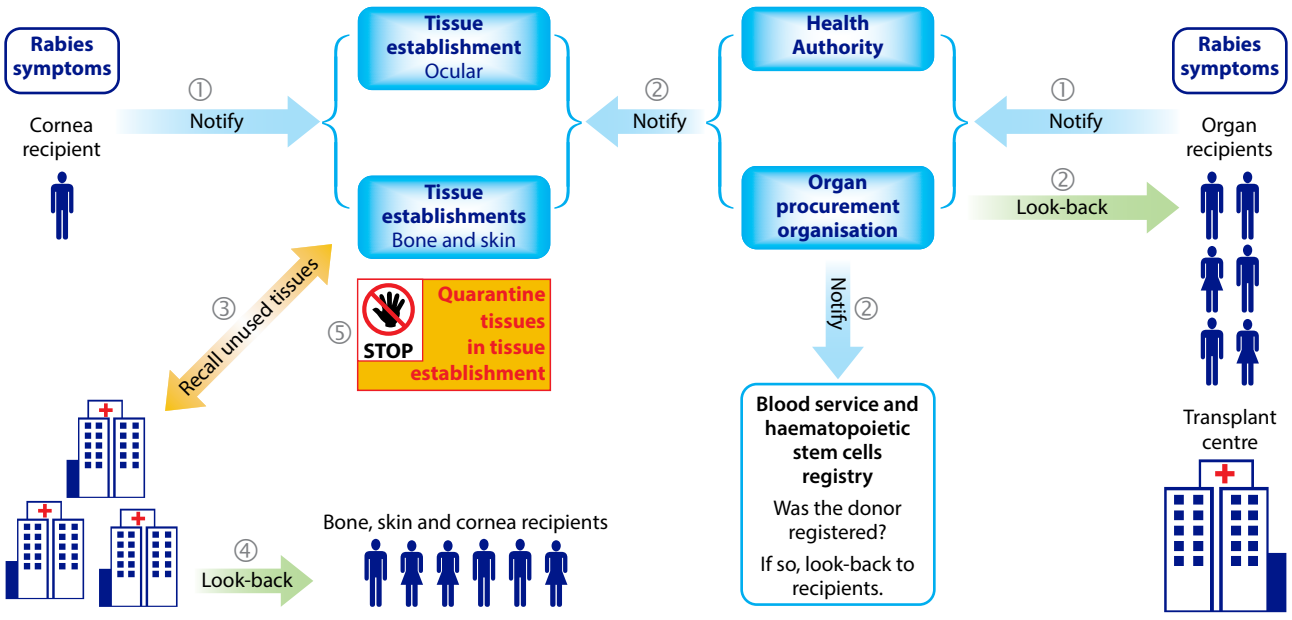
The healthcare professionals responsible for local biovigilance issue an initial report at an early stage after detection and without delay. This report has to be sent to the Health Authority in charge of the V&S system without delay (even if some information or test results are pending) in order to allow prompt forwarding of all rapid alerts to all recipients of the particular donor involved, in case of any SARE.

In cases of international organ exchange – especially when language barriers may interfere – all data and test results should be provided also in English language to avoid any misunderstanding. (For the timeline of reporting, see §15.4.3.)

15.4.3. Rapid alert

All suspected SAREs should be reported promptly by professionals by means of rapid communication and notification, based on appropriate preliminary data before investigations are finalised or confirmed. This enables healthcare professionals in charge of any other recipients of grafts from the same donor, beyond the scope of the case being reported, to initiate precautionary actions preventing avoidable harm to other patients. A 24/7 contact organisation has to be in place in order to ensure proper transmission of medical information. Such rapid alerts are essential for the healthcare professionals in charge to assess the relevance of the information received and the impact on their patients, and for setting up corrective measures if necessary (e.g. intensified monitoring only or pre-emptive antimicrobial treatment of the recipient in response to microbiological culture positive results from a sterile area, e.g. swab of inner organ packing). Depending on the kind of SARE, its circumstances and its impact on harm to the recipients, the experts receiving the initial report should decide immediately on the extent and timeframe acceptable to inform everyone properly (see figures 15.2 and 15.3).

Figure 15.2. **Actions that must be taken in the case of a report of suspected transmission of disease from a deceased organ and tissue donor (e.g. rabies)**



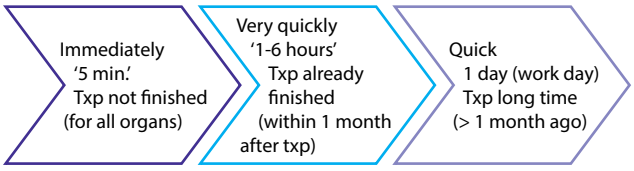
A recent publication has confirmed again that there is a significant association between the intensity of adverse outcomes in cases of a proven or probable donor-derived disease transmission (SAR) and the delay in communicating the event [9]. The failure to link the incident as early as possible to a (suspected) donor-derived disease transmission is the major reason for causing the death of the recipient in the worst case, due to incorrect clinical management based on missing information.

Figure 15.2 illustrates a scenario of actions that need to be taken in the case of a report of suspected transmission of disease (e.g. rabies) from a deceased organ-and-tissue donor: a complex network of institutions involved in organ transplantation and tissue use has to be considered, including look-back studies if indicated.

In some circumstances, a particular SARE will require rapid communication nationally or internationally to facilitate urgent actions, such as a recall of products or critical materials (e.g. contaminated preservation liquids). These rapid alerts beyond the scope of informing transplant centres and tissue establishments should only be issued in exceptional circumstances. The following criteria have been identified in the SoHO V&S project [10] as triggers for rapid alerts:

a. an ARE of a serious or potentially serious nature;
b. potential risk to other individuals, tissue establishments or institutions;
c. wider public health implications;
d. rapid intervention needed (preventive/corrective measures, urgent communication).

Figure 15.3. **Eurotransplant proposal for alert/rapid alert of an incident that might relate to an SARE**



Txp: transplantation. In the EU, specific procedures have been set down by the European Commission in Implementing Directive 2012/25/EU [11].

Where SAREs are detected in relation to organs that have been exchanged internationally, appropriate cross-border collaboration should ensure that all stakeholders in all countries involved are informed and collaborate in the investigation and follow-up actions. Figure 15.3 shows an example of proposed time frames for alerts (or rapid alerts) of transplant centres involved in the donation–transplant process when an incident has occurred that might be related to an SARE.

15.4.4. Assessment of serious adverse events or reactions

SARs and SAEs are assessed by the same procedure. During this procedure, an SAE might need to be reclassified as an SAR, or vice versa, depending on the data coming in and providing a new base of evidence.

For example, a donor has been tested negative for hepatitis C virus (HCV) antibodies, and all organs have been transplanted based on this knowledge. When afterwards a proper donor specimen is tested positive for hepatitis C virus (HCV) antibodies then, despite confirmation being still awaited, an SAE exists because of the potential risk of HCV transmission to any recipient. If at least one recipient develops symptoms of an HCV infection and this is linked to the donor, the SAE becomes an SAR. Whether this should be the time point when the recipient needs medical care because of symptomatic infection, or whether it should be when HCV-viraemia is measured for the first time, is a different issue. If, later on, confirmatory testing excludes HCV infection in the donor and complementary testing of all other recipients excludes HCV infection in the recipients too (by NAT, see Chapter 8), then the SAR and SAE may be unrelated to the donor. At this point all centres involved should concur on how to proceed since experts may advise that these findings do not rule out donor HCV infection in the eclipse period (see Chapter 8).

The above example illustrates that it is important to connect all relevant teams, professionals, experts, tissue establishments and others in a network for the proper exchange of information and for clarification of which preventive measures are deemed appropriate to prevent further harm to recipients, and how this is to be done (see §15.4.3). Classifying the above-mentioned case – as AE, SAE, AR, SAR or none – depends on the assumed imputability, as discussed below. Whenever there is a suspicion of an SARE, the case has to be managed by a multidisciplinary team co-ordinated by the corresponding Health Authority responsible for vigilance, with one person responsible for the case. If indicated, other specialists, e.g. microbiologist, oncologist, pathologist, should be consulted to take prompt and effective action. Although biovigilance is a retrospective risk-assessment analysis, all knowledge obtained may help to establish evidence for future advice, recommendations and guidelines.

Table 15.1. **Severity scale for adverse reactions and events**

Severity	Comments
Nil	no harm, no risk, patient not informed as there was no risk of harm
Non-serious	mild clinical/psychological consequences, with no need for hospitalisation and no anticipated long-term consequence/disability
Serious*	• hospitalisation or prolongation of hospitalisation, and/or • persistent or significant disability or incapacity, or • medical or surgical intervention to preclude permanent damage, or • transmission of a severe disease or prolongation of a disease
Life-threatening*	• the need by a living donor or transplant recipient for a major intervention (vasoactive drugs, intubation/mechanical ventilation, admission to intensive care) to prevent death, or • transmission of a life-threatening disease
Death*	death

* Mandatory reporting to the Health Authorities as SARE according to national regulation in the European Union.

Source: adapted from EUSTITE and SoHO V&S [14, 7].

Table 15.2. **Scale describing possible outcomes of an imputability investigation**

Grading	adapted from EUSTITE and SoHO V&S [10, 14, 7]	Criteria for infectious and malignant transmissions, adapted from the US Disease Transmission Advisory Committee [15]
Not assessable	Insufficient data for imputability assessment	Insufficient data for imputability assessement
0: Excluded	Conclusive evidence beyond reasonable doubt for attributing an adverse reaction to alternative causes There is evidence clearly in favour of attributing the adverse reaction to other causes than the process or transplanted organ.	Suspected transmission and fulfilment of at least one of the following conditions: • Clear evidence of an alternative cause; • The appropriate diagnostic tests performed have failed to document infection by the same pathogen in any transplant recipient from the same donor; • Laboratory evidence that the recipient was infected with the same pathogen or had a tumour before transplant.
1: Possible	The evidence is not clear for attributing the adverse reaction to the process or transplanted organ, or to alternative causes.	Suspected transmission and • Laboratory evidence of the pathogen or tumour in a single recipient or • Data suggest transmission but are insufficient to confirm it.
2: Probable	The evidence is clearly in favour of attributing the adverse reaction to the process or transplanted organ.	The following two conditions are met: • Suspected transmission and • Laboratory evidence of the pathogen or the tumour in a recipient. And it meets at least one of the following conditions: • Laboratory evidence of the same pathogen or tumour in other recipients; • Laboratory evidence of the same pathogen or tumour in the donor; If there is pre-transplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplant.
3: Definite; Certain	The evidence is conclusive beyond reasonable doubt for attributing the adverse reaction to the process or transplanted organ.	All the following conditions are met: • Suspected transmission; • Laboratory evidence of the pathogen or the tumour in a recipient; • Laboratory evidence of the same pathogen or tumour in other recipients (if multiple recipients); • Laboratory evidence of the same pathogen or tumour in the donor. If there is pre-transplant laboratory evidence, such evidence should indicate that the same recipient was negative for the pathogen before transplant.

The above-mentioned example also indicates that such an assessment becomes possible only with the support of experts, in this case infectious disease experts. During such investigations, the availability

of appropriate donor specimens, safely stored, is necessary to perform proper additional tests (see §8.2 to §8.3 and §15.4.6).

The process of SAE or SAR assessment itself can be split into five steps:

1. grade the severity of the event or reaction,
2. assess imputability,
3. assess likelihood of recurrence,
4. assess impact and consequences,
5. decide the level of response.

These five steps, which are discussed below, are partly based on the US DTAC decision tree [12-13], a comprehensive tool for assessing imputability (step 2), and on the EUSTITE impact-assessment tool in Appendix 19. The EUSTITE tool covers steps 3, 4 and 5, but it also includes step 1 because the severity of the incident is considered as part of the impact assessment. Whatever scheme is in use, it is self-evident that revision of the initial assessment becomes necessary each time relevant new data become available.

15.4.4.1. *SARE assessment, first step*

The severity of the event or reaction has to be determined (see Table 15.1). A severity scale should be used to grade the case as an ARE or SARE. The EUSTITE and SoHO V&S projects [14, 7] proposed a severity scale for vigilance in tissue and cell transplantation, based on the experience of vigilance applied to blood products. This scale can be used for organs too. At least in case of an AR or SAR, complete tracing of organs or all products and substances of human origin (SoHO) of this donor is required, e.g. recipients of the other organs or tissues, material still stored in tissue establishment (see Figure 15.2).

15.4.4.2. *SARE assessment, second step*

Imputability has to be assessed: is the donor responsible, or what happened during the procedure? In the case of an event, if no damage has occurred to any recipient yet, imputability cannot be assessed. In the case of a reaction, assessment of imputability becomes difficult without support from other experts in the field.

All ARs should be graded in terms of imputability using the scale provided by the EUSTITE and SoHO V&S projects [14, 7]. A version of the scale adapted to organ transplantation is shown in Table 15.2.

Table 15.2 includes also the approach to establishment of imputability for suspected donor-derived disease transmissions (infections or malignancies), as proposed by Garzoni and Ison [15]. Other methods to assess imputability exist [12-13]. There exists an overlap in all approaches on how to draw final conclusions. Common to all approaches is that the evaluation of imputability should be based on correct, evidence-based clinical and scientific knowledge. It might be helpful to use other resources as support in individual cases. For example, the ongoing Notify project [16] summarises cases with adverse reactions and events in organs and all other substances used which are of human origin (see §15.5); epidemiological data are supplied by the European Centre for Disease Control (ECDC), the World Health Organization, the Centers for Disease Control and Prevention in the United States, and other national and international institutions.

Imputability grades might change in the course of an investigation. They should be assigned at least during initial notification and again after completion of the AR investigations. Whenever an imputability grade is changed, then an explanation might be helpful.

15.4.4.3. *SARE assessment, third step*

For every AE or AR, the likelihood of recurrence in the future should be discussed and graded according to a scheme like that of the EUSTITE and SoHO V&S projects; see Table 15.3 [14, 7]. This issue has an impact on the final risk assessment and on future management processes in the healthcare system.

Table 15.3. **Assessing the likelihood of recurrence of an adverse reaction or event**

Likelihood of occurrence/recurrence of the ARE		
1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to occur again
3	Possible	May occur occasionally
4	Likely	Expected to occur again, but not persistently
5	Probable	Expected to occur again on many occasions

Note: The score for likelihood of recurrence (in the most left-hand column) should be entered in the impact matrix of Table 15.5.

For example, if a recipient died after organ transplantation due to an incompatible blood group match because this information was transmitted orally, then we can see, following the guidance in Table 15.3, that a recurrence of this 'extreme reaction' is more than possible. This conclusion will influence the fourth and fifth steps of the assessment as outlined below. Here corrective measurements will become necessary.

In order to avoid any high-probability recurrence of an SARE, the Health Authority can dissemi-

nate guidance or recommendations for improving the healthcare practice of professionals and organisations.

15.4.4.4. *SARE assessment, fourth step*

The impact and consequences of SARE should be assessed (see Table 15.4); for this purpose, a system based on the EUSTITE and SoHO V&S projects is recommended [14, 7]. The intention is help OPOs, transplant centres and Health Authorities responsible for SoHO to decide on the level of response that might be appropriate, depending on the impact score that is given to a specific case.

The impact can be divided into three categories: the individual, the system and the organ supply. For each category the impact may be assessed at different levels.

For example, the impact can be serious in the individual – e.g., death after virus transmission in the window period – while it is minor or moderate for the system and for organ supply, e.g., when virus infection is of low prevalence, so the event gains low publicity in the mass media without fear being transmitted to society and no transplantation procedure being cancelled. In contrast, the impact in the three categories is different for Zika virus infection when considering the issue of vigilance for blood products (see Chapter 8).

For safety reasons the worst-case scenario for each of the three categories should be considered before further conclusions are reached.

15.4.4.5. *SARE assessment, fifth step*

The two-dimensional impact matrix developed by the EUSTITE and SoHO V&S projects is designed to help Health Authorities responsible for monitoring biovigilance in SoHO to define the level of response that might be appropriate, depending on the final impact score (see Table 15.5). The likelihood of recurrence and impact of recurrence are considered as interacting factors. The response of a Health Authority to a specific SARE should be proportionate to the potential impact, as assessed by the matrix shown in Table 15.5. The following guidance may contribute to the further management of a specific SARE:

a. For values in the range of 0 to 3 the Health Authority is to file the report and keep a watching brief while the parties involved should manage the corrective and preventive actions.

b. For values in the range of 4 to 9 an interaction is required between the parties involved and the Health Authority, which may request an inspection that focuses on the SARE with the corrective and preventive actions to be followed up, including evidence of effective recall, where necessary. Written communication to professionals working in the field might be appropriate.

c. For values in the range of 10 to 20 the Health Authority will, in general, designate representatives to participate in developing or approving the corrective and preventive action plan (possibly a task force to address broader implications). Inspection, follow-up and written communication should be done as at the previous level; and possibly notification of Health Authorities in other countries where relevant.

d. It is important to note that the final impact score must be adjusted for confounders not covered by the assessment tool. Then the final score should be downgraded or upgraded, accompanied by a report explaining this deviation based on proper evidence. In the setting of organ transplantation, such deviations must be expected. This will require continuous research on how recommendations are to be adjusted (see §15.3.3).

- Example: in the case of an organ transport fluid contaminated by bacteria sensitive to almost all antibiotics, the likelihood of recur-

Table 15.4. **Assessing impact/consequences of an adverse reaction/event should it recur**

Impact level		On individual(s)		On the system		On organ supply
0	Insignificant	Nil	OR	No effect	OR	Insignificant
1	Minor	Non-serious	OR	Minor damage	OR	Some transplantations postponed
2	Moderate	Serious	OR	Damage for a short period	OR	Many transplantations cancelled or postponed
3	Major	Life-threatening	OR	Major damage to the system – significant delay to repair	OR	Significant cancellations of transplantations
4	Catastrophic/extreme (or Severe)	Death	OR	System destroyed – need to rebuild	OR	All transplantations cancelled

Note: The score for impact level (in the leftmost column) should be entered in the impact matrix of Table 15.5.
Source: adapted from EUSTITE and SoHO V&S [14, 7].

rence will be 'certain' and the impact of recurrence will be 'minor' because most recipients will be receiving prophylactic antibiotics at implantation. Nevertheless, it is possible that the profile of the perioperative antibiotic prophylaxis might not cover the specific pathogen and this could cause severe infection in the immunosuppressed recipient. Therefore, the impact of pathogens found in such conditions might equally be assessed as either 'moderate' or 'major'. This increases the impact score significantly, which might result in overestimation of the risks, even though the individual components of the matrix have been assigned correctly. In such cases, investigators should explain the issue clearly and could consider downgrading the impact score while performing root-cause analysis about contamination of organ transport fluids.

The response to a specific SARE should be proportional to the potential impact as described by the impact matrix in Table 15.5. The future impact may be decreased, either by reducing the likelihood of recurrence through preventive measures (horizontal axis) or by reducing the impact of any recurrence (vertical axis) by increasing the detectability of a risk factor or by improving the treatment options available.

Table 15.5. **Impact matrix**

Likelihood of recurrence → / Impact of recurrence ↓	1 Rare	2 Unlikely	3 Possible	4 Likely	5 Certain/almost certain
0 Insignificant	0	0	0	0	0
1 Minor	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Major	3	6	9	12	15
4 Catastrophic/extreme	4	8	12	16	20

Source: EUSTITE and SoHO V&S projects [14, 7].

The impact matrix may be useful in haemovigilance and biovigilance of tissues and cells – where processing of material of SoHO exists. In the case of human organ transplantation, the usefulness of such a matrix has to be evaluated because too many confounders exist: therefore it is recommended that the contribution of such an impact matrix should be evaluated for a defined time period (e.g. three years). After the evaluation period it must be decided whether modifications have become necessary, or not, and whether such a matrix should be used at all.

15.4.5. Final report

At the end of an investigation, the outcomes – along with details of the feedback, root-cause analysis and further surveillance of the case – have to be summarised in a final report by the Health Authority in charge of V&S. The report must be sent to all recipient centres and institutions involved in the specific case and it must communicate preventive and corrective measures. This information should be disseminated in order to prevent recurrence of the same biovigilance case and to be used as learning experiences. In best practice this is a consensus document supported by all parties and stakeholders involved.

The final report should include the following minimum data:

a. Reporter: identification, function, institution, contact data;
b. Report identification: confirmation date of the SARE, confirmation of identification number, confirmation of SARE, any change of type of SARE and (if so) specify the change;
c. Clinical outcome (if known): complete recovery, minor sequelae, serious sequelae, death;
d. Outcome of the investigation and final conclusions, root-cause analysis (details for SAE);
e. Recommendations for preventive and corrective actions.

15.4.6. Archive of appropriate donor specimen

It is highly recommended that frozen serum (and/or cells or DNA) samples are stored from every donor for the sole purpose of vigilance investigations (see Chapter 6). Sometimes it is necessary to repeat a previous blood test with other methods, either to confirm a result or to apply a new test with higher sensitivity and specificity for a particular question. For these reasons, having access to the donor serum archive is mandatory but without wasting material for inappropriate investigations. National legislation must ensure that all necessary measures are implemented to make such an archive available (including funding and maintenance in the long term). The system may differ from country to country, and donor co-ordinators should become familiar with the process by which the serum archive is managed for each donor in their own country. Also, the recipient's pre-transplant specimen (e.g. serum) should be stored to allow investigations needed to provide proper evidence for imputability assessment [7]. For analysis of donor-derived disease transmission due to a suspected malignancy, see section 9.8.

15.5. Vigilance communication

Effective communication of the results of vigilance systems is fundamental to ensure that the benefits of these programmes are realised in practice. Regular feedback to the health professionals involved is critical in supporting continued ARE notification.

In parallel with distributing information about SAEs or SARs across the network of stakeholders who are collecting the data and interpreting the facts, there should be tactful communication with recipients, living donors or donor family. Protocols should be set up for how and when to communicate with them, and who is responsible for doing this. In too many cases, the healthcare professionals are concerned merely with the medical case without taking into account, for example, the recipient's right to be informed in the gentlest manner about any undesired event or reaction. Consequently, unproven data and rumours can be discussed in hospitals and (deliberately or not) reach the recipient. Healthcare professionals should be aware that this kind of communication might cause severe consequences for the recipient, living donors, donor family or even for the donor programme in general. Health professionals have a duty of candour to patients, and transparency is part of their professional code of conduct. Proper communication should be based on face-to-face meetings led by competent experts, with help from specialists involved in the case in order to interpret the event or reaction in the correct manner without over- or underestimating the situation.

Furthermore, publication of the biovigilance investigation and its results, including corrective measures, is also crucial for improving quality and safety in the field. The publications should be prepared without disclosure of any personal information and without identifying individual centres, hospitals or individual people. Those centres directly involved in specific incidents should also consider publishing their experience to alert others to the means by which they detected and confirmed the event or reaction.

The Notify project is an initiative launched by the WHO, and supported by the Italian National Transplant Centre (CNT), that gathers information on documented types of adverse occurrences in transfusion, transplantation and assisted reproduction, and reviews the cases to identify general principles of detection and investigation. The database that has been constructed from the information gathered is openly accessible on a dedicated website [16]. The database will be maintained and updated on this platform and is intended as a communication hub for institutions and organisations worldwide collaborating in the facilitation of access to V&S information to improve safety and quality, and consequently efficacy. It is also intended to add didactic value to cases describing SAEs and SARs, for the benefit of individual healthcare professionals.

15.6. Registry and archive of information

All SARE cases with their datasets and accompanying reports should be properly registered and archived in a way that allows review in the future if it is necessary. This documentation could be part of the quality-management and quality-control documentation of the health establishment. The archiving documentation must also fulfil the requirements of any general rules for protecting personal and other medical data and national requirements if they exist.

15.7. Traceability, audit and record keeping

It is the responsibility of the national Health Authority to organise the system for ensuring quality and safety with the obligation of reporting all necessary data related to quality. The authority responsible for SoHO should issue appropriate guidance for the collection of relevant post-transplant information to evaluate the quality and safety of the organs transplanted. Any required follow-up will normally be considered as completed only when the SAE and SAR data are finalised.

More specific requirements for information about traceability, auditing and record keeping should be defined by national legislation, in the framework of the quality-management system of the health establishment, and included in the informatics system for donor and transplant programmes. Organising a transparent system, ensuring traceability, quality and safety and including the most important ethical principles, is a basic obligation of the Health Authority. How to include registration and archiving of SAE and SAR data depends on the individual approach of the country and its Health Authority, but it is highly recommended to work on this issue in co-operation with other countries, especially if the country is exchanging organs with other countries.

15.8. Education and training

All stakeholders, the Health Authority, OPOs and clinicians at transplant centres should promote a culture that encourages reporting in a non-punitive context for the benefit of patients and donors. It

should be accepted that mistakes happen and that no programme of transplantation is risk-free. Programmes of training and awareness should be organised to encourage reporting and to provide guidance on how to report and what information is needed. The message that reporting and disseminating V&S information can result in positive improvements for donors and patients should be promoted.

A high-quality educational programme with well-organised workshops is essential to run a functional biovigilance system. It is clear that functional biovigilance systems should be put in place at national and/or international level, depending on the system of organ allocation and exchange.

Consequently, the educational programme should be prepared and performed in co-operation with other countries involved in the system and/or it should be based on benchmarking. Given the very broad network of experts involved in reporting SAEs and SARs, the educational programme should include as many congresses and conferences where transplant medicine is discussed as possible, as well as specific workshops and seminars dedicated to the topic.

Notably a no-blame culture needs to be promoted and disseminated to clinicians and other healthcare professionals responsible, following WHO principles.

15.9. Surveillance for new risks (horizon scanning)

Horizon scanning is an integral part of risk surveillance. V&S programmes should include an activity of scanning for new risks that have not previously been recognised. New risks may be related to new donors, new techniques, new medical devices (including new ancillary products) or new reagents to which cells or tissues can be exposed during processing.

Newly emerging or re-emerging infectious diseases, for which targeted testing can be performed or which might imply the need for individual risk assessment of certain donors, represent an example of one type of risk that can be identified through monitoring of trends. The ECDC monitors the epidemiology of diseases in Europe and publishes a weekly Eurosurveillance report that provides useful data to support the basis for donor selection. Moreover, the ECDC has been recently mandated to provide risk assessment of particular epidemic agents, infectious diseases and new *in vitro* diagnostic techniques in the field of tissues and cells. An example of relevant surveillance is the mosquito monitoring in Europe by the ECDC for the detection of potential risks due to emerging vectors and implications for transmission risks (see Chapter 8).

15.10. Conclusions

V&S is a necessary element in optimising organ donation and transplant programmes, from donation to transplantation and follow-up care of transplant recipients and living donors. It includes alertness to the risks and systematic management of undesirable outcomes in both donors and recipients. V&S is a safeguard for donors, patients, health professionals and Health Authorities. V&S systems facilitate the monitoring of adverse occurrences, leading to preventive and corrective measures and to an overall improvement in safety and quality.

The reporting, investigation and management of biovigilance cases are critical in preventing recurrence of the problems, so V&S systems must promote a no-blame culture. The results of investigations should always be shared with the donation and transplant community. In fact, this sharing is a key element of any V&S system. It represents important learning opportunities that can help all OPOs, transplant centres and staff to improve their processes and to achieve higher levels of safety and quality [1-2], leading to prevention of harm in patients exposed to risk.

15.11. References

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Related material

- Appendix 18. Biovigilance standardised notification form for adverse events and reactions (France, English-language version)
- Appendix 19. Impact assessment tool for adverse events and reactions (Eustite and SoHO)

Chapter 16. Achieving and measuring quality in organ donation and transplantation

16.1. Introduction

This chapter outlines the general principles of quality management systems in organ donation and transplantation. It is addressed to Health Authorities, managers and health professionals directly involved in the process, with a special emphasis on donation and transplantation co-ordinators because they are central actors, involved in many steps in the chain from donation to transplantation. Moreover, because donation/procurement and transplant activities involve different aspects, different organisations and different health professionals, quality management is examined separately for these two types of activity.

After introductory remarks on quality management in general, and quality management applied to organ donation and transplantation in particular, this chapter provides separate reviews of government and Health Authority responsibilities, quality management in organ donation and finally quality management in organ transplantation.

16.2. General introduction to quality management

The quality of healthcare has always been a major concern for healthcare professionals who, in one way or another, even without using any specific or recognised methodology, have striven to achieve excellence in their work. That commitment is part of the job.

The development of instruments that enable quality to be measured has been essential in turning this concern into a way of working. Once it became possible to measure – or evaluate – quality, the focus shifted from quality control to quality assurance and, since the 1990s, towards continuous quality improvement.

As well as a commitment to excellence, continuous quality improvement requires a method. The aim is to continuously improve a process in an organisation for the purpose of fulfilling or even exceeding the (internal and/or external) customer's expectations and requirements. This can be achieved through quality management systems, these being any systems that help an organisation to establish the methodology, responsibilities, resources and activities needed to obtain good and measurable results.

Well-established models for quality management used in the healthcare sector are ISO (International Organization for Standardization), JCAHO (Joint Commission on Accreditation of Healthcare Organizations), EFQM (European Foundation for Quality Management) and KTQ (Cooperation for Transparency and Quality in Healthcare) [1-4]. A comparison of these models reveals the following:

a. There are few philosophical differences. All have the 'customer' as the focus of the organisation and of the quality.

b. In terms of practical application, all four models involve a monitoring scheme. The actual situation is compared with pre-established stand-

ards (ISO and JCAHO) or criteria (EFQM and KTQ) to identify where improvements need to be made within the aspects assessed in the respective models; problems then have to undergo cycles of improvement if the models are actually to be of use in the dynamics of quality improvement.

c. Although the JCAHO and KTQ models are the ones specific to healthcare services, the other two, which are either of generic or industrial origin, have tried to produce specific adaptations for healthcare services. In fact, since 2012 ISO has had a new standard specifically on quality management systems in healthcare services.

We can say that all four models can be facilitators of commitment to quality and may be used in the healthcare sector. However, their wider diffusion at international level and specific design directed at healthcare services make ISO and JCAHO the two most used models. In some European countries several donation and transplantation programmes have already been accredited (e.g. Spain: ISO 9001 accreditation).

16.3. Applied quality management in organ donation and transplantation

As in other healthcare activities, careful attention must be paid to all quality aspects of the entire process from donation to transplantation and follow-up in order to ensure their safety and efficacy and to maintain public and professional confidence. A number of quality systems can be applied throughout the transplant chain, from donor identification to allocation and transplantation or disposal of organs, including appropriate follow-up.

The quality management system is the responsibility of the healthcare professionals involved in donation and transplantation processes, but also of governments and Health Authorities in charge of healthcare systems in general and of the transplant system in particular.

In the EU, this common responsibility of Health Authorities and health professionals was confirmed with the adoption in July 2010 of Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation [5]. Indeed the EU member states 'shall ensure that a framework for quality and safety is established to cover all stages of the chain from donation to transplantation or disposal' (Article 4). To do so, Article 17 provides that 'Member States shall designate one or more competent authorities' to establish the framework for quality and safety, ensure that procurement organisations and transplantation centres are authorised and controlled or audited regularly, and take other measures described below. Regarding health professionals, Article 12 provides that 'Member States shall ensure that healthcare personnel directly involved in the chain from donation to transplantation or disposal of organs are suitably qualified or trained and competent to perform their tasks and are provided with the relevant training'.

The EU Action Plan on Organ Donation and Transplantation (2009-2015): Strengthened Cooperation between Member States [6] also explicitly provides for common action on quality improvement programmes (QIP), with its Priority Action 2: 'promote quality improvement programmes in every hospital where there is a potential for organ donation', while the other nine Priority Actions also refer to the 'exchange of best practices', 'twinning projects and peer reviews' and the development of common tools, thus fully in line with a logic of continuous quality improvement.

Applying a systematic approach to quality management in this context involves separate reviews of the following:

a. government and Health Authority responsibilities;

b. quality management in organ donation;

c. quality management in organ transplant.

16.4. Government and Health Authority responsibilities in organ donation and transplantation: a framework for quality and safety

If they are to reduce the risks and maximise the benefits of transplantation, Council of Europe member states need to ensure that a framework for quality and safety is established to cover all stages of the chain from donation to transplantation or disposal. That framework should act to integrate the activities carried out in all procurement and transplant centres, and in establishments responsible for allocation/distribution, in order to ensure the highest possible quality, safety and transparency of the process while increasing the number of organs available.

The recovery and distribution of organs has to be properly regulated. The Health Authorities of the state must play their key role in establishing a legal

and organisational framework to ensure the quality and safety of organs during the donation and transplantation process, and in evaluating their quality and safety throughout patient recovery and the subsequent follow-up. According to Directive 2010/53/EU [5], and other major recommendations [6-13] in the field of organ donation and transplantation, the quality and safety framework should include:

a. A system for authorisation and audit/inspection of procurement and transplant organisations by which quality and safety are ensured for both recipients and living donors. Such organisations should have in place proper organisation, suitably qualified or trained and competent personnel and adequate facilities and material.

b. Designation of a non-profit national or international body responsible for the allocation and distribution of organs. As emphasised by the Committee of Ministers of the Council of Europe in its recommendations to member states on the background, functions and responsibilities of a national transplant organisation, it is preferable to have a single, officially recognised, non-profit-making body with overall responsibility for donation, allocation, transport, traceability and accountability.

c. An organ-allocation system with strong guarantees, in terms of both equity and efficiency, to ensure optimal transplant use, especially considering the technical constraints inherent in organ recovery, transportation and quality maintenance. This system should support transparency, traceability and external audit of decision making. The rules for allocation should be clearly defined for each organ and made available to health professionals, patients and the public. The guidelines governing the allocation criteria and the distribution of organs should be developed and implemented by common agreement with a group of experts involved in organ transplantation. These rules must be regularly re-evaluated, taking technical advances into account.

d. A requirement to establish a comprehensive framework for quality and safety for the whole chain, with the adoption and implementation of standard operating procedures (SOPs) combined with standard documentation (protocols) for:

i. verification of donor identity;
ii. verification of the details of the consent authorisation (or absence of any objection) of the donor or his/her family, in accordance with the national rules that apply where donation and procurement take place;
iii. verification of the completion of the organ and donor characterisation;
iv. procurement, preservation, packaging and labelling of organs;
v. transport of organs;
vi. assurance of traceability;
vii. accurate, rapid and verifiable reporting and management of serious adverse events and reactions.

e. A traceability system that enables the path taken by each donation to be traced from donor to recipient or disposal and vice versa. This system must allow donor material to be traced to its source and to its destination with certainty. Each donor/component should be assigned a unique identifier, used to link the donor to all tests, records, transplants and other material and, for tracking purposes, to the recipient.

f. A vigilance system to provide mechanisms for the protection of donors and recipients, managed by national and/or supranational institutions. This should ensure rapid investigation of any undesirable event occurring in relation to donation and transplant services (e.g. unexpected transmission of an infectious or malignant disease from donor to recipient), so that corrective and preventive actions can be taken immediately. Any kind of serious adverse reaction in an organ recipient that is suspected to be of donor origin needs to be reported to all other institutions receiving organs or tissues from the same donor. The scope of such a system should cover all the steps of the process, from donation to transplantation, as well as the follow-up period, including a procedure for data collection according to legal requirements. The system must also inform all tissue banks in cases where tissues and/or cells have been procured from the same donor.

g. If necessary, a system to exchange organs with other countries and/or within international or European organ-exchange organisations, regulated and supervised by the Health Authorities, to increase the probability of providing organs for patients in special situations with lower chances of finding compatible organs within their own country (e.g. young children needing liver, intestinal or heart transplant, life-threatening conditions, recipients highly sensitised against human leukocyte antigens). Organ exchange with other countries should

be allowed only where equivalent standards of quality and safety are met.

h. A system to ensure that strict confidentiality rules and security measures are in place for the protection of donors' and recipients' personal data at all stages of the donation and transplant process, including traceability and vigilance systems. The Health Authority may also consult the national data-protection supervisory authority in relation to developing a framework for the transfer of data on organs to and from other countries.

i. A system to ensure that the healthcare personnel directly involved, at all stages of the chain from donation to transplantation or disposal, are suitably qualified or trained and competent, and to develop continuous education and specific training programmes for such personnel in order to maximise the required skills. The role of the donor co-ordinator or co-ordination team, appointed at hospital level, should be recognised as key to improving not only the effectiveness of the process of donation and transplant, but also the quality and safety of organs to be transplanted. Likewise, certain medical activities in procurement organisations, such as donor selection and evaluation, should be performed under the advice and guidance of a medical specialist/adviser.

j. A follow-up system for recipients and living donors that allows evaluation of outcomes. This is a prerequisite for quality improvements and for providing a means to stimulate and motivate the professionals involved. Whatever the evaluation system (local, regional, national), basic follow-up should include primary non-function, delayed graft function, re-transplantation and death-related/adjusted survival rates (graft and patient).

k. The implementation of quality assurance programmes (QAP) or QIP in the deceased donation process in order to address performance and identify areas where improvement is possible. International organisations, such as the Council of Europe and the European Commission, have recommended establishing and promoting QAP/QIP in every hospital where there is a potential for organ donation. These programmes should include access to and training on a specific methodology of QIP, and should also ideally be compatible at national or international level to adequately allow for comparison of the results obtained and to adopt the most appropriate measures for improving organ donation.

l. Harmonisation of regulatory rules and controls worldwide should be developed, in order to enhance the safety and quality of transplants.

For further details about the recommendations and regulations in the donation and transplant field at international level, see Chapter 1, section 1.5.

Nota bene: With the transposition of Directive 2010/53/EU into national laws, some of these principles (*a* to *l* above) are now mandatory requirements in EU member states and EEA countries, while some others remain fully under the competence of the member states. Nevertheless, all these principles remain crucial recommendations.

16.5. Quality management in organ donation

Implementation of a quality system in a procurement organisation will enable the achievement of four key objectives:

a. To ensure the quality and safety of the organs to be obtained and transplanted, minimising disease transmission to the recipient and ensuring that all possible risks are known and can be evaluated for the best risk–benefit analysis before transplantation.

b. To guarantee that the entire process is carried out ethically and legally, and is medically correct according to best medical practices and in compliance with legislation and ethical codes, including protection of living donors and prevention of commercial abuses.

c. To ensure good documentation and transparency throughout the process, from donation to transplantation, allowing full records and traceability of the entire process.

d. To establish a system of continuous improvement that will allow improvement of outcomes, by increasing the numbers of donors and organs transplanted, improving quality of life/survival of living donors and recipients, and by meeting other defined criteria.

In the context of organ donation, some areas have been identified which need work to improve quality, such as the development, implementation and evaluation of QAP/QIP [12-13], of best practices [14] and of quality indicators (QI) [15-16]. Quality criteria, also called 'best practice' or 'good practices', set standards that normal healthcare practice has to meet if it is to be considered as good-quality practice.

The Odequs Project (Organ Donation European Quality System, 2010-13), involving experts from 16 European countries, developed a quality system for the donation process which defines a methodology for evaluating organ procurement performance that can be used at hospital level [15]. The project identified 123 quality criteria and developed 31 relevant QI in the three types of organ donation – after brain death (DBD), after circulatory death (DCD) and from a living donor (LD) – regarding all three aspects of donation services: structure, procedures and outcomes [16].

Any of the quality management models mentioned earlier could help to achieve these objectives when applied to the process of organ donation in hospitals or donor-procurement organisations. The following description uses the basic outline of the ISO model, given its wider diffusion at international level.

The quality conditions that should be met in the different key activities of the donation process are reviewed below.

16.5.1. Organisational issues: legal framework, functional organisation and personnel

Procurement organisations for both living donation and deceased donation must be authorised and/or accredited by the Health Authorities competent to carry out these activities [5, 16].

Some steps of the *post mortem* organ donation process, such as the declaration of death, the approach to the family and the organisational aspects, must be undertaken and properly documented according to the laws of the country concerned [5].

There must be sufficient, suitably qualified personnel to carry out all tasks. Every donation team or group in charge of organising the donation process should consist of enough members to ensure that the donation activities can be carried out 24/7 [5, 14, 16]. Tasks and responsibilities must be clearly defined, understood and documented. All personnel should have clear, documented and up-to-date job descriptions.

All procurement organisations should include a key donation person and a medical specialist/adviser, who may or may not be the key donation person [5]. The key donation person should be responsible for developing a proactive donor-identification programme and for organising and monitoring the entire donation process and donor programme at the hospital [5, 11]. The ideal profile of the key donation person would include motivation, dedication, work capacity and good communication skills [14]. The key donation person should report directly to the head/director of their institution [16].

Every donor hospital should have an office for the exclusive use of the donation team. It should be identified by a sign, secure and equipped with means of communication (telephone, fax, Internet) [16].

In addition, the organisation should include an independent head of quality management, independent in the sense that this person is not directly involved in the organ donation programme [1-4].

16.5.2. Education, continuous training and research

Personnel involved should receive specific initial training under a programme certified by the corresponding national/European agency, organisation or professional association and appropriate to the duties assigned to them, and participate regularly in continuing medical training courses on specific topics related to donation [11, 14, 16]. The effectiveness of all training programmes should be monitored by regular assessment of the competence of personnel. Training should be documented and training records should be kept. Personnel should also be trained in quality principles relevant to their work.

Each donation team should also define objectives for research projects, conference communications and scientific publications relating to donation [16].

16.5.3. Donation process – implementation of protocols

The following aspects of the donation process should be included in the protocols and monitored [5, 16]:

a. Donor identification and referral, including a systematic approach to evaluating the potential for organ donation in every end-of-life care pathway (DBD or DCD) and the necessity of referring to the donation team all possible donors, whatever their medical situation is (age, past medical history, etc.). The donation team should also monitor the progress of each possible donor in the ICUs on a daily basis (for further information, see Chapter 2).

b. Donor assessment and donor selection. All potential donors should be carefully assessed by the donation team in order to establish their suitability for organ donation; they should be assessed and selected according to agreed principles and/or national regulations (see chapters 6 and 7).

c. Death diagnosis and proper certification of death. Each hospital should have developed

and implemented SOPs and standard documentation (protocols) to permit and regulate brain-death declarations in adults and children according to the legal framework. Every brain death should be promptly diagnosed following comprehensive, accurate and documented methodology (see Chapter 3).

d. Donor treatment/maintenance should be performed in an ICU with adequate means and under the supervision of an intensive care specialist according to best clinical practices; checklists and guidelines for donor maintenance should be available and updated regularly (see Chapter 5).

e. Family support and granting of consent, according to the regulations of the relevant member state (see Chapter 4).

f. Operating theatre organisation, organ procurement and organ sharing. There should be a clearly defined procurement protocol (including obligatory documentation) and every hospital should follow the established rules for organ sharing at a regional or national level (see Chapter 11).

g. Organ preservation and packaging, organ transport (in-hospital, inter-hospital) and logistics. There should also be procedures for packaging of organs, with the necessary biological samples and documentation, in shipping containers (e.g., as in Article 8 of Directive 2010/53/EU), and for transport of organs and biological specimens; traceability and donor anonymity should be guaranteed; logistical and auxiliary services for transport of organs and biological specimens should be ensured 24/7 (including air transport, if necessary); during the entire process, all containers should be clearly labelled and there should be instructions concerning the type and method of labelling (see Chapter 11).

h. Communication procedures with the national/regional co-ordination system should be in place, and the donation team should notify each potential donor in real time.

i. Development of training, promotional and educational activities to spread the culture of donation and transplant, directed at healthcare professionals, donor unit personnel (physicians and nurses) and the community (e.g. school activities, public conferences and mass media).

j. Archiving of documents, in accordance with national legislation.

16.5.4. Quality indicators

A quality system should periodically measure and evaluate relevant aspects of healthcare by means of quality indicators (QIs). QIs are measurements that indicate the presence of a phenomenon or event and its intensity. The objective of monitoring is to identify problems or situations that could be improved or deviations from standard practice; indicators act as alarms, warning us about possible anomalies [17].

Any set of indicators should ideally include a combination of the three types of evaluation:

a. structure: resources and organisation of care (e.g. protocol, circuit);

b. process: the way care is provided (e.g. adherence to protocol);

c. results: achievement of goals (e.g. mortality, adverse events and reactions, nosocomial infections).

In order to have sufficient information to determine the level of quality of the service, a selected group of indicators has to be monitored.

In relation to organ donation, two sets of indicators have been described which, although they complement each other, are quite different in terms of philosophy, objectives and methodology. One set of indicators was published in the *Guide of recommendations for quality assurance programmes in the deceased donation process*, developed by the DOPKI project (Improving the Knowledge and Practice of Organ Donation, 2006-09) [13], and the other set was developed in the ODEQUS project [15-16].

16.5.4.1. *Quality indicators developed by the DOPKI project*

These recommendations on QIs are based on the experience and knowledge acquired in the DOPKI project, particularly on the state of the art in QAP in the deceased donation process in each of the participating countries [18-22]. This project included group discussions on specific aspects and the pilot experience which took place in a group of 30 volunteer hospitals in 10 European countries, with the aim of validating the pre-agreed methodology.

QIs developed by the DOPKI Project were grouped as follows [13]:

a. Indicators of the potential for deceased organ donation.

b. Indicators of areas for improvement in the deceased donation process.

c. Indicators of global effectiveness in the deceased donation process.

Table 16.1. **The most important indicators applied in the DOPKI pilot (key indicators in blue)**

a. Indicators of the potential for deceased organ donation

Of the number of deaths:

$$\frac{\textbf{Brain deaths (possible and confirmed)}}{\textbf{Hospital deaths}} \times 100$$

$$\frac{\textbf{Brain deaths (possible and confirmed)}}{\textbf{ICU deaths}} \times 100$$

$$\frac{\text{Brain deaths (possible and confirmed)}}{\text{Number of persons who died within the hospital whose primary and/or secondary diagnosis contained at least one of the ICD codes [11] representing diseases potentially progressing towards a situation of brain death}} \times 100$$

$$\frac{\text{Brain deaths (possible and confirmed)}}{\text{Number of persons who died within the ICU whose primary and/or secondary diagnosis contained at least one of the ICD codes [11] representing diseases potentially progressing towards a situation of brain death}} \times 100$$

b. Indicators of areas for improvement in the deceased donation process

Of the number of brain deaths (possible and confirmed):

$$\frac{\text{Brain deaths not referred}}{\text{Brain deaths}} \times 100$$

$$\frac{\text{Brain deaths lost because of medical contraindications to organ donation}}{\text{Brain deaths}} \times 100$$

$$\frac{\text{Brain deaths lost because of maintenance problems}}{\text{Brain deaths}} \times 100$$

$$\frac{\text{Brain deaths lost due to refusal for organ donation}}{\text{Brain deaths}} \times 100$$

$$\frac{\text{Brain deaths lost due to coroner refusal for organ donation}}{\text{Brain deaths}} \times 100$$

$$\frac{\text{Brain deaths lost due to organisational problems}}{\text{Brain deaths}} \times 100$$

$$\frac{\text{Brain deaths lost for other reasons}}{\text{Brain deaths}} \times 100$$

Of the total number of families approached and judicial requests to proceed with organ donation:

$$\frac{\text{Number of families who refused organ donation}}{\text{Number of families approached to request organ donation}} \times 100$$

$$\frac{\text{Number of coroner refusals of organ donation}}{\text{Number of judicial requests for organ donation}} \times 100$$

c. Indicators of global effectiveness in the deceased donation process

Regarding the number of deaths:

$$\frac{\text{Actual donors}}{\text{Hospital deaths}} \times 100$$

$$\frac{\text{Actual donors}}{\text{ICU deaths}} \times 100$$

$$\frac{\textbf{Actual donors}}{\textbf{Brain deaths (possible and confirmed)}} \times 100$$

Other

$$\frac{\text{Multiple-organ donors}}{\text{Actual donors}} \times 100$$

$$\frac{\textbf{Utilised donors}}{\textbf{Actual donors}} \times \mathbf{100}$$

$$\frac{\textbf{Organs procured}}{\textbf{Actual donors}} \times \mathbf{100}$$

$$\frac{\text{Organs utilised}}{\text{Actual donors}} \times 100$$

$$\frac{\textbf{Organs utilised}}{\textbf{Utilised donors}} \times \mathbf{100}$$

Actual donor: A donor from whom at least one organ has been procured for the purpose of transplantation.
Utilised donor: An actual donor from whom at least one organ has been transplanted.
Source: [13].

Indicators developed during the DOPKI pilot experience are shown in Table 16.1. Out of those, six key indicators were identified (highlighted in blue in the table).

The DOPKI consortium stated that, in applying this set of indicators to specific hospitals, certain hospital variables or factors need to be taken into account that may justify the existence of differences between hospitals that, at least on the surface, seem to have similar characteristics. Among such factors, the following must be considered: the epidemiology of diseases concerned and hence the number of persons dead as a result of a devastating brain injury within a hospital or ICU; the presence of neurosurgical facilities in the hospital; the number of hospital and ICU beds; the ICU workload (the greater the workload in

an ICU, the lower the potential for *post mortem* organ donation) or differences in age and ethnicity between populations, which could have an influence on some areas (e.g. consent rate) [13].

A QAP in the deceased donation process is primarily a self-assessment of the whole process of organ donation, jointly performed by intensive care specialists and donor co-ordinators in every hospital. It involves a systematic review of all medical records of patients who have died in ICUs, and possibly in other similar units, being performed on a regular basis in order to analyse any undetected potential donors and establish means for improvement. After implementation of the self-assessment, the programme should be complemented by regular external audits performed by experts from other hospitals, regions or countries, in order to further improve the process and provide greater transparency.

For clinical use of this group of indicators, it is important to note the following [13]:

a. Dopki recommendations are exclusively focused on the process of DBD.

b. The groups of indicators form part of a QAP implemented at national/regional level and usually managed by the corresponding transplant organisations so, to a certain extent, they may be mandatory.

Table 16.2. **Quality indicators applied in the Odequs project**

Living donation	**Applies to**	**Type**	**Standard**
1 Approval for living donation from a council*	LD	process	100 %
2 Participation of the centre in a living donor registry	LD	process	100 %
3 Identification of potential living kidney donors	LD	outcome	20 %
4 Long-term follow-up of living donors	LD	process	100 %
5 Evaluation of potential living donors	LD	outcome	80 %
Deceased donation	**Applies to**	**Type**	**Standard**
1 Donation process procedures	DBD/DCD	structure	100 %
2 Proactive Donor Identification Protocol	DBD/DCD	structure	100 %
3 Donation team full-time availability	DBD/DCD	structure	100 %
4 Donation team members with ICU background	DBD/DCD	structure	50 %
5 Dedicated time Key Donation Person	DBD/DCD	structure	100 %
6a Documentation of key points of the donation process	DBD/DCD	structure	100 %
6b Documentation of reason for non-donation	DBD/DCD	process	100 %
7 Patient/ family consent	DBD/DCD	outcome	90 %
8 Identification of all possible donors in ICU	DBD	process	75 %
9 Uncontrolled in-hospital DCD donor identification	DCD	process	100 %
10 Controlled DCD donor identification	DCD	process	100 %
11 Existence of controlled DCD donation protocols	DCD	structure	100 %
12 Referral of possible DBD donors	DBD	process	100 %
13 Discarded organs documented	DBD/DCD	process	100 %
14 Evaluation of brain-dead donors	DBD	process	100 %
15 Donor management	DBD	process	90 %
16 Unexpected cardiac arrest	DBD	outcome	3 %
17 DCD organ donor preservation	DCD	process	85 %
18 Seminars on organ donation	DBD/DCD	process	≥1
19 Documentation of evaluation of potential donors	DBD/DCD	process	100 %
20 Brain death identification	DBD	outcome	50 %
21 Conversion rate in DBD donors	DBD	outcome	75 %
22 Conversion rate in uncontrolled DCD donors	DCD	outcome	85 %
23 Conversion rate in controlled DCD donors	DCD	outcome	90 %
24 Kidneys transplanted from uncontrolled DCD donors	DCD	outcome	80 %
25 Kidneys transplanted from controlled DCD donors	DCD	outcome	90 %

DBD: donation after brain death; DCD: donation after circulatory death; ICU: intensive care unit; LD: living donor.
*A council is an *ad hoc* multidisciplinary group that evaluates the LD to ensure safety and best outcome for both patients, following the principles laid down by the transplant centre's ethical committee.
Source: Project ODEQUS (Organ Donation European Quality System) [16].

c. Reference values (national or regional) should be available with which to compare the results obtained after implementing the indicators, particularly taking into account the socio-demographic characteristics, economic situation and available healthcare structure in the respective area.

d. By the very nature of the QAP, its scope is focused almost exclusively on the actions of individuals and outcomes, focusing less on the analysis and evaluation of processes and on the implementation of improvement plans.

16.5.4.2. *Quality indicators developed by the Odequs project*

The Odequs consortium developed a quality management system to assess the performance of organ procurement at hospital level. The specific objectives were to identify best practices in the three different types of organ donation (DBD, DCD and LD) and to design QIs to assess the organisational structures, clinical procedures and outcomes. Indicators developed were tested in selected hospitals in 12 European countries to assess their feasibility and usefulness. Healthcare workers were trained beforehand on how to use the QIs, checklists and auditing procedures [15].

The main fields considered in assessing the organisational structures were legal framework, accreditation and certification, organisation, human and material resources, education and research. In terms of clinical procedures and outcomes, the main aspects assessed were donor identification, clinical evaluation, death diagnosis, donor maintenance, family/personal consent, organ viability, surgical procurement/preservation and number of donors/organs/transplants.

From the analysis of best practices in organ donation conducted by the 16 donation experts, a quality criteria list of 123 items was compiled on the basis of expert opinions, literature review and evidential research. Once they had received specific training designed for this task, the same group of experts developed and agreed on a list of 31 key quality indicators based on the most important quality criteria previously identified [16]. The list of QIs developed by Odequs is shown in Table 16.2, specifying the type of organ donation where applicable (LD, DBD and/or DCD), type of indicator (structure, process or outcome) and level of the standard.

All the indicators developed have the same structure. As examples, Table 16.3 and Table 16.4 show two QIs of deceased donation: Documentation of reason for non-donation, valid for the DBD/DCD population (Table 16.3); and Controlled DCD donor identification (Table 16.4). Each one of the QIs includes the following data [16]:

a. name of the indicator,

b. justification (why the indicator is relevant and of practical use),

c. strength of evidence (Recommendation A: consistent, good-quality patient-oriented evidence; Recommendation B: inconsistent or limited-quality patient-oriented evidence; and Recommendation C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention or screening),

d. dimension (characteristics of the healthcare in order to be considered good-quality care, e.g. effectiveness and appropriateness, efficiency, etc.),

e. formula for rate-based indicators,

f. clarification of terms (explanation or definitions of terms included in the formula that are ambiguous),

g. type (structure, process or outcomes),

h. data source (medical records or other clinical documents, direct observation, questionnaires, etc.),

i. expected results,

j. comments and bibliography (scientific soundness, face validity, reliability, references to literature regarding scientific evidence, etc.).

The feasibility of implementation of the QI should be assessed by two types of evaluation:

a. Internal audit, performed by a team from the same hospital.

b. External audit, performed by an outside team (national or international).

The Odequs Quality System can be summarised as follows:

a. Odequs is designed as a quality management system that incorporates regular monitoring of a series of QIs that will allow us to identify problems or situations that can be improved, with the commitments to take action at the time when the practice evaluated presents below-standard results, to discuss these results, to analyse the causes and to define and implement improvement plans (e.g. Shewhart PDCA cycle: Plan–Do–Check–Act, sometimes called PDSA: Plan–Do–Study–Act).

b. It is focused on evaluating the three types of donation: LD, DBD and DCD.

c. It covers all three aspects of donation services: structure, procedures and outcomes, and therefore provides a broader evaluation.

d. It is a proactive approach to improvement of healthcare processes and systems that will lead to improved processes and outcomes, rather than improving the outcomes alone.

Table 16.3. **Deceased Donation indicator 6b in the ODEQUS project: documentation of reason for non-donation**

Name	**6b. Documentation of reason for non-donation**
Justification	Proper documentation of the cause of non-donation ensures that it will be possible later to review and analyse donor losses. This is the basis that will enable continuous improvement.
Strength of evidence	Recommendation C
Dimension	Appropriateness
Formula	$\frac{n_1}{n_2} \times 100$ where: n_1 = number of referred failed donors in whom the cause of no donation is properly documented n_2 = number of referred failed donors
Explanation of terms	Donor referral: see glossary (Appendix 2) Possible donor: see glossary (Appendix 2) Failed donor: Possible donor who did not become an actual donor Cause of non-donation properly documented: if in the records of the patient there is a note stating the cause by which the patient did not become an actual donor
Population	All possible referred donors who did not become actual donors
Type	Process
Data source	Donation team records
Expected result	100 %
Comments	Note: in order to standardise the evaluation of causes of donor's loss the recommendation is to implement a closed list of possible causes.

Source: Project ODEQUS (Organ Donation European Quality System) [15].

Another EU-funded project should be mentioned here: the ACCORD Joint Action (2012-15) has a work package (Work Package 5) focused on deceased donation and more specifically on collaboration between ICUs and donor co-ordinators. It applies the PDSA methodology, as a rapid improvement tool based on a common framework and the self-assessment of hospitals involved all over Europe, in 15 countries [28].

16.5.5. Audits, quality evaluation and outcomes

An audit is a documented review of procedures, records, personnel functions, equipment, materials and facilities to evaluate adherence to quality criteria and national/governmental laws and regulations. During an audit, performance is reviewed to ensure that items that should be carried out in terms of quality management are being done and documented; if this is not the case, it provides a framework to allow improvements to be made.

Auditing is an essential tool to ensure ongoing improvements, and may be performed in different ways:

a. Self-assessment: donation team personnel review each step in the process.

b. Internal audit: performed by the organisation's own quality personnel, who must be qualified for auditing.

c. External audit: carried out by independent bodies, often designated as approved or by competent authorities; external audit is often required for accreditation or licensing purposes.

Following international recommendations, as a complement to self-assessments, each procurement organisation should perform an annual external audit of the organ-donation process and should implement corrective measures when needed [12, 14, 16].

After each donation operation, a debriefing should take place with the donation team and all personnel involved in the operation (from the identification to the recovery, packaging and delivery of organs) in order to improve the process quality [16].

16.5.6. Documentation and registries

Documentation must enable all steps and all data affecting the quality and safety of the organs to be checked and traced, from donor to recipient and vice versa. Written documentation ensures that work is standardised and prevents errors that may result from oral communication. Where oral communication is necessary, audio recordings may be useful.

Documentation should be version-controlled, be regularly reviewed and cover at least the following items:

a. A quality manual.

Table 16.4. **Deceased Donation indicator 10 in the ODEQUS project: cDCD donor identification**

Name	10. Controlled DCD donor identification
Justification	Organ donation is a priority programme for the majority of a country's health systems. DCD donation has proved to be an adequate supply of organs for transplantation and can represent 10 %-20 % of the total number of organs available. These data confirm the importance of identifying all patients who undergo WLST in ICUs and who could become DCD donors.
Strength of evidence	Recommendation C
Dimension	Effectiveness
Formula	$\frac{n_1}{n_2} \times 100$ where: n_1 = number of patients who underwent WLST, were apparently medically suitable for organ donation AND were correctly identified and referred n_2 = number of patients who underwent WLST and were apparently medically suitable for organ donation
Explanation of terms	WLST: withdrawal of life-sustaining therapies, in an ICU patient Identified and referred: the patient is reported to the donation team (or transplant centre) as soon as the decision to withdraw life-sustaining therapies is made by the ICU medical team Apparently medically suitable for organ donation: at the moment of the decision to withdraw life-sustaining therapies it is not known if the patient has a malignancy (see Chapter 9 for details), sepsis with multiorgan failure or symptomatic HIV infection
Population	All patients admitted to the ICU to whom WLST is applied during the period studied Exclusion criteria: only withdrawing (not withholding) life support is considered
Type	Process
Data source	Medical records and donation team referral registry
Expected result	100 %
Comments	Note: In order to ensure the feasibility of the indicator the recommendation is to document accurately the time when WLST is decided, the time when it is performed and the time of death. The definition of Potential DCD Donor in the Critical Pathway includes the statement 'the cessation of circulatory and respiratory functions is anticipated to occur within a time frame that will enable organ recovery'. As the accuracy of the different systems to predict such an event is low, we have decided to exclude this point from the indicator. This eliminates subjectivity and improves its accuracy.

DCD: donation after circulatory death; ICU: intensive care unit; WLST: withdrawal of life-sustaining therapy.

Source: Project ODEQUS (Organ Donation European Quality System) [15].

b. SOPs, including standard documentation, i.e. protocols.
c. Records of performance of operations (e.g. donor selection, release, organ allocation).
d. Specifications.
e. Identification of risks and a risk-mitigation plan.
f. Other procedures (e.g. equipment validation, calibration, cleaning and maintenance).
g. Personnel training and records of competence.

Documents relating to the selection of donors, preparation and quality control should be retained for a minimum of 30 years after donation in EU member states, in accordance with Directive 2010/53/EU [5]. International and national regulations on data protection have to be taken into consideration. Data can also be stored in soft-copy form, for instance on computer or microfilm. Users should have access only to those categories of data for which they are authorised and for the purposes authorised.

A computerised record-keeping system ensures the authenticity, integrity and confidentiality of all records, but retains the ability to generate true paper copies. The hardware and software of computers should be regularly checked to ensure reliability. Computer programs should be validated before use. Only authorised persons should make changes to computerised systems and any such changes should be validated before use. In addition, appropriate hardware and software should be in place to guarantee secure back-up. Hospitals and other facilities should have an alternative record-keeping system that ensures continuous operation in the event that computerised data are not available.

16.5.7. Traceability

In accordance with the traceability system implemented in each country (or internationally, if applicable), each procurement organisation must maintain records that allow the location and unequivocal identification of each organ at any stage in the chain from donation to transplantation or disposal.

Each donor and component should be assigned a unique identifier that may also serve as a lot/batch number to identify the material during all stages, from collection to distribution and utilisation. This unique number should be used to link the donor to all tests, records, grafts and other material (e.g. preservation solutions, preservation devices) and, for tracking purposes, to the recipient. Records should include: identification, clinical and laboratory eval-

uation of the donor; verification of the conditions under which the material was procured, processed, tested and stored; and the final destination of the donor material. Records should indicate the identities of personnel involved in each significant step of the operation and the dates of those steps [5].

16.5.8. Investigation and reporting of non-conformance: vigilance system

Non-conformance includes deviations, incidents, accidents and adverse reactions and events.

Organisations involved in the donation–transplantation process should record and document incidents and deviations from established procedures and specifications. Procedures should be in place to identify the problems to be corrected, and to inform the relevant authorities as appropriate according to the national vigilance system [5]. For further details about the biovigilance system, see Chapter 15.

Priority should be given to the investigation and reporting of incidents with a demonstrated or potential risk to cause serious adverse reactions, for example, unexpected transmission of an infectious or malignant disease from a donor to a recipient or any incident during the process that might lead to a problem in a recipient. Unexpected infections or malignancies in recipients must be reported without delay, as early warning may facilitate interventions that could mitigate adverse outcomes in that recipient, and also in other recipients from the same organ donor (maybe in another country).

Open reporting of errors and incidents should be encouraged for improvement in practices to be shared among all institutions involved in all Council of Europe member states.

16.5.9. Risk assessment and mitigation

The procurement, manipulation and distribution of organs should be subject to a comprehensive risk assessment [5]. Where appropriate, a process-flow diagram listing all relevant steps, processes, re-agents, tests and equipment can form the basis for this assessment exercise. Risk-mitigation strategies should then be developed (specific protocols) to protect transplant-associated products, patients and personnel, as well as the process itself and other linked or related processes.

For example, risks might derive from: donor selection and screening, procurement procedures, preservation and transport, biological properties of procured organs, the absence of standardised quality control tests or the use of potentially infective materials.

16.5.10. Complaints and recalls

All complaints and concerns about donor material should be documented, carefully investigated and dealt with as quickly as possible. Effective written procedures must exist for recalling defective/suspect products [29]. These written procedures must encompass any review procedures that may be necessary. The procedures should be communicated to the end users. A mechanism for appropriate review and assessment of actions taken to address complaints should be established.

16.5.11. Premises, equipment, materials and contractual arrangements

Premises and equipment must be designed, located, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit operations to proceed in an orderly sequence.

a. Premises

Premises for each step in the transplant process should be specified (e.g. where the donation process will be carried out, allowing for confidential, personal interviews) and comply with existing recognised regulations.

All laboratory investigations (e.g. tissue typing for human leukocyte antigens and cross-matching, screening for infections, pathology investigations) should be done in certified laboratories, using methods and techniques that are certified and quality-controlled by internal and external methods. All outsourced activities should be handled with attention to ensure that all changes are communicated and managed.

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and components. There should be dedicated, secure and monitored areas for the storage of different types of organ. Storage conditions for organs and materials should be controlled, monitored and checked. Appropriate alarms should be present to indicate when storage temperatures fall outside acceptable levels in cases of donor material stored for further processing. Alarms should be regularly checked. SOPs should define the actions to be taken in response to alarms.

b. Equipment

Adequate and standardised equipment for the entire organ retrieval process should be available 24/7 (surgical equipment, preservation fluids, transport boxes, etc.) [15].

All equipment that might influence the quality or safety of transplant-associated products should be designed, validated and maintained to suit its intended purpose and to minimise any hazard to donors, recipients or operators. Maintenance, monitoring, cleaning and calibration should be documented and these records should be appropriately maintained.

c. Materials

Detailed specifications of re-agents and other materials that might influence the quality or safety of transplant-associated products are required. Only materials from qualified suppliers that meet the documented requirements should be used. Manufacturers should provide a certificate of compliance for every lot/batch of such materials.

Equipment and materials should conform to international standards and European and national licensing arrangements, where these exist.

Inventory records should be kept for traceability and to prevent use of materials after their expiry date. Deviations in the quality and performance of equipment and materials should be investigated and documented promptly [28]. The outcomes of these investigations should be reported in a timely manner to the person responsible and corrective actions taken. For substantial deviations, a notice should be sent to the manufacturer and, where appropriate, reported to the Health Authority.

d. Contractual arrangements

Arrangements relating to procurement, testing (laboratories), processing, storage or distribution functions should be documented, and compliance with professional standards should be ensured by all parties involved.

16.6. Quality management in organ transplantation

The characteristics of transplantation, regardless of organ type, make this process a model of multidisciplinary care. The complexity, involvement of different specialties, levels of care and speed required in transplant situations make the combination of co-ordination and quality management essential in this area of healthcare.

Table 16.5. **Some quality indicators that can be used in deceased organ transplantation, regardless of organ**

Indicators for evaluation and consensus
Patients studied within 30 days of referral to the TC
• Definition: percentage of patients who have been evaluated (whether placed on the waiting list or not, after an evaluation) by the TC within 30 days of the appointment request. • Formula: Number of patients in a given period with study completed within 30 days of request for appointment for transplant evaluation/Number of patients in the same period referred for transplant evaluation × 100. • Type: Process
Quality of clinical report by doctor responsible for referring a candidate to the TC
• Definition: percentage of clinical reports that are full clinical reports (those specifying all the information contained in the evaluation checklist for the potential recipient) sent by the doctor responsible for referring a transplant candidate to the multidisciplinary committee. • Formula: Number of full reports sent to the committee in a given period/Total reports sent to the committee in the same period × 100. • Type: Process
Indicators of management of patients waiting for a transplant
Frequency of pre-transplant follow-up visits
• Definition: percentage of patients on the transplant waiting list who are seen in follow-up visits at a frequency of more than 60, 90 or 120 days (as applicable). • Formula: Number of patients on the waiting list seen in visits in a given period at a frequency of more than 60, 90, 120 days (as applicable)/Total number of patients on the waiting list × 100. • Type: Process
Mortality of patients on the waiting list
• Definition: percentage of patients excluded from the transplant waiting list because of death or disease progression. • Formula: Number of patients excluded from the waiting list in a given period (because of death or disease progression)/Total number of patients placed on the waiting list in the same period × 100. • Type: Outcome
Peri-operative indicators
Peri-operative mortality
• Definition: percentage of transplant patients who die during a period starting from the start of surgery and including the first 24 h post-transplant. • Formula: Number of deaths during the first 24 h of transplantation/Total number of transplant patients for the same period × 100. • Type: Outcome
Occurrence of primary graft failure
• Definition: percentage of transplant patients who develop 'primary graft dysfunction'. • Formula: Number of transplant patients in a given period who develop 'primary graft dysfunction' causing re-transplantation or death/Total number of transplant patients × 100. • Type: Outcome

Cold ischaemia time
- Definition: percentage of organs preserved by cold ischaemia (time between clamping blood supply to the organ in the donor and restoring blood supply in the recipient) for more than 3, 5, 10, 15 and 20 h (as applicable, depending on the type of transplantation).
- Formula: Number of organs in a given period preserved by cold ischaemia for more than 3, 5, 10, 15 and 20 h (as applicable)/Total number of organs transplanted in the same period × 100.
- Type: Process

Rate of non-transplanted organs with no justifiable objective reason
- Definition: percentage of non-transplanted organs after initial acceptance, with no justifiable objective reason (ideally, a histological study showing the impossibility of use).
- Formula: Number of non-transplanted organs after acceptance in a given period/Number of transplanted organs (based on applicable national acceptance criteria for deceased donors) in the same period × 100.
- Type: Outcome

Indicators of post-transplant hospitalisation

In-hospital mortality post-transplant
- Definition: percentage of transplant patients who die within the first 24 h/up to 30 days post-transplantation.
- Formula: Number of transplant patients who died within the first 24 h and up to 30 days post-transplantation/Number of transplant patients × 100, for the same period.
- Type: Outcome

Early re-operation rate
- Definition: percentage of transplant patients requiring a second, unscheduled operation in the subsequent 15 days because of a complication.
- Formula: Number of transplant patients in a given period undergoing re-operation in the first 15 days/Number of transplant patients in the same period × 100.
- Type: Outcome

Early mortality post-transplant with functioning transplanted organ
- Definition: percentage of transplant patients who die during hospitalisation post-transplant with a correctly functioning transplanted organ.
- Formula: Number of transplant patients who died during post-transplant hospitalisation with normal transplanted organ function/Number of transplant patients × 100, for the same period.
- Type: Outcome

Post-transplant follow-up indicators

Re-transplant rate
- Definition: percentage of re-transplants overall in the series of transplants (not valid in kidney transplantation).
- Formula: Number of re-transplants in a given period/Total number of transplants in the series × 100.
- Type: Outcome

Survival of transplant patients
- Definition: survival rate of transplant patients in the series at 1, 3, 5 and 10 years post-transplant.
- Formula: Number of transplant patients alive at the time of each threshold or analysis (1, 3, 5 and 10 years)/Number of transplant patients at the beginning of the period. Actuarial survival curves (Kaplan–Meier method).
- Type: Outcome

Graft survival
- Definition: overall rate of graft survival in the series of transplants at 1, 3, 5 and 10 years post-transplant.
- Formula: Number of functioning organs at the time of each threshold or analysis (1, 3, 5 and 10 years)/Number of grafts transplanted at the beginning of the period. Actuarial survival curves (Kaplan–Meier method).
- Type: Outcome

Mortality post-transplant with functioning transplanted organ
- Definition: percentage of transplant patients who die with a well-functioning transplanted organ.
- Formula: Number of transplant patients who died with normal transplanted organ function/Number of transplant patients × 100, for the same period.
- Type: Outcome

Transplant patients' satisfaction
- Definition: level of overall satisfaction of transplant patients evaluated by means of a satisfaction survey.
- Formula: overall measurement of user satisfaction after scoring each item on the survey.
- Type: Outcome

TC: transplant centre.

Source: [31, 39].

Multiple variables affect organ transplantation (type of organ transplant, living or deceased donors, urgent or elective transplant etc.), and a global approach needs to be taken for the transplant process. In general, the term 'transplant/transplantation centre' will be used for all those health centres that, by fulfilling the established requirements, are duly authorised to perform some type of organ transplant.

Following the same outline as in the previous section, the different quality criteria used for organ transplant are now reviewed.

16.6.1. Organisational issues: legal framework, functional organisation and personnel

A transplant centre that performs any type of organ transplant, with organs from living and/or deceased donors, must have specific authorisation/accreditation from the competent Health Authority to conduct such activity [7].

As multidisciplinary functional units, transplant centres must have an establishment plan and an organisational structure with well-defined responsibilities and hierarchies in all areas of activity (medical, surgical, anaesthesia, nursing, etc.). In all cases, functional management positions must be filled by doctors and nurses who specialise in the area in which they work. Transplant centres must have specific and qualified personnel, in adequate and sufficient number so that each stage of the process can be carried out throughout the year, including the holidays. There must also be an organisational and functional description of the different positions, which should include the profiles and qualifications

required, and the activities corresponding to each functional group [30].

Transplant centres must have formal internal communication in the form of regular meetings in which all healthcare personnel concerned take part (and administrative personnel if necessary). In these meetings, key issues are analysed, such as:

a. Evaluation of recipients and consensual decision on transplant indication and patient prioritisation.
b. Information on and evaluation of morbidity of transplant centre patients.
c. Decisions made on treatment strategies for patients who are to be placed on a waiting list.
d. Follow-up of the status of patients on a waiting list.
e. Analyses of outcomes individually and compared with other groups or areas.
f. Other informational or organisational issues.

A record of the issues dealt with at each meeting should be kept in the form of minutes. The outcomes achieved by the programme should be made public on a regular basis (usually annually) with the publication of a report on healthcare, teaching and research activities.

Centres should ensure that they carry out the required procedures in the study and follow-up of patients. Centres must ensure that they carry out the examinations considered necessary, either at the centre itself or through co-ordinating centres.

Transplant centres must have adequate physical space to suit the needs of the different areas for inpatients and outpatient follow-up visits.

In addition, transplant centre personnel should also include an independent head of quality management, independent in the sense that this person is not directly involved in the organ donation programme.

Finally, following Directive 2010/53/EU, member states in the EU shall ensure that the Health Authority draws up and makes publicly accessible an annual report on activities of procurement organisations and transplant centres, including the types and quantities of organs procured and transplanted [5].

16.6.2. Education and continuous training

All staff involved in transplant activities must be suitably qualified or trained, competent to perform their tasks and provided with the relevant training [5]. Transplant centres must have an integration plan for new members of staff. This plan should include a description of the activities to be performed, the people responsible for training and mentoring at each stage and the duration of each stage, and the person responsible for validating the new staff member's training.

There should be a continuous professional development programme for all transplant centre personnel, based on properly identifying training requirements (through surveys, analysing complaints, adding new procedures, etc.), which should be communicated to all members. All training activities should be properly recorded, along with the training outcomes achieved, and the training's effectiveness in meeting the envisaged objectives should also be evaluated.

16.6.3. Transplant process: implementation of protocols

The healthcare activities needed to perform transplants and the quality characteristics they entail must be described. The transplant process includes different stages, which should be properly monitored and written into procedures and protocols [30]:

a. Assessment and consensus, with the aims of assessing and agreeing whether a transplant is indicated for the patient and, if so, establishing a degree of urgency or priority and specific measures to optimise results. Transplant centres should have procedures and protocols that define and provide for the process of assessing a patient as a transplant candidate in order to ensure that it can be done in the shortest time possible. Subsequently, a multidisciplinary committee must decide whether to place a patient on the corresponding waiting list, leaving a written record of the decisions taken.
b. Management of patients awaiting a transplant, which includes:
   i. clinical, organisational and administrative criteria for placing patients on the transplant centre's waiting list and regional/national registries (as applicable);
   ii. clinical monitoring of patients on the waiting list to enable optimisation of the overall situation of patients so that they arrive in the best condition possible for transplantation;
   iii. establishing the level of priority for transplantation (based on the use of prognostic scores);
   iv. appropriate distribution of grafts in accordance with donor–recipient eligibility;
   v. communication: at this stage, patients (and in most cases their immediate family members) should be properly informed, both verbally and in writing, of the need for transplant, as well as

the different phases of the process and the possible complications. Patients who agree must grant their consent to be placed on the waiting list as well as to undergo the transplantation when the time comes. There should be an educational programme for patients and families on the care required for getting into the best physical and psychological shape possible and preventing early and late post-transplant complications and on the importance of complying with the therapeutic regimen.

c. Peri-operative management of transplanted patients, which should be defined and written into protocols related to:
   i. procuring donor organs of all types (living or deceased donors, in hospital or out of hospital, whether obtained by the centre's staff or by another centre) and ensuring the validity of the organ obtained;
   ii. transportation of organs, including medical team, packaging, labelling, safety and integrity, identification, real-time monitoring of temperature and traceability of the organ during the process; the transport procedure should be validated and also performed by a qualified courier;
   iii. correctly allocating organs to recipients;
   iv. correctly preparing patients;
   v. optimising the time to start of surgery and immediate results in transplanting the organ;
   vi. transplanting the appropriate organ in line with the recipient's clinical characteristics;
   vii. organising and co-ordinating the various professionals and units involved in order to ensure that needs are met and possible contingencies accounted for.

d. Post-transplant hospitalisation, which establishes the care required for patient recovery during the immediate and early post-operative periods after transplantation (in the ICU and the subsequent hospitalisation in the ward) and the monitoring of complications and optimisation of treatment to prevent organ rejection and immuno-suppression-associated toxicity.

e. Post-transplant follow-up, which establishes appropriate clinical follow-up after hospital discharge in order to increase patient survival and quality of life and to minimise and/or anticipate the possible complications that frequently occur during the first year after transplantation: infections, acute drug-related toxicity, immune disorders, reactivation of the underlying disease, etc. For this post-transplant follow-up, there should be clinical protocols (e.g. follow-up visits, possible complications and treatment for them) and drug treatment (e.g. immuno-suppression, use of antibiotics). The mid- and long-term follow-up of transplanted patients should also be ensured and continuously documented. This is crucial not only for the survival of the patient and their graft, but also more generally for the whole scientific community to learn from past transplants.

16.6.4. Quality indicators

Some medical societies and working groups have defined their systems of transplant quality management by selecting various QIs that, when monitored, enable relevant aspects of the process to be measured and evaluated periodically [31-39]. These monitoring systems should include, as a minimum, the frequency of measurements, the system of collecting information and the person(s) responsible for collection.

Adopting a monitoring system based on indicators involves a commitment from the transplant centre to act – whenever the practice being evaluated gives results outside the established standards – by analysing the results obtained, identifying the causes and implementing improvement cycles where appropriate (e.g. the PDCA/PDSA cycles). It is crucial that all professionals involved keep this commitment in mind; otherwise the measurement becomes routine and has no utility in the management of the unit [17].

In order to avoid a too-exhaustive description, we have selected some indicators that could be used, with minor modifications and regardless of the type of organ transplant, to evaluate organ transplantation in the different phases discussed in section 16.6.3.

The list of selected indicators is shown in Table 16.5, specifying definition of the indicator, formula used to calculate it and the type of indicator (process, structure or results). The standards to be met have not been included, because these differ for each type of organ transplant. More detailed information is available in references [31-39].

16.6.5. Audits and quality evaluation

As in the donation process (see §16.5.5), the viability of a QI monitoring system should be evaluated by internal and external audits, thus enabling improvement measures to be subsequently taken as needed.

16.6.6. Documentation and registries, traceability, vigilance system, assessment and mitigation of risks, complaints and recalls, and resource management

The entire process – starting from reception of the organ through to the transplantation and post-operative care – should be clearly documented, and criteria for each aspect should be defined. It is not exceptional to find that errors occurred because the documentation before transplantation was lacking. Clinicians should be made very attentive to documenting each step after receiving the transplant organ.

In order to detect possible inconsistencies in data collection, it is important to have a data-control system. Relevant data should be reviewed at transplant centre level, and at the allocation office, as a measure to automatically control the plausibility of data (e.g. laboratory values with normal creatinine and very high values for urea are not plausible).

The quality criteria relating to all of these support processes can be superimposed on those mentioned in the respective sections on quality management in organ donation, and so the reader is encouraged to review sections 16.5.6 to 16.5.11.

16.7. Final remarks

Although implementing a quality management system in the process of donation and organ transplantation may seem to be a complex process likely to involve an increased workload for the healthcare professionals concerned, the many advantages of doing so offset the initial effort. Some of these advantages include:

a. Task systematisation and standardisation of criteria in daily activities.
b. Support in visualising, analysing and improving workflow.
c. Involvement of personnel in daily activities, which contributes to better teamwork.
d. Definition, measurement and analysis of QIs, which makes results-based decision-making easier.
e. Increased transparency and satisfaction of patients and healthcare professionals, and therefore improved trust in the transplant system (which in turn might be beneficial for organ donation).
f. Valuable management tool, and increased motivation of healthcare personnel.
g. Promotion of continuous improvement.

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Chapter 17. Measuring outcomes in transplantation

17.1. Introduction

The aim of organ donation and transplantation is to try to provide all recipients on the waiting list with a chance to survive with an adequate quality of life. Therefore organ transplantation should preferably occur just in time before end-stage organ failure becomes life-threatening.

For donor relatives and/or the donors we are obliged to use any organ with the best chance of long-term function in the recipient selected. For organs and recipients with a limited functional and survival expectancy due to medical, biological (e.g. age) or transplantation factors, we have to find a compromise on how to use such organs and transplant them into such recipients properly. Therefore we have to weigh these factors and we have to make the best decision for both the recipient and the donor. This means that we have to realise that sometimes it might be the best option not to choose the patient with the highest priority on the waiting list, but instead someone lower on the waiting list, in order to avoid a futile transplantation.

This concept is probably best described with a 'benefit score'. We are still dealing with a serious shortage of donor organs, so decisions are sometimes not in the best interest of a specific patient, but decisions should always be in the best interest of all patients in need of an organ. In order to monitor whether such decisions are correct or not, we have to ask ourselves whether all factors have been considered properly. Measuring and analysing outcomes will help to properly weigh all the factors involved.

In organ transplantation we are dealing with a complex combination of donor, recipient and transplantation factors, including a large number of confounders that interact with each other in generating the outcome. Caution is also needed in the interpretation of data, because stakeholders and shareholders have various interests in the perception of results. Besides, the number of subjects investigated is usually limited and outcomes may be skewed.

The aim of this chapter is to provide some guidance on how to measure outcomes after transplantation in order to prove the correctness of guidance in previous chapters on improving quality and safety, and how to best deal with the current shortage of organs with regard to allocation.

17.2. End-points to measure, study period and confounders

In any study, end-points should be clearly defined. It should be explained what outcomes (patient or graft survival, death-censored or non-death-censored) are to be measured and whether short- or long-term results are evaluated. Furthermore, it is important to describe the intention and possible applications of the study results.

17.2.1. End-points to measure

Outcomes are usually measured by survival analysis. A survival analysis measures the time from the starting point of an observation, e.g. transplantation or entry onto waiting list, until occurrence of

an event, e.g. graft failure or recipient death, and it is analysed for a certain study period. Another way of measuring outcome is by follow-up of a recipient until a fixed time point when someone checks whether some event or measurement has been observed or not, e.g. returning to work or glomerular filtration rate (GFR) at one year after transplantation. Each method has its advantages and limitations.

Most commonly end-points are measured by survival analysis [1-4]:

- Patient survival: time interval from transplantation to death of a recipient independently of graft-failure events. Therefore, the observation of patient survival should be extended beyond the end-point of graft-failure events or the record should state that observation has ended at this point.
- Graft survival: time interval from transplantation to graft failure, regardless of whether graft failure or recipient death occurs first.
- Graft survival death-censored: time interval from transplantation to graft failure, with the event of recipient death with a functioning graft censored, assuming that the recipient left the observation of the study with an appropriate graft function. This may be used to mitigate the issue of competing risks such as death with functioning graft *versus* graft failure caused by other issues. Then the assumption of proper graft function needs to be explained well because the event of death related due to insufficient poor graft function cannot be excluded.

Each end-point has its justification with pros and cons [2-3]. Best practice is to report all end-points or to clarify the use of only one particular end-point, e.g. graft survival, because multiple risk factors can cause graft failure in a set of combinations, e.g. death with a suboptimal functioning graft and recipient-related factors.

A second issue is the definition of graft failure, which should be explained well. For example, disregarding the event of re-transplantation, graft failure may be defined as:

- in kidney transplantation: return to dialysis, or GFR below a threshold value;
- in liver transplantation: return to waiting list due to malfunction;
- in pancreas transplantation: need for use of exogenous insulin (and how much), or Hb1Ac > 48 mmol/mol (> 6.5 %) according to the WHO diabetes definition.

It is obvious that, for such alternative failure events, the first occurrence of one of the alternative events is imputed.

17.2.2. Study period

Occurrence of a particular complication can also be analysed in relation to the time interval from transplantation until manifestation of the complication, e.g. diagnosis of ischaemia-type bilary lesion (ITBL) in liver transplantation. Then again, the issue of competing risks should be considered, e.g. death of the recipient for other reasons or re-transplantation for other reasons.

This is a key problem: what to do with subjects in a study who cannot be observed for occurrence of an event because they have dropped out of the study due to competing failure events. In such a case the subject has no chance to experience the event of interest. One example of how to handle this problem would be a decision, when conducting survival analysis that focuses on graft failure, to censor deaths during the observation period; equally problematic are fixed measurements at certain time points, such as numbers returning to work within one year after transplantation, if some recipients have died postoperatively with a non-transplanted related issue.

It should also be clearly indicated whether outcome is measured on the basis of intention to treat or on the basis of an actually occurring intervention. In both cases it should be mentioned what was or is done with the cases not receiving the intervention or cases where there was deviation from the intention to treat.

17.2.3. Confounders

The examples in section 17.2.2 show that looking exclusively at one risk factor will not give a correct view without adjustment for confounders. On the other side, failure events or complications may be caused by one common bundle of risk factors e.g. graft failure and/or ITBL may be caused as a result of prolonged ischaemia times, incorrect flush of organ and bile ducts at procurement, prolonged anastomosis time or arteriosclerosis. This requires careful analysis of all single factors and their contribution to a global result.

For survival analysis, the following methods are often used:

- Kaplan–Meier analysis, which shows up the influence of a single risk factor on the time interval after transplantation until the failure event occurs, without adjustment for con-

founders. The risk factor can be dichotomous or a group of classes, or it may be a metric variable split into certain categories. With 'increasing risk' of the risk factor, a monotonously increasing sequence of curves should be visible without any crisscrossing of the curves. Furthermore, the number of cases at risk diminishes with time and therefore care should be taken in deriving strong conclusions if 'the numbers at risk' are too low.

- In Cox regression models, multiple variables can be considered for their combined influence on outcome. This may be stated as adjustment for confounders. The risk of a specific risk factor is described by the Hazard ratio: the risk is significantly increased when the Hazard ratio and the 95 % confidence interval are above 1, and there is protection from risk when both are below 1. When the 95 % confidence interval crosses 1, there is no significant change in risk. Still no adjustment exists for confounders not considered in the model. Therefore, selection of variables in the statistical model is crucial and should be explained properly. For metric variables in the model, the Hazard ratio should be explained as related to increment in one unit or increment over the whole population. In such multivariable models, conclusions about a single factor require careful consideration of the confounders analysed too. For proper analysis of competing risk events the sub-distribution hazards according to the method of Fine and Gray can be used – especially for long-term analysis. Otherwise the same principles apply as have been mentioned for Cox regression [5-9].

It is recommended that the analyst should plan studies and discuss the results with an expert in medical statistics because pitfalls exist in the interpretation of data in survival analysis. For further details please refer to the specific literature (e.g. further statistical test used). Some examples of survival analysis are shown in Table 17.1.

In outcome analysis, static end-points need exact definitions, which need to be specified. These end-points can be categorical measurements or metric measurements associated with a time point. Also, the defined parameters must include the time that is to elapse before checking whether this event has occurred or not (see Table 17.1 describing examples of organ-specific end-points). Absolute numbers of cases and their percentages are of interest in dichotomous factors as well as in the distribution of metric factors. It is helpful to adjust single parameters for confounders by appropriate regression models. Again it is recommended that results are discussed with an expert in medical statistics as pitfalls exist in interpretation of data.

17.3. Selection of and adjustment for covariates or treatment bias

Care is required when selecting variables to be included in an outcome analysis study [2-3, 11]. Enough data exist to show that outcome depends on donor quality and the recipient's condition, but also on the expertise of a centre and other transplantation factors such as organ preservation and donor management. Overlooking important confounders will result in incorrect analysis. Without proper consideration of this risk, the study might become questionable.

Depending on the case-mix of the population investigated, different results may be expected: naturally, centres specialising in paediatric transplantation will have different data from centres specialising in adult transplantation, but (less obviously) due to the allocation rules it cannot be predicted which graft will go to which centre with its own special case-mix. Proper correction for case-mix will be required. The use of propensity scores is currently advocated as a method to compensate for the bias caused by confounders not expected, e.g. overlay due to effects of immune-suppressive treatment in a study. However, adequate identification of possible confounders and correction for risk factors is essential before methods such as propensity scores are used.

Therefore it is important to adjust for covariates by multivariable methods before a result of single variable analysis can be confirmed [2-3, 11]. The study report should include all details about risk factors considered or not considered, due to lack of data or sample size, for example. When an association exists between multiple risk factors, which all have an impact on outcome, then using a single risk factor – that subsequently depends on the other factors – has to be done with caution [12].

When defining end-points for measuring outcomes and selecting risk factors that potentially influence these outcomes, it has to be kept in mind that all relevant clinical factors are to be included in the statistical model [2-3]. A transparent explanation of this process is mandatory. Best practice is to perform external validation of the thesis in an independent study group [13]. It is recommended that validation of

such risk factors is repeated over time, because their influence might be due to chance or they might even become outdated in their prognostic contribution (e.g. the risk factor of donor hepatitis C viraemia will change in its relevance due to the possible treatment by direct-acting antiviral agents in the recipient).

When outcome-prediction models are to be imported from one healthcare system into another, it is essential that the validation process is repeated with a representative study population within such a healthcare system. However, discrimination and calibration of the prognostic system might then fail and the whole process of developing a prognostic scoring system would have to be repeated. Two important limitations exist. For investigation of a particular risk factor in many populations, there may be an insufficient number of cases and/or events observed and therefore no conclusions with proper risk adjustment are possible. Furthermore, for most study groups in the range of the extreme values of risk factors, a predictive model performs well, whereas in the majority of the cases within the range of intermediate values of the risk factor no acceptable degree of discrimination exists; e.g. Donor Risk Index for kidneys [14]. These issues have to be explained well.

17.3.1. Long-term follow-up *versus* short-term follow-up

Ideally, we would have decades of data from monitoring the long-term function of grafts, using patient-, graft- and death-censored measures of graft survival as well as quality-of-life measurement of the recipient over the timeline of survival. Manifestation of complications due to existing risk factors or avoidance of complications by interventions could be monitored precisely in their short-term and long-term effects.

Unfortunately we cannot wait decades to adapt interventions and decisions while withholding optimised organ-replacement therapy for future recipients. Therefore science has to look for surrogate markers to predict long-term function by short-term observations and extrapolation of the assumed risk into the future, e.g. by patient-, graft- and death-censored graft survival as well as quality-of-life measurement of the recipient, limited to short periods of one, two, three or five years. In a second step, studies should confirm the primary assumptions by long-term follow-up.

Most complications occur during the early period after transplantation (typically the first two years) but, after this first and steep incline of risk, complication rates plateau to a more constant level over time. However, some risk factors have a higher impact during the early post-transplant period (e.g. infection during the early phase of intensive immunosuppression) whereas others become more important in the longer term (e.g. death due to cancer after many years of immunosuppression). This requires adjustment in the methods of measuring outcome. It is evident that early complications could be well described with only a short follow-up period, whereas long-term complications and outcomes would be missed in such a study.

The issue of time-dependent covariates and competing risks should be considered too. For example, when monitoring outcomes for patients put on the waiting list, then it would be of interest to know what happens in candidates not being given a transplant *versus* candidates with transplants after having survived a certain waiting time and being exposed to the event of graft failure [15].

17.3.2. Surrogate markers for long-term function

Surrogate markers for long-term survival or assumed indicators for reliable prognosis in long-term survival should be described in the researcher's consideration of their assumptions. The proof of concept should be provided by long-term measurement of hard end-points, e.g. by survival analysis or description of quality of life achieved. For example, enough data exist for the surrogate marker GFR measured [16] and prognosis after kidney transplantation regarding graft survival. On the other hand, several studies have shown that kidney grafts from donors with acute kidney injury can be used without impact on outcome, while they also report the need for post-operative dialysis requirements. Clearly, delayed graft function (DGF) cannot be used as a surrogate marker in such studies because all patients would fall within the definition for DGF. This needs careful explanation of what is being investigated.

17.3.3. Centre effect and duration of study period

Adjustment for centre effect and length of study period should be considered too [17-18]. Depending on the case-mix of the donor and recipient populations investigated, different results are observed. For a study with a long period of recruiting cases, a bias for changes in medicine should be considered. This can be corrected by noting specific study periods in relation to known milestones in medicine or, if they

are not applicable, by including a metric factor of study time.

In a small series there is a risk of bias caused by the interest of the study and recruiting of subjects. Pilot studies are under pressure to push patients through the study period in order to obtain results. This issue requires confirmation by monitoring the usability of study data in clinical practice by independent control studies and proper follow-up of the initial study population.

In the case of an analysis of a single centre, all adjustments for confounders or involved risk factors should be applied in order to eliminate the issue of a policy of avoiding risk behaviour due to external control with open access. Since we have an organ shortage, single centres should not be punished for using higher-risk organs when they are able to achieve results equivalent to other centres. However, transparency should be promoted and therefore it is essential to show or publish results. Of course, results should be shown in the context of donor quality and recipient condition, and adequate correction for involved risks (case-mix) is essential. This does not exclude careful monitoring of a trend analysis towards failure accumulation in a single institution caused by other issues.

Furthermore, due to different policies in healthcare systems, centre effects may not be attributable to donor-, recipient- or procedure-related risk factors but to other issues based on the concept of that particular healthcare system [19].

Table 17.1. **Some examples of organ-specific outcome measurements**

Indicator	Heart	Lung	Liver	Kidney	Pancreas	Intestine
Patient survival	**Time interval: death; Clarify cause of death**					
Graft survival (uncensored for death of recipient)	Time interval until death with functioning graft *or* re-transplantation *or* return to assist device *or* graft-ectomy, whichever occurs first.	Time interval until death with functioning graft *or* re-transplantation *or* graft-ectomy *or* return to ECMO, whichever occurs first.	Time interval between transplant and graft loss secondary to either re-transplantation *or* recipient death, whichever occurs first.	Time interval until return to dialysis *or* death, whichever occurs first. Alternatively time interval to return to dialysis can be determined by a cut-off value of the glomerular filtration rate (GFR).	Time interval until return to exogenous insulin use (e.g. ≥ 0.5 IU/kg/day for > 90 consecutive days) *or* HbA1c > 48 mmol/mol (6.5 %) (diabetes according to WHO) *or* recipient death, whichever occurs first.	Time interval until death with functioning graft *or* re-transplantation *or* failure (e.g. re-introduction of enteral nutrition) *or* graft-ectomy, whichever occurs first.
	Currently several definitions are used, so this parameter requires clarification, including the cause of failure.					
Graft survival (censored for death of recipient)	As above but censored for death of recipient with functioning graft as a no-failure event. This is a very critical issue, because authors must meticulously state the exact definitions, being used in the article, of when they consider a graft as still functioning *or* not functioning. In cases of marginal *or* impaired organ function, the interaction of recipient death and poor graft function cannot be ruled out.					
Graft-related complications	It is arguable whether occurrence of particular complications may be used as an outcome measurement *or* not, and also how the time interval between transplantation and event is considered. This must be defined in the study protocol.					
	e.g. coronary heart disease	e.g. bronchiolitis obliterans	e.g. biliary leakage; ITBL	e.g. proteinuria	e.g. pancreatitis, thrombosis	
Functional parameter	e.g. cardiac output	e.g. gas exchange	e.g. coagulation, liver enzymes	e.g. GFR	e.g. HbA1c, amount of insulin used	
Delayed graft function (DGF)	Usually defined as a yes/no event based on items listed below and as outlined in the study protocol					
	e.g. until weaned off inotropics *or* assist device	e.g. until weaned off ventilator *or* ECMO	In liver transplants, it is referred to as slow *or* intermediate graft function (SGF *or* IGF). In that case, cut-off levels need to be stated in the manuscript.	Despite multiple definitions of DGF in kidney transplants, 69 % of studies use this definition: DGF is the need for dialysis within the first week after transplantation [10]	e.g. until weaned off insulin	
Primary non-function of graft (PNF)	e.g. never weaned off inotropics or assist device	e.g. never weaned off ventilator and/or ECMO	e.g. re-transplantation or death without initial function	e.g. never weaned off dialysis	e.g. never weaned off insulin	
Reperfusion damage						
Duration of stay at ICU	Time interval					
Duration of hospital stay	Time interval					
Quality of life	Parameters to be extracted from rehabilitation medicine					

ECMO = extracorporeal membrane oxygenation.

Time interval: can be either two measurements as fixed time points (start time, end time) or a single measurement of duration of transplantation or elapsed time until specific event occurs. This list is not exhaustive, and the factors mentioned can be combined with each other. In the literature, multiple definitions are used for graft function or failure that might be justified in the context of that specific published study.

17.3.4. Pressure to publish

Most studies are under pressure to publish quickly. Exhaustive waiting for long-term results might not be in the interest of stakeholders or shareholders. Furthermore, study results might be misinterpreted to better match the interests of the readers.

17.4. Challenge of statistics

For readers of studies who are not familiar with all details of statistics, the interpretation of data and conclusions is difficult. Authors should consider this. When talking about models, authors should always state clearly how good the prognostic values are and what limitations exist.

Regarding the quality of predictive models, c-statistics might be helpful: according to Harrell, a c-value of 0.5 corresponds to a random experiment of flipping a coin, while values of > 0.7 are acceptable as predictions and values of > 0.9 can be regarded as perfect predictions. In the transplantation setting it will be difficult to achieve a c-index of > 0.7 because we want to predict outcomes for people who have received an organ transplant, a procedure that is always influenced by many uncontrollable factors and events, with low numbers of cases. This should be well considered, especially when such models are used to discard or to use donor organs without further individual risk–benefit assessment of the donor–recipient combination.

17.4.1. Profiles of risk factors change over time

Established models used in discussion of risk factors have to be re-evaluated regularly for their validity because donor populations and recipient populations change in their case-mix over time (e.g. donor age, cause of death, co-morbidities, recipient age, human leukocyte antigen immunisation, therapy concepts or other technologies). Risk factors themselves may change, or new risk factors may become apparent. New procedures (e.g. machine perfusion, normothermic regional reperfusion) may improve outcome and may subsequently change donor-risk evaluation. Therefore it is necessary to continually re-examine the models and concepts in use in order to identify changes and re-educate users with the aim of changing attitudes to risk–benefit assessment to ensure that it is properly performed.

17.4.2. Monitoring of trends in performance

Although we are faced with limited resources financially as well as in the number of organs, we have to ensure that an appropriate and optimal quality is achieved for each transplantation [2, 20]. Centres and/or regions that, after correction for risk factors based on the case-mix of recipients and donor grafts, show a performance above average should be monitored to help other centres in copying best practice. At the same time, outliers below average should be evaluated for identification of known or possible new risk factors. It is important to keep in mind that unavoidable differences may exist between various centres, regions and countries [19].

Within centres and healthcare systems a drift of outcome data should be monitored too in order to identify changes in risk factors at an early stage [21]. When monitoring such data it is important to identify whether, either at single institutions or in the healthcare system as a whole, there is any extreme risk-avoiding behaviour when selecting transplant recipients and grafts with the sole purpose of positively influencing outcome measures. Note that monitoring of outcomes of transplantation should include the whole process, starting with entry of patients onto the waiting list and their exposure to transplant-associated risks later on [15, 17-18]. Transplantation outcomes well below average may be explained by risk avoidance or risk acceptance in the choice of recipients or grafts.

Different methods have been applied to monitor such trends, each method having its own strengths and weaknesses. Despite careful interpretation of the data, a low number of cases per transplantation unit might be a limiting factor for the application of regression models. In order to have an appropriate set of primary data in registries, all resources of electronic data availability should be used (e.g. waiting list database, donor database, allocation database) so that double documentation of existing data is avoided and clinically relevant data can be added to the registry. Personal data protection should be assured when analysing registry data.

For research purposes, secondary data analysis might help to monitor for trends in the whole healthcare system. For a primary approach, some quality indicators exist and are in use, with and without adjustment for risk factors (see Chapter 16 and published national data).

17.5. Conclusion

Measuring outcome after transplantation is complex. No perfect method exists to give the user a complete picture. Instead, each approach has its limitations and merits. If a combination of methods produces an easy-to-understand result,

then the outcome reported should be regarded as suspect and needing further investigation, regardless whether it is a desirable or undesirable result. In the case of a user left with a gut feeling of distrust or alert about a change in the trend of results, the user should seek for clarification of this issue in order to avoid misunderstandings.

Especially when performing analysis for quality assurance of centre-specific performance, all efforts must be undertaken to educate all staff about what is inappropriate risk-avoiding behaviour, so that medical professionals and non-medical people do not try to avoid all risk. On the other hand, it cannot be accepted that a poorly performing institution can hide behind multiple excuses (e.g. data protection, burden of data collection for quality assessment). Therefore, central data collection, analysis and quality assessment are essential in any organisation to monitor and further improve outcomes after transplantation.

17.6. References

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Appendix 1. **Abbreviations and acronyms**

ABO	blood group according to the ABO system
ACLD	deaths with acute primary or secondary cerebral lesions
ADEM	acute disseminated encephalomyelitis
ADH	anti-diuretic hormone
ADM	aggressive donor management
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
AFP	alpha fetoprotein and placental
AHA	American Heart Association
AJCC	American Joint Cancer Committee
ALAT	alanine aminotransferase
ALL	acute lymphoblastic leukaemia
ALT	alanine aminotransferase
anti-CMV	antibodies against *cytomegalovirus* (total antibodies of IgG and IgM)
anti-EBV	antibodies against Epstein–Barr virus
anti-HBc	antibodies against the core antigen of the hepatitis B virus
anti-HBc-IgM	IgM-antibodies against the core antigen of the hepatitis B virus
anti-HBs	antibodies against the HBsAg-molecule of hepatitis B virus
anti-HCV	antibodies against hepatitis C virus
anti-HIV	antibodies against HIV
anti-HIV-1/2	antibodies against HIV subtypes 1 or 2
anti-HIV-1	antibodies against HIV subtype 1 only
anti-HIV-2	antibodies against HIV subtype 2 only
AOTDTA	Australian Organ and Tissue Donation and Transplantation Authority
APTT	activated partial thromboplastin test
AR	adverse reaction
ARE	adverse reactions and events
ASAT	aspartate aminotransferase
AST	American Society of Transplantation
AST	aspartate aminotransferase
ATP	adenosinetriphosphate
ATP	ancillary therapeutic product
BAL	broncho-alveolar lavage
Banff	Banff classification of renal allograft pathology
BCG	bacillus Calmette–Guérin
BD	brain death
BDD	brain death diagnosis
BKPyV	BK polyomavirus
BKV	BK virus
BM	bone marrow
BMI	body mass index
BNP	B-type natriuretic peptide
CA	cardiac arrest
CA	competent authority
CAD	coronary artery disease
CALM	contact–appoint–look ahead–make a decision [dealing with strong reactions]
CB	cord blood
CBF	cerebral blood flow
CDC	Centers for Disease Control and Prevention (USA)

cDCD	controlled donation after circulatory death
CD-P-TO	Committee of Experts on Organ Transplantation of the Council of Europe
CEA	carcinoembryonic antigen
CEN	European Committee for Standardization
CETC	Certification of European Transplant Co-ordinators
CGH	comparative genomic hybridisation
CHIKV	chikungunya virus
CI	cardiac index
CIT	cold ischaemia time
CJD	Creutzfeld–Jakob disease
CKMB	creatine kinase MB isoenzyme
CML	chronic myeloid leukaemia
CMV	*cytomegalovirus*
CNS	central nervous system
CNT	Centro Nazionali di Trapianti (Italy)
CO	carbon monoxide
CPAP	continuous positive airway pressure
CPK	creatinine phosphokinase
CPK-MB	creatinine phosphokinase-MB fraction
CPP	cerebral perfusion pressure
CPR	cardio-pulmonary resuscitation
CQI	continuous quality improvement
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant *enterobacteriaceae*
CR-KP	carbapenem-resistant *Klebsiella pneumoniae*
CT	computed tomography
CTA	computed tomographic angiography
CTC	circulating tumour cells
CVP	central venous pressure
D+/R–	donor has been infected by the pathogen, recipient is naïve (not infected)
D+/R+	both donor and recipient have been infected by the pathogen
D–/R+	donor is naïve (not infected), recipient has been infected by the pathogen
D–/R–	both donor and recipient are naïve (not infected by the pathogen)
DAA	direct-acting anti-viral agents
DBD	donation after brain death
DBI	devastating brain injury
DCD	donation after circulatory death
cDCD	controlled donation after circulatory death
uDCD	uncontrolled donation after circulatory death
DD	deceased donor
DENV	dengue virus
DGF	delayed graft function
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DKG	Double Kidney Transplant Group
DNA	deoxyribonucleic acid
DRI	donor risk index
DSO	Deutsche Stiftung Organtransplantation (Germany)
DTAC	Disease Transmission Advisory Committee (USA)
EBV	Epstein–Barr virus
ECD	expanded-criteria donor
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
ECLS	extracorporeal life support
ECMO	extracorporeal circulation with membrane oxygenation
ED	emergency department
EDD	European Donation Day
EEA	European Economic Area
EEG	electroencephalogram
EF	ejection fraction
EFQM	European Foundation for Quality Management
EG	ethylene glycol
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ELWI	extra-vascular lung water index
ENTV	elective non-therapeutic ventilation
EPAS	ET-pancreas allocation system
ERC	European Resuscitation Council
ESBL	extended-spectrum beta-lactamases
ESCIM	European Society of Intensive Care Medicine
ESGICH	ESCMID Study Group of Infection in Compromised Hosts
ESP	European Senior Program
ET	essential thrombocythemia (or Eurotransplant)
$EtCO_2$	end-tidal carbon dioxide level
ETT	endotracheal tube
EU	European Union
EuSCAPE	EUropean Survey on CArbapenemase-Producing *Enterobacteriaceae*
FAP	familiar amyloid polyneuropathy
FDG	fluorodeoxyglucose
FFP	fresh frozen plasma
FiO_2	inspired oxygen fraction

FISH	fluorescence *in situ* hybridisation
FMF	familial Mediterranean fever
FOUR	full outline of unresponsiveness (coma scale)
FP	framework programmes
FSME	endemic viral tick-borne encephalitis
FWIT	functional warm ischaemic time
GBM	glioblastoma multiforme
GCS	Glasgow Coma Scale
G-CSF	granulocyte-colony stimulating factor
GDRI	geographical disease risk index
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GIST	gastro-intestinal stromal tumours
GLP	good laboratory practice
GMP	good manufacturing practice
GN	Gram negative
HAM	HTLV-associated myelopathy
HAV	hepatitis A virus
HBsAg	surface antigen of hepatitis B virus
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis D virus
HEA	hydroxyethylamidons
HELLP	syndrome of haemolysis, elevated liver enzymes, low platelets
HES	hydroxyethyl starch
HEV	hepatitis E virus
HR	heart rate
HHV8	human herpes virus-8
HIV	human immunodeficiency virus
HIV-1-p24-Ag	p24-antigen of HIV, subtype 1
HLA	human leukocyte antigen
HMPAO	hexamethylpropyleneaminoxime
HOTT	Combatting trafficking in persons for the purpose of organ removal
HPA	hypothalamic-pituitary axis
HPC	haematopoietic progenitor cell
HPyVs	human polyomaviruses
HRP	hypothermic regional perfusion
HSV	*Herpes simplex* virus
HTK	Histidine-tryptophan-ketoglutarate
HTLV1/2	human T-cell-leukaemia virus subtype 1/2
ICHS	intracerebral haemorrhage scale
ICOD	intensive care to facilitate organ donation
ICP	intracranial pressure
ICU	intensive care unit
ID-card	identification card
IGRA	interferon-gamma release assay
IHS	intracerebral haemorrhage scale
ILCOR	International Liaison Committee of Resuscitation
INR	international normalised ratio
IPITTR	Israel Penn International Transplant Tumor Registry
IRI	ischaemia/reperfusion injury
ISHLT	International Society of Heart and Lung Transplantation
ISN	International Society for Nephrology
ISOL	intracranial space-occupying lesion
ISUP	International Society of Urological Pathology
ITBL	ischemia-type biliary lesions
ITBVI	intra-thoracic blood volume index
IV	intravenous
IVC	inferior vena cava
IVS	intraventricular septum
IVSd	thickness of intraventricular septum in diastole
iVx	inactivated vaccine
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations
JCI	Joint Commission International
JCPyV	JC polyomavirus
JPAC	Joint Professional Advisory Committee
KDIGO	*Kidney disease: improving global outcomes* guidelines
KDP	key donation person
KPD	kidney paired donation
KSHV	Kaposi sarcoma herpes virus
LCMV	lymphocytic choriomeningitis virus
LD	living donor
LDH	lactate dehydrogenase
LD-LR	living donor liver resection
LDLT	living donor liver transplantation
LDN	living donor nephrectomy
LH	left hepatectomy
LLH	left lateral hepatectomy
LOD	living organ donation
LTBI	latent tuberculosis infection
LVEF	left ventricular ejection fraction
LVx	live vaccine
MALORY	MALignancy in Organ donors and Recipient safetY
MAP	mean arterial pressure
MCL	medio-calvicular line
MDR	multidrug-resistant
MELD	model of end-stage liver disease
MERS-CoV	Middle East respiratory symptom coronavirus
MGUS	monoclonal gammopathies of undetermined significance
MI-LDN	minimally living donor nephrectomy

MPHO	medical products of human origin
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MRT	magnetic resonance tomography
MRSA	methillicine-resistant *Staphylococcus aureus*
MSM	men who have sex with men
NAT	nucleic acid amplifying technique ('nucleic acid testing')
NEC	neuro-endocrine carcinoma
NET	neuro-endocrine tumour
NHMRC	National Health and Medical Research Council
NIHSS	National Institute for Health Stroke Severity Scale
Notify	WHO Vigilance and Surveillance Database for MPHO
NR	non-reactive
NRP	normothermic regional perfusion
NSE	neuron-specific enolase
NTO	national transplant organisation
NURSE	naming–understanding–respecting–supporting–exploring [dealing with emotions]
OHES	out-of-hospital emergency services
OMF	osteomyelofibrosis
ONT	Organización Nacional de Trasplantes (Spain)
OPO	organ procurement organisation
OPTN	Organ Procurement and Transplantation Network (USA)
OTC	ornithine transcarbamylase
pa	pulmonary artery
$PaCO_2$	partial pressure of carbon dioxide
PanIN	pancreatic intraepithelial lesions
PaO_2	partial pressure of oxygen
paO_2	pulmonary artery oxygen
PAOP	pulmonary arterial occlusion pressure
PASS	pheochromocytoma of the adrenal gland: scaled score
PBC	primary biliary cirrhosis
PBPC	peripheral blood progenitor cells
PCC	pheochromocytoma
PCR	polymerase chain reaction
PDCA	plan–do–check–act cycle
PDSA	plan–do–study–act cycle
PEEP	positive end-expiratory pressure
PET	positron emission tomography
PGL	paraganglioma
PHS	public health service (USA)
PLAP	placental alkaline phosphatase
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
PNF	primary non-function
PNF	permanent non-function
P-PASS	pre-procurement pancreas allocation: suitability score
PSA	prostate-specific antigen
PT	prothrombin time
pTis	tumour *in situ*
PTLD	post-transplant lymphoproliferative disorders
PV	polycythemia vera
pvO_2	pulmonary vein blood-gas determination
QA	quality assurance
QAP	quality assurance programme
QC	quality criterion
QI	quality indicator
QIP	quality improvement programme
QMS	quality management system
RCC	renal cell carcinoma
RH	right hepatectomy
RL	risk level
RP	responsible person
SaBTO	Advisory Committee for the Safety of Blood, Tissues and Organs (UK)
SAE	serious adverse event
SAR	serious adverse reaction
SARE	serious adverse reaction or event
SCD	standard criteria donor
SIRS	systemic inflammatory response syndrome
SMA	superior mesenteric artery
SoHO	Substances of Human Origin
SOL	space-occupying lesion
SOP	standard operating procedure
SOT	solid-organ transplantation
SPECT	single-photon-emission computed tomography
SPIKES	setting–perception–invitation–knowledge–emotions–strategy/summary [breaking bad news]
SSRI	selective serotonin re-uptake inhibitors
STD	sexually transmitted disease
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TA-NRP	thoraco-abdominal NRP
TB	tuberculosis
TBE	tick-borne encephalitis
TC	transplant centre
TCA	tricyclic anti-depressants
TCD	transcranial Doppler

TPHA	*Treponema pallidum* haemagglutination
TPM	transplant procurement management
TSE	transmissible spongiform encephalopathies
TST	tuberculosis screening test
TTS	The Transplantation Society
uDCD	uncontrolled donation after circulatory death
UK	United Kingdom
UNOS	United Network for Organ Sharing (USA)
UTI	urinary tract infection
UW	University of Wisconsin
V&S	vigilance and surveillance
VCA	vascularised composite allograft
VZV	varicella–zoster virus
WHO	World Health Organization
WIT	warm ischaemia time
WLST	withdrawal of life-sustaining therapy
WNV	West Nile virus
X-ray	X radiation

Appendix 2. **Glossary**

Acirculatory time See 'Primary warm ischaemia time'.

Actual organ donor A consented eligible organ donor in whom an operative incision has been made with the intention of organ recovery for the purpose of transplantation. An actual deceased organ donor is defined as a person from whom at least one organ has been recovered for transplant purposes.

Adverse event An undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to harm in solid-organ transplant recipients or living organ donors. See also 'Serious adverse event'.

Adverse reaction An unintended response, including a communicable disease, in the recipient or in the living donor that might be associated with any stage of the chain from donation to transplantation. See also 'Serious adverse reaction'.

Agonal phase The period from withdrawal of ventilatory support until circulatory arrest.

Allocation The process for the assignment and distribution of organs.

Ancillary tests Auxiliary or supplementary tests used for the determination of death by neurologic criteria. Ancillary tests can assess electro-physiological activity or brain blood flow.

Apnoea test Procedure to evaluate the cessation of the spontaneous breathing reflex regulated by the respiratory centres located in the brainstem.

Asystolic time See 'Primary warm ischaemia time'.

Audit Periodic, independent, documented examination and verification of activities, records, processes and other elements of a quality system to determine their conformity with specific internal or external requirements. Audits may be conducted by professional peers, internal quality system auditors or auditors from certification bodies.

Banff classification Schema for nomenclature and classification of renal allograft pathology, established in 1991 by Kim Solez and Lorraine Racusen in Banff, Canada. This classification has become the main instrument for setting standards in renal transplant pathology and is widely used in international clinical trials of new anti-rejection agents.

Brain death Death determined by neurologic criteria on the basis of evidence of irreversible loss of neurological functions, in persons with acute primary or secondary devastating cerebral lesions, induced by intracranial events or the result of extracranial phenomena, such as hypoxia.

Cell The smallest transplantable and functional unit of life.

Circulatory death Death determined by circulatory criteria based on evidence of irreversible or permanent loss of the circulatory function.

Clinical triggers Specific medical criteria that, when met, should result in referral of the possible deceased organ donor to the donor co-ordinator or the staff of the corresponding organ procurement organisation by the treating physician.

Cold ischaemia time The elapsed time between the cooling of an organ after its blood supply has been cut off and the time when the organ is reperfused by circulation in the recipient. This interval can occur while the organ is still in the body or after it is removed from the body and applies only to organs stored by static cold storage. In cases of machine perfusion, it is not appropriate to use the term without providing more detailed information on the conditions (solutions, temperatures, oxygenation etc.) applied.

Compensation Reimbursement strictly limited to making good the expenses and inconvenience related to the donation.

Competent Authority See 'Health Authority'.

Consent to donation/authorisation of donation Legally valid permission from a person to donate an organ. In cases of living donation, this person must be given appropriate information beforehand about the purpose and nature of the intervention as well as its consequences and risks.

Controlled donation after circulatory death Donation from a person whose death has been established by circulatory criteria, following an expected circulatory arrest.

D+/R– Combination of a seropositive donor and a seronegative recipient for a given infectious disease. This combination should raise questions about the prophylactic measures to be taken to protect the recipient from harm.

D+/R+ When both the donor and the recipient have been infected by a given pathogen.

D–/R+ Combination of a seronegative donor and a seropositive recipient for a given infectious disease.

D–/R– When both the donor and recipient are naïve for (i.e. have not been infected by) a given pathogen.

Delayed graft function Manifestation of acute graft injury, with attributes unique to the transplant process, in which the graft takes up function with some delay after implantation.

Devastating brain injury Neurological injury where there is an immediate threat to life from a neurologic cause and where limitation of therapy is being considered in favour of palliative and end-of-life care.

Diabetes insipidus Form of diabetes caused by a deficiency of the pituitary hormone vasopressin, which restricts the rate of water excretion in the kidney. Clinical triggers for identification of this complication in deceased organ donors, related to the failure of the hypothalamic-pituitary axis, are polyuria (in the case of appropriate volume therapy) and hypernatraemia.

Distribution The process of transport and delivery of organs after they have been allocated.

Donation after brain death Donation from a person who has been declared dead on the basis of the irreversible loss of neurological functions.

Donation after circulatory death Donation from a person who has been declared dead on the basis of circulatory criteria. Depending on the clinical scenario in which cardiac arrest occurs, it can be classified as controlled or uncontrolled and in one of the four Maastricht categories. See also 'Controlled donation after circulatory death' and 'Uncontrolled donation after circulatory death'.

Donor A person, living or deceased, who is a source of one or several organs.

Donor assessment and selection The process of determining the suitability of a potential donor, living or deceased, to donate. This process allows a prediction of whether the transplantation of one or several of his/her organs will be safe for the recipient(s).

Donor card Personal document stating agreement to organ donation.

Donor characterisation The process of collecting the relevant information on the characteristics of the donor needed to evaluate his/her suitability for organ donation, in order to undertake a proper risk assessment, minimise the risks for the recipient and optimise organ allocation.

Donor co-ordinator Person responsible for the proactive identification of potential donors at hospital level and for co-ordination and support of all the subsequent steps supporting organ donation, including organ procurement and distribution. They may also be called 'transplant co-ordinator', 'key donation person' or other names.

Donor risk index Scoring system describing organ quality in a population from whom this score has been derived by multivariable statistical methods.

Elective non-therapeutic ventilation The initiation of mechanical ventilation, in patients with a devastating brain injury in whom further treatment is deemed futile, with the aim of incorporating the option of organ donation into their end-of-life care.

Eligible organ donor A person who has been found medically suitable to become an organ donor.

Expanded-criteria donor A donor in whom co-morbidities exist that may compromise organ function. This concept should not be confused with the non-standard-risk donor. See also 'Non-standard-criteria donor'.

Export The process of transporting human organs, tissues or cells intended for human application to another country where they are to be processed further or used.

False negative A test result which improperly indicates absence of a condition (the result is negative) when in reality the condition is present. An example of a false negative would be if a test designed to detect a given infection returned a negative result but the person actually did have the infection. Some common causes of a 'false negative' result include haemodilution, window period, investigation of the incorrect body compartment or inappropriate test quality.

False positive A test result which improperly indicates presence of a condition (the result is positive) when in reality the condition is absent. An example of a false positive would be if a test designed to detect a given infection returned a positive result but the person actually did not have the infection. Some common causes of a 'false positive' include contamination, cross-reactivity or inappropriate test quality.

Follow-up Subsequent evaluation of the health of a patient, living donor or recipient, for the purposes of monitoring the results of the donation or transplantation, maintenance of care and initiation of post-donation or post-transplant interventions.

Functional warm ischaemia time The period between the first episode of significant hypoperfusion and the start of *in situ* preservation.

Good practice A method or technique that has consistently shown results superior to those achieved by other means and which is currently used as a benchmark.

Graft Part of the human body that is transplanted in the same person or another person to replace a damaged part or to compensate for a defect.

Haemodilution Dilution of serum or blood sample used for laboratory investigations, due to infusions and transfusions.

Health Authority In the context of this Guide, a national or regional body to which the government has delegated the responsibility for ensuring that organ donation and transplantation are appropriately promoted, regulated and monitored in the interests of patient safety and public transparency. The terms Regulatory Authority, Regulatory Agency or, in the EU, Competent Authority, are equivalent to it.

Import The process of transporting human organs, tissues or cells into one country from another for the purpose of further processing or use.

Imputability Assessment of the probability that a reaction in a living donor or a recipient may be attributed to the process of donation or transplantation, or to an aspect of the safety or quality of the transplanted organ, tissue or cell.

Informed consent A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to donate an organ or to undergo a diagnostic, therapeutic or preventive procedure.

Intensive care to facilitate organ donation The initiation or continuation of intensive care measures in patients with a devastating brain injury, in whom further treatment is deemed futile, with the aim of incorporating the option of organ donation into their end-of-life care.

Intermediate graft function The terms 'slow graft function' and 'intermediate graft function' are used in liver transplantation as equivalent to DGF in kidney transplantation for the delayed start of graft function after transplantation. See also 'Delayed graft function'.

Ischaemia time The period during which an organ is deprived of its blood supply. See 'Cold ischaemia time' and 'Warm ischaemia time'. See also 'Functional warm ischaemia time', 'Lukewarm ischaemia time', 'Primary warm ischaemia time' and 'Total ischaemia time'.

Labelling The process, including the steps taken to identify the packaged material, of attaching all appropriate information to a container or package so that the information is clearly visible on the exterior of the carton, receptacle or packaging.

Living donor A living person from whom organs, tissues or cells have been removed for the purpose of transplantation. A living donor has one of these possible relationships with the recipient:

A. Related
A1. Genetically-related:
First-degree genetic relative: parent, sibling, offspring.
Second-degree genetic relative: grandparent, grandchild, aunt, uncle, niece, nephew.
Other than first or second degree genetically related, e.g. cousin.
A2. Emotionally related:
Spouse (if not genetically related), in-law, adopted, friend.

B. Unrelated = Non-related
Not genetically or emotionally related.

Lukewarm ischaemia time The uncontrolled period between the events of stopping of organ perfusion and proper storage of the graft in cold storage or on machine perfusion.

Lung-protective treatment Strategy applied in potential organ donors with the goal of increasing the number of lungs eligible for transplant. It includes these methods to prevent atelectasis and infection: continuous mucolysis, humidification of respiratory gases, aspiration of secretions, changes of body position and head-of-bed elevation (if no contraindications).

Model for end-stage liver disease Scoring system for predicting survival in end-stage liver disease based on laboratory data for bilirubin, creatinine and INR.

Negative Any 'negative' test result indicates only that the pathogen has not been detected. The medical community documents this as 'negative' without knowing whether the pathogen was missed or whether it did not exist. Equivalent to 'non-reactive'.

Next of kin A person's closest living relative(s).

Non-resident donor or recipient A person donating an organ or receiving a transplant who does not reside permanently in the country where donation or transplantation takes place.

Non-standard-criteria donor Donor in whom evidence of disease-transmission risk exists. The risk can be graded according to risk levels (which differ for infectious diseases and malignancies). This concept should not be confused with the expanded-criteria donor concept.

Normothermic regional perfusion *In situ* perfusion of organs with oxygenated blood using a device applied at normothermic temperatures.

Notify WHO Vigilance and Surveillance Database for MPHO.

Operating procedure See 'Procedure'.

Opting-in donation system A system where consent to donation has to be given explicitly from the donor or the next of kin. Also called 'explicit consent' or 'informed consent' system.

Opting-out donation system A system where donation can take place if there is no objection registered to donation. In practice, operational variations exist, just as with the 'opting-in' system in Europe, because the family still plays a prominent role in the decision-making process. Also (inappropriately) called 'presumed consent' system.

Organ A differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularisation.

Organ characterisation The process of collecting the relevant information on the characteristics of the organ, needed to evaluate its suitability, in order to undertake a proper risk assessment, to minimise the risks for the recipient and to optimise organ allocation.

Organ procurement organisation A healthcare establishment, a person, a team or a unit of a hospital, or any other body which undertakes or co-ordinates the procurement of organs and is authorised to do so by the responsible Health Authority under the regulatory framework in the member state concerned.

Positive Any 'reactive' test result that indicates either current or past exposure to a pathogen, after exclusion of a false positive result. Equivalent to 'reactive'.

Possible organ donor A patient with a devastating brain injury or lesion or a patient with a circulatory failure who is apparently medically suitable for organ donation.

Potential organ donor A potential DBD (donation after brain death) donor is a person whose clinical condition is suspected to fulfil brain-death criteria. A potential DCD (donation after circulatory death) donor is either a person whose circulatory and respiratory functions have ceased, and cardio-pulmonary resuscitation measures are not to be attempted or continued, or a person in whom the cessation of circulatory and respiratory functions is anticipated to occur within a time frame that will enable organ recovery.

Pre-emptive transplantation In renal transplantation this term is used for cases where transplant is performed prior to the start of dialysis as renal replacement therapy.

Preservation The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or inhibit biological or physical deterioration of organs between procurement and transplantation.

Presumed consent See 'Opting-out donation system'.

Primary non-function The situation when a graft never functions following transplantation.

Primary warm ischaemia time Primary WIT (asystolic or acirculatory time) is the period between circulatory arrest and the start of *in situ* preservation.

Procedure Description of the operation(s) or process(es) to be carried out, the precautions to be taken and measures to be applied that relate directly and indirectly to the transplant process from donation to transplantation.

Procurement The removal of organs, tissues or cells from a donor for the purpose of transplantation. The term 'recovery' is equivalent to it.

Protocol A combination of a standard operating procedure and standard documentation.

Quality assurance Describes the actions planned and performed to provide confidence that all systems and elements that influence the quality of the product are working as expected, individually and collectively.

Quality control Part of quality management, focused on fulfilling quality requirements.

Quality criteria Conditions that have to be met by the healthcare practice in order to be considered a good-quality practice.

Quality improvement Describes the actions planned and performed to develop a system to review and improve the quality of a product or process.

Quality indicator A defined measurement that indicates the presence and intensity of a phenomenon or event.

Quality management A system that monitors and coordinates activities in an organisation to ensure consistent quality in care, safety and use of resources. This general term encompasses everything that can affect the final quality of organs, tissues and cells.

Quality system The organisational structure, defined responsibilities, procedures, processes and resources for implementing quality management, including all the activities that contribute to quality (directly or indirectly).

Recipient A person who receives transplanted organs, tissues and/or cells.

Recovery See 'Procurement'.

Registry A repository of data collected on organ donors and/or transplant recipients for the purpose of outcome assessment, quality assurance, healthcare organisation, research and surveillance.

Risk assessment Identification of potential hazards, with an estimate of the likelihood that they will cause harm and of the severity of the harm should it occur.

Self-assessment A comprehensive and systematic review of the organisation's activities and results, referenced against the quality management system or a model of excellence, which can help identify areas requiring improvement.

Serious adverse event Any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity.

Serious adverse reaction An unintended response – including a communicable disease in the living donor or in the recipient, and which might be associated with any stage of the chain from donation to transplantation – that is fatal, life-threatening, disabling or incapacitating, or which results in (or prolongs) hospitalisation or morbidity.

Slow graft function The terms 'slow graft function' and 'intermediate graft function (IGF)' are used in liver transplantation as equivalent to DGF in kidney transplantation for the delayed start of graft function after transplantation.

Standard-criteria donor A donor manifesting no evidence of disease-transmission risk and no co-morbidities compromising organ function.

Strout test Concentration test for the diagnosis of acute Chagas disease. This test has a sensitivity of 80-90 % and is recommended in the case of patients strongly suspected of having acute Chagas disease and returning negative results for the direct fresh-blood exam.

Surveillance The systematic ongoing collection, collation and analysis of data for public health purposes, and the timely dissemination of public health information for assessment and public health response, as necessary. See also 'Follow-up' (which includes surveillance).

Tissue An aggregate of cells joined together by, for example, connective structures and performing a particular function.

Total ischaemia time The time from cessation of adequate circulation to an organ (cross-clamping) in a donor until arterial reperfusion in the recipient. During this period, multiple organ-preservation technologies can be applied.

Traceability Ability to locate and identify an organ at each stage in the chain from donation to transplantation/disposal, including the ability to identify the donor, the donor hospital and the recipient(s) at the transplant centre(s), and to locate and identify all relevant non-personal information relating to products and materials coming into contact with that organ.

Transmissible disease Any clinically evident illness (i.e. with characteristic medical signs and/or symptoms of disease) that results from – or could result from – the infection, presence and growth of micro-organisms in an individual recipient, having originated from the organs, tissues or cells applied.

Transplantation/implantation/grafting Surgical procedure in which an organ (or organs) from a donor is (are) inserted into a recipient with the aim of restoring function(s) in the body.

Transplant centre A healthcare establishment which undertakes the transplantation of organs and is authorised to do so by the Health Authority under the national regulatory framework.

Uncontrolled donation after circulatory death Donation from persons whose death has been established by circulatory criteria, following an unexpected circulatory arrest.

Utilised organ donor An actual donor from whom at least one organ has been transplanted.

Vigilance	Alertness to or awareness of adverse events, adverse reactions or complications related to the donation and clinical application of human organs, tissues and cells, involving an established process for reporting at local, regional, national or international level.
Warm ischaemia time	The time an organ remains at body temperature after its blood supply has been reduced or cut off but before it is cooled or reconnected to a blood supply.
Warm ischaemia time: international usage	Netherlands: WIT means primary WIT. UK: WIT means functional WIT. US: WIT means time from WLST in donor to *in situ* preservation.
Warm ischaemia time in uncontrolled DCD	In uDCD, total WIT extends from the moment the donor suffers the sudden and unexpected cardiac arrest until the start of *in situ* preservation (with cold preservation fluid or abdominal regional perfusion).
Warm ischaemia time in controlled DCD	In cDCD, total WIT extends from the moment when ventilatory support is withdrawn until the start of *in situ* preservation (with cold preservation fluid or abdominal regional perfusion). It includes the agonal phase, primary WIT and functional WIT.
Window period	The time between potential exposure to an infectious pathogen and the point when the test will give an accurate result. During the window period a person can be infected with the pathogen and transmit it to others but have a negative or non-reactive test result.

Appendix 3. Criteria for the identification of potential donors after brain death in a retrospective clinical chart review (Spain)

The Spanish quality assurance programme for the deceased donation process has established criteria to identify potential donation after brain death (DBD) donors during a retrospective clinical chart review.* By using these criteria, professionals performing potential donor audits can classify patients in one of five categories of potential DBD donor – confirmed, highly probable, possible, not assessable or not potential – in a consistent and reproducible manner. A conservative assessment of the potential donor pool would take into account only the 'confirmed' or 'highly probable' DBD donor cases. A less conservative approach would also take into account the 'possible' DBD donor cases.

Situation 1: confirmed potential DBD donor

To consider a patient as a confirmed potential DBD donor, any of the following circumstances must be present:

- All legal requirements to confirm brain death have been properly reflected in the clinical chart.
- A neurologist or a neurosurgeon has examined the patient and has recorded that brain death has occurred, and there is no evidence against this diagnosis.
- An intensive care physician has recorded that brain death has occurred, and there is no evidence against this diagnosis.

Situation 2: highly probable potential DBD donor

A patient is considered a highly probable potential DBD donor in the following circumstances:

- aetiology + conditions + 1 finding (at least) in clinical examination + 1 clinical sign (at least); or
- aetiology + conditions + 2 findings (at least) in clinical examination.

For more detail, see Table A.

Situation 3: possible potential DBD donor

A patient is considered a possible potential DBD donor in the following circumstances:

- aetiology + conditions + 1 finding (at least) in clinical examination; or
- aetiology + conditions + 1 clinical sign (at least).

For more detail, see Table A.

Situation 4: not assessable as a potential DBD donor

A patient is not assessable as a potential DBD donor in any of the following circumstances:

- The aetiology of the process is known, severe and consistent with brain death, but there is no

* De la Rosa G, Domínguez-Gil B, Matesanz R *et al.* Continuously evaluating performance in deceased donation: the Spanish Quality Assurance Program. *Am J Transplant* 2012;12:2507-13.

additional information in the clinical chart or the clinical chart is not available.

- The aetiology of the process is known, is severe and can lead to brain death, but the diagnosis could not be confirmed because life-sustaining therapies were withdrawn.
- The aetiology of the process is known, is severe and can lead to brain death, but the patient was exposed to barbiturates or neuromuscular blocking drugs at the moment of cardiac arrest.
- Infratentorial processes with no legal diagnosis of brain death.

Situation 5: not considered as a potential DBD donor

In circumstances other than those described above, the patient will not be considered a potential DBD donor.

Table A. **Issues to be considered, based on the available information in the clinical chart, when defining a person as being a highly probable or a possible potential donor after brain death**

Aetiology of the process causing death
It must be one of the known aetiologies of brain death and must be severe enough to cause brain death.
Conditions
Absence or no evidence of spontaneous breathing and movements.
Findings in clinical examination
• Progressing non-reactive mydriasis, i.e. *de novo* non-reactive mydriasis in a patient with a severe neurological condition, in the context of a severe clinical deterioration and which is not explained by drug interference. • Absence of at least one of the following brainstem reflexes: corneal, oculocephalic, oculovestibular, cough and gag. • Negative atropine test.
Clinical signs
• Abrupt arterial hypotension, other causes apart from brain death having been discarded. • Abrupt polyuria, other causes apart from brain death having been discarded. • Refractory and progressive intracranial hypertension (intracranial hypertension which has evolved in the minutes or hours prior to death, towards limits that provoke a cerebral perfusion pressure of 0 or close to 0 mmHg, with no response to therapy).

Appendix 4. Procurement surgery in brain-death donors: tasks for the anaesthesiologist

This appendix gives information on the management of procurement surgery by the anaesthesiologist in the operating room (theatre), with specific goals and strategies to optimise the outcome for the organ recipient.

General

1. Donor management will be continued until organ preservation (see Chapter 5).
2. Often volume depletion will be underestimated at the intensive care unit (ICU) prior to procurement surgery: volume resuscitation until urine output > 1 mL/kg/h, mean arterial pressure (MAP) > 60 mmHg, central venous pressure (CVP) 4-8 mmHg.
3. If diabetes insipidus continues to persist: antidiuretic hormone (ADH) substitution, correct Na^+ (< 155 mmol/L). Avoid hypokalaemia (may result in ventricular fibrillation, e.g. by electrocoagulation): K^+ 3.5-4.5 mmol/L). Try to achieve a blood glucose < 180 mg/dL.
4. If the donor is haemodynamically unstable. During preparation of the large retroperitoneal vessels, alteration in blood pressure occurs (e.g. vena cava compression due to manipulation of the vessels), which may be corrected by short-acting agents. Thereby the effect of intervention is seen with delay, and inverse events may occur because the cause of lack of venous return does not exist anymore (e.g. no longer vena cava compression). In cases of arterial hypertension, the MAP usually drops by itself. After tapering catecholamines, sevoflurane may be used because of its controllable side-effect of vasodilation and its short action. Haemodynamic instability may be exacerbated by hypovolaemia (before and during procurement). Hypotension with hypoperfusion impact on long-term organ function is higher than when using vasopressors.
5. Spinal reflexes exist in brain-death donors. They occur during positioning on the table, incision of abdominal walls (skin nerves) and retroperitoneal preparation (e.g. plexus solaris). They should be blocked by muscle-relaxing agents (as well as opiates to block the spinal receptors). During further surgery such spinal vegetative reactions may induce tachycardia up to 120 bpm, flushing and sweating when preparing area of plexus solaris and/or adrenal glands.
6. Avoid uncontrolled hypothermia.
7. Continue lung-protective ventilation (to achieve PaO_2 > 100 mmHg, O_2-saturation > 98 %, PEEP ≥ 8 cmH_2O). In cases of lung procurement, the lung team will suggest adjustment of ventilation. If no lung procurement, ensure proper oxygenation and ventilation of other organs without further consideration of long-term lung damage.

Preparation prior to surgery in intensive care unit

1. All relevant documents should go to the operating room (cross-check with co-ordinator).
2. Transfusions are usually not needed (if Hb > 7 g/dL). The only exception might be heart

preservation with normothermic machine perfusion when appropriate erythrocyte function is needed for priming the system (check with co-ordinator and heart team): then Hb should be at 10.0 g/dL. In case of untraceable bleeding (e.g. rupture of vertebral artery) you may need multiple units without prior crossmatch and may want to switch to cDCD/uDCD technology.

3. Actual monitoring data, blood gas analysis (BGA), coagulation, electrolytes and haemoglobin.
4. All syringe pumps and/or infusion pumps are continued during transport and in the operating room (with backup for 3 h).
5. For transport to the operating room: prepare according to standards of transfer for any ICU patient (consider transport and emergency equipment); many hospitals apply muscle relaxants before departure from ICU (spinal reflexes, see point 5 above). During transport, spinal-vegetative reflexes may occur (MAP goes up).
6. Pre-operative antibiotics according to indication at hospital standards if requested at all. Selective decontamination of the intestine is not necessary unless requested. Acid-blocking agents are no longer required. Continue thrombosis prophylaxis.
7. Check for special medications with co-ordinator and teams (e.g. 250-500 mg bolus methylprednisolone).

Preparation prior to surgery in operating room

1. See above, standard emergency equipment for a patient haemodynamically unstable with severe systemic pro-inflammatory response (SIRS). Prepare Heparin 25 000 I.U.
2. Ensure access available to draw blood samples for BGA etc., convenient monitoring including diuresis. For positioning: ask surgeons.
3. Before skin incision: team timeout.
4. For organ preservation, have available two infusion poles: 10-15 L physiologic sterile flush solution (e.g. 0.9 % NaCl), check whether defibrillator and/or sterile paddles are available in case of a heart procurement. During organ preservation, the scrub nurse will need enough suction equipment to collect about 20 L within a few minutes.
5. Avoid heat loss until organ preservation.

Special issues per organ

Basic surgery: Recycle knowledge from the modules of hemicolectomy with retroperitoneal inspection, Whipple surgery, sternotomy, lung surgery until organ preservation.

Pancreas: Depending on surgical strategy, pancreas with duodenal segment will be mobilised prior to organ preservation (inclusive gastrectomy). Prior to stapling, some centres prefer to decontaminate the duodenum with 300-500 mL of diluted Povidone–iodine and they will ask to remove the gastric tube. Controversy exists about indication of further intestinal decontamination. During mobilisation of the pancreas, vasoactive mediators will be delivered, causing severe fluctuation of MAP.

Liver: In stable donors, *in situ* splitting may be considered (consider basic knowledge of hemihepatectomy).

Heart: During opening of the pericardium and marking of the large vessels, depression of the circulation may occur with arrhythmia (especially in case of volume depletion and electrolyte disorders).

Lung: Bronchoscopy by lung team ($FiO_2 = 1$, multiple BGA, equipment provided by lung team). Lung team may perform recruitment under visual and manual protection of the lung against barotrauma. Then adjust ventilation according to instruction of the lung surgeon. Optionally, BGA from the lung veins may be helpful to check whether a single lung can be used or whether lung segments may be resected at the recipient hospital if indicated. Continue ventilation during organ preservation according to the instructions of the lung surgeon.

Intestine: Pre-procurement briefing necessary with responsible surgeon.

For every organ: Blood specimen must be drawn before organ preservation (ask co-ordinator).

After dissection of all organs and vessels

The following steps (depending on kind of procurement) occur after dissection of all organs and vessels. Heparinisation (20 000-30 000 I.U. IV, or 300 I.U./kg IV) prior to cannulation (of abdominal aorta for preservation of all abdominal organs, of ascending aorta for the heart, of pulmonary artery for lung). Some teams apply prostacyclin (100-200 µg IV) before crossclamp (please be aware of immediate vasodilation: blood pressure drops irreversibly within a few seconds). Prior to crossclamp, the heart team will/should ask for removal of central venous catheter. After crossclamp, lung ventilation should be continued in accordance with lung surgeon's advice. In case of normothermic heart preservation, 1 000 mL of blood may be drawn from aorta with an acceptable hypotension of < 30 seconds. Please note

that, for all these steps, instructions have to be given by the procurement teams.

Then crossclamp of aorta and opening of vena cava/ left ear of heart and start of flush by organ. The use of the preservation solution is done according to manufacturer's guidance by the procurement teams. All anaesthesiologic interventions are stopped except for continued lung ventilation. Here the lung surgeon will ask for targeted ventilation manoeuvres prior to stapling of trachea upon removal of the lung from the thoracic cavity. During organ preservation with vascular flushout by preservation solution, topical cooling will be applied by a sludge prepared from 4 °C cold solution by the procurement team. After the flush the procurement teams must perform final dissection of each organ, which will leave the body in this sequence:

a. heart,
b. lung,
c. intestine,
d. liver,
e. pancreas,
f. kidney,
g. spleen or lymphnodes for compatibility testing,
h. vessel tool kits (arteriovenous iliaca communis, aortic arch) for reconstruction.

Surgery is done when the wound has been closed. After organ preservation and during final dissection of all organs, all venous and arterial lines as well as other indwelling material must be removed with the aim that proper post-procurement respect is possible for donor relatives. (Only exception: coroner or state attorney explicitly requests hospital not to remove any line).

Suggested further reading

Anderson TA, Bekker P, Vagefi PA. Anesthetic considerations in organ procurement surgery: a narrative review. *Can J Anaesth* 2015 May; 62(5):529-39.

Appendix 5. **Checklist for the anaesthesiologist in the operating room**

Specific goals and strategies to optimise the outcome for the organ recipient

General

1. Volume resuscitation until:
   - urine output > 1 mL/kg/h ☐ yes ☐ no ☐ n/a
   - MAP > 60 mmHg ☐ yes ☐ no ☐ n/a
   - CVP 4-8 mmHg ☐ yes ☐ no ☐ n/a
2. Diabetes insipidus persists?
   - ADH substitution ☐ yes ☐ no ☐ n/a
   - correct Na^+ (< 155 mmol/L) ☐ yes ☐ no ☐ n/a
   - correct K^+ to 3.5-4.5 mmol/L) ☐ yes ☐ no ☐ n/a
   - achieve a blood glucose < 180 mg/dL ☐ yes ☐ no ☐ n/a
3. Haemodynamically unstable?
   - need to use short-acting agents to increase MAP? ☐ yes ☐ no ☐ n/a
   - need to use sevoflurane in case of arterial hypertension? ☐ yes ☐ no ☐ n/a
4. Are spinal reflexes present during procedure?
   - need to use muscle-relaxing agents? ☐ yes ☐ no ☐ n/a
   - need to use opiates to block the spinal receptors? ☐ yes ☐ no ☐ n/a
   - need to control spinal vegetative reactions? ☐ yes ☐ no ☐ n/a
5. Uncontrolled hypothermia avoided? ☐ yes ☐ no ☐ n/a
6. Lung-protective ventilation with PEEP ≥ 8 cmH_2O (to achieve PaO_2 > 100 mmHg, SpO_2 > 98 %) ☐ yes ☐ no ☐ n/a

   or adjusted according to the lung team (only for lung procurement) ☐ yes ☐ no ☐ n/a

Preparation at the intensive care unit prior to surgery

7. Transfusions needed (Hb < 7g/dL)? **or** ☐ yes ☐ no ☐ n/a
   - > 10 g/dL (exception for heart preservation with normothermic machine perfusion) ☐ yes ☐ no ☐ n/a
8. Chart with updated data:
   - monitoring ☐ yes ☐ no ☐ n/a
   - blood-gas analysis (BGA) ☐ yes ☐ no ☐ n/a
   - coagulation ☐ yes ☐ no ☐ n/a
   - electrolytes ☐ yes ☐ no ☐ n/a
   - haemoglobin ☐ yes ☐ no ☐ n/a
9. All syringe and/or infusion pumps are maintained and have backup battery for 3 hours ☐ yes ☐ no ☐ n/a
10. For transport to the operating room:
    - standard precautions as for critically ill patient (including emergency equipment) ☐ yes ☐ no ☐ n/a
    - donor paralysed before departure from ICU ☐ yes ☐ no ☐ n/a
11. Preoperative antibiotics administered? ☐ yes ☐ no ☐ n/a
12. Thrombosis prophylaxis continued? ☐ yes ☐ no ☐ n/a
13. Need of special medications confirmed with co-ordinator and teams (e.g. 250-500 mg bolus methylprednisolone) ☐ yes ☐ no ☐ n/a

Note: ADH anti-diuretic hormone; CVP central venous pressure; ICU intensive care unit; MAP mean arterial pressure; n/a not applicable; OR operating room.

Preparation prior to surgery in the operating room			
14. Adequate monitoring including arterial line, urinary output; for positioning, ask surgeons	❑ yes	❑ no	❑ n/a
15. Avoid heat loss until organ preservation	❑ yes	❑ no	❑ n/a
16. Prepare Heparin 25 000 I.U.	❑ yes	❑ no	❑ n/a
17. For organ preservation, have available two infusion poles and 10-15 L of adequate sterile solution (4 °C)	❑ yes	❑ no	❑ n/a
18. During organ preservation, prepare suction equipment to collect about 20 L within a few minutes	❑ yes	❑ no	❑ n/a
19. Check that defibrillator and/or sterile paddles are available in case of heart procurement	❑ yes	❑ no	❑ n/a
20. Before skin incision: team timeout	❑ yes	❑ no	❑ n/a
21. Prepare to draw blood specimen before organ preservation (ask co-ordinator for which organs)	❑ yes	❑ no	❑ n/a

Special issues			
Follow instructions given by the procurement team depending on kind of procurement	❑ yes	❑ no	❑ n/a
Stop all anaesthesiology interventions when lung ventilation is no longer indicated	❑ yes	❑ no	❑ n/a
Sequence of organ procurement is: heart, lung, intestine, liver, pancreas, kidney, spleen or lymph nodes	❑ yes	❑ no	❑ n/a
Surgery is done when the wound has been closed	❑ yes	❑ no	❑ n/a
For proper post-procurement protocol/respect by donor relatives:			
Remove all venous and arterial lines as well as other indwelling material. (Only exception: coroner or state attorney explicitly requests hospital not to remove any line.)	❑ yes	❑ no	❑ n/a

Note: ADH anti-diuretic hormone; CVP central venous pressure; ICU intensive care unit; MAP mean arterial pressure; n/a not applicable; OR operating room.

Appendix 6. Rationale document for medical and social history questionnaire (United Kingdom)

This appendix shows the *Rationale Document for Medical and Social History Questionnaire (Information document INF947/4)*, including the questionnaire itself, as used in the United Kingdom since October 2017. The Rationale Document is adjusted to all formal and informal rules valid in the healthcare system of the United Kingdom. In the healthcare systems of other member states, different formal and informal rules exist and questionnaires must be adjusted to the rules that apply in their jurisdiction (e.g. see Appendix 9).

Rationale document for medical and social history questionnaire

Introduction

- The purpose of donor characterisation is to determine whether a potential donor is suitable to donate **any** organ or tissue, and then to determine **which** organs and tissue can be donated. Whilst following assessment of an individual's medical and social history, organ and tissue donation may be possible, it may be that not all organs or tissues are suitable due to specific organ/tissue requirements.
- This document aims to provide a rationale for specific information that is required to assess a potential donor's suitability for organ/tissue donation and should be used in conjunction with the NHS Blood and Transplant FRM4211 Medical and Social History Questionnaire (MaSH).
- The purpose of the MaSH questionnaire is to collate relevant information for donor characterisation; this can help determine risk factors for the transmission of disease from donor to recipient. It is the responsibility of the Specialist Nurse Organ Donation/Specialist Nurse Tissue Donation/Tissue Donor Co-ordinator to collect comprehensive information on medical, behavioural and travel history and relay all the information obtained to the organ recipient and tissue procurement centres. In addition, for organs it is the responsibility of the implanting surgeon to assess the risk-benefit of transplant for their individual patients. For tissue, the final decision on donor acceptance is often made after reviewing additional information available post donation and it is the responsibility of the tissue establishment to make the final decision on donor suitability.
- All specialist nursing staff trained to use this document must recognise when to expand questions in order to obtain more details, what additional information might be required and recognise when to seek advice. It is expected that the donors referred for tissue donation meet donor selection guidelines (see link below) or have had an individual risk assessment on donor suitability.
- The conditions which will cause the deferral of a potential donation vary significantly between organs and tissue, including ocular tissue. For many of the questions asked, the principle will be to gain as much relevant information as pos-

sible, clearly document the information and inform recipient centres. For tissue donation this is also relevant, however suitability can also be confirmed by reference to the current version of the UKBTS Tissue Donor Selection Guidelines for Deceased Donors (TDSG-DD).*

- This rationale is a guide and should not replace discussions with transplant centres, tissue establishments, microbiologist and other experts where necessary. SaBTO guidance on the microbiological safety of human organs, tissue and cells used in transplantation will also provide more information on many of the questions below.

* www.transfusionguidelines.org.uk/dsg/ctd/guidelines.

Patient assessment section

Whilst the MaSH document does give 'unknown' as an option to minimise organ/tissue deferrals it is preferred wherever possible this option is not used. As such when opening the conversation with the family we request they answer with 'yes or no.'

In terms of the country of residence question, you are classed as a resident if you have lived somewhere for 6 months and over.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
For paediatric donation: has your child been breast-fed in the last 12 months?	There is a risk of vertical transmission of some blood-borne viral infections from the mother to her child via breast milk. Although testing of the milk donor would be desirable, it is acknowledged that this may not be possible and this should not be a contraindication for donation; discuss accordingly. Transplant centres should be informed. Prior to donating breast milk, microbiological screening will have been carried out in the maternity unit.	The mother's medical, social and behavioural history should be assessed and both a maternal and infant blood sample must be taken for full microbiological screening.	As organ donation.
Note: for all patients under the age of 18 months and any infant who has been breast-fed in the last 12 months, a blood sample is required from both the mother and the infant.	Some infections can be transmitted from the mother *in utero*, at birth, perinatally and through breast feeding. Examples of some of those blood-borne viruses, which are also transmissible by transplantation, are CMV, HIV, HBV, HTLV and HCV. Testing the mother identifies potential infectious risk for the baby and if positive, will inform need for further testing in the case of organ donation; for tissue donation, positive maternal results is a contraindication for infant donation (see additional action on the right). Donor characterisation testing portfolio has expanded over time; to avoid difficulties in obtaining sufficient blood sample from small babies, there are instances when a maternal sample can be used as a surrogate.	If the death of the neonate falls within 28 days from birth, maternal microbiological screening alone is sufficient. SNOD must make the virology laboratory fully aware of what is being tested. Appropriate interpretation of results is required and further additional testing of the mother and baby may be required. Before the age of 18 months, antibodies found in the baby may have been passively acquired from the mother or may reflect infection; if positive, discuss. From 29 days up to 18 months of age, full microbiological screening of the infant and the mother are both required.	As organ donation. Under EU Tissues and Cells Directive, *if the mother is infected with HIV/HBV/HCV/HTLV or is at risk of these infections*, an infant under the age of 18 months or who has been breastfed in the past 12 months *cannot be accepted as a tissue donor*, regardless of the results of the tests; maternal sample is required to establish mother's status and assess donor suitability.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
For ALL female patients aged between 13 and 53 years of age: Is there a possibility that your relative could be pregnant?	If there is a possibility that the patient could be pregnant then a pregnancy test should be performed to determine whether the foetus is viable.	If a pregnancy test is confirmed as positive, the donation process should be paused and expert advice should be sought to enable individual case assessment.	As organ donation.
General health information Was/did your relative or you (if completing as mother of paediatric donor):			
1. Did your relative visit a general practitioner in the last two years? 2. Was your relative currently seeing or waiting to see a general practitioner or any other healthcare professional?	These are broad questions to ascertain if there are any long-term/current health problems. If the answer to either is yes, it is important to obtain as much information as possible including symptoms, diagnosis, investigations and medications prescribed include names of hospitals if relevant to allow further clarification as required. Note: It is important to obtain accurate information on past/current medical history. Therefore it is a requirement that the GP is contacted to complete the NHSBT GP questionnaire (FRM1602).	Attempts should always be made to contact the GP prior to the retrieval of organs. If, following these attempts, the GP cannot be contacted, the NHSBT GP assessment MUST be sent by the next working day. Any new relevant information must be shared appropriately. If the patient has no GP then ensure this is information is documented for recipient centres to be aware.	As organ donation.
3. Did your relative ever take regular medication?	This is a broad question to ascertain if there are any long-term/current health problems. Include type of medication, length of therapy and reason for treatment. Rationale for acne, prostate and psoriasis medication: Finasteride (prostate), Dutaseride (Avodart) or one of the following acne treatments: roaccutane, etretinate, acitretin, isotretinoin, alitretinoin, tamoxifen and duasteride – All these medications are teratogenic and are excreted from the body at different rates at different times and can therefore be transmitted through tissue.	Document information clearly to alert accepting surgeons.	Refer to TDSG-DD guidelines re deferral period required for each of the named drugs – if donation will take place beyond the deferral period accept donation; if donation take place within the deferral period for the medication defer donor unless the tissue bank can perform individual risk assessment based on risk–benefit analysis.
4a. Did your relative have a history of allergies to medication, food or other substances?	Aiming to establish all substances that the donor was allergic to; if the donor does have a history of allergy it is important to get information as to the type of allergy, i.e. mild rash or severe anaphylactic-type reaction. There is the potential that the organ recipient would develop the same type of allergy as the donor.	Document information clearly to alert accepting surgeons.	No action required.
4b. Did your relative have any health problems due to exposure to toxic substances such as pesticides, lead, mercury, gold, asbestos, agent orange, etc.?	Some toxic substances may linger in the body for several years and could potentially be transmitted through transplanted tissue/organs.	Document information clearly to alert accepting surgeons.	It is HTA requirement based on EU commission Directive 2006/17/EC that tissue donation from donors with the history of 'ingestion of or exposure to a substance (such as cyanide, mercury, lead, gold) that may be transmitted to recipients in a dose that could endanger their life' must be excluded. Expert advice must be sought for individual risk assessment.
5a. Is your relative a diabetic? If yes, were they on insulin? 5b. Is there a family history of diabetes? If yes, is it insulin-dependent diabetes?	Because diabetes can have an affect on a number of organs, particularly development of diabetic nephropathy in the kidneys, this information helps inform transplant centres when considering organs for transplantation. Increased risk of kidney disease runs in families.	If yes, absolute contraindication for pancreas and islet donation. Refer to POL188 (Contraindications to Organ Donation).	If yes, absolute contraindication for pancreas and islet donation. No action required for other tissues.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
6. Did your relative suffer from any chronic or long-term illness or disease?	Some diseases of unknown aetiology, such as multiple sclerosis, inflammatory bowel and Crohn disease, may have an as yet unrecognised infectious cause. More importantly, if there is a current condition that is suspected to be of infectious origin but a cause has not been identified, there is a risk of transmission. Some chronic neurological or cardiac conditions, for instance, may have an infectious aetiology which is unsuspected at time of death such as Chagas disease, a condition that is not commonly considered in the UK as it is not endemic.	Clinical assessment as appropriate. In light of other relevant information, including epidemiology; e.g. family or own history of gastrointestinal dysmotility, cardiac arrhythmia and residency in Chagas endemic area.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
7. Did your relative ever suffer from any bone, joint, skin or heart disease?	Responses will inform transplant centres and tissue establishments when assessing the patient's suitability to donate.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
8. Did your relative ever have hepatitis, jaundice or liver disease?	Jaundice can have infectious causes, such as viral hepatitis, and non-infectious causes, such as gallstones. Enquire regarding dates, causes, diagnosis, investigations.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
9. Did your relative recently suffer from significant unplanned weight loss?	Recent unplanned weight loss may be an indication of illness, including malignancy. It is important therefore to obtain the reason for the weight loss, the estimated amount of weight loss, if it was investigated or accompanied by other problems.	Document weight loss information clearly to alert accepting surgeons.	As organ donation.
10. Did your relative ever undergo any investigations for cancer or were they ever diagnosed with cancer?	The presence, or previous history, of malignancy poses a risk of transmission of malignant cells to a recipient. If yes, obtain further information regarding dates, diagnosis and treatments. If investigations such as mammograms, smear tests, PSA testing for prostate cancer and so on have been completed, ensure it is clearly stated whether these were part of routine national screening or due to any concerns or symptoms to allow a risk/benefit assessment of the likely implications.	It is important to assess the type, grade and time scales of any malignancy, as certain types are contraindicated in organ donation. Refer to POL188 (Contraindications to Organ Donation).	If organ and tissue donation is contraindicated, corneal donation may be possible. Refer to current version of TDSG-DD.
11. Did your relative have a history of eye disease, receive any medications for eye problems (e.g. eye drops), or undergo eye surgery or laser treatment?	This question is specifically designed to assess the suitability of ocular tissue; of note, glaucoma surgery might involve the use of allogeneic scleral tissue and it is therefore important to elicit whether a patient with glaucoma has undergone surgery and where even if further surgical details are not known to the family at the time of the family interview.	Not applicable to organ donation	If answer yes to this question refer to current TDSG-DD as donation may be contraindicated.
12. Did your relative ever have any operations?	If the answer is yes, it is important to obtain as much information as possible, such as reasons for surgery, as this may provide important past medical history. In particular. any operations for malignancy, neurosurgery or operations where organs/tissue were transplanted.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
13. Did your relative ever have any surgery on the brain or spine?	Before 1993 dura mater from deceased donors, has been documented to transmit CJD, may have been used in brain and spinal surgery. Therefore where this answer is yes, the patient is at increased risk of CJD. Clarity should be sought on type of procedure, dates and location/hospital where procedure occurred.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
14. Did your relative ever have an organ or tissue transplant?	This will provide information regarding any previous requirement of immunosuppression, risk of CJD transmission if within specific time frames, and inform decision making.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
15. Was your relative ever told not to donate blood?	If answered yes, reason for this must be clarified. Some deferrals are due to reasons such as a patient's age or weight, however there may be other reasons such as infection risk including being at CJD risk for public health purposes.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
16. Did your relative receive a transfusion of blood or blood product(s) at any time?	This should include type of product, such as Fresh Frozen Plasma (FFP), Platelet, Cryoprecipitate or Immunoglobulin as these are human derived products. The reason for the transfusion should also be obtained as this may provide significant medical history. Establish in which country the transfusion occurred as donor screening policies vary by date and country and this information is helpful. Transfusions have been known to transmit bacterial, viral, protozoal and prion infections, such as variant CJD. Testing of blood donors for markers of infection varies by country and by date, so level of risk will also vary. Please document all transfusions given during this admission, as well as historical transfusions if known.	Any transfusions should be noted and the laboratory completing the microbiology testing should be informed if the potential donor received any transfusions within the last 3 months. Antibodies can be acquired passively through transfusions so a positive antibody test in a post transfusion sample may need to be interpreted accordingly. The laboratory interpretation must take this into account and the information should be passed on to the transplant centres. Transfusion history should be explored as part of the review of medical records and importantly the prescription chart for the current admission (NB if a potential donor has had more than one admission within the 3 days prior to the current, then prescription charts for these admissions should also be reviewed). Documenting all transfusions (not just the ones relevant for haemodilution calculation) would give a full picture should there ever be the need to investigate a potential transfusion-transmitted infection.	As organ donation.
17. Did your relative suffer from any type of brain disease such as Parkinson's or Alzheimer's disease, or dementia?	Neurological disease may be of infectious or non-infectious origin or a neurodegenerative condition of unknown aetiology e.g. Parkinson's disease or Alzheimer's disease.	Not applicable to organ donation.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
18. (A-D) Did your relative suffer from any one or more of the following problems: memory problems or confusion, change in personality or behaviour, or were they unsteady on their feet?	CNS conditions have a range of underlying pathologies, and for the purposes of organ and tissue donation it is important to identify and exclude those that might be of infectious origin or of unknown aetiology such as neurodegenerative conditions (e.g. Parkinson's disease or Alzheimer's disease). As relevant CNS conditions are not necessarily always fully diagnosed at time of death, it is important to identify potentially relevant clinical signs and symptoms as possible indicators of relevant disease processes. Slowly progressive neurological symptoms, including paraparesis, may have a yet undiagnosed viral aetiology (e.g. HTLV). New symptoms such as behavioural changes, confusion with or without fever and other symptoms, may be part of a yet undiagnosed infectious CNS process. It is important to establish time of onset, duration, severity and trend of neurological and psychiatric symptoms in order to assess their relevance. For example, patients with sporadic CJD would be expected to deteriorate noticeably from month to month. Being unable to live independently is a good indication of severity of any neurological condition, e.g. a patient with dementia is usually unable to live on their own. Clinical assessment will exclude other relevant underlying conditions that may also be present beside the primary cause of death (e.g. altered behaviour of new onset, which may be infectious in origin, followed by a fall or RTA). The cause of death may not be a deferral for donation, however the underlying, as yet undiagnosed condition, may have led to the incident leading to death.	Not applicable to organ donation.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
19. Did your relative have a family history of prion disease, such as CJD, or were they ever told that they were at risk of prion disease?	Individuals at familial risk of prion-associated disease are those who have two or more blood relatives with a prion-associated disease or where the family has been informed they are at risk following genetic testing and counselling. These patients are at increased risk of prion disease transmission.	Assessment must be made on a case by case basis and expert advice sought where necessary. 'At risk' and familial history is not an absolute contraindication to organ donation. Refer to POL188 (Contraindications to Organ Donation).	If answer yes, patient is contraindicated for tissue donation. If the donor has had genetic testing and been found not to be at risk for prion disease – accept.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
20. Did your relative ever receive human pituitary extracts, e.g. growth hormones or fertility treatment or test injections for hormone imbalance?	Human pituitary extracts have been known to have been contaminated and have led to the transmission of CJD. They have not been used in the UK since 1985; however it is uncertain when their use was stopped in other countries. Metrodin HP was an infertility treatment used up to 2003. However, patients treated after 2003 will not have been treated with this. Metrodin HP was manufactured from urine sourced in Italy and therefore was a risk of CJD. Donated eggs are classed as tissue donation due to the risk of CJD transmission.	Document information clearly to alert accepting surgeons.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
21. Did your relative ever have any significant infection?	Significant infections can be regarded as any infection where an individual has required investigations, hospitalisation or a specialist referral. Infections identified in this section may be transmittable during transplantation depending on the detail. Therefore it is important to ascertain diagnosis, treatments, and dates.	Refer to POL188 (Contraindications to Organ Donation). Initiate discussions at early stages, as appropriate.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
22. Did your relative come into contact with an individual with an infectious disease within the last month?	Potential donors who have been in recent contact with an infectious disease may be in the asymptomatic stage of an infection at the time of donation. It is also helpful to know what type of contact the patient had.	Initiate discussions at early stages, as appropriate.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated.
23. Did your relative have any signs of infection, e.g. colds, flu, fever, night sweats, swollen glands, diarrhoea, vomiting or skin rash within the last month?	Answers to this question will add to the clinical picture. It is important to enquire as to any treatment given, investigations, duration of illness. Further investigations may be required.	Initiate discussions at early stages, as appropriate.	Night sweats may be secondary to menopausal symptoms – having this information documented is important as this type of night sweats allows the tissue to be released.
24. Did your relative have any immunisations within the last 2 months?	Immunisations with live vaccine may cause severe illness in people who are immunosuppressed. By eight weeks any infection caused by the immunisation should have been controlled and so should not be passed on through donated organs or tissues. Very recent vaccination with HBV vaccine for instance (7 days) can give positive result for HBsAg during screening, which does not mean infection. (No other vaccines affect the result of routine donor characterisation tests.) Asking for type of flu vaccination i.e. injection versus nasal spray will help confirm whether the vaccination used was inactivated or a live vaccine. List of common live and inactivated vaccines should be checked at: http://www.transfusionguidelines.org/dsg/ctd/appendicies/appendix-4-table-of-immunizations.	Laboratory completing the donor microbiological screen must be informed if recent HBV vaccination.	As organ donation.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
25. Did your relative have tattooing, body piercing, botox injections, acupuncture, colonic irrigation, faecal transplantation, or any other cosmetic treatments that involve piercing the skin in the last 3 months?	Any piercing of the skin for these reasons may carry a risk of viral disease transmission depending on the standards of practice. It is important to confirm when and where the treatment has been carried out, i.e. in the UK or not, and whether in licensed premises or not. If carried out in certain establishments, i.e. NHS or otherwise licensed establishments, tissue donation will be possible. During the 3-month period, if infection has occurred, it may not be detected by serological tests (window period). Colonic irrigation may be unregulated if not on NHS. As such there may be an increased risk of rectal mucosa damage and infection. Faecal microbiota – one of a number of treatments that can be done through the NHS or non-NHS – is human-derived and so gives rise to risk of blood-borne virus.	Document information clearly to alert accepting surgeons. Include relevant information in the virology request form to aid interpretation of results.	If answer yes to this question refer to current TDSG-DD as tissue donation may be contraindicated depending on where and when this happened. If faecal microbiota is carried out in the NHS or by a registered professional so we know the donor is being screened and tested then accept the donor; if done outside the NHS/not by a registered professional then defer if the treatment was in the last 3 months – if more than 3 months ago accept. If the donor or donor family state that tattoo/body piercing etc. was done in a high-street shop, we assume the shop is abiding by the law and is therefore licensed – there is no need to look for further evidence as to whether the shop was licensed or not.

Appendix 6 continues

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
26. Has your relative ever been bitten or scratched by any animal including strays, pets, wild or farm. Or have they been bitten or in close contact with ticks or bats?	Exposure to animal secretions (e.g. bites or exposure to saliva through broken skin) may result in infections, for example rabies. In the UK the risk of rabies comes from contact with infected bats. Outside the UK, bites and scratches from infected mammals (most commonly dogs and cats but any mammal can get infected – see below), can be a source of rabies in endemic countries. A potential exposure to rabies is significant at any time, so if the patient's family mentions a significant exposure, obtain information regardless of time elapsed. Close contact with animals, including domestic family pets, may lead to zoonotic infections (infections transmitted between animals and humans), which may then be transmitted through transplantation. A significant number of families will have family pets. The main risk is if the donor has been bitten by an animal or there has been unusual contact between an animal (particularly if unwell) and the donor. *Exposure to bats:* in the UK, bat handlers are encouraged to receive rabies vaccination. Exposure is regarded as direct contact of bat saliva or neuronal tissue with broken skin or mucosa. If a bat is found in the room of a sleeping, previously sleeping, or intoxicated person or child this is classed as exposure as the person may not be aware they have been bitten and bites may not be visible. Otherwise, just being close to a bat does not constitute an exposure. *Exposure to terrestrial (predominantly land living) mammals:* knowledge of any transdermal bite or scratch, lick to broken skin, contact of saliva with mucous membranes requires further discussion. Examples of animals known to have transmitted rabies: racoons, foxes, monkeys. Transmission of rabies through transplantation has been described when diagnosis of rabies in the donor had been missed despite presence of compatible signs and symptoms at the time of death. Tick bites can transfer infections, e.g. the agents that cause Lyme's disease, tick-borne encephalitis, etc.	If the answer to this question is yes, as much information as possible must be ascertained. Important questions to ask include: • Place of incident (country, region, area). • Type of animal (raccoon, skunk, fox, etc). • What was the injury (bite, scratch, lick to broken skin, mucosal exposure to saliva?) When did it happen? • Was the animal vaccinated against rabies? Was the animal observed by anyone in the 14 days following the incident (animals with active rabies would die within 2 weeks)? • Circumstances of incident – e.g. Was the bat dead or alive? Was the dog bite provoked or unprovoked? Was it directly on bare, broken or unbroken skin? • Was any medical advice sought afterwards? Any treatment? (e.g. Rabies hyperimmunoglobulin and rabies vaccine). • Would any one else have further information or have witnessed the incident?	Tissue donation is contraindicated if the patient has ever been bitten by a non-human primate, has any animal bite where the wound is infection or not healed, or if it is less than 12 months since being bitten anywhere in the world by any mammal outside the British Isles. Refer to current TDSG-DD.

Appendix 6 continues

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
Travel risk assessment This group of questions is designed to establish the risks of a potential donor being/having been at risk of an infection which is not endemic within the UK. Due to the evolving patterns of infections worldwide, when a detailed travel history has been obtained it is necessary to consult both the TDSG-DD (link above) and the Geographical Disease Risk Index (GDRI) (www.transfusionguidelines.org.uk/dsg/gdri) for up-to-date information on the risk assessment criteria. It is the responsibility of the specialist nursing staff to gather appropriate information, including date, duration of travel, destination and purpose of trip; and whether the donor was well or unwell during their travel and on returning to the UK – the travel-associated risk may vary by region with some countries, e.g. malaria risk only in some parts of Turkey or Zika risk in the USA. It is important to get as much information as possible, to document it and communicate it to transplant centres.			
27. Did your relative ever travel or live outside the UK (including business trips)?	Certain infections are distributed geographically and the risk of exposure will depend on the length of time and activities performed in the area. For some infections, risk is highest for residents of endemic areas (e.g. malaria and Chagas), regardless of how long ago they have left the area. Individuals who have lived in malaria-affected areas, particularly from early age, may develop a partial immunity to malaria through repeated exposure; they very often have no symptoms, despite infection being present. The malaria antibody screening test will identify that the donor had infection at some point; a NAT test will identify detectable parasite in the blood at the time of donation. In general terms, most risk of tropical acute infections such as Dengue, Chikungunya and Zika exists during the 4 weeks after return from endemic areas hence dates of recent travel are important part of the risk assessment.	Due to continual changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed. Initiate discussions at early stages, as appropriate.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
28. In the last 12 months, did your relative travel outside the UK (including business trips)?	Any travel within 12 months may trigger further investigations for potential diseases such as malaria. Certain infections are distributed geographically and the risk of exposure will depend on the length of time and activities performed in the area. Full details are important including area, dates, duration, nature of visit, type of activity.	Due to continual changing guidance in relation to travel refer to current GDRI. Document if any additional tests are being processed. Initiate discussions at early stages, as appropriate.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
29. Did your relative ever have malaria or an unexplained fever which they could have picked up whilst abroad?	Malaria and other endemic infections such as West Nile Virus and *T. cruzi* can be transmitted by blood, organs, tissues and cells. Full details are required, including date and duration of visit, and any treatments or investigations undertaken.	Due to continual changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
30. Was your relative unwell whilst abroad or in the first month on their return to the UK?	If patient was unwell while abroad or within 1 month of returning to the UK the infection may have been contracted while abroad – depending on the country visited this may include infections that would require additional tests to be processed, or would contra-indicate tissue donation e.g. malaria, Zika, West Nile Virus, etc. History of relevant epidemiology and symptoms are important and an individual risk assessment needs to be initiated as early as possible to enable appropriate discussions and any testing, if required.	Depending on country visited check GDRI to see what infection risk if any is linked with that country/region of country and decide whether additional tests are required, e.g. malaria testing, and discuss with transplant surgeons and document.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
31. Did your relative ever live or travel outside the UK for a continuous period of 6 months or more?	Certain infections are distributed geographically and the risk of exposure will depend on the length of time and activities performed in the area. For some infections, risk is highest for residents of endemic areas, regardless of how long ago they have left the area. Individuals who have lived in malaria-affected areas, particularly from early age, may develop a partial immunity to malaria through repeated exposure; they very often have no symptoms, despite infection being present.	Due to continual changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
32. Did your relative ever go to Central America, Mexico or South America for a continuous period of 1 month or more?	Individuals who have ever been in certain areas such as impoverished, rural communities (refer to SaBTO guidelines) of Central America, Mexico or South America for a period of 4 weeks or more may be at risk of *T. cruzi* infection. Full details are important including area, dates, duration, nature of visit, type of activities. For those who were born, or who have lived for a prolonged time or whose mothers were born in endemic areas for Chagas disease, family history or own history of cardiac (e.g. arrhythmia) or Gastro Intestinal abnormalities are significant and should be noted.	Due to continual changing guidance in relation to this aspect refer to current GDRI. Document if any additional tests are being processed.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
33. Was your relative's mother born in Central America, Mexico or South America?	*T. cruzi* infection can be passed vertically from mother to child so that a child born outside this area and who has never travelled to this area is still at risk of infection if their mother was born within the stated areas.	Document if any additional tests are being processed.	Due to continual changing guidance in relation to this aspect refer to current TDSG-DD and GDRI.
Behavioural risk assessment To the best of your knowledge did your relative:			
34a. Consume alcohol?	The effect of alcohol can impact on the quality of liver tissue. If yes, it is important to obtain as much information as possible. How much did the patient drink per day? What they drank (e.g. beer, spirits, wine, etc.)?	Document information clearly to alert accepting surgeons.	
34b. Smoke tobacco or any other substances?	If yes, give details of substance, frequency, history of smoking time and time elapsed since giving up.	Document information clearly to alert accepting surgeons.	
34c. Take any recreational drugs?	Looking for evidence of precarious/risky behaviours particularly if the patient is taking a substance that cannot be obtained legally.	Document information clearly to alert accepting surgeons.	Evidence of a potentially precarious/risky life style – if only smoking cannabis, accept; if injected illegal drugs in the last 12 months defer, if taking other oral recreational drugs would need a risk assessment.

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
Based on information obtained from blood donors who tested positive and epidemiological data from larger populations, it is known that certain groups of people may be at increased risk of infection by HIV, HCV, HTLV and HBV. Unfortunately it is not possible to exclude all cases of infection by relying on blood testing alone as infected donors may not be identified in the very early stages of infection, commonly referred to as the 'window period'. This refers to the period between being infected and the appropriate test being able to detect the infection. It takes several days/weeks for an infected individual to start forming antibodies, and a number of weeks before the antibody levels are high enough to be detected by using an antibody detection test; however, tests that are based on antigen detection will identify the infection earlier. During this window period the potential 'negative' donor is infectious. The focus of this group of questions is to identify behavioural risks that can be associated with increased risk of infection. It is particularly important to note recent risks; whilst established blood-borne infections will be detected through screening, very recent ones may not. Information must be passed on to the testing laboratory and transplant centres.			
35. Is it possible any of the following apply to your relative:			
35a. Was, or may have been infected with HIV, hepatitis or HTLV?	These blood-borne viruses can all be transmitted via organ/tissue donation.	Refer to POL188 (Contraindications to organ donation).	If yes to this question tissue donation is contraindicated.
35b. Within the last 12 months have they injected or been injected with non-prescribed drugs, including performance enhancing drugs or injectable tanning agents?	Individuals with a history of intravenous drug use remain the largest group diagnosed with HCV infection in the UK. They also have a higher rate of HIV and HBV infection. Ascertain if there was frequent exposure and dates of any exposure. Injectable tanning agents are illegal and their manufacture is not controlled.	Document information clearly to alert accepting surgeons.	Carry out risk assessment depending on the details provided.
35c. Been in prison or a juvenile detention centre for more than 3 consecutive days in the last 12 months? NB: This excludes those who have been in a police cell for < 96 hours.	Individuals in prison are at a higher risk of being exposed to transmissible viruses through sexual contact and intravenous drug abuse. Ascertain details of dates and duration.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
35d. Taken medication to prevent HIV infection, e.g. PrEP/ pre-/post-exposure prophylaxis?	There is the potential for a significantly reduced antibody response to HIV in an HIV-infected individual taking PrEP – a low titre infection (being treated) or a lower, blunted antibody response will means that the HIV infection may be missed with current testing methods.	This information must be passed to the testing laboratory and discussed at early stages as modification of the testing algorithm may be required.	As organ donation.
36. Has your relative ever had sex – consensual or otherwise?	This question needs to be asked of all donors irrespective of age. This includes the mother of neonates.	Document information clearly to alert accepting surgeons.	
If yes, it is possible that your relative:			
36a. Was given payment for sex with money or drugs in the last 3 months?	Individuals who receive payment for sex are at a higher risk of contracting HIV/HBV/HCV and other sexually transmitted diseases. The increased risk could be related to the high number of sexual partners, the potential promiscuity of these partners and possible drug-related habits.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
36b. Has ever had a sexually transmitted infection?	If the answer is yes, ascertain type of infection, treatment and dates and where treated. Untreated STIs may eventually cause damage to many organs and tissues or could be transmitted to the recipient.	Document information clearly to alert accepting surgeons.	Acceptance criteria are specific for each condition, refer to current TDSG-DD.
37. Did your relative have sex, consensual or otherwise in the last 3 months?		Document information clearly to alert accepting surgeons.	

Question	Reason for asking the question	Additional action to take re organ donation	Additional action to take re tissue donation
If yes, is it possible that in the last 3 months your relative had sex with:			
37a. (For male patients only) another man?	Men who have sex with men have a much higher prevalence of HIV infection and other sexually transmitted diseases.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
37b. (For female patients only) a man who has ever had sex with another man?	The sexual partners of individuals who fall into the above category (37a) are at higher risk of HIV infection and other sexually transmitted diseases.	Document information clearly to alert accepting surgeons.	If yes to this question tissue donation is contraindicated.
37c. Anyone who is HIV- or HTLV- positive? 37d. Anyone who has hepatitis? 37e. Anyone who had a sexually transmitted disease? 37f. Anyone who has ever been given payment for sex with money or drugs? 37g. Anyone who in the last 12 months has injected, or been injected, with non-prescription drugs, including performance enhancing drugs, injectable tanning agents.	Transmission of blood-borne sexually transmitted diseases is higher in individuals who fall into these categories.	Document information clearly to alert accepting surgeons.	Other than Q37i (see below) – If yes to any of these questions tissue donation is contraindicated.
37h. Anyone who may ever have had sex in a part of the world where AIDS/HIV is very common (this includes most countries in Africa)?	There is a higher risk of contracting some sexually transmitted infections in some parts of the world where they are more common.		
37i. Anyone who has developed an illness related to travel such as Zika?			If the donor has had sexual contact with anyone with a diagnosed infection in the previous 6 months, e.g. Zika, then there needs to be a risk assessment – when was the infection/sexual contact, can we test, do we need to defer or can we accept based on the type of tissue?
38. Having answered all the previous questions, is there anyone else who you think may provide more information?	The highest ranking/nearest relative may not be the person with the most relevant and current information to answer questions of a sensitive nature about the donor. If the answer is 'yes' to this question, every effort should be made to identify and contact that individual to get the relevant information from that person as well.		

Medical and Social History Questionnaire in its original (2014) form

NHS
Blood and Transplant

Tissue Donor Number | | | | | | | | | | ODT Donor Number | | | | | | |

Medical and Social History Questionnaire

Directions for completion

1 This form must be completed in **black or dark blue ink** by the Specialist Nurse – Organ Donation (SNOD)/Specialist Nurse – Tissue Donation (SNTD)/Tissue Donor Co-ordinator (TDC) and signed where required.

2 The original copy should be retained by the **SNOD/SNTD/TDC** for the donor file.

3 A copy should be made for the patient's medical records.

4 In the event of organ and tissue donation, a legible copy should be sent to the relevant **Tissue Establishment**, where required.

NOTE: The term patient is used throughout the form to refer to the potential donor.

The term relative is used throughout the form to refer to the relationship between the patient and the interviewee.

In order to ensure the safety of organs and tissue for transplant I will need to ask you some questions about *(name of patient)* medical and lifestyle history. Some of the questions are of a sensitive and personal nature. They are similar questions to those asked when someone donates blood. I will read and discuss each question with you and ask that you answer to the best of your knowledge with either a "Yes" or "No."

PATIENT INFORMATION

Patient's Forename(s) Please print

Patient's Surname Please print

Donating Hospital

NHS/CHI Number

Hospital Number

Cause of Death

Date of Birth (dd/mm/yyyy)

Occupation

Country of Birth

Country of Residency

INTERVIEWEE INFORMATION

Information discussed with

Name Please print

Relationship Please print

For patients under the age of 18 months, or those who have been breast-fed or fed breast milk by a donor in the last 12 months, the mother is required to answer these questions with regard to her own and her child's health.

For children: has your child been breast-fed in the past 12 months? Yes ☐ No ☐ Unknown ☐

NOTE: for all patients under the age of 18 months and any child who has been breast-fed in the last 12 months, a blood sample for microbiological testing is required from the mother, as well as from the patient.

For ALL female patients between 13 and 53 years of age: Is there a possibility that your relative could be pregnant? Yes ☐ No ☐ Unknown ☐

GENERAL HEALTH INFORMATION

1. Did your relative visit a general practitioner in the last two years? Yes ☐ No ☐ Unknown ☐

If YES, give details

2. Was your relative currently seeing or waiting to see a general practitioner or any other healthcare professional? Yes ☐ No ☐ Unknown ☐

If YES, give details

3. Did your relative ever take regular medication? Yes ☐ No ☐ Unknown ☐

If YES, give details of any current or previous medication including any medication for acne, prostate or psoriasis

4a. Did your relative have a history of allergies to medication, food or other substances? Yes ☐ No ☐ Unknown ☐

If YES, please provide details of the substance they were allergic to and describe the reaction

4b. Did your relative have any health problems due to exposure to toxic substances such as pesticides, lead, mercury, gold, asbestos, agent orange etc? Yes ☐ No ☐ Unknown ☐

If YES, please provide details of the toxic substance and treatment

5a) Was your relative a diabetic? Yes ☐ No ☐ Unknown ☐

If YES, were they on insulin? Yes ☐ No ☐ Unknown ☐ N/A ☐

5b) Is there a family history of diabetes? Yes ☐ No ☐ Unknown ☐

If YES, is it insulin-dependent diabetes? Yes ☐ No ☐ Unknown ☐ N/A ☐

6. Did your relative suffer from any chronic or long term illness or disease? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment if possible

7. Did your relative ever suffer from any bone, joint, skin or heart disease? Yes ☐ No ☐ Unknown ☐

If YES, specify which and give details

8. Did your relative ever have hepatitis, jaundice or liver disease? Yes ☐ No ☐ Unknown ☐

If YES, give dates, diagnosis, treatment and hospital /clinic name if known

GENERAL HEALTH INFORMATION

9. Did your relative recently suffer from significant unplanned weight loss? Yes ☐ No ☐ Unknown ☐

If YES, give details

10. Did your relative ever undergo any investigations for cancer or were they ever diagnosed with cancer? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment, if possible

11. Did your relative have a history of eye disease, receive any medications for eye problems (e.g. eye drops), or undergo eye surgery or laser treatment? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment, if possible

12. Did your relative ever have any operations? ***If NO go to question 15*** Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment, if possible

13. Did your relative ever have any surgery on the brain or spine? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details including hospital name and dates of treatment if possible. **Surgery before 1993** is particularly significant

14. Did your relative ever have an organ or tissue transplant? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details including hospital name and dates of treatment if known

15. Was your relative ever told not to donate blood? Yes ☐ No ☐ Unknown ☐

If YES, give details of where, when and the reason

16. Did your relative receive a transfusion of blood or blood product(s) at any time? Yes ☐ No ☐ Unknown ☐

If YES, give details including country, hospital name, dates and reason for transfusion

GENERAL HEALTH INFORMATION

17. Did your relative suffer from any type of brain disease such as Parkinson or Alzheimer disease or dementia? Yes ☐ No ☐ Unknown ☐

If YES, give details including hospital name and dates of treatment if possible

18. Did your relative suffer from any one or more of the following problems: memory problems or confusion, change in personality or behaviour, or were they unsteady on their feet? If **NO** go to Question 19, If **YES** Yes ☐ No ☐ Unknown ☐

18a. Were you aware of a condition causing these symptoms? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, please specify condition

18b. When did these symptoms start?

Please give details

18c. Did they worsen noticeably over time?

Please give details

18d. Was your relative able to live independently?

Please give details

19. Did your relative have a family history of prion disease, such as CJD, or were they ever told that they were at risk of prion disease? Yes ☐ No ☐ Unknown ☐

If YES, please give details

20. Did your relative ever receive human pituitary extracts, e.g. growth hormones or for fertility treatment or test injections for hormone imbalance? Yes ☐ No ☐ Unknown ☐

If YES, give details including dates and hospital/clinic name if known

21. Did your relative ever have any significant infection? Yes ☐ No ☐ Unknown ☐

If YES, give details, and any treatment received and hospital/clinic name if known

RECENT HISTORY

22. Did your relative come into contact with an individual with an infectious disease within the last month? Yes ☐ No ☐ Unknown ☐

If YES, please specify details, dates, symptoms, diagnosis, and treatment

23. Did your relative have any signs of infection, e.g. colds, flu, fever, night sweats, swollen glands, diarrhoea, vomiting or skin rash within the last month? Yes ☐ No ☐ Unknown ☐

If YES, please specify dates, symptoms, diagnosis, and treatment

24. Did your relative have any immunisations within the last 2 months? Yes ☐ No ☐ Unknown ☐

If YES, give details including travel vaccinations and flu vaccination or flu nasal spray

25. Did your relative have tattooing, body piercing, botox injections, acupuncture colonic irrigation, faecal transplantation, or any other cosmetic treatments that involve piercing the skin in the last 3 months? Yes ☐ No ☐ Unknown ☐

If YES, give details including where and when including unlicensed clinics in UK or abroad

26. Has your relative ever been bitten or scratched by any animal including strays, pets, wild or farm. Or have they ever been bitten or in close contact with ticks or bats? Yes ☐ No ☐ Unknown ☐

If YES, give details of incident, circumstances, animal, place, dates, and treatment

TRAVEL HISTORY

27. Did your relative ever travel or live outside the UK (including business trips)? Yes ☐ No ☐ Unknown ☐
If NO go to question 33

28. In the last 12 months did your relative go outside the UK (including business trips)? Yes ☐ No ☐ Unknown ☐ N/A ☐

Give details of dates and destinations visited

29. Did your relative ever have malaria or an unexplained fever which they could have picked up whilst abroad? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give date of fever/illness, places visited, duration and dates

30. Was your relative ever unwell whilst abroad or in the first month of their return to the UK? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details

31. Did your relative ever live or travel outside the UK for a continuous period of 6 months or more? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details of dates and destinations

32. Did your relative ever go to Central America, Mexico or South America for a continuous period of 1 month or more? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details of dates, places (remote/rural/urban areas), nature of visit

33. Was your relative's mother born in Central America, Mexico or South America? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details

BEHAVIOURAL RISK ASSESSMENT

34. Did your relative
(a) Consume alcohol? Yes ☐ No ☐ Unknown ☐

If YES, give details

(b) Smoke tobacco or any other substance? Yes ☐ No ☐ Unknown ☐

If YES, give details of substance, frequency, history of smoking time and time elapsed since giving up.

(c) Take any recreational drugs? Yes ☐ No ☐ Unknown ☐

If YES, give details of route of administration and dates

35. Is it possible that any of the following apply to your relative?

(a) Was, or may have been infected with HIV, hepatitis or HTLV? Yes ☐ No ☐ Unknown ☐

(b) Within the last 12 months have they injected, or been injected, with non-prescription drugs, including performance enhancing drugs or injectable tanning agents? Yes ☐ No ☐ Unknown ☐

(c) Been in prison or a juvenile detention centre for more than 3 consecutive days? Yes ☐ No ☐ Unknown ☐

(d) Taken medication to prevent HIV infection e.g. (PrEP/ Post exposure prophylaxis)? Yes ☐ No ☐ Unknown ☐

If YES to any of the above questions a-d, give details, including dates for question c

36. Has your relative **ever** had sex – consensual or otherwise?
If no, go to question 38. If yes, is it possible that your relative: Yes ☐ No ☐ Unknown ☐

If YES, is it possible that your relative:

(a) Was given payment for sex with money or drugs in the last 3 months? Yes ☐ No ☐ Unknown ☐ N/A ☐

(b) Ever had a sexually transmitted disease? Yes ☐ No ☐ Unknown ☐ N/A ☐

If YES, give details, including hospital/clinics, dates, treatments.

37. Did your relative have sex, consensual or otherwise in the last 3 months?	Yes ☐	No ☐	Unknown ☐	N/A ☐
If no, go to question 38. If yes, is it possible that in the last 3 months your relative had sex with:				
(a) *(for male patients only)* another man?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(b) *(for female patients only)* a man who has had sex with another man?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(c) Anyone who is HIV or HTLV positive?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(d) Anyone who has hepatitis?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(e) Anyone who had a sexually transmitted disease?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(f) Anyone who has ever been given payment for sex with money or drugs?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(g) Anyone who in the last 12 months has injected or been injected with non-prescription drugs including performance enhancing drugs or injectable tanning agents?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(h) Anyone who could have had sex, in any part of the world, where AIDS/HIV is very common (this includes most countries in Africa)?	Yes ☐	No ☐	Unknown ☐	N/A ☐
(i) Anyone who has developed an illness related to travel such as Zika?	Yes ☐	No ☐	Unknown ☐	N/A ☐
38. Having answered all the previous questions, is there anyone else who you think may provide more information?	Yes ☐	No ☐		

If YES, please specify

Question number	Relevant additional information. If any questions have been answered as unknown, give an explanation

Signature of healthcare professional obtaining information

Please print name

Designation of healthcare professional obtaining information

Date of interview | | | | | 2 | 0 | | |

Time of interview | | | | |

Appendix 7. Donor patient history questionnaire (Germany, English-language version)

	Patient's history questionnaire		
	identification		
	date and time		
	interviewer	☐ attending physician ☐ co-ordinator	
	kind of interview	☐ personal ☐ telephone	
	resources used	☐ hospital physician ☐ general practitioner ☐ donor relative ☐ other	
	any obstacles during interview		

1.	Medical treatment (during past 12 months)	☐ yes ☐ no ☐ unknown
	outpatient treatment	☐ yes ☐ no ☐ unknown
	contact data to outpatient treatment	
	reason for outpatient treatment	
	inpatient treatment	☐ yes ☐ no ☐ unknown
	contact data to inpatient treatment	
	reason for inpatient treatment	
	any transfusions during outpatient or inpatient treatment?	☐ yes ☐ no ☐ unknown
	if yes, where and indication	

2.	**Pre-existing illness/disease or past medical illness/previous surgery**	☐ **yes**	☐ **no**	☐ **unknown**
	diabetes*	☐ yes	☐ no	☐ unknown
	arterial hypertension*	☐ yes	☐ no	☐ unknown
	coronary artery disease*	☐ yes	☐ no	☐ unknown
	hepatitis/jaundice*	☐ yes	☐ no	☐ unknown
	tuberculosis*	☐ yes	☐ no	☐ unknown
	venereal disease or sexually transmitted disease*	☐ yes	☐ no	☐ unknown
	other infections (e.g. malaria)*	☐ yes	☐ no	☐ unknown
	breast tumour/malignancy*	☐ yes	☐ no	☐ unknown
	melanoma or skin tumour/malignancy*	☐ yes	☐ no	☐ unknown
	intestinal/colon tumour/malignancy*	☐ yes	☐ no	☐ unknown
	prostatic tumour/malignancy *	☐ yes	☐ no	☐ unknown
	gynaecological or obstetric tumour/malignancy*	☐ yes	☐ no	☐ unknown
	other tumour/malignancy*	☐ yes	☐ no	☐ unknown
	disease of central nervous system/neurological or psychiatric illness*	☐ yes	☐ no	☐ unknown
	autoimmune diseases*	☐ yes	☐ no	☐ unknown
	haematologic diseases/coagulation disorders	☐ yes	☐ no	☐ unknown
	if yes: received coagulation products of human origin*	☐ yes	☐ no	☐ unknown
	any other pre-illness*	☐ yes	☐ no	☐ unknown
	previous surgery*	☐ yes	☐ no	☐ unknown
	* if yes, specify details			

3.	**Medications/substance abuse/drugs/injections, etc.**			
	regular medications*	☐ yes	☐ no	☐ unknown
	if yes: specify *medication*			
	regular use of pain medications/analgesics	☐ yes	☐ no	☐ unknown
	smoking*	☐ yes	☐ no	☐ unknown
	if yes: *duration, amount (pack-years)*			
	alcohol abuse*	☐ yes	☐ no	☐ unknown
	if yes: *duration, amount*			
	injections without medical indication (iv, im, sc) during past 12 months*	☐ yes	☐ no	☐ unknown
	evidence for drugs consumed (e.g. stimulants, amphetamine, LSD, marijuana, cocaine)*	☐ yes	☐ no	☐ unknown
	drugs consumed iv/nasal*	☐ yes	☐ no	☐ unknown
	tattoos, piercings, acupuncture (during past 12 months)*	☐ yes	☐ no	☐ unknown
	* if yes, specify details			

4.	**Abnormality during past 12 months (B-Symptoms)**	☐ yes	☐ no	☐ unknown
	fever/unexplained fever attacks or elevation of body temperature	☐ yes	☐ no	☐ unknown
	night sweats	☐ yes	☐ no	☐ unknown
	headache	☐ yes	☐ no	☐ unknown
	loss of weight	☐ yes	☐ no	☐ unknown
	diarrhoea	☐ yes	☐ no	☐ unknown
	swelling of lymph nodes	☐ yes	☐ no	☐ unknown
	dysmenorrhoea/haemorrhage	☐ yes	☐ no	☐ unknown

5.	**Affiliation to at-risk group for recent HIV HBV HCV infection***			
	appropriate information not available*	☐		
	prostitution*	☐ yes	☐ no	☐ unknown
	frequently changing sexual partner (during past 12 months)*	☐ yes	☐ no	☐ unknown
	sexual partner with HIV, HBV or HCV infection or at-risk group (during past 12 months)*	☐ yes	☐ no	☐ unknown
	imprisonment (during past 12 months)*	☐ yes	☐ no	☐ unknown
	men who have sex with men (MSM) (during past 12 months)*	☐ yes	☐ no	☐ unknown
	children of mothers HIV-infected or at-risk group for HIV infection (especially < 18 months or breastfed during past 12 months)*	☐ yes	☐ no	☐ unknown
	long-term stay in area with high prevalence for HIV, HBV or HCV*	☐ yes	☐ no	☐ unknown
	other evidence for increased risk (e.g. contact to open wound/blood/mucosa of persons at risk for HIV, HCV, or HBV infection, *Treponema pallidum* antibody reactive or other window-period-infection)*	☐ yes	☐ no	☐ unknown
	* if yes, specify details			

6.	**Exclusion from blood donation***	☐ yes	☐ no	☐ unknown
	* if yes, specify (reason, bloodbank)			

7.	**Stay (during past 3 months) or immigration from outside northern or central Europe***	☐ yes	☐ no	☐ unknown
	* if yes, specify where, duration of stay			

8.	**Vaccinations (within the past 4 weeks)***	☐ yes	☐ no	☐ unknown
	if yes, please mark			
	☐ influenza (if inhaled)	☐ varicella	☐ tick-borne encephalitis	☐ rotavirus
	☐ polio (if oral)	☐ measles	☐ mumps	☐ rubella
	☐ cholera (if oral)	☐ yellow fever		
	☐ BCG	☐ smallpox	☐ *Salmonella typhi* (if oral)	☐ other

9.	**Multidrug resistant organisms**	☐ yes	☐ no	☐ unknown
	if yes, specify (what kind)			

10.	**Animal bite/injury by animal**	☐ yes	☐ no	☐ unknown
	if yes, specify which animal			

11.	**Exist signs of pregnancy**	☐ yes	☐ no	☐ unknown
	if yes, specify			

12.	Additional remarks	☐ yes ☐ no

Date and name of physician/signature _____

Date and name of donor co-ordinator/signature _____

This questionnaire aims to ensure that disease transmission risks are not missed although limitations may exist. If in any section a 'yes' is marked, the donor co-ordinator should initiate appropriate investigations in order to clarify whether risk factors for transmissible diseases exist or not in a particular donor.

Appendix 8. Physical examination of an organ or tissue donor (American Association of Tissue Banks)

The rationale for this form is to standardise the physical examination for potential organ and tissue donors. This form is equivalent to the one shown in the *Guide to the quality and safety of tissues and cells for human transplantation*, 3rd edition, Appendix 13.

Sample Tissue Donor Physical Assessment Form

Identification

Name stated on Consent (Authorization) : _____
Age: _____ days months years Recovery Agency ID#: _____
Sex/gender: Male Female Race: _____ _____ID#:_____
Weight: _____ lbs. kgs Weight is: estimated/team, reported (source: _____) , /actual
Height: _____ft. in. cm. Height is: estimated/team, reported (source: _____), /actual
Manner identified by: hospital ID band, toe tag, other (describe) _____

Identification Band/Tag

ID re-created as closely as possible,

or circle N/A (if not present).

Personnel confirming donor identification: _____Date/time:_____

Evidence of Donation/Autopsy

Eye donation: whole eyes, corneas only, N/A ; Organ donation: Yes No UNOS#: _____
Autopsy: tissue recovery is pre, or post autopsy (full, limited); no autopsy planned; or, plan unknown

Recovery Team Assessment:

Is there evidence of:
Jaundice ——— Yes ——— No
Genital lesions ——— Yes ——— No
Enlarged lymph nodes ——— Yes ——— No
Tattoo/piercing ——— Yes ——— No
White spots in the mouth ——— Yes ——— No —— Unable to visualize
Non-medical injection sites ——— Yes ——— No
Enlarged liver (hepatomegaly) ——— Yes ——— No
Insertion trauma/perianal lesions ——— Yes ——— No
Rash/scab/skin lesion (non-genital) ——— Yes ——— No
Blue/purple (gray/black) spots/lesions ——— Yes ——— No
Trauma/infection to potential retrieval sites ——— Yes ——— No
Abnormal ocular finding (e.g., icterus, scarring)—— Yes ——— No —— Unable to visualize
Notes/Explain if "unable to visualize", or if any answers are "Yes": _____

_____

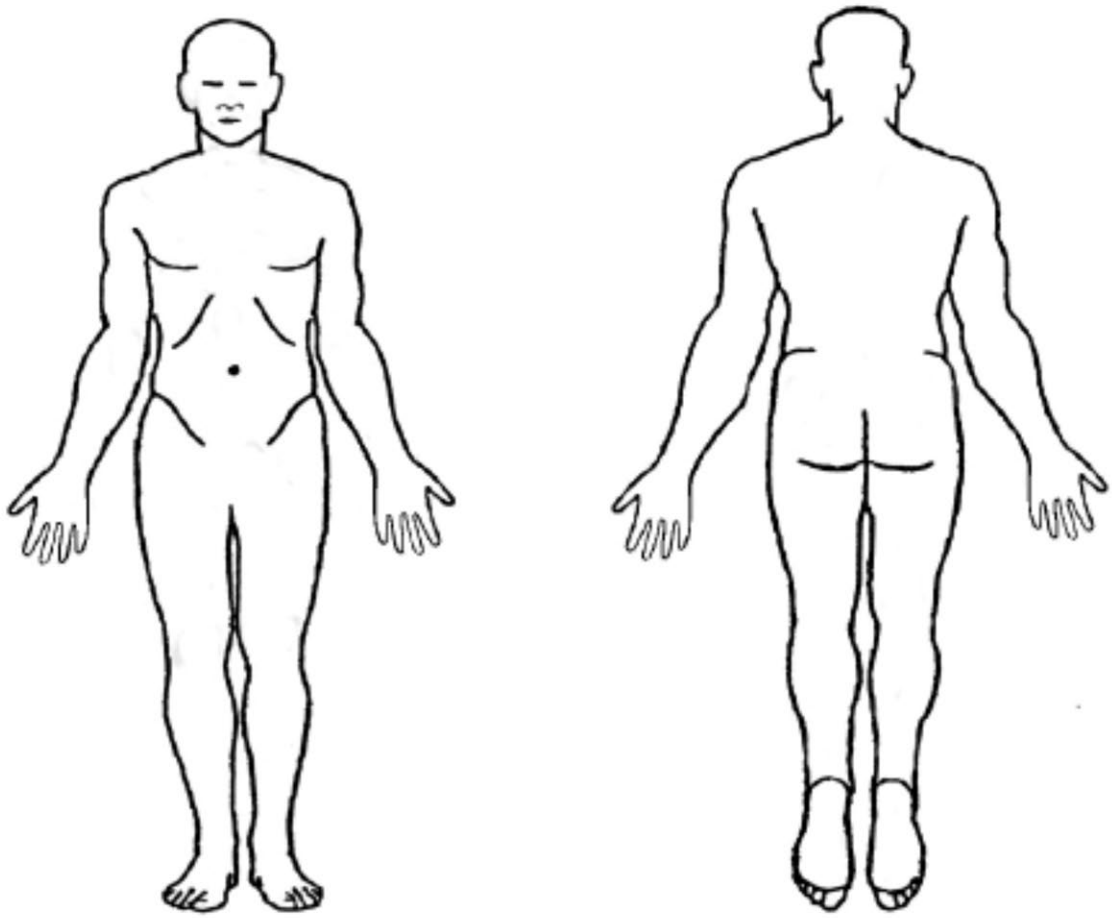
General Appearance
Cleanliness: Good Poor; Describe if "poor" _____
Personnel performing physical assessment: _____Date/time:_____

_____	_____	_____	_____
Name of Person Completing Form (Print)	Signature	Initials	Date

AATB Sample Tissue Donor Physical Assessment Form

Recovery Agency ID#: _____

Recovery Team Assessment: (continued)



Key to schematics:

(A) Abrasion	(J) Team blood draw site	(T) Tattoo – requires description
(B) Bruise/Contusion	(L) Laceration/Wound	(U) Urethral catheter
(C) Cast/Ortho device	(M) ID band/tag	(V) Skin lesion
(D) Dressing/Bandage	(N) Needle entry site	(W) Scab
(E) ET tube/NG tube	(O) Organ recovery incision	( ) _____
(F) Fracture/Dislocation	(P) Body Piercing – requires description	( ) _____
(H) Hematoma	(R) Rash	( ) _____
(I) IV/Arterial line	(S) Scar (surgical/trauma)	( ) _____

Summary

A review of available medical records & physical assessment findings were completed & found to be acceptable/not acceptable prior to recovery. _____ _____

(Circle one) (Responsible person) (Date/time)

Appendix 9. **Donor and organ information forms**

Appendix 9.1. Donor information form (Eurotransplant, English-language version)

Appendix 9.2. Organ information form of the Foedus project (Agence de la biomédicine, France, English-language version)

The two forms shown in this appendix are used for donor characterisation as well as for data exchange between European countries when cross-border organ exchange is intended.

9.1. Donor information form (Eurotransplant, English-language version)

The Donor information form is used within the Eurotransplant area (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands) for data exchange during organ offer by the allocation office according to the data provided by the organ procurement organisation. This form is modified in its design when used within the IT systems of the different states. The donor and organ characteristics described in this questionnaire are based on the considerations outlined in Chapter 6 and Chapter 7.

EUROTRANSPLANT DONOR INFORMATION FORM

Registration date / time	ET donor nr	Region Center	ABO Rh	NHBD: Y / N	Date of birth	Age	Sex	Weight	Height
				Type: I / II / III / IV					
DSO identity nr			Bloodgroup remarks						

TT lab	HLAmethod	A	A	A	A	B	B	B	B	Bw	Bw	Cw	Cw
	DNA Serology												
material	date / time	DR	DR	DR	DR	DR	DR	DQ	DQ	DQ	DQ	Cw	Cw

Microbiology (* is mandatory) date: Other microbiology results:

HIV Ab *	HIV Ag	HBsAg*	HBsAb	HBcAb*	HCV Ab*	CMV IgM *	CMV IgG *	Lues (VDRL / TPHA)	Toxo. Ab	EBV	Sepsis	Meningitis

Remarks on microbiology

Organs	Repor-ted	Explant. by local team	Reason not reported (specify)	Reason for withdrawal (specify)	Preservation fluid used	Consent to research
Heart	Y / N	☐				Y / N
Left lung	Y / N	☐				Y / N
Right lung	Y / N	☐				Y / N
Liver	Y / N	☐				Y / N
Pancreas	Y / N	☐				Y / N
Left kidney	Y / N	☐				Y / N
Right kidney	Y / N	☐				Y / N
Intestine	Y / N	☐				Y / N

Donor information

Donor identity:	Permission given:
Country of citizenship:	**Register checked :**

Contact data

Donor hospital:	Hospital tel nr:
Contact person (DSO coord):	Contact tel nr:
Hospital department: ESP region:	Contact other (GSM) tel nr:
ET office coordinator:	Explantation planned on date / time:

General Clinical data

Cause of death:	
Brain death date / time:	
Admission date / time:	Admission on ICU date / time:
Mechanical ventilation since date / time:	Urine catheter since date / time:
Cardiac arrest:	Total duration of cardiac arrest:
Date / time of last reanimation:	Duration of last reanimation:
Number of times the donor was reanimated:	
Donor comments:	

F1.1.2 Donor information form 31-01-2014 Also available on: www.eurotransplant.org

EUROTRANSPLANT DONOR INFORMATION FORM

Donor center	ET donor nr	ABO Rh	Date of birth

Medical History			
Hypertension:	since:	Treated:	
Diabetes Mellitus Type:	since:	Treated:	
Alcohol Abuses:	since:	Intake:	
Smoking: since:	packyears:	IV Drug abuse: since:	
Malignant Tumor	since:	Treated:	
Comments / other known illnesses:		Medication before admission:	

Physical data			
Diuresis:	ml in last …… hours	Diuresis last hour:	ml

Clinical data	Date:	Date:	Date:
Temperature	°C	°C	°C
Heart Frequency	/min	/min	/min
Systolic Bloodpres.	mmHg	mmHg	mmHg
Diastolic Bloodpres.	mmHg	mmHg	mmHg
CVP	cm H2O/ mmHg	cm H2O/ mmHg	cm H2O/ mmHg
Clinical deviations	Date / time:	Date / time:	Date / time:
Highest art BP	min. mmHg	min. mmHG	min. mmHg
Duration of low BP	min	min	min

Medication	Date: Dose:	Date: Dose:	Date: Dose:
Adrenaline			
Noradrenaline			
Dopamine			
Dobutamine			
Other vasopressor			
Blood transfusions: last 24 hours:			
Plasma expanders: last 24 hours:	product:	product:	product:
Other bloodproducts	product:	product:	product:
Antibiotics:	therapeutic / profylactic	therapeutic / profylactic	therapeutic / profylactic
Antidiuretics:			
Other medication (last 24 hours):			

General Remarks

EUROTRANSPLANT DONOR INFORMATION FORM

Donor center	ET donor nr	ABO Rh	Date of birth

Laboratory Values (* is mandatory)

Date / time							Normal values	calc. →	Normal values
Hb *						mmol/l / g/dl	7.5-11 mmol/l	X 1.6	12-16 g/dl
Ht *						%	40-54 %	X 0.01	0.4-0.54
Leuco's *						x 10^9/l	4.0-11.0 x 10^9/l		
Platelets *						x 10^9/l	130-400 x 10^9/l		
Ery's						x 10^{12}/l	3.5-5.9 x 10^{12}/l		
Na^{+*}						mmol/l	135-147 mmol/l		
K^{+*}						mmol/l	3.5-5.0 mmol/l		
Ca^{2+}						mmol/l	2.2-2.55 mmol/l		
Cl^-						mmol/l	95-105 mmol/l		
Glucose *						mmol/l / mg/dl	3.9-6.1 mmol/l	x 17.9	70-110mg/dl
Creatinine *						mmol/l / mg/dl	62-132 mmol/l	x 0.011	0.7-1.5mg/dl
Urea *						mmol/l / mg/dl	3 – 9 mmol/l	x 6	18-54 mg/dl
LDH *						U/l	50-240 U/l	x 0.016	0.8-3.8µkat/l
CPK *						U/l	0-150 U/l	x 0.016	0-2.5 µkat/l
CKMB *						U/l	<5 U/l <10%cpk	x 0.016	<0.08 µkat/l
Troponine						µg/l	< 0,1 µg/l		
ASAT / SGOT*						U/l	0-35 U/l	x 0.016	0-0.58 µkat/l
ALAT / SGPT*						U/l	0-35 U/l	x 0.016	0-0.58 µkat/l
γGT *						U/l	0-30 U/l	x 0.016	0-0.50 µkat/l
Bilirubin tot. *						µmol/l / mg/dl	3.4-20.4 µmol/l	x 0.058	0.2-1.2 mg/dl
Bilirubin dir. *						µmol/l / mg/dl	0-4 µmol/l	x 0.058	0-0.2 mg/dl
Alk. Phos. *						U/l	40-130 U/l	x 0.016	0.64-2.1µkat/l
Amylase *						U/l	0-130 U/l	x 0.016	0-2.17 µkat/l
Lipase						U/l	0-160 U/l	x 0.016	0-2.66 µkat/l
HBa1C						%	4-6 %		
Tot. Protein						g/l	60-80 g/l	x 0.10	6-8 g/dl
Albumin						g/l	25-60 g/l		60-65%
Fibrinogen						g/l / mg/dl	1.5-3.5 g/l	x 100	150-350 mg/dl
Quick / PT *						% / sec	70-100 %		10-13 sec
INR *							0.9-1.1		
APTT *						sec	26-34 sec		
AT III						%	70-120 %		
CRP*						mg/l	< 8 mg/l	x 0.10	< 0.8 mg/dl

Bloodgas and Ventilation

Date / time								Normal values	Normal values
FiO_2 (%) *						100 %	For 10 minutes		
PEEP *						+5 CM H_2O			
pH *								7.35-7.45	
pO_2 *							mmHg / kPa	80-100mmHg	9.5-13.5 kPa
pCO_2 *							mmHg / kPa	35-45mmHg	4.6-6.0 kPa
HCO_3 *							mmol/l	21-25mmol/l	
BE *							mmol/l		
O_2 sat. *							%	96-100%	

EUROTRANSPLANT DONOR INFORMATION FORM

Donor center	ET donor nr	ABO Rh	Date of birth

Bacteriology		**Urinalysis**	date/time	date/time
Urine:	date:	**Glucose:**		
		Protein:		
Sputum / Tracheal:	date:	**Sediment:**		
		ery's:		
Blood:	date:	**leuco's**		
		cyl.:		
Other:	date:	**bact.:**		
		other:		
Remarks Bacteriology:		**Remarks Urinalysis:**		

Other Diagnostics (* is mandatory)

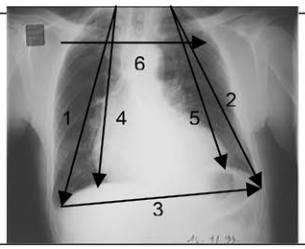
Chest X-Ray * date:

ECG * date:

Ultrasound heart date:

Bronchoscopy date:

Lung measurements	
1. Right apex to Right CPA	cm
2. Left apex to left CPA	cm
3. Right CPA to left CPA	cm
4. Right apex to diaphragma	cm
5. Left apex to diaphragma	cm
6. Thoraxwidth at lvl aortic arch	cm
Xray at 1m (end expiratory)	
CPA is costo phrenic angle	



Ultrasound abdomen * date:

Other diagnostics (ie. coronary angiography, CT Thorax, CT Abdomen:

9.2. Organ information form of the Foedus project (Agence de la biomédicine, France, English-language version)

This Organ information form is used within the Foedus project to ensure safe and effective organ exchange across borders between different countries and their organ-exchange organisations. The donor and organ characteristics described in this questionnaire are based on the considerations outlined in chapters 6 and 7.

agence de la biomédecine

To be contacted:
Tel : **00 33 1 49 46 50 74**
Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

ORGAN(S) OFFER

Please advise within less than 1 hour whether you wish to accept this offer

Procurement/ Retrieval site: _____
Closest opened airport: _____

Heart *(coeur)* ☐	**Heart/Lungs** *(coeur –poumons)* ☐	**Small Bowel** ☐	**Pancreas** ☐
Lungs ☐	*Right Lung* ☐	*Left Lung* ☐	
Kidneys ☐	*Right Kidney* ☐	*Left Kidney* ☐	
Liver ☐	*Right lobe* ☐	*Left lobe* ☐	

Procurement/Retrieval time: : hrs *or planned* at : : hrs
Aortic cross clamp time: : hrs *on* DD/MM/YY
If DCD planned time for switch off: : *hrs*

DONOR:

Donor code/ ID: Type of Donor: DCD ☐ DBD…. ☐

ABO group O Rh+ ☐ Rh- ☐ *(Groupe sanguin)*	Age	Gender: ♂☐ ♀☐	Weight (kg) *(Poids)* *kg*	Height (cm) *(Taille)* *cm*
HLA	*A*	*B*	*DR*	*DQ*

Admission date in Hospital *(date d'admission)*: / /
Admission date in ICU *(date d'admission)*: / /

Ventilated from *(date de ventilation)*: / /

Cardiac arrest *(arrêt cardiaque)*: Yes ☐ / No ☐, No flow for min on / / ,

Immediate actions: External defibrillator *(choc électrique externe)* ☐

select drug if other => *specify:*

Date & Time of Death: / / & : hrs

Cause of Death : Select diagnosis

Chest: Yes ☐ No ☐ / Head: Yes ☐ No ☐ /Abdominal: Yes ☐ No ☐ /Other => specify: _____

If intoxication ☐ => select substance, if other => *specify:* _____

Other cause of death : ☐ => specify:_____

agence de la biomédecine

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Past History:

Alcohol consumption (*Alcool*) : ☐/ quantity: since:

Stopped: ☐ since

Smoking status (*Fumeur*) : ☐/ quantity: since:

Stopped: ☐/since

Drug Abuse (*Drogues*) : ☐/ by IV: ☐/ Stopped: ☐/since comment *if any*:

Cardiovascular Disorders : ☐/, => ***Select type*** : ☐/ => specify: _____ Since :
DD/MM/YYYY & treatment : => specify:

Cancer : ☐ =>***Select*** : : Remission for more than 5 years : Yes ☐/ No ☐

Diabetes mellitus ☐/ & Type: ___

Chronic Infection : ☐/ => ***Select Chronic Infection*** Other ☐/ => specify: _____

Risk of pre-immunization : ☐/ => ***Select***

Other ☐/ => specify: _____

Previous Surgery *(Antécédants chirurgicaux)*: _____

Previous Treatment *(traitements antérieurs)*: _____

Clinical Data:

	: hrs *on*	: hrs *on*	: hrs *on*
Blood pressure : Average Haemodynamic unbalance : Yes ☐/ No ☐ /	mmHg	mmHg	mmHg
Heart rate	beats/ min	beats/ min	beats/ min
Diuresis	ml/h	ml/h	ml/h

Blood transfusion =>Last 24 h: Yes ☐/ No ☐

Current infections : ☐ select data Antibiotics => Last 24 h:Yes ☐ No ☐; if yes =>

_____

agence de la biomédecine

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Email : **regulation.nationale@biomedecine.fr**

Laboratory Data:		*At admission on* : hrs *on*	*Latest on* : hrs *on*
Haemoglobin	g/dl		
White cell	count /mm^3 X10 g/l		
Platelets	count /mm^3 X10 g/l		
Haematocrit	%		
Fibrinogen	g/l		
INR ☐ or PT ☐ or TQ ☐	% seconds		
Lactate	mmol/l		
Amylases	mmol/l		
Other /specify:			

Biological test (Add a X)	*Negative*	*Positive*	*Indeterminate (unreliable result)*	*In Process*	*Not tested*
HIV AgP24					
HIV Ab					
HCV Ab					
HBs Ag					
HBs Ab					
HBc Ab					
HTLV: I & II Ab					
HCV Ab					
CMV Ab					
Syphilis:(TPHA/VDRL)					
EBV Ab					
Toxoplasma Ab					
Others : _____					

Medication:	: hrs *on*	: hrs *on*	: hrs *on*
Dopamine/ Dobutamine : γ/kg/min µg/kg/min			
Adrenaline/ Noradrenaline: mg/h µg/kg/min			
Antidiuretic hormone µg			
Corticoids mg			
Others: _____ => specify units			

agence de la biomédecine

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Email : **regulation.nationale@biomedecine.fr**

Organs Characterisation:

LIVER		: hrs *on*	: hrs *on*
ASAT	UI/l		
ALAT	UI/l		
GGT	UI/l		
Alk. Phos.	UI/l		
LDH	UI/l		
Albumin	g/l		
Bilirubin	mg/l		

Echography / Ultrasounds Yes ☐ No ☐	Hepatic size *(fleche hépatique)*	138mm
	Abnormalities	Steatosis ☐ at %
		Biliary duct dilatation ☐
		Vena cava : Permeability defect ☐ Thrombosis ☐
		Other ☐ => specify

KIDNEY		: hrs *on*	: hrs *on*
Na+	mmol/l		
K+	mmol/l		
Urea	mmol/l		
Creatinine	µmol/l		
Proteinuria	g/l		

Echography / Ultrasounds Yes ☐ No ☐	**Right**	Size **cm** (*taille D*)	
		Abnormaliries	Cyst/Tumor: ☐ size **cm** Biopsy in process : ☐
			Atherosclerosis : ☐
			Thrombosis : ☐
			Signs of obstruction : ☐
			Other: ☐ => specify
	Left	Size **cm** (*taille G*)	
		Abnormaliries	Cyst/Tumor: ☐ size **cm** Biopsy in process : ☐
			Atherosclerosis : ☐
			Thrombosis : ☐
			Signs of obstruction : ☐
			Other ☐ => specify

agence de la biomédecine

To be contacted:
Tel : **00 33 1 49 46 50 74**
Fax : 00 33 1 48 22 66 05
Email : **regulation.nationale@biomedecine.fr**

LUNGS		: hrs *on*	: hrs *on*
FiO_2		%	%
pH			
$PaCO_2$	mmHg		
PaO_2	mmHg		
HCO^{3-}	mmol/l		
PEEP	mmHg		
O_2 sat		%	%

Chest X-Ray Yes ☐ No ☐	Thoracic perimeter **cm** Abdominal perimeter **cm** Sternal height **cm**	
	Abnormaliries	Effusion ☐ *(épanchement)*
		Atelectasis ☐
		Pneumonia ☐
		Cyst/Tumor: ☐ size **cm** Biopsy in process : ☐
		Broncoscopy ***Select***
		Adenopathy ☐
		Other ☐ => specify

HEART		: hrs *on*	: hrs *on*
CPK	UI/l		
CKMB	UI/l		
Troponin	ng/ml		

Electrocardiogram Normal ☐ Abnormal ☐		If Abnormal why:
Vascular pathology		Yes ☐/ No ☐ If YES specify:
Echography/ Ultrasounds Yes ☐ No ☐	**Abnormaliries**	Aortic injury ☐
		Atheroma ☐
		Aortic dissection ☐
		Aortic/ Vascular shrinkage ☐
		Other ☐ => specify

LVEF *(fract° d'éjection)*	%
And / or SF *(fract°raccourcissement)*	%
Septum size **mm**	
Dilation Right	Yes ☐/ No ☐
Left	Yes ☐/ No ☐
Contractility	Normal ☐ Abnormal ☐

Reason for non-acceptance in country of origin : ***Select reason***
(Raison du refus dans le pays d'origine)
if other => *specify:*_____

FOEDUS
FACILITATING EXCHANGE OF ORGANS DONATED IN EU MEMBER STATES

This form arises from the project FOEDUS (grant agreement 2012 21 01) which has received funding from the European Union, in the framework of the Health Programme. The sole responsibility lies with the author and the Executive Agency is

Co-funded by the Health Programme of the European Union

Appendix 10. **Donor examination by various means**

- 10.1. Donor examination by chest X-ray or alternative imaging (Eurotransplant, English-language version)
- 10.2. Donor examination by bronchoscopy (Eurotransplant, English-language version)
- 10.3. Donor examination by echocardiography (Eurotransplant, English-language version)
- 10.4. Donor examination by electrocardiogram (Eurotransplant, English-language version)
- 10.5. Donor examination by coronary angiography or alternative imaging (Eurotransplant, English-language version)
- 10.6. Donor examination by abdominal ultrasound or alternative imaging (Eurotransplant, English-language version)
- 10.7. Donor examination by standardised blood gas analysis with lung recruitment (Eurotransplant, English-language version)

10.1. Donor examination by chest X-ray or alternative imaging (Eurotransplant, English-language version)

X-Ray Chest

Date of examination	Date	Time	Identity (Id-#)		
Trachea in the middle	☐ yes ☐ no				
ET tube cranial to carina	☐ yes ☐ no				
Left lung	Clear: any changes or pathologies?		☐ no	☐ yes	☐ not assessable
	Rib fracture		☐ no	☐ yes	☐ not assessable
	Pneumothorax		☐ no	☐ yes	☐ not assessable
	Pleura effusion		☐ no	☐ yes	☐ not assessable
	Pleura thickening		☐ no	☐ yes	☐ not assessable
	Atelectasis		☐ no	☐ yes	☐ not assessable
	Infiltrates		☐ no	☐ yes	☐ not assessable
	Bronchial thickening		☐ no	☐ yes	☐ not assessable
	Space occupying lesion		☐ no	☐ yes	☐ not assessable
	Emphysema		☐ no	☐ yes	☐ not assessable
	Interstitial lung disease		☐ no	☐ yes	☐ not assessable
Right lung	Clear: any changes or pathologies?		☐ no	☐ yes	☐ not assessable
	Rib fracture		☐ no	☐ yes	☐ not assessable
	Pneumothorax		☐ no	☐ yes	☐ not assessable
	Pleura effusion		☐ no	☐ yes	☐ not assessable
	Pleura thickening		☐ no	☐ yes	☐ not assessable
	Atelectasis		☐ no	☐ yes	☐ not assessable
	Infiltrates		☐ no	☐ yes	☐ not assessable
	Bronchial thickening		☐ no	☐ yes	☐ not assessable
	Space occupying lesion		☐ no	☐ yes	☐ not assessable
	Emphysema		☐ no	☐ yes	☐ not assessable
	Interstitial lung disease		☐ no	☐ yes	☐ not assessable
Foreign body	☐ no ☐ left lung ☐ right lung ☐ both lungs ☐ trachea				☐ not assessable
Prominent Hilum	☐ no ☐ yes				☐ not assessable
Mediastinum enlarged	☐ no ☐ yes				☐ not assessable
Heart shadow enlarged	☐ no ☐ yes				☐ not assessable
Remark					
Examiner					

10.2. Donor examination by bronchoscopy (Eurotransplant, English-language version)

Bronchoscopy

Date of examination	Date	Time	Identity (Id-#)		
Trachea	Epithelium: any changes or pathologies	☐ no	☐ yes		☐not assessable
	Inflammation	☐ no	☐ yes		
	Bleeding	☐ no	☐ yes		
	Ulceration	☐ no	☐ yes		
	Tumour	☐ no	☐ yes		
	Aspiration	☐ no	☐ yes		
	Putrid secretion	☐ no	☐ yes		
	Amount, colour, consistency of secretions :				
	Additional bronchus	☐ no	☐ yes		
Bronchus left	Epithelium: any changes or pathologies?	☐ no	☐ yes		☐not assessable
	Inflammation	☐ no	☐ yes		
	Bleeding	☐ no	☐ yes		
	Ulceration	☐ no	☐ yes		
	Tumour	☐ no	☐ yes		
	Putrid secretion	☐ no	☐ yes		
	Localization of secretion in bronchus		☐ main b.	☐ lobar b.	☐ sublobar b.
	Secretion after suction	☐ clean	☐ refilling from peripheral		
	Aspiration	☐ no	☐ yes		
Bronchus right	Epithelium: any changes or pathologies?	☐ no	☐ yes		☐not assessable
	Inflammation	☐ no	☐ yes		
	Bleeding	☐ no	☐ yes		
	Ulceration	☐ no	☐ yes		
	Tumour	☐ no	☐ yes		
	Putrid secretion	☐ no	☐ yes		
	Localization of secretion in bronchus		☐ main b.	☐ lobar b.	☐ sublobar b.
	Secretion after suction	☐ clean	☐ refilling from peripheral		
	Aspiration	☐ no	☐ yes		
Remark (Bronchus):					
Tracheal / bronchial aspirate sent to microbiological laboratory		☐Yes	☐no		
BAL (bronchoalveolar lavage) sent to microbiological laboratory		☐Yes	☐no		
Examiner					

10.3. Donor examination by echocardiography (Eurotransplant, English-language version)

Echocardiography

Date of examination		Date	Time	Identity					
Type of examination		☐ TTE ☐ TEE		(Id-#)					
Visualisation		☐ normal ☐ limited ☐ severely limited							
Haemodynamic measurement at time of echocardiography									
MAP			mmHg	Inotropes at examination ☐ yes↓ ☐ no					
Heart rate			BPM	Kind and					
CVP			mmHg	Dosage					
Left heart									
If case of measurement not possible please describe qualitative	LA		mm (≤59)						
	LV-EDD		mm (≤59)	LV-PWd		mm (≤10)	IVSd		mm (≤10)
	LV-ESD		mm (≤38)	LV-PWs		mm	IVSs		mm
	LV-EF		% ☐ Simpson (≥55) ☐ Teichholz ☐ estimated				or LV-FS		% (≥25)
	LVH Hypertrophy	☐ normal	☐ moderate	☐ severe					☐ not assessable
	LVF Function systolic	☐ normal	☐ mildly reduced	☐ moderately reduced		☐ severely reduced			☐ not assessable
	LV Function diastolic*	☐ normal	☐ abnormal relaxation	☐ pseudo normalisation		☐ restrictive filling			☐ not assessable
		☐ none	☐ regional akinesia↓		☐ hypokinesia↓				☐ not assessable
LV-regional wall motion disorder (please specify)									
Right Heart									
If case of measurement not possible please describe qualitative	RV-EDD		mm (<35)	RV-TAPSE		mm (>15)			
	RV-ESD		mm (<25)	RV-Wand		mm (≤5)			
				RA		mm (≤45)			
	RV function	☐ normal	☐ function reduced						☐ not assessable
	RV size	☐ normal	☐ hypertrophy						☐ not assessable
	RV morphology	☐ normal	☐ moderate dilated		☐ dilated				☐ not assessable
Aorta and Valves									
Aorta	Aortic-Annulus		mm (<28)	Aorta-ascendens		mm(<30)	☐ not assessable		
	Morphology								
Aortic valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Morphology	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Mitral valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Anterior leaflet	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
	Posterior leaflet	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Pulmonary valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Morphology	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Tricuspid valve	Insufficiency	☐ none	☐ 1	☐ 2	☐ 3	☐ not assessable			
	Stenosis	☐ none	☐ mild	☐ moderate	☐ severe	☐ not assessable			
	Morphology	☐ normal	☐ thickened	☐ calcification		☐ not assessable			
Pericardial effusion		☐ no	☐ yes	Thickness		mm	☐ not assessable		
Further measurements, remarks (e.g. suspicion of endocarditis, malformation (ASD / VSD))									
Examiner									

***LFV diastolic only when LVF systolic normal**

10.4. Donor examination by electrocardiogram (Eurotransplant, English-language version)

ECG (Electrocardiogram)

Date of examination	Date	Time	Identity	
ECG plot at ET	☐ no ☐ yes		(Id-#)	
Heart rate (BPM)				
Sinus-Rhythm (SR)	☐ SR (yes) ☐ absent (no)			☐ not assessable
AV-Block	☐ none ☐ present (yes)			☐ not assessable
Atrial arrhythmia	☐ none ☐ present (yes)			☐ not assessable
Ventricular arrhythmia	☐ none ☐ present (yes)			☐ not assessable
QRS-changes	☐ none ☐ left bundle bloc ☐ bifsc. bloc ☐ Infarct like ☐ right bundle bloc ☐ other ☐ not assessable			
remark				
ST-T-Segment changes	☐ none ☐ present (yes)			☐ not assessable
remark				
LV-hypertrophy	☐ none ☐ present (yes)		☐ not assessable	
QTc-time	☐ normal ☐ prolonged (yes) (QTc time in ms: ☐)		☐ not assessable	
Remark				
Examiner				

10.5. Donor examination by coronary angiography or alternative imaging (Eurotransplant, English-language version)

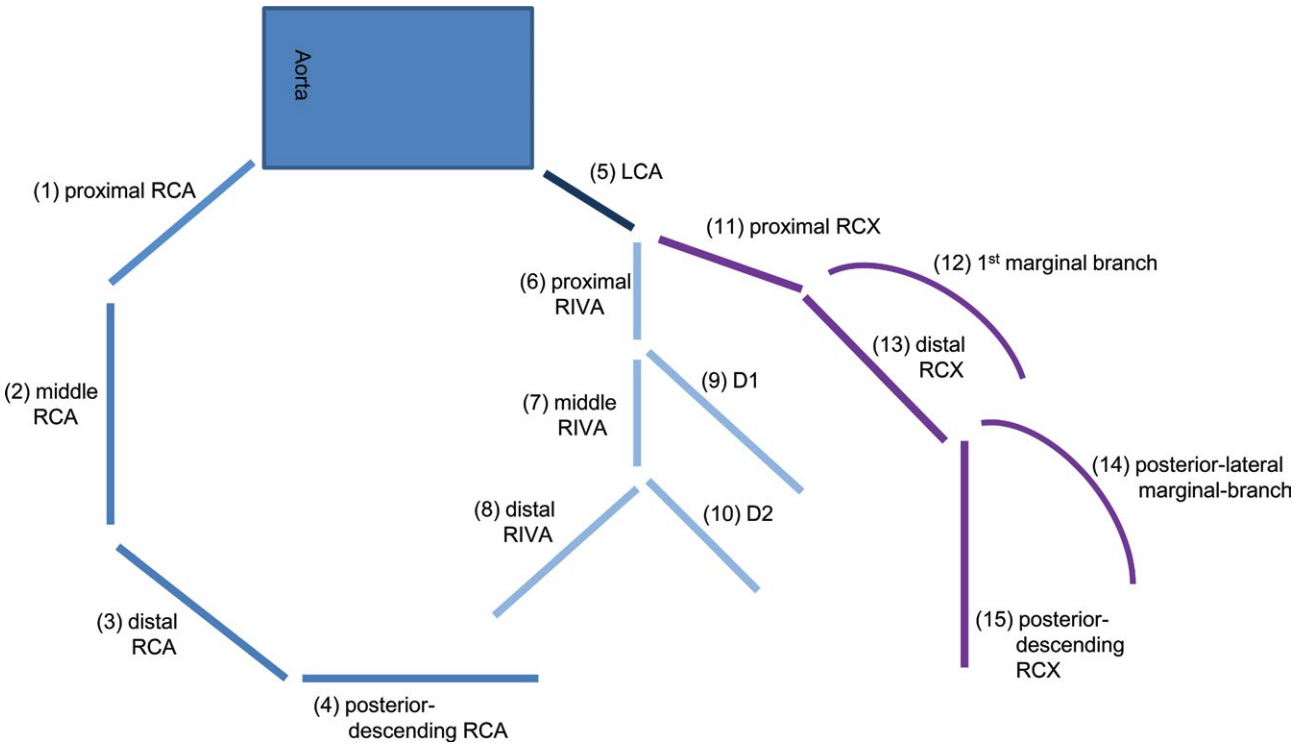
Coronary angiography

Date of examination	Date	Time	Identity (Id-#)	

	Degree of stenosis (in % or luminal irregularities (LIR))							
Vessel	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
RCA and branches	☐	☐	☐	☐	☐	☐	☐	☐
↳proximal RCA (1)	☐	☐	☐	☐	☐	☐	☐	☐
↳middle RCA (2)	☐	☐	☐	☐	☐	☐	☐	☐
↳distal RCA (3)	☐	☐	☐	☐	☐	☐	☐	☐
↳post.-descend. RCA (4)	☐	☐	☐	☐	☐	☐	☐	☐
↳ **Type of stenosis**		☐ LIR	☐ A concentric <1cm		☐ B eccentric 1-2cm		☐ C diffuse > 2cm	
	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
LM/LCA- (5)	☐	☐	☐	☐	☐	☐	☐	☐
	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
LAD/RIVA and branches	☐	☐	☐	☐	☐	☐	☐	☐
↳proximal RIVA/LAD (6)	☐	☐	☐	☐	☐	☐	☐	☐
↳middle RIVA/LAD (7)	☐	☐	☐	☐	☐	☐	☐	☐
↳distal RIVA/LAD (8)	☐	☐	☐	☐	☐	☐	☐	☐
↳1st diagonal branch/D1 (9)	☐	☐	☐	☐	☐	☐	☐	☐
↳2nd diagonal branch /D2 (10)	☐	☐	☐	☐	☐	☐	☐	☐
↳ **Type of stenosis**		☐ LIR	☐ A concentric <1cm		☐ B eccentric 1-2cm		☐ C diffuse > 2cm	
	none	LIR-25%	26-50%	51-75%	76-99%	100%	not existent	not assessable
RCX/LCX and branches	☐	☐	☐	☐	☐	☐	☐	☐
↳proximal RCX/LCX (11)	☐	☐	☐	☐	☐	☐	☐	☐
↳1st marginal branch/OM (12)	☐	☐	☐	☐	☐	☐	☐	☐
↳distal RCX/LCX (13)	☐	☐	☐	☐	☐	☐	☐	☐
↳posterolat. marginal/PL (14)	☐	☐	☐	☐	☐	☐	☐	☐
↳post.-descend. RCX/PD (15)	☐	☐	☐	☐	☐	☐	☐	☐
↳ **Type of stenosis**		☐ LIR	☐ A concentric <1cm		☐ B eccentric 1-2cm		☐ C diffuse > 2cm	

Major supply	☐ right ☐ left ☐ not assessable
Vessel variant	☐ normal ☐ variant
Levocardiography↓	☐ no ☐ yes (not necessary in case of good echocardiography assessment)
Other measurement	
Remark:	
Examiner	

☐ In case of complex findings use drawing provided at opposite



The rationale and indication for this investigation is outlined in Section 7.2.5. The pathway of standardised examination corresponds to Figure 7.5 and Table 7.4. For further convenience the design of the form can be adopted to national requirements as long as the contents remain identical in order to assure electronic data exchange.

10.6. Donor examination by abdominal ultrasound or alternative imaging (Eurotransplant, English-language version)

Sonography -Abdomen

Date of examination	Date Time		Identity (ID-Nr.)	
Liver	Parenchyma	☐ normal	☐ slightly hyper-echogenous ☐ severely hyper-echogenous ☐ cirrhosis	☐ n.a.
	Diameter MCL (cm)		if MCL not measured size: ☐ normal ☐ small ☐ large ☐ enlarged	☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation in segment	☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??	
			Specify	
	liver edge	☐ sharp	☐ blunt	☐ n.a.
	bile duct Intrahepatic	☐ normal	☐ dilated	☐ n.a.
	bile duct Extrahepatic	☐ normal	☐ dilated ☐ Choledocholithiasis	☐ n.a.
	Portal vein	☐ free	☐ thrombosis	☐ n.a.
	Vena cava	☐ normal	☐ yes ☐ volume depleted ☐ volume overload	☐ n.a.
	remarks			
Gall bladder		☐ normal	☐ cholecystolithiasis ☐ cholecystitis ☐ cholecystectomy ☐ other pathologies	☐ n.a.
	space occupying lesion	☐ no	☐ yes	☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ cyst ☐ ??	
			Specify	
Pan-creas	Parenchyma	☐ normal	☐ lipomatosis ☐ edema ☐ fibrosis ☐ other	☐ n.a.
	Calcification	☐ no	☐ yes	☐ n.a.
	Pancreatitis	☐ no	☐ yes	☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation: ☐ head ☐ corpus ☐ tail ☐ multiple	☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??	
			Specify	
	remarks			
Spleen	Size	☐ normal	☐ splenomegaly ☐ haematoma ☐ liquid fringe ☐ multiple	☐ n.a.
			splenomegaly (cm) haematoma (cm) liquid fringe (cm)	
	Remarks			
Kidney left	Longitudinal diameter (cm)		Short diameter (cm) Mass of renal cortex (cm)	
	Parenchyma	☐ normal	☐ reduced- atrophic ☐ atrophic ☐ nephrectomy ☐ other pathologies	☐ n.a.
	renal calculi	☐ none	☐ yes (Nephrolithiasis)	☐ n.a.
	signs of obstruction	☐ none	☐ yes	☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation: ☐ upper pole ☐ middle ☐ lower pole ☐ multiple	☐ n.a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??	
			Specify	
	remarks			
Kidney right	Longitudinal diameter (cm)		Short diameter (cm) Mass of renal cortex (cm)	
	Parenchyma	☐ normal	☐ reduced- atrophic ☐ atrophic ☐ nephrectomy ☐ other pathologies	☐ n.a.
	Renal calculi	☐ none	☐ yes (Nephrolithiasis)	☐ n.a.
	Signs of obstruction	☐ none	☐ yes	☐ n.a.
	space occupying lesion	☐ no	☐ yes, localisation: ☐ upper pole ☐ middle ☐ lower pole ☐ multiple	☐ n. a.
			Possibly ☐ tumour ☐ abscess ☐ angioma ☐ contusion ☐ haematoma ☐ cyst ☐ ??	
			Specify	
	remarks			
Free liquid / ascites		☐ none	☐ minimal ☐ significant	☐ n.a.
	amount / distribution			
Aorta		☐ normal	☐ single plaques ☐ severe arteriosclerosis ☐ aneurysm ☐ stenosis	☐ n.a.
	diameter (cm)		morphology	
Paraaortic lymphoma		☐ none	☐ yes if yes size lymphoma (cm)	☐ n.a.
	remarks			
Small pelvis		☐ normal	☐ pathological	☐ n.a.
Prostate		☐ normal	☐ enlarged ☐ pathological	☐ n.a.
Urinary bladder		☐ normal	☐ pathological	☐ n.a.
Remarks				
Examiner				

Possibly =Possible explanation of space occupying lesion; n.a.=not assessable.

10.7. Donor examination by standardised blood gas analysis with lung recruitment (Eurotransplant, English-language version)

Standardized bloodgas evaluation at FIO2=1.0 after lung recruitment

Date of examination	Datum	Uhrzeit	Identity (D.-Nr.)			
Suction of secretion performed			☐ yes	☐ no	☐ not possible	
Lung recruitment (back squeezing performed)			☐ yes	☐ no	☐ not possible	
Sample drawn after at FIO_2=1.0 for 10 min.			☐ yes	☐ no	☐ not possible	
PEEP (cmH_2O)						
pH						
paO_2 (mmHg temperature corrected)*				or paO_2 (kPA temperature corrected)*		
$paCO_2$ (mmHg temperature corrected)*				or $paCO_2$ (kPA temperature corrected)*		
HCO_3^- (mmol/l temperature corrected)						
Base-Excess (mmol/l temperature corrected)						
examiner						

***mmHg * 0,1333224 = kPA; kPA * 7,5006150504 = mmHg**

Appendix 11. Grading for biopsies at histopathological examinations (English-language version)

This table summarises a proposed lexicon of standard terms which can be used when investigating biopsies of livers, or other samples, during donor characterisation or at procurement. The preferred concept is to use a standardised list of values instead of free text because this will allow correlation of clinical data with findings of histopathological examination. Further exchange of samples and images of samples or technology of telemedicine should be used to compare data between investigating institutions and second-opinion experts as well as donor and recipient centres.

Field label	List of values	Item needed	
date of specimen	dd.mm.yyyy hh:mm	liver	other
specimen from	• brain • heart • lung left • lung right • lymph node (localisation sampling point) • liver • pancreas • spleen • stomach • intestine (localisation see sampling point) • kidney left • kidney right • urinary bladder • prostate • ovary • other (localisation see sampling point)	liver	other
sampling point/additional information/indication/ leading question/clinical data	free text to describe localisation	liver	other
localisation of specimen	• localised lesion • representative for whole organ • other (please specify)	liver	other
specimen ID (laboratory)	free text	liver	other
specimen incoming (date/time)	dd.mm.yyyy hh:mm	liver	other
macroscopic aspect of specimen	free text	liver	other

Field label	List of values	Item needed	
kind of specimen/biopsy	• sub-capsular wedge biopsy (liver) • wedge-biopsy • biopsy histology • core biopsy (via skin puncture) • other	liver	other
kind of investigation	• frozen section • final report (after formalin fixation and paraffin embedded) • other	liver	other
macrovesicular steatosis (% of parenchyma as integral of the parenchymal surface examined)	• none (0-5 %) • 5-10 % • 11-20 % • 21-30 % • 31-40 % • 41-50 % • 51-60 % • > 60 % • not assessable	liver	
additional lipid staining	• no • yes	liver	
fibrosis	• none • slight (portal) fibrosis • portal fibrosis with early stages of septum formation • fibrosis with septa formation and changes of liver architecture • cirrhosis • not assessable	liver	
microvesicular steatosis (not relevant for use of liver for transplantation)*	• none (or slight) • moderate • severe • not assessable	liver	
steatohepatitis*	• none or slight inflammation (no steatohepatitis) • moderate inflammation (steatohepatitis) • severe inflammation (steatohepatitis) • not assessable	liver	
inflammatory changes of portal fields*	• none or mild portal inflammation • moderate portal inflammation • severe portal inflammation with periportal spread into parenchyma • not assessable	liver	
inflammatory changes of parenchyma*	• none or slight inflammation • moderate acinar inflammation • severe acinar inflammation • not assessable	liver	
cholangitis*	• none • chronic (see comment for specification) • florid (see comment for specification) • not assessable	liver	
necrosis*	• none or insignificant • necrosis (see comment for specification) • not assessable	liver	
cholestasis*	• none • cholestasis (see comment for specification) • not assessable	liver	
neoplasia/malignancy	• no evidence for neoplasia in specimen • benign neoplasia (see comment for specification) • malignancy (see comment for specification) • uncertain dignity (see comment for specification	liver	other
comment/further results/additional findings	free text to describe or explain any other relevant finding (e.g. malignancy) as well as to mention other pathologies (e.g. pigmentations in liver biopsy)	liver	other

Field label	List of values	Item needed	
consult investigating pathologist for medical issues	free text for comment by investigating pathologist	liver	other
→ at phone number	free text	liver	other

* facultative fields which should be considered according to the indication for investigation.

Appendix 12. Hepatitis C – direct-acting antiviral drugs and interaction with immunosuppressive drugs or genotype HCV-DAA and interaction with immunosuppressive drugs

Thorough understanding of the Hepatitis C (HCV) structure, replication mechanism and cell cycle has led to the development of the direct-acting antiviral drugs (DAA). These drugs are small molecules that target nonstructural (NS) viral proteins and inhibit HCV replication. Four classes of DAAs exist, namely NS3/4A protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), non-nucleoside polymerase inhibitors (NNPIs) and NS5A inhibitors [1-2].

The introduction of these agents and further ones has been and will be changing the treatment of patients with HCV infection. Sustained virological response (SVR) can be achieved in over 95 % of patients [1-2] either when treatment is initiated pre-emptively in the recipient before he or she is exposed to the grafts procured from an HCV-viraemic donor or if the infection is treated later after transplantation.

Different combinations of DAAs can be administered if the HCV genotype is known, but pan-genotypic effectiveness exists, especially in those combinations suggested to be used in organ transplantation (Table A) [2]. Therefore prospective determination of the donor genotype or viral load is not necessary. Interaction of DAAs exists with immunosuppressive drugs (Table B) and other drugs [1-2]. The major advantage of the interferon-free treatment regimens is that the risk associated to acute allograft rejection caused by interferon application is mitigated.

Table A. Recommended DAA combinations for patients with HCV but without impaired liver-function

Please check further details (e.g. treatment duration, combination with ribavirin based on resistance testing, co-infection, organ dysfunction) and the most recent data available at the European Association for the Study of the Liver (EASL) webpage at www.easl.eu/research/our-contributions/clinical-practice-guidelines.

Genotype / DAA combination	1a	1b	2	3	4	5	6
sofosbuvir + velpatasvir	2 tx	2 tx	1 tx	1 tx	2 tx	2 tx	2 tx
sofosbuvir + daclatasvir	5 tx	5 tx	2 tx	2 tx	5 tx	3 tx	3 tx
sofosbuvir + ledipasvir	1 tx	1 tx	no	no	1 tx	1 tx	1 tx
paritaprevir + ombitasvir + ritonavir + dasabuvir	3	3	no	no	no	no	no
paritaprevir + ombitasvir + ritonavir	no	no	no	no	3	no	no
elbasvir + grazoprevir	4	4	no	no	4	no	no

Numbers from 1 to 6 indicate the EASL preferred treatment option [2] when genotype is known.

no = not recommended.

tx = combination can be used after organ transplantation, in accordance with the specific recommendations [2].

option for possible combination with ribavirin in treatment experienced patients or liver transplant recipients [2].

Table B. Drug interactions between DAAs and immunosuppressive drugs

This table is based on the data made available by the University of Liverpool website [3], modified according to [2]. In the combinations listed, at least one drug is associated to the interaction as shown.

Immunosuppressive drug / DAA combination	Myco-phenolate	Azathio-prine	Ciclo-sporin	Tacro-limus	Sirolimus	Evero-limus	Etaner-cept
sofosbuvir + velpatasvir	✓	✓	✓	✓	✓	○	✓
sofosbuvir + daclatasvir	✓	✓	✓	✓	✓	○	✓
sofosbuvir + ledipasvir	✓	✓	✓	✓	✓	○	✓
paritaprevir + ombitasvir + ritonavir + dasabuvir	○	✓	○	○	○	💣	✓
paritaprevir + ombitasvir + ritonavir	?	?	?	?	?	?	?
elbasvir + grazoprevir	✓	✓	💣	○	○	○	○
ribavirin	✓	○	💣	?	?	?	○

Key	
✓	No clinically significant interaction expected.
○	Potential interactions require dosage adjustment, altered timing of administration or additional monitoring.
💣	These drugs should not be co-administered.
?	No clear data available.

References

1. Hézode C. Pan-genotypic treatment regimens for hepatitis C virus: Advantages and disadvantages in high-and low-income regions. *J Viral Hepat* 2017;24(2):92-101; DOI: 10.1111/jvh.12635.
2. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol* 2017;66:153-94.
3. University of Liverpool: HEP drug interactions [available at www.hep-druginteractions.org, accessed 13 Sep 2018].

Appendix 13. World Health Organization 2007 classification and grading of central nervous system neoplasms

From Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization, *Classification of Tumours of the Central Nervous System*. IARC, Lyon, 2007.

For the WHO 2016 classification, see Table 9.4 in Chapter 9.

Astrocytic tumours	**I**	**II**	**III**	**IV**
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours	**I**	**II**	**III**	**IV**
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours	**I**	**II**	**III**	**IV**
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours	**I**	**II**	**III**	**IV**
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours	**I**	**II**	**III**	**IV**
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuro-epithelial tumours	**I**	**II**	**III**	**IV**
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours	**I**	**II**	**III**	**IV**
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuro-epithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours	**I**	**II**	**III**	**IV**
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours	**I**	**II**	**III**	**IV**
Medulloblastoma				•
CNS primitive neuro-ectodermal tumour (PNET)				•
Atypical teratoid/rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves	**I**	**II**	**III**	**IV**
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours	**I**	**II**	**III**	**IV**
Meningioma	•			
Atypical meningioma		•		
Anaplastic/malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region	**I**	**II**	**III**	**IV**
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Source: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization, *Classification of Tumours of the Central Nervous System*. IARC, Lyon, 2007.

Appendix 14. **Reporting form for rare diseases and intoxication (France, English-language version)**

agence de la biomédecine

RECORD SHEET:
CANCER – INFECTION – POISONING – RARE DISEASE
Click here to enter a date.

Area	**Donor N°** Click here to enter text.	**ICD-10***

DONOR: selected/not selected DONOR: organ removed/ organ not removed

CAUSE (*if answer is negative*): Click here to enter text.

PATHOLOGY, PROGRESSION AND TREATMENT, BRIEF DESCRIPTION

CANCER[1] ☐ INFECTION ☐ POISONING ☐ RARE DISEASE ☐ OTHER[2] ☐

[1] ***if cancer:***
History of the disease (mandatory): - active cancer at the time of collection NO ☐ YES ☐
- donor's history of "cured" cancer NO ☐ YES ☐
- family history of cancer NO ☐ YES ☐

System: Click here to enter text. Organ (mandatory): Click here to enter text.
Histological type: Click here to enter text. Extent of invasion: Click here to enter text.
Date of diagnosis: Click here to enter text.
Treatments: Click here to enter text.

[2] ***if other,*** *specify the condition (e.g. morbid obesity, allergy, polydipsia leading to water intoxication, etc…):* Click here to enter text.

Description: **Click here to enter text.**

EXPERT CONSULTED NO ☐ YES ☐ Speciality: Click here to enter text.

Expert's opinion: Click here to enter text.

ORGANS removed (☒)	**H** ☐	**H-L** ☐	**RL LL DL** ☐ ☐ ☐	**TL RL LL** ☐ ☐ ☐	**RK LK DK** ☐ ☐ ☐	**Pa** ☐	**In** ☐
Not removed owing to the disease?	?	?	? ? ?	? ? ?	? ? ?	?	?
Transplanted (Y/N)	?	?	? ? ?	? ? ?	? ? ?	?	?
Not transplanted owing to the disease?	?	?	? ? ?	? ? ?	? ? ?	?	?
Anat. path. (AP) Transf. (Valves) Destruc. (DST)	?	?	? ? ?	? ? ?	? ? ?	?.	?.
Recipient No.	?	?	? ? ?	? ? ?	? ? ?	?.	?.

* INTERNATIONAL CLASSIFICATION OF DISEASES

H: heart; H-L: heart- lung; RL: right lung; LL: left lung; DL: double lung; TL: total liver; RL: right liver; LL: left liver; RK: right kidney; LF: left kidney; DK: double kidney; Pa: pancreas; In: intestine

Appendix 15. **Quality forms (Dutch Transplant Foundation)**

Nederlandse Transplantatie Stichting
QUALITY FORM TRANSPLANTATION

Logged in: Print

Overview procurement | Overview transplantation | Missing QFT | QFT with devi

Pancreas quality form transplantation

Cancel Save

Organ detail

ET Donornumber		Organ	Pancreas
Donor type	Heart Beating	Organ status	Transplanted
Transplantation center			
Transplantation surgeon		Registration date	

Registered Quality Form Donation discrepancies.

Please select Agree or Disagree. If 'Disagree', please specify

Packaging

Packaging Agree

Packaging adequate	Yes	Number of bags below 3	No
		Leakage	No
		Low amount of fluid	No
		Organ frozen	No
		Blood samples included	Yes
		Spleen sample included	Yes

General information

End pancreatectomy

Detailed procurement information

Detailed procurement information Agree

Pancreas procurement with duodenum	Yes
Pancreas procurement with spleen	
Entire pancreas procured	Yes
Head of pancreas procured	Yes
Neck of pancreas procured	Yes
Body of pancreas procured	Yes
Tail of pancreas procured	Yes

Reason for partial procurement

Reason for partial procurement Agree

Right aberrant hepatic artery from SMA	
Injury before procurement	
Injury during procurement	
Other reason for partial procurement	
Specify reason for partial procurement	

Duodenum related information

Duodenum related information Agree

Length of duodenum more than 12 cm	
Both sides of duodenum closed with stapler	
Haematoma of the duodenum wall	
Decontamination solution for duodenum used	
Injury/perforation of the duodenum wall	
Leakage of duodenum content	

Arterial anatomy/status

Arterial anatomy/status Agree

Superior Mesenteric Artery (SMA)	Yes
SMA with aortic patch	Yes
Coelic axis with pancreas	No
Coelic axis with aortic patch	No
Splenic artery cut and ligated	
Splenic artery cut and marked with suture	

Gastroduodenal artery cut and ligated
Gastroduodenal artery cut and marked with suture
Right aberrant hepatic artery
Dorsal pancreatic artery recognizable
Dorsal pancreatic artery arisen from

Arterial toolkit

Arterial toolkit Agree

Iliac arteries (common, external, internal) Yes
Brachio-cephalic arteries
Brachiocephalic trunk
Brachial artery
Carotid artery (common, external, internal)
Subclavian artery
Thoracic aorta arch with branches
Other artery(ies)
Please specify other artery(ies)
Quality of arterial toolkit

Venous anatomy/status

Venous anatomy/status Agree

Length of portal vein (distance to parenchyma) (long is > 2 cm) Short

Venous toolkit

Venous toolkit Agree

Iliac veins (common, external, internal) Yes
Other veins
Please specify other veins
Quality of venous toolkit

Parenchymal anatomy/status

Parenchymal anatomy/status Agree

Injury of parenchyma and/or capsule
Injury of parenchyma/Head
Injury of parenchyma/Neck
Injury of parenchyma/Body
Injury of parenchyma/Tail
Injury of parenchyma/Hilus of spleen
Aspect perfusion Good
Common bile duct ligated
Haematoma of the parenchyma
Location of haematoma

Transplant data

Transplant data Agree

Morphological variations
Additional comments

Final evaluation

Final evaluation Agree

Quality of pancreas Good
Organ injured No

Final result

Organ transplanted Yes

Nederlandse Transplantatie Stichting
QUALITY FORM TRANSPLANTATION

Logged in: Print

Overview procurement | Overview transplantation | Missing QFT | QFT with devi

Kidney quality form transplantation

Cancel Save

Organ detail

ET Donornumber
Donor type Heart Beating
Transplantation center
Transplantation surgeon

Organ Right Kidney
Organ status Transplanted
Registration date QFT

Registered Quality Form Donation discrepancies.

Please select Agree or Disagree. If 'Disagree', please specify

Packaging

Packaging Agree

Packaging adequate Yes

Number of bags below 3 No
Leakage No
Low amount of fluid No
Organ frozen No
Blood samples included Yes
Spleen sample included Yes

General information

End nephrectomy
Preservation method Machine preservation

Arterial anatomy/status

Arterial anatomy/status Agree

Number of arteries 1
Aortic patch Yes
Arteriosclerosis None
Artery abnormal

Intima dissection
Partial/complete transsection
Partial/complete ligation
Unidentified arteries
Origin/renal artery stenosis

Venous anatomy/status

Venous anatomy/status Agree

Number of veins 1
Caval patch Yes
Vein abnormal

Venous tear
Partial/complete transsection
Partial/complete ligation
Unidentified veins

Ureter anatomy/status

Ureter anatomy/status Agree

Number of ureter
Length of ureter (long is > 10 cm) Long

Parenchymal anatomy/status

Parenchymal anatomy/status Agree

Aspect perfusion Good
Biopsy
Parenchyma abnormal No

Tear(s) in capsule
Subcapsular hematoma
Parenchymal rupture
Cyst(s)
Tumor(s)

Perirenal fat

Perirenal fat Agree

Perirenal fat removed

Transplant data

Transplant data Agree

Morphological variations

Additional comments

Final evaluation

Final evaluation Agree

Quality of kidney Good

Organ injured No

Final result

Organ transplanted Yes

Cancel Save

Overview procurement | Overview transplantation | Missing QFT | QFT with deviation | Print | Home

Nederlandse Transplantatie Stichting
QUALITY FORM TRANSPLANTATION

Logged in:

Print

Overview procurement | Overview transplantation | Missing QFT | QFT with devi

Liver quality form transplantation

Cancel Save

Organ detail

ET Donornumber		Organ	Liver
Donor type	Heart Beating	Organ status	Transplanted
Transplantation center	Transplantation		
surgeon		Registration date	

Registered Quality Form Donation discrepancies.

Please select Agree or Disagree. If 'Disagree', please specify

Packaging

Packaging Agree

Packaging adequate	Yes	Number of bags below 3	No
		Leakage	No
		Low amount of fluid	No
		Organ frozen	No
		Blood samples included	Yes
		Spleen sample included	Yes

General information

End hepatectomy

Arterial anatomy/status

Arterial anatomy/status Agree

Normal arterial anatomy	No
Coeliac axis with aortic patch	
Right hepatic artery from SMA	
SMA with aortic patch	
Left hepatic artery from gastric artery	
Coeliac axis with aortic patch	
Present after dissection	
Common hepatic artery	
Arteriosclerosis	None
Artery injury	No
Coalic axis injury	
Common hepatic artery injury	
Proper hepatic artery injury	
Left hepatic artery injury	
Right hepatic artery injury	
Aberrant left hepatic artery injury	
Aberrant right hepatic artery injury	

Venous anatomy/status

Venous anatomy/status Agree

Length of portal vein (long is over 3 cm)	Long
Vein injury	No
Hepatic vein(s) injury	
Portal vein injury	

Parenchymal anatomy/status

Parenchymal anatomy/status Agree

Aspect perfusion	Good
Biopsy	
Parenchyma abnormal	No
Tear(s) liver capsule	
Subcapsular hematoma	
Parenchymal rupture	
Steatosis	

Liver congested	
Cyst(s)	
Tumor(s)	
Cholecystectomy	No
Galbladder flushed	Yes
Cystic duct ligated	
Bile duct flushed	Yes
Bile duct injury	

Toolkit

Toolkit Agree

Iliac artery included	Yes
Iliac vein included	Yes
Brachio-cephalic arteries	

Transplant data

Transplant data Agree

Morphological variations	
Additional comments	Consultation with centre: toolkit can be split for both pancreas and liver

Final evaluation

Final evaluation Agree

Quality of liver	Good
Organ injured	No

Final result

Organ Transplanted Yes

Cancel Save

Overview procurement | Overview transplantation | Missing QFT | QFT with deviation | Print | Home

Appendix 16. **Donation after circulatory death – reporting form (Belgium, English-language version)**

DCD- Report Centre : BGETP Coordinator : Hospital : .... ET Donor #:..... Date: ..../..../.....	*Label*	DCD Category I ☐ II ☐ III ☐ IV ☐ V (Euthanasia) ☐ Technique: ☐ DBTL catheter Time : ... h ... ☐ rapid sterno-laparatomy + direct canulation
Start resuscitation procedure (only for NHBD I and II)	... h ...	
Stop resuscitation procedure (only for NHBD I and II)	... h ...	
Stop ventilation and supportive therapy	... h ... Extubation: YES /NO Time : Ré-intubation : YES/NO Time :	***Acirculatory*** (donor) WIT = ET = ... min ***Absolute*** (donor) WIT = ... min ***Total*** (donor) WIT = ...min
Mean Arterial Pressure < 60 mmHg	... h ...	
Asystoly or circulatory arrest (= start "no touch")	... h ...	
Incision time (= end "no touch")	... h ...	
Start of aortic flush	... h ...	

Time of RIGHT pneumectomy : ... h ...
Time of hepatectomy : ... h ...
Time of RIGHT nephrectomy : ... h ...

Time of LEFT pneumectomy : ... h ...
Time of pancreatectomy : ... h ...
Time of LEFT nephrectomy : ... h ...

Appendix 17. **Donation after circulatory death – reporting form (Netherlands, English-language version)**

ET Donor number: ######

Report generated on: ##.##.2018 ##:##+0100 / Database environment: beta1

Eurotransplant Donor Data

Extra Information Non-Heart-Beating Donor for

General data

Center	Date	Donor Nr	Cadaver type	Contact person	Contact tel.nr.	Contact person OR	Contact tel.nr. OR

ABO	Rh	NHBD category	Reason for Non-heartbeating

Course

Switch off at		Diuresis total (ml)	
Saturation <80% or MAP <50 mmHG at			
Circulatory arrest (mean ABP=0) at			
Cross clamp aorta at			

Explantation/preservation data

DBTL catheter inserted / laparotomy executed at		Carried out by	
Kootstra signs: left		Catheter insertion checked with röntgen	
right		Perfusion technique	

Clinical data

Date	Sys. bloodpressure mm HG	Dia. bloodpressure mm HG	Heart freq. /min	Saturation %	Diuresis ml	Breath freq. /min	Comments

Appendix 18. **Biovigilance standardised notification form for adverse events and reactions (France, English-language version)**

BIOVIGILANCE NOTIFICATION FORM

(Source : Agence de la biomédecine - FRANCE)

ORGAN	☐
TISSUE	☐
CELLS	☐
Ancillary therapeutic products	☐

Cadre réservé à l'ANSM
Fiche BV N°

1. Reporter

To be filled up by the reporter	***To be filled up by the local biovigilance coordinator (LBC)***
Identity of the reporter Surname: First name:	Identity of the LBC Surname: First name:
Title:	Title:
Details of the reporter Telephone number: Fax : E-mail : Address :	Details of the local biovigilance coordinator Telephone number: Fax : E-mail : Address :
	Date of notification λ_____μ λ_____μ λ_____μ
	Internal reference number:
	☐ initial notification ☐ notification follow-up (specify the BV number)

2. Product(s) concerned

Type of graft, identification number ☐ Allogeneic ☐ Autologous	
Name of the ATP (1), producer, batch number	
Location of the preparation* or location of the procurement * or producer's address* (regarding ATP)	
Specify, if need be, if : ☐ the graft or product was imported ☐ the graft or product was exported Origin*/destination* of the import*/export* : Date of import*/export* : λ_____μ λ_____μ λ_____μ	

(1) ATP: Ancillary Therapeutic Product (preservation liquid, media)* Delete whichever does not apply

3. Donor and recipient(s) involved *(or potentially involved)*

Donor			
Status : ☐ Living ☐ BD & HB (2) ☐ DCD (3) ☐ PMT (4) Donation between relatives : ☐ yes ☐ no			
Identification N°:	Sex : ☐ M ☐ F	Birth date: λ_____μ λ_____μ λ_____μ	
Date of procurement: λ_____μ λ_____μ λ_____μ	Location of the procurement:		
Recipient			
Identification N°:	Sex : ☐ M ☐ F	Birth date: λ_____μ λ_____μ λ_____μ	
Date of transplantation: λ_____μ λ_____μ λ_____μ	Location of the transplantation:		

Other organ and/or tissue** and/or cells** **recipients**: ☐ yes (specify in the table below) ☐ no

Identification N°					
Type of graft					
Date of transplantation	λ___ λ___ λ_____	λ___ λ___ λ_____	λ___ λ___ λ_____	λ___ λ___ λ_____	λ___ λ___ λ_____
Location of the transplantation (hospital and city)					

**: With regard to tissues and cells, specify the name of the tissue bank or the cell therapy unit concerned

(2) BDD&HBD: brain-death donor and heart-beating donor; (3) DCD: donor after circulatory-death leading to the implementation of organ preservation techniques. (4) PMT: post-mortem tissues retrieved at the morgue

4. Description of the adverse event and/or reaction

If need be, attach a more exhaustive description on a plain unheaded paper. Specify the number of attached pages (Please write the name of the sender on each page):

Date (of occurrence*or detection*)

λ_____μ λ_____μ λ_____μ

☐ of the event

☐ of the adverse reaction (donor* or recipient*)

* Delete whichever does not apply

Description:

Level of the adverse reaction:

Initial ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Final ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

1-Insignificant: clinical or biological manifestations that do not need any care or medical treatment.

2-Moderate: clinical or biological manifestations presenting with no vital threat on the short or long term. Hospitalisation is not necessary.

3-Severe: clinical or biological manifestations :

- leading to disability or incapacity,
- inducing, prolonging or complicating hospitalisation or any other morbid state or,
- necessitating medical or surgical intervention to preclude permanent damage or impairment of a body function.

Important: Serious infections likely to be transmitted by the graft or during procurement or transplantation must be systematically declared at a severity level higher than or equal to 3.

4-Major: imminent vital threat

5-Death

Investigation: ☐ pending ☐ not performed* ☐ not performable*

☐ completed – closing date : λ_____μ λ_____μ λ_____μ

Detail the analysis of the causes (and their conclusion when investigation has been completed)

* If the investigation has not been performed, please explain the reasons for taking this decision

Imputability (link between the product or the procurement or the transplantation activity and the adverse reaction at the beginning and at the end of the investigation):

Initial: ☐ 1-Excluded/unlikely ☐ 2- Possible ☐ 3- Likely/probable ☐ 4- Certain ☐ not assessable

Final: ☐ 1-Excluded/unlikely ☐ 2- Possible ☐ 3- Likely/probable ☐ 4- Certain ☐ not assessable

5. Local assessment of the criticality and of the measures taken

Probability of recurrence of the adverse event or reaction (probability that the event occurs again in view of the controls implemented) :

☐ R1-rare ☐ R2-unlikely ☐ R3-possible ☐ R4-likely ☐ R5-almost certain ☐ not assessable

Potential consequences of the adverse reaction or event on the patients, on the stock of grafts or on ATP

☐ C1 ☐ C2 ☐ C3 ☐ C4 ☐ C5 ☐ not evaluable

1-**Insignificant** (no clinical and/or biological manifestations or no consequence for the stock of products).

2-**Moderate** (moderate clinical and/or biological manifestations that do not absolutely require medical intervention or treatment or to report transplantation or applications).

3-**Serious** (disability or permanent incapacity, medical intervention and treatment or cancellation or delay in several transplantations or applications).

4-**Major** (vital threat for the patient(s) or significant number of transplantations or applications cancelled that request the use of imported products).

5-**Extreme** (death of the patient(s) or cancellation of all transplantations and applications).

Description of the measures locally implemented to reduce criticality (RxC)

6. Dissemination of information

Other biovigilance correspondent(s) informed: ☐ No ☐ Yes (specify location and date)

The biomedicine Agency (SRA* and/or biomedicine Agency's LBC) was informed on: λ_____μ λ_____μ λ_____μ

Other vigilance body(ies) informed: ☐ No ☐ Yes (specify)

Other transplantation team(s) informed : ☐ No ☐ Yes (specify location and date)

Date and reporter's signature

Date and signature of the local biovigilance correspondent

*Regional unit

Appendix 19. **Impact assessment tool for adverse events and reactions (EUSTITE and SoHO)**

An impact assessment tool was developed by the EUSTITE and SoHO projects to be of use to vigilance and surveillance systems in the field of tissues and cells.[1] The impact assessment tool assists practitioners and regulators in planning their response to a given Adverse Reaction or Event (ARE), taking into account broad consequences beyond the individual patient affected or potentially affected. The assessment should be based on available data, past experience and scientific expertise.

Step 1: Assessing the likelihood of occurrence/ recurrence of the ARE

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to occur again
3	Possible	May occur occasionally
4	Likely	Expected to occur again, but not persistently
5	Probable	Expected to occur again on many occasions

Step 2: Assessing impact/consequences of the ARE should it recur

Impact level		**On individual(s)**		**On the system**		**On organ supply**
0	Insignificant	Nil	OR	No effect	OR	Insignificant
1	Minor	Non-serious	OR	Minor damage	OR	Some transplantations postponed
2	Moderate	Serious	OR	Damage for a short period	OR	Many transplantations cancelled or postponed
3	Major	Life-threatening	OR	Major damage to the system – significant delay to repair	OR	Significant cancellations of transplantations
4	Catastrophic/extreme	Death	OR	System destroyed – need to rebuild	OR	All transplantations cancelled

Steps 3 and 4 follow.

1 SoHO V&S Guidance for Competent Authorities: Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells. Available at: www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Communication%20and%20Investigation%20Guidance.pdf. Access: 11 March 2018.

Step 3: Applying the impact matrix

Likelihood of recurrence → / Impact of recurrence ↓	1 Rare	2 Unlikely	3 Possible	4 Likely	5 Certain/ almost certain
0 Insignificant	0	0	0	0	0
1 Minor	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Major	3	6	9	12	15
4 Catastrophic/extreme	4	8	12	16	20

Step 4

The response of a Health Authority to a specific ARE should be proportionate to the potential impact as assessed by the matrix described.

White The procurement organisation or transplantation centre to manage the corrective and preventive actions, and the Health Authority to file the report and keep a 'watching brief' (values 0-3 after multiplication of the two score-values).

Pale shading Requires interaction between the procurement organisation or transplantation centre and the Health Authority, which may request an inspection that focuses on the ARE and corrective and preventive actions to be followed up. Written communication to professionals working in the field might be appropriate (values 4-9 after multiplication of the two score-values).

Dark shading Health Authority will generally designate representatives to participate in developing or approving the corrective and preventive action plan, possibly a task force to address broader implications. Inspection, follow-up and written communication as previously and possibly notification of Health Authorities in other countries where relevant (values 10-20 after multiplication of the two score-values).

The effectiveness of the response can be assessed by re-applying the impact matrix following the implementation of the corrective and preventive actions. The impact can be reduced by decreasing the probability of recurrence through preventive measures; increasing the detectability of the risk; or reducing the severity of the consequences, if it should recur.

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