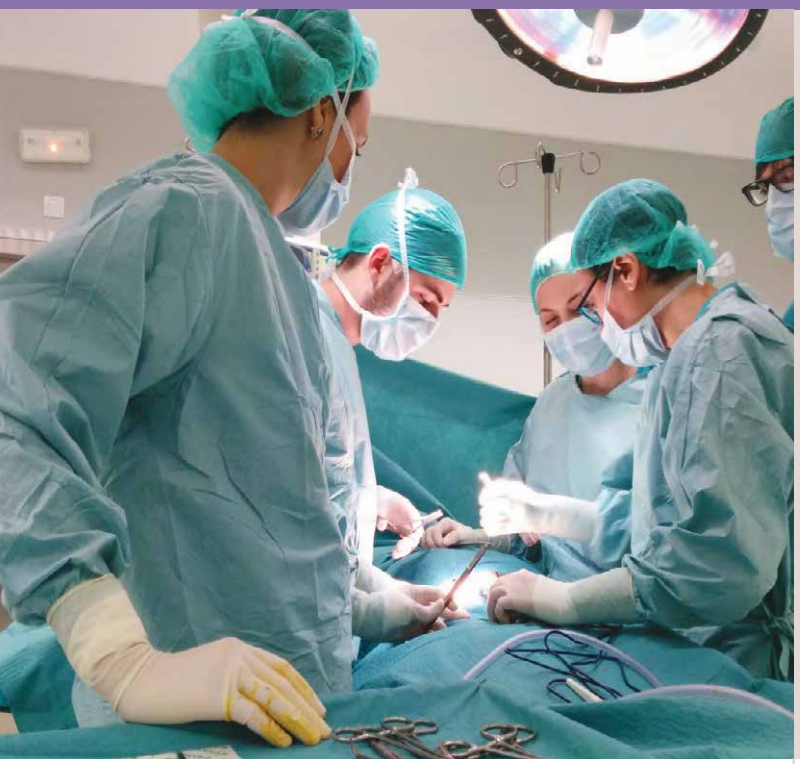
Guide to the quality and safety of ORGANS FOR TRANSPLANTATION



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

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6th Edition

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Guide to the quality and safety of organs for transplantation

6th 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.[1] One of its founding principles is that of increasing co-operation between member states to improve the quality of life of all European citizens. Within 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.

The European Directorate for the Quality of Medicines & HealthCare (EDQM) 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. This directorate co-ordinates activities in the field of substances of human origin, with a long-standing co-operation with the European Commission.

Organ transplantation has progressed during recent decades in a way hard to imagine in earlier years. Still the demand of organs for transplantation far outweighs the available supply. This has important consequences because organ transplantation is the best – and in some cases the only available – treatment for end-stage organ failure. Additionally, as with all substances of human origin, transplantation of human organs entails risks of disease transmission that must be minimised by the 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 6th edition of the *Guide to the quality and safety of organs for transplantation*. The Guide aims to improve the rate of successful and safe organ transplantation. It supports professionals on a practical level. Updated information is collated to provide professionals with the most recent advances in the field as well as technical guidance to ensure the safety and quality of organs of human origin that are intended for transplantation. It is essential that all 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 and health authorities responsible for overseeing donation and transplantation programmes should all have easy access to this information. Technical guidance for the donation and transplantation of human tissues

1 Albania, Andorra, Armenia, Austria, Azerbaijan, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Republic of Moldova, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, San Marino, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, 'the former Yugoslav Republic of Macedonia', Turkey, Ukraine, United Kingdom.

and cells has now been moved to a dedicated *Guide to the quality and safety of tissues and cells for human application*. For blood and blood products, please refer to the Council of Europe *Guide to the preparation, use and quality assurance of blood components*.

This Guide contains the instructions considered to be the 'minimum standards' that align with principles set out in the relevant European Union (EU) Directives in the field, thereby providing technical support to EU member states in their implementation and assistance for those states outside the EU that are considering adopting EU requirements in their legislation. These minimum 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, expert opinion and the results of many EU-funded projects. 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 recent developments that may be reflected in future updates of the EU legislation, where necessary and relevant, thereby providing advance information and recommendations regarding developments in the field. Throughout this Guide, use of the word 'must' indicates mandatory compliance in alignment with Council of Europe recommendations and resolutions as well as with EU Directives, whereas the use of the word 'should' indicates recommended compliance in accordance with commonly accepted good practice.

In this 6th edition, all chapters have been thoroughly revised according to the state of the art, and new and important chapters have been incorporated. Chapter 2, 'Identification and referral of possible deceased organ donors', provides recommendations for succeeding in one of the weakest steps of the deceased donation process – since failure to identify and refer possible organ donors is the main reason for differences in deceased donation rates across countries. Chapter 3, 'Determination of death by neurologic criteria', addresses the fundamental principles of brain death diagnosis and expands on the key decisions that follow. There is still today great inconsistency in the extent to which brain death is tested when this is a likely diagnosis, and in the practices followed once death is determined and organ donation is not a possibility. Chapter 4, 'Consent/authorisation for *post mortem* organ donation', is built from the perspective of differences and commonalities in the European setting, but most importantly, from the perspective of respect for the wishes of the deceased and care for the donors' families. Chapter 5, 'Management of the potential donor after brain death' has been updated based on current knowledge in the field, stressing that the potential organ donor must be treated and managed as any neurocritical patient would be from the therapeutic and diagnostic standpoints.

Another enhancement to the Guide has been the division of the former chapter on assessment of donors into two new, more comprehensive chapters: Chapter 6, 'Deceased donor and organ characterisation', and Chapter 7, 'Donor and organ assessment and selection criteria'. Chapter 6 is expected to be particularly useful in the development of operating procedures for donor and organ characterisation. It provides very detailed guidance on the data to be compiled from a variety of sources in order to evaluate donor and organ suitability, to undertake an adequate risk–benefit analysis and to optimise organ allocation. Chapter 7 clarifies the difference between expanded criteria and non-standard risk donors, a quality versus a safety concept. From the safety perspective, it provides a classification of donors in terms of risk of disease transmission. Importantly, a different grading has been used for infectious diseases and malignancies. Chapter 7 is then expanded in detail in the three chapters that follow. These three chapters will be particularly useful not only to donor co-ordinators and organ procurement organisations, but also to transplant physicians in charge of evaluating the risk of transplanting an organ versus the risk of declining an opportunity of transplantation. This is an invaluable tool for the fast decision-making processes needed in any donation and transplantation procedure.

Chapter 8, 'Risk of transmission of infectious diseases', has been fully revised to include up-to-date developments in the field of emerging pathogens. Additionally, screening algorithms have been extensively updated and a new section on infections of the central nervous system has been included. Chapter 9 'Risk of transmission of neoplastic diseases' was prepared taking into account the work carried out by Council of Europe experts for previous editions of the Guide, initially inspired by the Spanish Guidelines for evaluating the risk of malignancy transmission. But it also considers the recommendations of the Disease Transmission Advisory Committee in the United States and the Advisory Committee on the Safety of Blood, Tissues and Organs in the United Kingdom. The result is an extremely informative guidance text, with assessment and grading of the risk of transmission for an extensive list of malignancies present in the donor history or incidentally identified at the time of organ recovery. Additionally, Chapter 10, 'Risks related to the use of organs from donors with other conditions

and diseases', provides recommendations on topics such as poisoning and inherited diseases, but also on the use of organs from donors with such other conditions as allergies and autoimmune, neuro-degenerative and demyelinating diseases: a list of conditions that raise frequent doubts about the safety (and quality) of organs to be transplanted in daily practice.

Chapter 11, 'Organ procurement, preservation and transportation', details up-to-date information on organ preservation and novel technologies for organ perfusion and preservation, including important considerations to be weighed when developing operating procedures, in accordance with the EU directives.

Chapter 12, 'Donation after circulatory death', focuses on donation from persons declared dead using circulatory criteria. It gives concrete recommendations for the development and optimisation of both controlled and uncontrolled donation after circulatory death programmes. At a time when the pool of potential donors after brain death is declining in western European countries, donation after circulatory death is becoming a necessary source of organs for transplantation. This chapter provides useful guidance to authorities and professionals initiating or consolidating this practice.

Chapter 13, 'Living donation', provides an overview of an activity that is progressively expanding in the European landscape. Although living donation really requires a guide of its own, this chapter is useful in addressing a number of legal, ethical, medical, technical and organisational aspects of this practice. Very importantly, special emphasis is made on donor evaluation and selection, with specific considerations from the perspective of the donor, but also from that of the prospective recipient.

Chapter 14, 'Biovigilance', has been expanded, particularly describing how to identify, report, assess and manage severe adverse reactions and events. In strict alignment with the EU directive, the chapter is outstanding in clarifying concepts and providing guidance on the implementation of good vigilance and surveillance practices. Lastly, Chapter 15, 'Quality management in organ donation and transplantation', has been fully rewritten to provide detailed principles of quality management for organ donation and procurement, and for transplantation activities, separately.

Acknowledgements

A dedicated working group, composed of well-recognised international experts nominated by member states, was convened for the elaboration of this Guide. This group was chaired by Beatriz Domínguez-Gil (Organización Nacional de Trasplantes [ONT], Spain) and Carl-Ludwig Fischer-Fröhlich (Deutsche Stiftung Organtransplantation [DSO], Germany). This expert group contributed to different aspects of the book and did a tremendous job in sharing their expertise, in reviewing the literature and in extracting knowledge from numerous international guidelines, collaborative projects and diverse publications and websites, with the aim of ensuring accessibility to all this information. Members of the group co-ordinated the preparation of the chapters and ensured proper expertise through the engagement of a number of additional experts, from European countries and beyond, who co-authored and contributed to the discussions on various parts of this Guide. The names of all members of the working group and other experts who have participated in the elaboration of the Guide can be found in Appendix 14.

All the professionals who participated in the open consultation, and provided extremely useful comments and suggestions, must also be acknowledged.

Special thanks should be given to the European Commission, in particular to Hélène Le Borgne, who ensured appropriate reference was made to the directives of the EU in the field, to the EU Action Plan on Organ Donation and Transplantation: Strengthened Cooperation between Member States, and to the results from EU-funded projects related to the different chapters of this Guide.

Additionally, the European Society for Organ Transplantation (ESOT) and very particularly the European Donation and Transplant Coordination Organisation (EDTCO, a section of ESOT) should also be thanked for sharing their expertise and knowledge.

The drafting and publication of the 6th edition of the Guide was co-ordinated by Marta López Fraga (Scientific Officer in charge of the CD-P-TO) with the assistance of Ahlem Sanchez, Mar Lomero, Michael Wraith, David Crowe 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 towards 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. Regarded as an experimental procedure until the 1980s, today it is the best life-saving treatment for end-stage organ failure and is performed in 112 countries all over the world [1]. According to the Global Observatory and Database on Donation and Transplantation, 118 127 solid-organ transplants (kidney, liver, heart, lung, pancreas, small bowel) were performed in 2013, the majority of which, about 79 000, were kidney transplants, followed by about 2 000 liver transplants [2]. 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 2014, more than 60 000 patients were waiting for a kidney, liver, heart, lung, pancreas, intestinal or composite tissue transplant in member states of the European Union (EU), and 11 of those patients on the waiting list died every day because there was no organ available.

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 technical activities and services (removal, transportation, processing, preservation, quality control and, where necessary, storage) and safeguarding 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 much evolved since then.

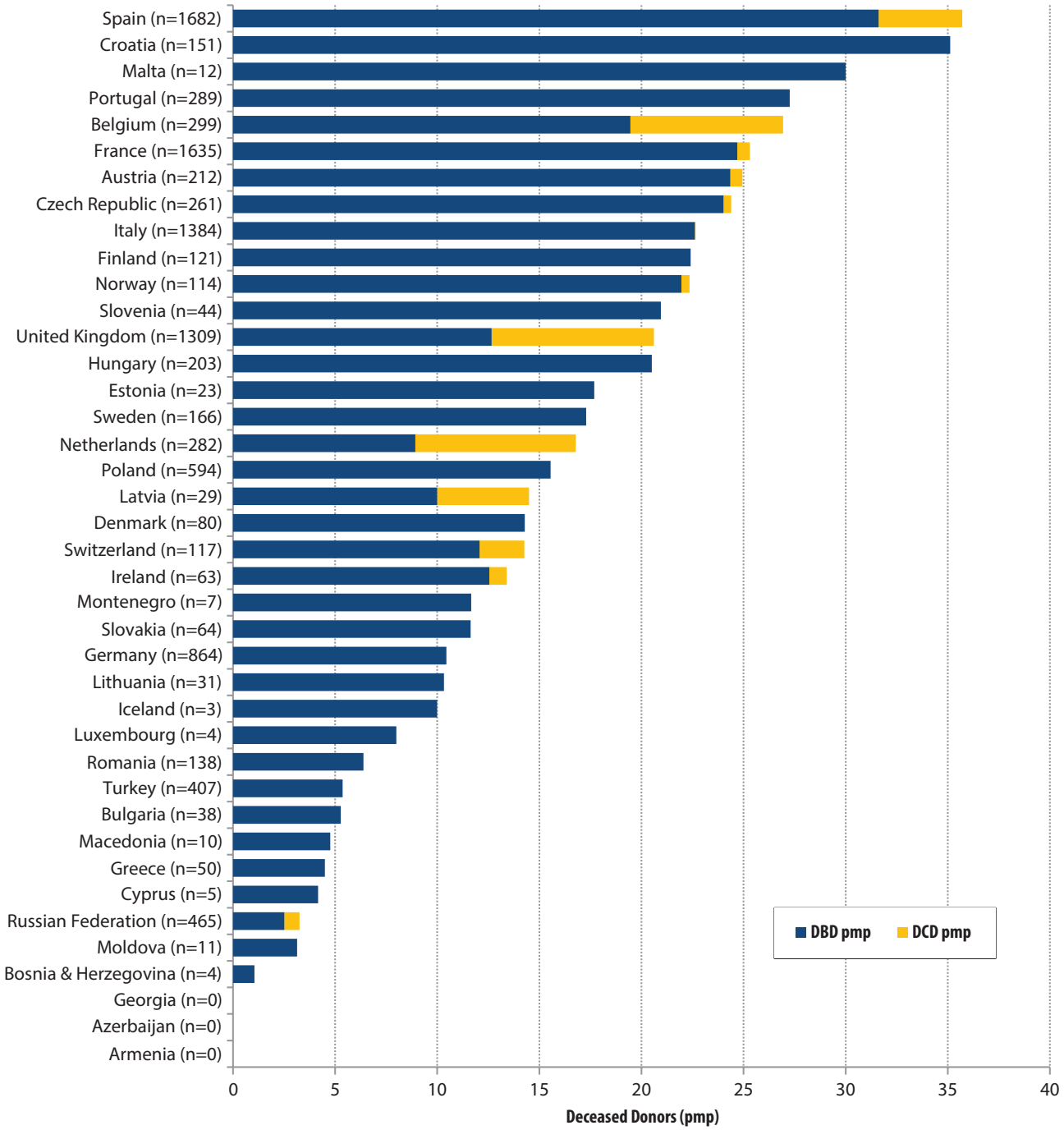
This is the 6th edition of the *Guide to the quality and safety of organs for transplantation* of the Council of Europe. This Guide has two main objectives. Firstly, it aims to provide sound information and guidance for all professionals involved in donation and transplantation of human organs, to optimise 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 national 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

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



Source: *Newsletter Transplant*. Data from 2014.

DBD = donation after brain death; DCD = donation after circulatory death; pmp = per million population. Data in parentheses: total number of deceased organ donors in 2014.

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 14 and 15). 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, amongst other objectives, to avoid duplication of efforts.

It is under the mandate and aegis of this 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, 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 cost-effective 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 in recent decades (see Figures 1.1 and 1.2). For kidneys, the numbers of living donors are also largely 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 the waiting lists.

The scarcity of organs to cope with transplantation needs 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 to 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 (ECD) and from non-standard risk donors. All of these aspects will be discussed at length in dedicated chapters of this Guide.

1.3.1. Risks and benefits of transplantation

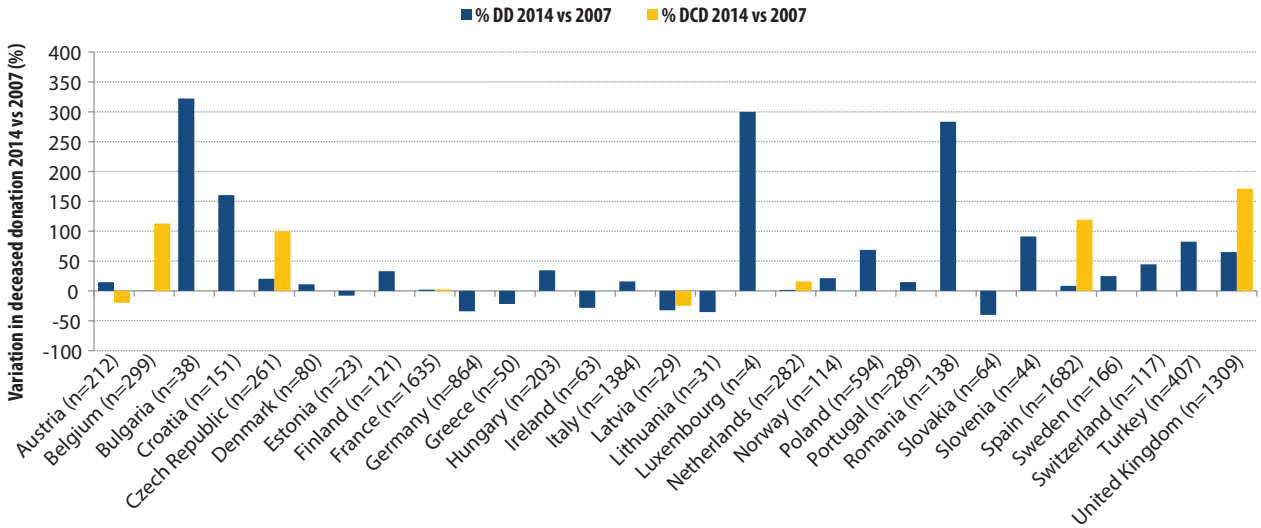
Transplantation is not without risks, and only organs procured under strict quality and safety parameters are likely to function properly and provide the best clinical outcomes for the recipients. Transplantation carries the risk of the operative procedure itself, of the lifelong immuno-suppression that will be necessary, and of disease transmission. The factors influencing the clinical outcome of transplantation are complex: 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

Figure 1.2. **Variation in deceased donation activities 2014 v. 2007**



Source: *Newsletter Transplant*.

In parentheses: total number of deceased donors in 2014.

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

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].

Unlike most solid-organ transplantations, the transplantation of VCA is not usually life-saving, and its primary aim is to increase a patient's quality of life. However, while form and function 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, it must be critically balanced whether functional ability, e.g. grasping and lifting objects, may be more easily 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 large sized donor–recipient populations.

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 relatives or the general practitioner in charge of a person do not know all the data for multiple reasons.

Therefore, 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 of 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.

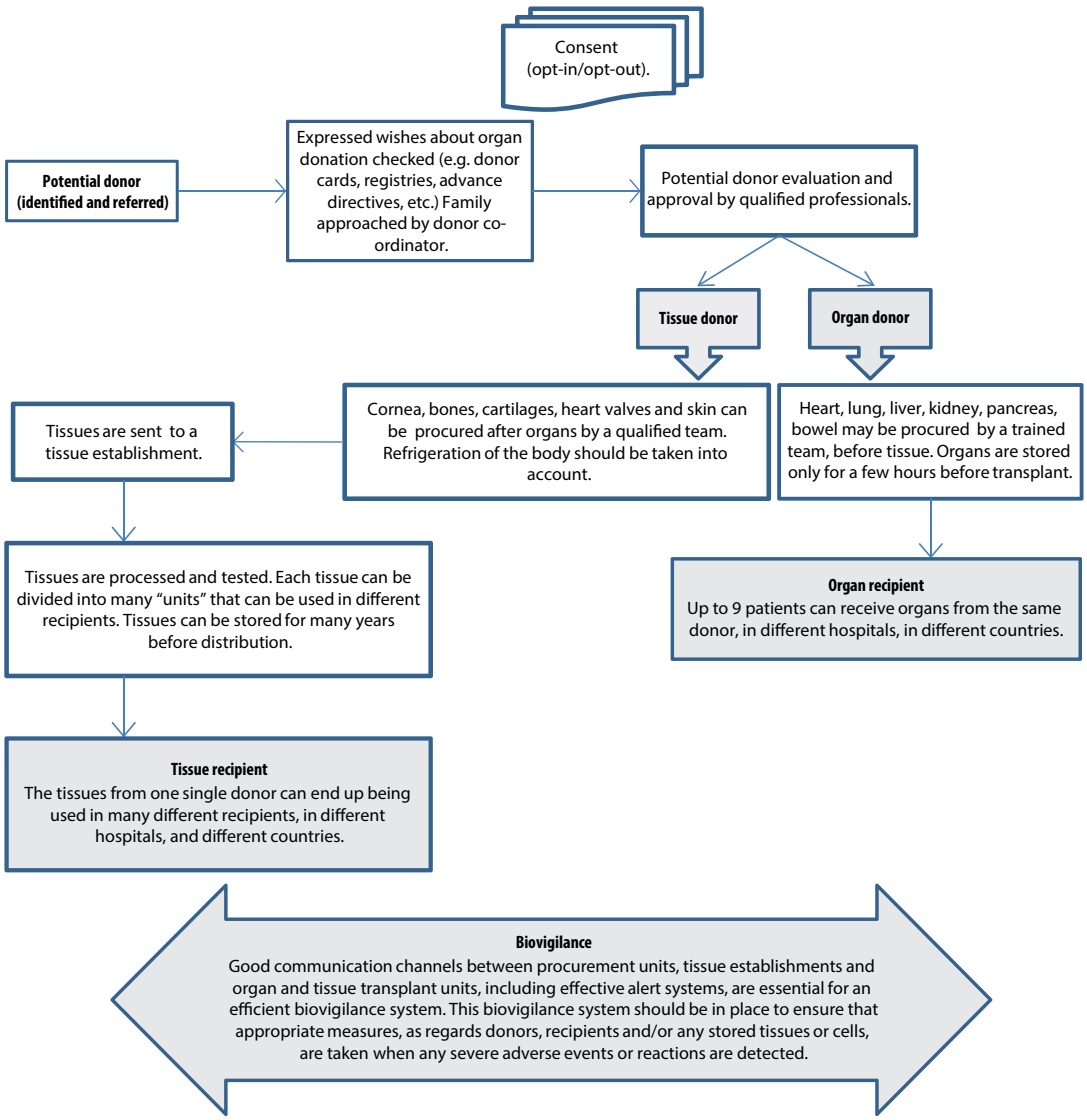
All patients (or parents/legal guardians of underage patients) who are candidates for transplant waiting lists, or those changing their status on waiting lists, should know about these risks.

1.3.2. Process of donation and transplantation of organs

Organ donation and transplantation continue to be fast-moving fields, requiring control of all 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 from 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

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



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 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-ordinators' 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 of 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 experiences 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 situ*ations in which the requirement for a high degree of matching or phenotypical similarities 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 them are meant 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:

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 transplants that should be financially covered by national 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 haemopoietic stem cell transplants, including the importing of haemopoietic stem 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 the EU, Directive 2010/53/EU requires that member states designate one or more competent authorities (and delegated bodies) to implement a number of tasks that cover many of the functions described above, and defines broadly their tasks and responsibilities.

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 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 receive 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 and should be regularly trained. 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 regards to transparency, free will and other legal and ethical considerations. Their professional activities should include:

a. detecting and identifying possible donors;
b. facilitating the determination of death, when needed;
c. supervising the 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 the 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.

Donor co-ordinators 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 not only be responsible 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.

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 section 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 World Health Organizsation (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 [9]. 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 case of organ donation after death, the 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 [10]. These provisions, along with other relevant information, 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, 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 [9]. This motion is reiterated in the Additional Protocol to that Convention, in its Article 21 [10].

The Council of Europe Convention against Trafficking in Human Organs [22] 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 living 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 the 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 the 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 cannot be directed to a particular individual. 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 therefore often also 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 from their current donors), 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, whilst 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 [16]. 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) [17] 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) [18], 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) [19], 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.[1]

The Additional Protocol (European Treaty Series, No. 89) [20], opened for signature on 24 June 1976 and which entered into force on 23 April 1977, provides for the accession of the European Community 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 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 that the body and its parts, as such, give rise to financial gain.

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 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 and its Explanatory Report (European Treaty Series, No. 197) [21], which was opened for signature in Warsaw on

1 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.

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 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 [22] 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 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 the 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 a national transplant organisation [35], 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 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 [36], 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 a 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 [37], recommending that the 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 [38] 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 [39], 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 [40] and its Explanatory Memorandum [41] 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 [42] 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 [43] sets out the general guidelines for the construction of such national/international registries. In addition, the Explanatory Memorandum [44] 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.

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* [1], 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, Mediterranean Network). The *Newsletter Transplant* database is connected with other international projects on data collection (e.g. WHO Global Observatory on Organ Donation and Transplantation, Eurocet database) 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 6th edition of the *Guide to the quality and safety of organs for transplantation*, the 2nd edition of the *Guide to the quality and safety of tissues and cells for human application* and the 18th 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 [45]. 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, the 63rd World Health Assembly adopted resolution WHA63.22 [46] on 21 May 2010, 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 [47] 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 [46] 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 [2].

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 [48]. 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 [49, 50].

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 [51] have a standing collaboration aimed, amongst 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 [52] (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 [53] was adopted on 7 July 2010 (see Corrigendum [54] 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, as well as 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 [55]. This last 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 [56] 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 [57]. 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 [58], recalling the main principles and objectives. In addition, based on the Actor Study [59], the Commission issued a document where efforts at national and European levels were mapped [60].

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 (FP), Horizon 2020 – and under the (Public) Health Programmes run by the Consumers, Health, Agriculture and Food Executive. Some of these projects [61] are:

- Alliance-O [62] (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 7 countries involved.
- Dopki [63] (Improving the 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 [64] (European Living Organ Donation, 2010-2012, FP7): this project focused on living organ donation as a complementary approach to bridge the gap between demand and supply of organs. Living organ donation presents opportunities, but 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 practices on living organ donation programmes.
- EDD [65] (European Donation Day, 2009-2011): this project aimed at developing guidelines for organising European organ donation days. The EDD celebration is envisaged as becoming a primary awareness-raising 'voice' and event regarding 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 [66] (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 (Ethical, Legal and Psychosocial Aspects of Transplantation) [67] organised by this section of the European Society for Organ Transplantation were also supported by the European Commission in 2003, 2007 and 2010.
- Eulid [68] (European Living Donation and Public Health, 2008-2010) and Elipsy [69] (European Living Donor – Psychosocial Follow-up, 2010-2012) projects and the Lidobs Conference [70] (Living Donor Observatory, 2014): the main objective of these two projects and the conference, led by the same consortium, 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 [71, 72] (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 [73] (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 Organización Nacional de Trasplantes 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 practices 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 practices 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.

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 [79] (European Standards and Training in the Inspection of Tissue Establishments) and
- SoHO V&S [80] (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 projects BIO-DrIM (BIOmarker-Driven personalised Immuno-suppression) [81], COPE (Consortium on organ preservation in Europe) [82], HepaMAb (Human monoclonal antibody therapy to prevent hepatitis C virus reinfection of liver transplants) [83], and the One Study (A unified approach to evaluating cellular immunotherapy in solid organ transplantation) [84]. All these projects have strengthened the collaboration among national health authorities and between these latter and 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 [85], 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) regarding the responsibility of the community towards living kidney donors [86, 87]. A subsequent international conference of transplant physicians, surgeons and allied health professionals was held in Vancouver, Canada, to address the care of living lung, liver, pancreas, and intestine organ donors. 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 [88].

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, because transplant commercialism targets impoverished and otherwise vulnerable donors and leads inexorably to inequity and injustice, it should also be prohibited. 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: 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.

1.6. References

1. International figures on donation and transplantation 2014. *Newsletter Transplant* 2015; 20 (1) [available from: www.edqm.eu/sites/default/files/newsletter_transplant_2015_2.pdf, accessed: 30 January 2016].
2. Global observatory on donation and transplantation [available from: www.transplant-observatory.org, accessed: 30 January 2016].
3. 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, available at www.edqm.eu/medias/fichiers/Joint_Council_of_EuropeUnited_Nations_Study_on_tra1.pdf; see also Executive Summary [available from: www.edqm.eu/medias/fichiers/

Executive_summary_of_the_Joint_Council_of_EuropeUn.pdf, accessed: 30 January 2016].

4. Council of Europe Organ Transplantation Guides [available from: www.edqm.eu/en/organ-tissues-cells-transplantation-guides-1607.html and Council of Europe Blood Guide [available from: www.edqm.eu/en/blood-transfusion-guides-1608.html, accessed: 9 March 2016].
5. Conclusions of the Third Conference of European Health Ministers (1987), 16-17 November 1987 [available from: wcd.coe.int/com.instranet.InstraServlet?command=com.instranet.CmdBlobGet&InstranetImage=1909381&SecMode=1&DocId=1778468&Usage=2, accessed: 30 January 2016].
6. European Directorate for the Quality of Medicines & HealthCare (EDQM) [available from: www.edqm.eu, accessed: 30 January 2016].
7. European Committee on Organ Transplantation (CD-P-TO) [available from: www.edqm.eu/en/organ-transplantation-work-programme-72.html, accessed: 9 March 2016].
8. Rahmel A. Vascularized composite allografts: procurement, allocation, and implementation. *Curr Transpl Rep* 2014; (1): 173-82.
9. Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities of a National Transplant Organisation (NTO) [available from: www.edqm.eu/en/recommendations-organ-transplantation-1515.html, accessed: 30 January 2016].
10. Council of Europe (1997) 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 [available from: http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm, accessed: 30 January 2016].
11. Council of Europe (2002) Additional Protocol to the Convention on human rights and biomedicine, on transplantation of organs and tissues of human origin [available from: http://conventions.coe.int/Treaty/en/Treaties/Html/186.htm, accessed: 30 January 2016].
12. Resolution (78) 29 on harmonisation of legislations of member states relating to removal, grafting and transplantation of human substances [available from: www.coe.int/t/dg3/healthbioethic/texts_and_documents/Res(78)29E.pdf, accessed: 9 March 2016].
13. World Health Organization (2010), WHO guiding principles on human cell, tissue and organ transplantation [available from: www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf, accessed: 30 January 2016].
14. Steering Committee of the Istanbul Summit (2008). Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. *Lancet* 2008; 372 (9632): 5-6; see also The Declaration of Istanbul Custodian Group (2008), The Declaration of Istanbul on Organ Trafficking and Transplant Tourism [available from: www.declarationofistanbul.org/index.php?option=com_content&view=article&id=73&Itemid=59, accessed: 30 January 2016].
15. Report from the Nuffield Council on Bioethics Human bodies: donation for medicine and research [available from: http://nuffieldbioethics.org/project/donation/, accessed: 30 January 2016].
16. Council of Europe *Conventions, Resolutions, Recommendations and Reports in the field of organs, tissues and cells* [available from: www.edqm.eu/en/organ-transplantation-recommendations-resolutions-74.html, accessed: 30 January 2016].
17. Convention for the Protection of Human Rights and Fundamental Freedoms [available from: www.coe.int/en/web/conventions/full-list/-/conventions/treaty/005, accessed: 30 January 2016].
18. European agreement on the exchange of therapeutic substances of human origin [available from: http://conventions.coe.int/Treaty/en/treaties/html/026.htm, accessed: 30 January 2016].
19. European Agreement on the Exchange of Tissue-Typing Reagents [available from: http://conventions.coe.int/Treaty/en/treaties/html/084.htm, accessed: 30 January 2016].
20. Additional Protocol to the European Agreement on the Exchange of Tissue-Typing Reagents [available from: http://conventions.coe.int/Treaty/en/treaties/html/089.htm, accessed: 30 January 2016].
21. Council of Europe Convention on action against trafficking in human beings and its Explanatory Report [available from: http://conventions.coe.int/treaty/en/Treaties/Html/197.htm, accessed: 30 January 2016].
22. Council of Europe Convention against Trafficking in Human Organs [available from: http://www.coe.int/en/web/conventions/search-on-treaties/-/conventions/treaty/216, accessed: 31 August 2016].
23. Explanatory Report to the Council of Europe Convention against Trafficking in Human Organs [available from: https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=0900001680d3840, accessed: 31 August 2016].
24. Organ shortage: current status and strategies for the improvement of organ donation – a European Consensus Document [available from: www.edqm.eu/medias/fichiers/Organ_shortagecurrent_status_and_strategies_for_improvement_of_organ_donation_A_European_consensus_document.pdf, accessed: 30 January 2016].

25. Council of Europe *Resolutions, Recommendations and Reports related to Safety, Quality and Ethical Matters Concerning Procurement, Storage and Transplantation of Organs, Tissues and Cells* [available from: www.edqm.eu/medias/fichiers/organ_tissue_and_cells_free_publication.pdf, accessed: 30 January 2016].
26. Recommendation No. R (97) 15 of the Committee of Ministers to member states on xenotransplantation [available from: www.edqm.eu/medias/fichiers/Recommendation_No_97_15_of_the_Committee_of_Ministers_to_member_states_on_xenotransplantation.pdf, accessed: 30 January 2016].
27. Recommendation No. R (97) 16 of the Committee of Ministers to member states on liver transplantation from living related donors [available from: www.edqm.eu/en/organ-transplantation-recommendations-resolutions-74.html, accessed: 30 January 2016].
28. Recommendation Rec (2001) 5 of the Committee of Ministers to member states on the management of organ transplant waiting lists [available from: www.edqm.eu/sites/default/files/recommendation_no_2001_5_of_the_committee_of_ministers_to_member_states_on_the_management_of_organ_transplant_waiting_lists.pdf, accessed: 9 March 2016].
29. Recommendation Rec (2003) 10 of the Committee of Ministers to member states on xenotransplantation [available from: www.edqm.eu/sites/default/files/recommendation_no_2003_10_of_the_committee_of_ministers_to_member_states_on_xenotransplantation_2.pdf, accessed: 9 March 2016].
30. Explanatory memorandum to Recommendation Rec (2003) 10 [available from: https://wcd.coe.int/ViewDoc.jsp?id=39603, accessed: 9 March 2016].
31. Recommendation Rec (2003) 12 of the Committee of Ministers to member states on organ donor registers [available from: www.edqm.eu/sites/default/files/recommendation_no_2003_12_of_the_committee_of_ministers_to_member_states_on_organ_donor_registers.pdf, accessed: 30 January 2016].
32. Recommendation Rec (2004) 7 of the Committee of Ministers to member states on organ trafficking [available from: www.edqm.eu/sites/default/files/recommendation_no_2004_7_of_the_committee_of_ministers_to_member_states_on_organ_trafficking.pdf, accessed: 30 January 2016].
33. Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities [available from: www.edqm.eu/sites/default/files/recommendation_no_2004_19_of_the_committee_of_ministers_to_member_states_on_criteria_for_the_authorisation_of_organ_transplantation_facilities.pdf, accessed: 30 January 2016].
34. 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") [available from: www.edqm.eu/sites/default/files/recommendation_no_2005_11_of_the_committee_of_ministers_to_member_states_on_the_role_and_training_of_professionals_responsible_1.pdf, accessed: 30 January 2016].
35. Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities of a National Transplant Organisation [available from: www.edqm.eu/sites/default/files/recommendation_no_2006_15_of_the_committee_of_ministers_to_member_states_on_the_background_functions_and_responsibilities_of_a_national_transplant_organisation_nto1.pdf, accessed: 30 January 2016].
36. Recommendation Rec (2006) 16 of the Committee of Ministers to member states on quality improvement programmes for organ donation [available from: www.edqm.eu/sites/default/files/recommendation_no_2006_16_of_the_committee_of_ministers_to_member_states_on_quality_improvement_programmes_for_organ_donation.pdf, accessed: 30 January 2016].
37. Resolution CM/Res (2008) 4 on adult-to-adult living donor liver transplantation [available from: www.edqm.eu/medias/fichiers/Resolution_CMRes20084_on_adult_to_adult_living_donor_liver_transplantation.pdf, accessed: 30 January 2016].
38. Resolution CM/Res (2008) 6 on transplantation of kidneys from living donors who are not genetically related to the recipient [available from: www.edqm.eu/medias/fichiers/Resolution_CMRes20086_on_transplantation_of_kidneys_from_living_donors_who_are_not_genetically_related_to_the_recipient.pdf, accessed: 30 January 2016].
39. Resolution CM/Res (2013) 55 on establishing procedures for the collection and dissemination of data on transplantation activities outside a domestic transplantation system [available from: www.edqm.eu/sites/default/files/medias/fichiers/resolution_cmres201355_on_establishing_procedures_for_the_collection_and_dissemination_of_data_on_tr.pdf, accessed: 30 January 2016].
40. Resolution CM/Res (2013) 56 on the development and optimisation of live kidney donation programmes [available from: www.edqm.eu/sites/default/files/medias/fichiers/resolution_cmres201356_on_the_development_and_optimisation_of_live_kidney_donation_programmes.pdf, accessed: 30 January 2016].

41. Explanatory Memorandum to Resolution CM/Res (2013) 56 [available from: www.edqm.eu/sites/default/files/explanatory_memorandum_cm_2013145.pdf, accessed: 30 January 2016].
42. Resolution CM/Res (2015) 10 on the role and training of critical care professionals in deceased donation [available from: www.edqm.eu/sites/default/files/resolution_cmrs_201510_role_and_training_critical_care_professionals_in_deceased_donation.pdf, accessed: 30 January 2016].
43. Resolution CM/Res (2015) 11 on establishing harmonised national living donor registries with a view to facilitating international data sharing [available from: www.edqm.eu/sites/default/files/resolution_on_establishing_harmonised_national_living_donor_registries_with_a_view_to_facilitating_international_data_sharing_2015_11.pdf, accessed: 30 January 2016].
44. Explanatory Memorandum to Resolution CM/Res (2015) 11 [available from: www.edqm.eu/sites/default/files/explanatory_memorandum_resolution_cm_res201511_on_harmonised_national_living_donor_registries_2015.pdf, accessed: 30 January 2016].
45. World Health Assembly (1991), Human organ transplantation: WHA44.25 [available from: www.transplant-observatory.org/SiteCollectionDocuments/wha44resen.pdf, accessed: 30 January 2016].
46. World Health Assembly (2010), Human organ and tissue transplantation: WHA63.22 [available from: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R22-en.pdf, accessed: 30 January 2016].
47. World Health Assembly (2004), Human organ and tissue transplantation: WHA57.18 [available from: http://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf, accessed: 30 January 2016].
48. Notify: Exploring vigilance notification for organs, tissues and cells [available from: www.transplant-observatory.org/SiteCollectionDocuments/glorepnotify.pdf, accessed: 30 January 2016].
49. Access to safe and effective cells and tissues for transplantation [available from: www.who.int/transplantation/cell_tissue/en/, accessed: 30 January 2016].
50. Aide-mémoire on key safety requirements for essential minimally processed human cells and tissues for transplantation [available from: www.who.int/transplantation/cell_tissue/en/, accessed: 30 January 2016].
51. European Union: European Commission General Directorate on Public Health, Organ Transplantation Section [available from: http://ec.europa.eu/health/blood_tissues_organs/organs/index_en.htm, accessed: 30 January 2016].
52. Treaty on the Functioning of the European Union [available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012E/TXT&from=EN, accessed: 30 January 2016].
53. European Parliament and Council of the European Union: Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. *Official Journal of the European Union* 2010; (53): 14-29 [available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX-:32010L0053:EN:NOT, accessed: 30 January 2016].
54. Corrigendum to Directive 2010/45/EU [available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:243:0068:0068:EN:PDF, accessed: 30 January 2016].
55. Commission Implementing Directive 2012/25/EU of 9 October 2012 laying down information procedures for the exchange, between member states, of human organs intended for transplantation [available from: http://ec.europa.eu/health/blood_tissues_organs/docs/organs_impl_directive_2012_en.pdf, accessed: 30 January 2016].
56. European Commission Campaign 'Europe for Patients' on organ donation and transplantation: Commission Action plan on Organ Donation and Transplantation (2009-2015) [available from: http://ec.europa.eu/health-eu/europe_for_patients/organ_donation_transplantation/index_en.htm, accessed: 30 January 2016].
57. Communication from the Commission: Action plan on Organ Donation and Transplantation (2009-2015): Strengthened Cooperation between Member States [available from: http://ec.europa.eu/health/archive/ph_threats/human_substance/oc_organs/docs/organs_action_en.pdf, accessed: 30 January 2016].
58. Council conclusions on organ donation and transplantation (2012/C 396/03) of EU Member States [available from: http://ec.europa.eu/health/blood_tissues_organs/docs/organs_council_ccl_2012_en.pdf, accessed: 30 January 2016].
59. Actor study: Study on the set-up of organ donation and transplantation in the EU Member States, uptake and impact of the EU Action Plan on Organ Donation and Transplantation (2009-2015) [available from: http://ec.europa.eu/health/blood_tissues_organs/docs/organs_actor_study_2013_en.pdf, accessed: 30 January 2016].
60. Commission Staff Working Document on the mid-term review of the EU Action Plan on Organ Donation and Transplantation [available from: http://ec.europa.eu/health/blood_tissues_organs/docs/midtermreview_actionplan_organ_en.pdf, accessed: 30 January 2016].
61. EU Programmes of Community Action in the Field of Health. More information available at: http://

ec.europa.eu/health/programme/policy/index_en.htm, http://ec.europa.eu/health/programme/policy/2008-2013/index_en.htm and http://ec.europa.eu/eahc/projects/database.html, all accessed: 30 January 2016].

62. Alliance-O (European Group for Co-ordination of National Research Programmes on Organ Donation and Transplantation) [available from: http://ec.europa.eu/research/fp7/pdf/era-net/fact_sheets/fp6/alliance-o_en.pdf, accessed: 30 January 2016].
63. Dopki (Improving the Knowledge and Practices in Organ Donation) [available from: http://ec.europa.eu/research/fp6/ssp/dopki_en.htm and www.ont.es/internacional/Documents/DOPKI.pdf, accessed: 30 January 2016].
64. Eulod (European Living Organ Donation) [available from: www.eulod.org and www.eulod.eu, accessed: 30 January 2016].
65. Project EDD (European Donation Day) [available from: http://ec.europa.eu/chafea/documents/health/conference_27-28_06_2013/EDD_-_Toolkit_for_European_Donation_Days.pdf, accessed: 9 March 2016].
66. Efretos (European Framework for the Evaluation of Organ Transplants) [available from: www.efretos.org, accessed: 30 January 2016].
67. Elpat Conferences [available from: www.esot.org/ELPAT/home, accessed: 30 January 2016].
68. Eulid (European Living Donation and Public Health) [available from: www.eulivingdonor.eu/eulid/what-is-eulid.html, accessed: 30 January 2016].
69. Elipsy (European Living Donor – Psychosocial Follow-up) [available from: www.eulivingdonor.eu/elipsy, accessed: 30 January 2016].
70. Lidobs Conference [available from: www.eulivingdonor.eu/lidobs, accessed: 30 January 2016]. Etpod (European Training Program on Organ Donation) [available from: www.etpod.eu, accessed: 30 January 2016].
71. Etpod (European Training Program on Organ Donation) available at: www.etpod.eu.
72. Manyalich M, Guasch X, Paez G *et al.* Etpod (European Training Program on Organ Donation): a successful training program to improve organ donation. Transpl Int 2013; 26 (4): 373-84.
73. 'Transplant co-ordinators train the trainers' course [available from: www2.iavante.es/en, accessed: 7 April 2016].
74. Project Odequs (Organ Donation European Quality System) [available from: www.odequs.eu, accessed: 30 January 2016].
75. Coorenor (Coordinating a European initiative among national organisations for organ transplantation) [available from: https://coorenor.ders.cz/, accessed: 30 January 2016].
76. Joint action Mode (Mutual Organ Donation and Transplantation Exchanges) [available from: http://ec.europa.eu/chafea/documents/health/conference_27-28_06_2013/MODE_-_Mutual_Organ_Donation_and_Transplantation_Exchanges.pdf, accessed: 7 April 2016].
77. Joint action Accord (Achieving Comprehensive Coordination in Organ Donation throughout the European Union) [available from: www.accord-ja.eu, accessed: 30 January 2016].
78. Joint Action Foedus (Facilitating Exchange of Organs Donated in EU Member States) [available from: www.foedus-ja.eu, accessed: 30 January 2016].
79. Eustite project [available from: http://ec.europa.eu/chafea/documents/health/conference_27-28_06_2013/Projects_presented_at_the_meeting_-_27th_and_28th_of_June_2013_Madrid.pdf, accessed: 30 January 2016].
80. SoHO V&S project [available from: http://ec.europa.eu/chafea/documents/health/conference_27-28_06_2013/Transplantation_and_Blood_Transfussion_in_EU_programme_conference_27-28_06_2013.pdf, accessed: 31 August 2016].
81. BIO-DrIM project [available from: www.biodrim.eu, accessed: 30 January 2016].
82. Cope project [available from: www.cope-eu.org, accessed: 30 January 2016].
83. HepaMAb project [available from: www.hepamab.eu, accessed: 30 January 2016].
84. One Study [available from: www.onestudy.org, accessed: 30 January 2016].
85. Technical Assistance and Information Exchange (TAIEX) [available from: http://ec.europa.eu/enlargement/tenders/taiex/index_en.htm, accessed: 7 April 2016].
86. The Ethics Committee of the Transplantation Society. Consensus Statement of the Amsterdam Forum on the Care of the Live Kidney Donor. *Transplantation* 2004; 78 (4): 491-2, [available from www.tts.org/images/stories/pdfs/ConsensusStatementfinal.pdf, accessed: 30 January 2016].
87. Ethics Committee of The Transplantation Society. A Report of the Amsterdam Forum on the care of the kidney donor: data and medical guidelines – Amsterdam 2004 International Forum on the Care of the Live Kidney Donor. *Transplantation*. 2005; (79): S53-S66 [available from: www.livingdonorsonline.org/ConsensusStatementLong.pdf, accessed: 30 January 2016].
88. Report on the Vancouver Forum. *Transplantation* 2006; (81): 1373-85. Barr ML, Belghiti J, Villamil FG *et al.* [available from: www.tts.org/images/stories/pdfs/Vancouver_Forum.pdf, accessed: 30 January 2016].

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 i.e. to satisfy comprehensively the transplantation needs of their patients by using resources within their own population [1]. Addressing self-sufficiency entails a combination of strategies targeted at decreasing the burden of diseases treatable through transplantation and at maximising the availability of organs, with priority given to donation from the deceased. 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 the deceased. However, the persisting shortfall in the availability of organs 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 9.3% of all deceased organ donors reported to the Global Observatory on Donation and Transplantation (2013 data), although this activity is developed only in a limited number of countries because of legal, organisational and technical constraints specific to this particular type of donation [2, 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 transplants, although the process may be structured in various ways. The Madrid Resolution yielded a list of practical recommendations for self-sufficiency in transplantation. One of its products was the WHO Critical Pathway for Deceased Donation, classifying organ donors on the basis of the subsequent phases of the deceased donation process [4].

Although some aspects of deceased donation are equally apparent in both DBD and DCD, there are also important differences between the two, and DCD poses some very specific challenges. However, in both types of donation, organ donors should be identified at a specific point in time which marks the beginning of the organ donation pathway. The identification and subsequent referral of organ donors by treating physicians, 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 most critical step of the deceased donation process. The identification of opportunities for organ donation by treating physicians depends on whether they see donation as a routine part of end-of-life care, a principle that still needs to be upheld by adequate regulatory frameworks and professional and public debate [1]. Failure to identify and refer organ donors is the main reason

for substantial differences in deceased donation rates between countries, regions and hospitals.

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 then focuses on the steps of identification and referral of organ donors. Recommendations for succeeding in the subsequent phases of the deceased donation process are provided in other chapters of this guide.

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

Deceased organ donors are of two types, depending on the criteria used to determine death before the recovery of organs: DBD and DCD donors.

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

DCD refers to donation from persons who have been declared dead based on circulatory criteria. Depending on the clinical scenario in which cardiac arrest occurs, there are four different categories of DCD, first described in Maastricht (Netherlands) in 1995 and updated in Paris (France) in 2013 (see Table 2.1) [5, 6]. Categories I and II describe donors in whom death has occurred following an unexpected circulatory 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)]. 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 (during or after BD diagnosis, but before organ recovery).

DCD is an activity performed by 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 circulatory – and 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 brain death diagnosis process, but before organ recovery

Modified Maastricht classification, Paris 2013.

* 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 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 builds upon 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).

2.3.1. Possible deceased organ donors

A possible deceased organ donor is a patient with a devastating brain injury or lesion or a patient with a circulatory failure, who is apparently medically suitable for organ donation.

This is frequently a patient with devastating brain damage already admitted to an ICU and receiving mechanical ventilation. However, a possible organ donor may also be a person with devastating brain damage in whom further therapy is deemed futile either in the emergency department or the hospital ward, and for whom admission to an ICU, and even the initiation of mechanical ventilation, is not deemed therapeutically indicated because further

treatment is not considered to be in the patient's best interests. In this context, intubation and initiation of mechanical ventilation (elective non-therapeutic ventilation) and admission to an ICU could be considered with the purpose of incorporating donation into the end-of-life care pathway of the patient [7]. However, this practice is not widely applied in Europe.

A patient with a circulatory failure is also a possible organ donor. If 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 (Category II) process.

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

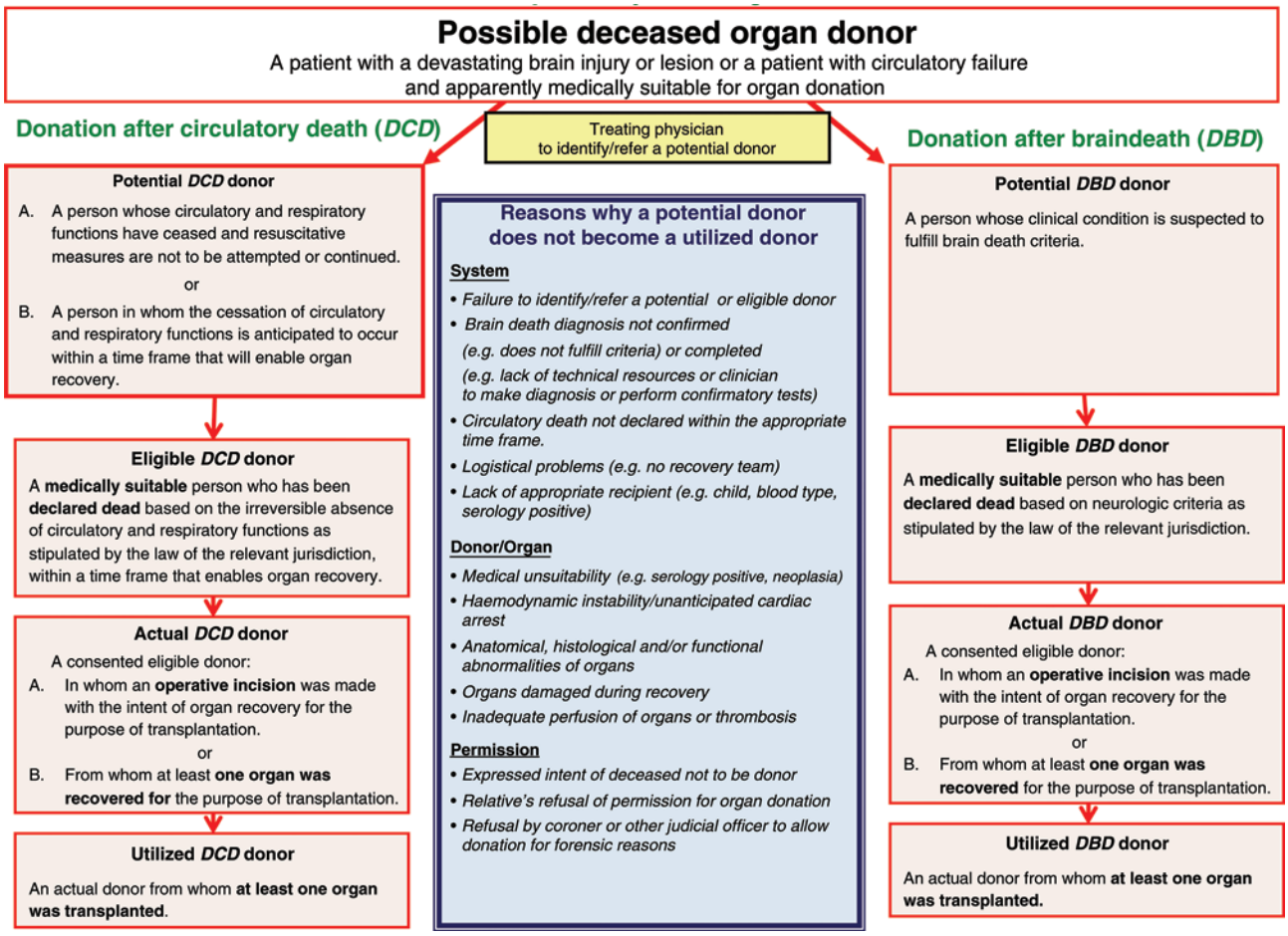
The WHO Critical Pathway for Deceased Donation identifies the possible organ donor as the ideal point for identification and referral of the case by the treating physician to the donor co-ordinator or staff of the corresponding OPO. However, early referral is not considered appropriate or is not legally possible in all jurisdictions, which leads to the need for delaying 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.

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 for whom CPR measures are not to be attempted or continued (potential uDCD donor), 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 (potential cDCD donor). This last scenario refers to persons with a devastating brain injury in whom further treatment has been deemed futile and the decision has been made to withdraw life-sustaining therapy [6]. Potential cDCD donors also include patients with end-stage neurodegenerative or cardiac/respiratory diseases in whom the WLST has been decided. Although the majority

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



* The 'dead donor rule' must be respected. That is, patients may only become donors after death, and the recovery of organs must not cause a donor's death.
Reprinted with permission from *Transpl Int* 2011; 24 (4): 373-8) [4].

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 [8]. The study revealed that the incidence of BD was significantly higher in southern 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 made evident that the practice of withdrawing therapy when further treatment is considered futile, is frequent in northern Europe, while 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 devastating brain injury (possible organ donors) – were also made evident at the recently held Accord Joint Action [10].

2.3.3. Eligible deceased organ donors

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

A potential DBD donor might not become eligible for organ donation because the diagnosis of death by neurologic criteria has not been confirmed, or in exceptional cases not completed – e.g. because of the lack of technical and human resources needed for confirmation. It is worth noting that in some European countries 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 [9, 10]. In circumstances where BD is not confirmed or completed, cDCD might be activated, but substitution of DBD by cDCD 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. However, cDCD will only occur if the cardio-respiratory arrest follows soon after WLST. This time limit has been most commonly established at 2 h, but it is being extended in some countries (for example, to 3 h in the United Kingdom), although death following WLST not infrequently occurs beyond this time limit.

In the uDCD setting, non-eligibility frequently follows 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 not be eligible because they are considered medically unsuitable. Although there are very few absolute contraindications to organ donation, 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 11 % of the decisions not to refer a potential DBD donor on medical grounds to be incorrect [11]. Therefore, the medical assessment of organ donors should be made by the donor co-ordinator and the relevant transplant teams, and not only by the treating physician.

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 intent of organ recovery for the purpose of transplantation. An actual deceased organ donor is also defined as the 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 his/her lifetime or by their relatives. Consent rates to organ donation are influenced by a variety of factors – both modifiable and not modifiable. At the Accord Joint Action, within a dedicated study undertaken at 67 hospitals from 15 European Union (EU) member states, 24 % and 33 % of families approached to discuss organ donation declined authorisation for organ recovery in the DBD and DCD process respectively [10]. Consent declined for organ recovery in the DBD process was however underestimated since the rate referred only to those families approached about organ donation from persons with death already confirmed by neurologic criteria.

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 organ has been transplanted.

Once organs are recovered, these might not be transplanted because of anatomical or histological findings in the donor or the organs themselves, 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 compared to the DBD process (see Chapter 12). Non-utilisation rates are also higher in uDCD than in the cDCD setting [3].

2.4. Identification and referral of possible organ donors

Failure to identify and refer organ donors is one of the most important reasons for not realising the deceased donation process as described in Figure 2.1. In the ACCORD project, 35 % of patients dead as a result of a devastating brain injury were never referred to the donor co-ordinator or the staff of the OPO, thus ruling out the possibility of organ donation [10].

Identification of opportunities for deceased organ donation by treating physicians, 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 and nor have uniform criteria been established for donor referral. The stage for referral has been defined only in some national guidelines, with revealing differences between countries. However, if legally possible, referral should ideally occur early in the process, i.e. 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 treatments switch from active therapy to palliative and end-of-life care [12]. Referral can also systematically occur based on a poor prognosis of the patient, even if active medical treatment is to be continued. Referral at this point is considered a sort of notification that 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 family. If needed, expert assistance for BD testing or physiological optimisation of the donor can be identified. Early referral also allows better planning of the family approach and a prompt identification and resolution of potential coroner/judicial issues.

Figure 2.2. **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 Camilo Hospital (Rome, Italy), as part of a cycle for improvement in organ donation during the European Union co-funded project ACCORD.

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

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

Clinical triggers	Ischaemic brain injury	Intra-cerebral haemorrhage	Secondary cerebral anoxia	CNS tumour	CNS infection	Cerebral trauma
Recommended referral	NIHSS ≥ 27	ICH or Hunt–Hess ≥ 4		GCS ≤ 6		
Required referral	GCS 3 and progressive absence of at least 3 out of 6 brain stem reflexes or FOUR score of E0M0B0R0					

Note: CNS: central nervous system; GCS: Glasgow coma scale; IHS: 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 [16].

2.4.1. 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 medical criteria which, when met, should result in referral by the treating physician. They should be agreed upon by consensus and developed by an interdisciplinary panel of experts inclusive of all professionals who care for patients with a devastating brain injury (e.g. personnel from the intensive and emergency care departments, neurology and neurosurgery). Clinical triggers should be simple, clearly defined, and easy to audit. They should focus on prognostic factors and lead to referral regardless of a patient's age and comorbidity, since limiting referral based on age or apparent medical contraindications to donate may lead to an important number of lost opportunities for organ donation. Clinical triggers should be easily available to critical care professionals, e.g. through simple posters containing the relevant information and located at visible places in critical care units (see Figure 2.2).

The next sections 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 devastating brain injury does not evolve to a BD condition and the decision to allow WLST is made.

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

The Glasgow Coma Scale (GCS) is most commonly used to define triggers for referring donation after brain death (DBD) donors (e.g. GCS < 8). In Croatia, certain scores of different neurologic 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 stroke severity scale ≥ 27 [13];
b. For patients with cerebral haemorrhage, an intra-cerebral haemorrhage scale [14] or a Hunt–Hess scale [15] ≥ 4;
c. For patients with secondary cerebral anoxia, CNS tumours or infections, or severe cerebral trauma, a GCS ≤ 6.

Patients at this stage may still be subject to active treatment. However, according to Croatian guidelines, those patients should be reported as possible donors to the donor co-ordinator [16] (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 [16, 17]. 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 [17, 18].

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

Group of cerebral lesion	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 codes with three figures – e.g. G93.1 – all sub-classifications should be included.

Sources: Achieving Comprehensive Coordination in Organ Donation through the European Union–Accord Joint Action [10]; 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 [21].

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 [19]. In patients with a catastrophic brain injury, referral is recommended in the absence of one or more brainstem reflexes and a GCS score ≤4 that is not explained by sedation, 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 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 [20]. 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).

There is an ongoing area of research on clinical and radiological factors to predict progression to BD in patients with a devastating brain injury in whom the decision has been made of not to treat on the ground of futility. Derived new prognostic scores may become clinical triggers for the referral of possible DBD donors and support physicians to make difficult decisions on elective non-therapeutic intensive care to facilitate organ donation [21].

Some ICD-10 codes are related to potentially devastating cerebral lesions that can lead to BD (see Table 2.3) [10, 22]. The review of this codified data collection (or that 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 devastating brain injury. 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.

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

Controlled donation after circulatory death (cDCD) and uncontrolled donation after circulatory death (uDCD) are developed in very different clinical scenarios that necessitate separate clinical triggers for identification and referral.

The potential for cDCD should be considered in any critically ill patient in whom the decision of WLST has been made because treatment is no longer in the best interests of the patient [22]. Most cDCD donors have suffered a devastating brain injury similar to DBD donors. It is always important that the treating physician considers if death by neurologic criteria might be determined if active treatment is maintained and WLST is delayed. 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 and neuromuscular disease. An undesired replacement of DBD by cDCD is not a possibility in this particular context.

The possibility of cDCD will always be raised as a different and separate decision from that of WLST. Following the decision to withdraw treatment, the case should be referred to the donor co-ordinator or the OPO. This timely referral will avoid unnecessary delays in the withdrawal of therapy that may cause distress to relatives of the potential cDCD donor. After the referral, the donor co-ordinator or the OPO should assess any obvious contraindication to DCD. Discussions with the relatives of the potential cDCD donors should be initiated by the donor co-ordinator in close co-operation with the treating physician.

The identification of uDCD donors provides a different set of challenges because of the obvious 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 [23]. Activation of the uDCD process requires carefully planned co-operation between teams in charge of CPR (emergency and intensive care) 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 developed in most countries where DCD is standard practice [23-26]. More detailed information is provided in Chapter 12.

2.5. Training and education

An effective system for the routine identification and referral of organ donors requires close co-operation between healthcare professionals caring for critically ill patients (personnel from the intensive and emergency care departments, but also from neurology and neurosurgery) 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 this continuous education and training through various means that must include dedicated courses at least twice a year. 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 devastating brain damage. The type and duration of these training courses, as well as the frequency of attendance, are to be agreed upon at a 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 Organization – UEMS 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 [28].

2.6. Quality system

As part of the quality control system (see Chapter 15), a proactive donor-referral programme must be developed at national, regional or local level and be 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 regarding both types of deceased organ donors, DBD and DCD [29]. These quality criteria and indicators were proposed to evaluate 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) [11, 30]. 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 at the ICU of procurement hospitals to then identify potential DBD and, if appropriate, potential cDCD donors [11, 30-33]. 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 caused by a devastating brain injury, 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 at the Spanish Quality Assurance Programme are described in Appendix 3 [11]. 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.

2.7. Conclusion

Without an active donor identification and referral programme 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 must be established at each hospital. Donor coordinators will play a key role in ensuring the quality of the donor detection and referral policies. Efforts should be made to ensure education and training of all healthcare professionals who care for patients with a devastating brain injury, especially in intensive care units, 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 devastating brain injury is to preserve life. However, when the patient has evolved to a BD condition or the futility of further care 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.

Table 2.4. **Quality criteria proposed in the ODEQUS project on donor identification and referral**

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.	Each hospital should implement a systematic approach to evaluate the possibility for organ donation in every end-of-life care.
The written definition of 'possible donor' is available and known by the personnel of the units of the hospitals where possible donors may be found.	The written definition of 'possible donor' is available and known by the personnel of the units of the hospitals where possible donors may be found.
A possible donor is always referred to the donation team whatever the medical situation is (age, past medical history, etc).	A possible donor is always referred to the donation team whatever the medical situation is (age, past medical history, etc.).
	In all potential donors, the timing of treatment withdrawal should not be agreed 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 collaboration 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, eventually facilitating early brain death diagnosis as soon as the clinical criteria are fully met.	
The Donation Team monitors the evolution 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 the 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.

2.8. References

1. Third WHO Global Consultation on Organ Donation and Transplantation: Striving to achieve self-sufficiency, 23-25 March 2010, Madrid, Spain. *Transplantation* 2011: 91 (Suppl 11): S27-8.
2. Global Observatory on Organ Donation and Transplantation [available from: www.transplant-observatory.org/Pages/home.aspx, accessed: 30 January 2016].
3. Domínguez-Gil B, Haase-Kromwijk B, Van Leiden H *et al.* Current situation of donation after circulatory death in European countries. *Transpl Int* 2011; (24): 676-86.
4. Domínguez-Gil B, Delmonico FL, Shaheen FAM *et al.* The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. *Transpl Int* 2011; (24): 373-8.
5. Kootstra G, Daemen JH, Oomen A. Categories of non-heart-beating donors. *Transplant Proc* 1995; (27): 2983-94.
6. Thuong M, Ruiz A, Evrard P *et al.* New classification of donation after circulatory death donors, definitions and terminology. *Transplant Int.* 2016 Jul; 29 (7): 749-59.
7. Gillett G. Honouring the donor: in death and in life. *J Med Ethics*. 2013; 39 (3): 149-52.
8. Sprung CL, Cohen SL, Sjokvist P *et al.* End-of-life practices in European intensive care units: the Ethicus Study. *JAMA* 2003; (290): 790-7.
9. Groot YJ, Wijdicks EFM, van der Jagt M *et al.* Donor conversion rates depend on the assessment tools used in the evaluation of potential organ donors. *Intensive Care Med* 2011; (37): 665-70.
10. Achieving Comprehensive Coordination in Organ Donation through the European Union–Accord Joint Action [available from: www.accord-ja.eu, accessed: 30 January 2016].
11. De la Rosa G, Domínguez-Gil B, Matesanz R *et al.* Continuously evaluating performance in deceased donation: the Spanish quality assurance program. *Am J Transpl* 2012; (12): 2507-13.
12. Domínguez-Gil B, Murphy P, Procaccio F. Ten changes that could improve organ donation in the intensive care unit. *Intensive Care Med* 2016; (42): 264-7.
13. Brott T, Adams HP, Olinger CP *et al.* Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; (20): 864-70.
14. Hemphill JC, Bonovich DC, Besmertis L *et al.* The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001; (32): 891-7.
15. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28 (1): 14-20.
16. Župan Ž. Proposal of the National Strategy for Optimisation of Organ Donation Pathway 2011-2016; *Medix* 2011; 17 (92): 149-55, [available from http://hrcak.srce.hr/].
17. De Groot YJ, Jansen NE, Bakker J *et al.* Imminent brain death: point of departure for potential heart-beating organ donor recognition. *Intensive Care Med* 2010; (36): 1488-94.
18. Wijdicks E, Bamlet W, Maramatton B *et al.* Validation of a new coma scale: The FOUR score. *Ann Neurol* 2005; (58): 585-93.
19. Timely identification and referral of potential organ donors. A strategy for implementation of best practice [available from: www.odt.nhs.uk/donation/deceased-donation/professional-resources/reference-documents, accessed: 30 January 2016].
20. Nathan HM, Conrad SL, Held PJ *et al.* Organ donation in the United States. *Am J Transpl* 2003; 3 (Suppl 4): 29-40.
21. 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. *Transpl Int* 2016 Mar; 29 (3): 299-306.
22. Matesanz R, Coll E, Domínguez-Gil B *et al.* Benchmarking in the process of donation after brain death: a methodology to identify best performer hospitals. *Am J Transpl* 2012; (12): 2498-506.
23. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth* 2012; 108 (51): i108-i121.
24. Donation after circulatory death in Spain: current situation and recommendations. National consensus document 2012 (in Spanish) [available from: www.ont.es/infesp/Paginas/DocumentosdeConsenso.aspx, accessed: 30 January 2016].
25. Consensus statement on Donation after Circulatory Death from the British Transplantation Society and Intensive Care Society [available from: www.odt.nhs.uk/donation/deceased-donation/donation-after-circulatory-death, accessed: 30 January 2016].
26. National recommendations for donation after circulatory death in Canada. *CMAJ* 2006; (175): S1-S24.
27. Bernat JL, D'Alessandro AM, Port FK *et al.* Report of a national conference on donation after cardiac death. *Am J Transplant* 2006; (6): 281-91.
28. Manyalich M, Guasch X, Paez G *et al.* Etpod (European Training Program on Organ Donation): a successful training program to improve organ donation. *Transpl Int* 2013; (26): 373-84.
29. Odequs project website [available from: www.odequs.eu, accessed: 30 January 2016].
30. Dopki Guideline for quality programmes in organ donation [available from: www.ont.es/internacional/Documents/DOPKI.pdf, accessed: 30 January 2016].

31. Barber K, Falvey S, Hamilton C *et al.* Potential for organ donation in the United Kingdom: audit of intensive care records. *BMJ* 2006; (332): 1124-7.
32. Wesslau C, Grosse K, Krüger R *et al.* How large is the organ donor potential in Germany? Results of an analysis of data collected on deceased with primary and secondary brain damage in intensive care unit from 2002 to 2005. *Transpl Int* 2007; (20): 147-55.
33. Procaccio F, Ricci A, Ghirardini A *et al.* Deaths with acute cerebral lesions in ICU: does the number of potential organ donors depend on predictable factors? *Minerva Anestesiol* 2015; (81): 636-44.

Related document: 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]. 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. In 1959, Mollaret and Goulon published the cases of comatose and apnoeic patients in *coma dépassé* or 'irreversible coma'. These patients had lost consciousness, brainstem reflexes and respiration, and their electro-encephalograms were permanently flat.

The 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, or brain death (BD). In 1976, the Conference of Medical Royal Colleges and their Faculties in the United Kingdom published a statement on the diagnosis of BD defined as the 'complete, irreversible loss of brainstem function', which pointed to the brainstem as the centre of brain function [2]. 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.

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 (BDD), 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).

BD 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 BD 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.

The purpose of this chapter is to provide some recommendations on BDD 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 BDD.

3.2. Epidemiology and aetiology of brain death

Up to 15 % of patients dying in European ICUs are expected to present with a clinical condition consistent with BD [3]. Other data collected in European countries suggest that 50-65 % of all deaths with

acute primary or secondary cerebral lesions (ACLDs) in ICUs (traumatic brain injury, haemorrhagic and ischaemic stroke, subarachnoid haemorrhage, meningitis, encephalitis, central nervous system neoplasia, anoxia, toxic and poisoning cerebral lesions) may fulfil BD criteria [4].

As only mechanically ventilated patients with acute cerebral lesions may eventually deteriorate to BD, 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 BD 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 BD. In particular, traumatic brain injury and stroke are the two acute cerebral lesions most frequently linked with BD 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 BD. Case reports of BD declaration followed by successful DBD have been published, in which cerebral catastrophic events were due to poisoning by methanol, tricyclic antidepressants, insulin, carbon monoxide, ecstasy, etc.

It is feasible that death from traumatic uncontrolled intracranial pressure may be less frequent in young patients than in the past [5]. 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 the last 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 BD is no longer the gold standard for organ donation in most European countries, where stroke will be frequently the leading cause of BD and DBD in the near future. In addition, stroke mortality is decreasing, whereas the ageing European population will continuously increase the absolute number of cases. European mortality rates are also higher in eastern countries compared to northern and western countries, with a substantial number of deaths including both sexes and younger individuals. 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.

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

Prerequisites for clinical determination of brain death (BD)

1. Clinical history, known aetiology and irreversible condition compatible with BD diagnosis.
2. Exclusion of medical conditions which could influence clinical examination (severe disturbances in electrolytes, acid-base or endocrine metabolism).
3. Exclusion of central nervous system-depressant drugs intoxication.
4. Body temperature >35 °C.

Three mandatory clinical signs

1. 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.
2. Absence of brainstem reflexes (see text).
3. Absence of spontaneous breathing – Apnoea test (see text).

Absence of brainstem reflexes

During progression to BD, the loss of brainstem reflexes follows a rostro-caudal direction, from the midbrain (mesencephon) to the pons and at the end, the medulla (oblongata).

1. No pupil reactivity: lack of photo-reactivity, with no response to bright light of the fixed pupils (pupil diameter 4 to 9 mm).
2. 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).
3. Corneal reflex loss (avoid cornea damage): no palpebral movement when touching cornea edge using a sterile compress.
4. Lack of cough at bronchial suctioning, lack of pharyngeal and tracheal reflexes.

Apnoea test

Lack of spontaneous breathing due to the loss of respiratory centre function (medulla location):

- Pre-oxygenation requirement under FIO_2 100 % – minimal PEEP 5cmH_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 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 6-12 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 procedure without ventilator disconnection (CPAP mode).
- Collect sample of arterial blood after an interval of about 5 minutes and reconnect the ventilator.

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.

In practice, the age of stroke patients dying in ICUs is continuously increasing and becomes the real

limitation for DBD potentiality. Nevertheless, the increasing age of utilised DBD donors strongly suggests that these potential donors should be considered medically suitable.

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 BD. 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. Reasonably, elective ventilation for stroke patients who could progress to BD could be an important area for increasing organ donation over the next few years and thus could be recognised as indication for ICU admission.

The progression towards BD 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 the withdrawal of life support is very different between countries in northern and southern Europe (BD 3.2 % v. 12.4 %; withdrawal of life-sustaining therapy 47.4 % v. 17.9 %) [6]. 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 [7].

Actually, DBD 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 BD strongly depends on the absolute number and the ratio between severe brain injuries and strokes 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 in Germany and fewer than 5 in Portugal. 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, intensive care bed resources, ethical principles for end-of-life management and admission policy to ICU for elderly patients with stroke, BD 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 ICUs.

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 BD 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 running in European countries, with a view to defining efficiency indicators in the DBD process [3]. A simple and effective method for obtaining retrospective but objective data is the standard use of ICD-10 codes (see Table 2.3 and 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 [8]. Prospective national registries including all deaths with acute cerebral lesions, inside and outside the ICU, could be useful for calculating the potentiality of BD 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 BD 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 BDD. 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 BD should be clearly requested by any national guidelines about the determination of BD.

3.3. Clinical diagnosis of brain death

Brain death diagnosis (BDD) first relies on a clinical examination and the study of brainstem function. It is the most immediate, reliable and easy way to determine BD 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 BD are summarised in Table 3.1.

3.3.1. Preconditions for clinical examination

BD diagnosis should follow a strict step-by-step pathway, beginning with two absolutely mandatory criteria [9-11]:

a. A structural cause for coma must be identified. Comas of unknown origin are not suitable for BDD. Catastrophic brain damage, when demonstrated, supports the conclusion of irreversibility of such condition (e.g. massive brainstem haemorrhage).

b. Any situation that can simulate BD must be excluded.

The absence of external causes (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 related to the structural cause identified above (and not to another condition that can simulate the pattern). BD may also be simulated by neurologic special comas, such as minimally conscious states or persistent vegetative states. In such cases, the presence of any kind of motricity, spontaneous reactivity of the body or spontaneous breathing are key aspects for excluding BD. 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 and early period after cardio-respiratory arrest) – may be necessary. Rare cases of Guillain–Barré syndrome involving all peripheral and cranial nerves (potentially reversible) can mimic BD leading to a potential and dangerous diagnostic error if ancillary tests are not performed.

As the interpretation of a clinical examination is dependent on these two items and evidence of irreversibility is required for the final conclusion of BDD, it is recommended that physicians experienced in neurologic-critical situations perform this diagnosis. Many protocols recommend a team of two physicians: one intensivist (the attending physician), who can easily identify possible situations that exclude BD, and one neurologist or neurosurgeon or other intensivist from another ICU, who can help in assessing the impact of the detected structural injury and confirming the impossibility of reversal [12].

The clinical examination performed for BDD needs of a set of preconditions in which basic physiologic parameters allow, without any doubt, a correct interpretation of the clinical signs observed (see Chapter 5) [13]:

a. Haemodynamic stability (mean arterial blood pressure > 65 mmHg (> 8.7 kPa);

b. Euvolemia or positive fluid balance within the previous 6 h (to avoid immediate shock);

c. Absence of complicated metabolic conditions that may confound the clinical assessment (no severe electrolyte, acid-base or endocrine disturbance);

d. Core temperature > 35 °C (and < 38 °C). Brainstem reflexes disappear when core temperature drops below 28 °C. Moreover, the response to light is lost at core temperatures between 28 °C and 32 °C. All deficits are potentially reversible in a non-definite time frame. Long-term accidental hypothermia, alcohol, CNS-depressant drugs and head injury are confounders for wrong BDD. In situations of anoxic brain injury and to preserve neurologic function, the recently introduced therapeutic hypothermia (32 °C to 34 °C) can be a confounder for BD. No presence of CNS-depressant drugs and neuromuscular blocking agents: barbiturates, benzodiazepines, tricyclic anti-depressants (to name common clinically used drugs that affect arousal or movement reactions). 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, proposed by Wijdicks, 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 [9]. 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;

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. propofol and baclofen. An appropriate time for neurologic recovery should be allowed or confirmatory tests used to increase clinical certainty about the irreversibility of neurologic findings [14];

f. Other examples of pitfalls in BDD are: severe facial or high cervical trauma, pre-existing pupillary abnormalities, sleep apnoea or severe pulmonary disease resulting in chronic reten-

tion of CO_2. In these circumstances, confirmatory tests are recommended [13].

Irreversibility of brain function loss, in association with a known cause of death, is a key feature to establish BDD. In some cases, its demonstrability is obvious, e.g. massive haemorrhages, but it may be difficult in many other cases, e.g. in anoxic lesions following a cardiac arrest. Irreversibility has 3 factors requiring clinical judgment:

a. Cause of death must be sufficient, according to the physician's judgment, to be directly linked to the total brain destruction;

b. Reversible medical conditions known to depress brain function should not exist. Drugs, hypotension, hypothermia, ongoing hypoxia and severe endocrine disorders should be corrected or excluded. Nevertheless, if not excluded, they must be reversed before performing BDD. In certain cases, where some medical conditions cannot be totally reversed, BDD must be completed with confirmatory ancillary tests;

c. The absence of brain function should be confirmed during an observation period, the length of which depends on the physician's judgment in each specific case: shorter periods (e.g. less than 6 h) for an obvious brain physical destruction, longer periods (e.g. 12-24 h) when the cause is unclear, or in case of hypoxia or metabolic and toxic conditions, as well as in children. Confirmatory ancillary tests, mainly those demonstrating absence of brain perfusion, should be applied whenever there is a reasonable doubt for definitive BDD. These confirmatory tests, once performed, may shorten the observation period in some countries. On this issue, clear formal rules exist in each country based on a particular national consensus, which physicians must adhere to.

3.3.2. Clinical examination

The confirmation of BD through clinical examination is established by neurologic testing of patients in a coma which fulfils the above-mentioned preconditions (see section 3.3.1) and in whom there are no spontaneous breathing movements and no brainstem reflexes.

Neurologic tests should be performed when the best physiologic stable conditions (haemodynamic, metabolic, respiratory, and non-hypothermic) are provided, making possible a response from any living neurons. In case of an invalid BDD, these conditions mitigate the risk of further brain injuries. Therefore, the apnoea test should be the last to be performed, when the necessary rise in partial carbon dioxide pressure ($PaCO_2$) increases intra-cranial pressure with the risk of further brain damage [9, 11]. If any brainstem function reflex is positive, or if in any way there are reasonable doubts about the BDD, the apnoea test should not be performed. Also, in rare cases where brainstem reflexes are absent but breathing movements are detected, the apnoea test should be aborted immediatel, and controlled ventilation restarted.

It is recommended to ventilate the patient with FIO_2 100 % and adjust the ventilator to obtain normocapnia during 15-30 minutes before beginning brainstem physical tests.

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 can 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 nerves) [9]. 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 with 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) is 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 which are not possible in BD. The physical examination of brainstem reflexes is summarised in Table 3.1.

3.3.2.1.1. Photomotor reflex

In the Collaborative Study Criteria, dilated and fixed pupils were considered mandatory, because mid-position fixed pupils can be seen in cases of drug intoxication [13]. Nowadays, careful history and drug screening obtained before any BDD allows mid-position fixed pupils to be judged consistent with

BD 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 [11].

3.3.2.1.2. Corneal reflexes

In BD, 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.

3.3.2.1.3. Oculocephalic and oculovestibular reflexes

In oculocephalic reflexes, 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.

For oculovestibular reflexes, 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, the normal response consists of a deviation of one eye's axis, or both, which does not occur in BD. Stimulation of the opposite auditory canal should be performed with a 5-minute delay.

Assessment of one or both reflexes depends on the physician's judgment, but oculovestibular tests are more popular, mainly in trauma cases, where cervical sharp movements may aggravate subclinical cervical lesions difficult to detect.

3.3.2.1.4. Pharyngeal (nausea or gag) and cough reflexes

No response to tracheo-bronchial suctioning and no response after posterior pharynx stimulation with a tongue blade must be observed to confirm BD. No respiratory movements should occur at all during these procedures.

3.3.2.1.5. Facial sensation and facial motor responses

No response to central pain is also a key feature of BD. Painful stimulus on body somatic areas such as pressure on the nail bed of a finger, and in selected sensitive areas of the face like temporomandibular joint zones or the supraorbital nerves (at the supraorbital ridges), should not yield any reaction or grimacing.

It is always important to remember that any demonstration of arousal or awareness is not compatible with a BD state.

3.3.2.1.6. 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. Sometimes, these complications create barriers for completing the test, leading to the need for additional confirmatory studies. End-tidal carbon dioxide levels have been frequently documented as a surrogate for $paCO_2$. Prior to this test, the patient is pre-oxygenated with FIO_2 100 % for at least 5 minutes (peripheral oxygen saturation 100 %) 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 for no longer than 10 minutes, receives passive oxygenation with 6-12 L/min of O_2 through a tracheal tube, while careful observation of the chest is made for any respiratory efforts. 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 [15]. 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 when no efforts for respiration were observed. In some countries, it is recommended that the terminal $paCO_2$ is over ≥ 60 mmHg (≥ 8.0 kPa).

Once an apnoea test is performed for the diagnosis of BD and this is to be followed by organ procurement, disconnecting from the ventilator can be harmful for the lungs to be recovered because there may be immediate lung collapse, resulting in atelectasis. One alternative is the single recruitment manoeuvre performed immediately after the apnoea test: it may improve the paO_2/FIO_2 ratio and prevent the loss of potential lung donors [16]. Then, an approach could be to perform the apnoea test without ventilator disconnection using a continuous positive airway pressure mode: set up the mechanical ventilator to this mode and change the trigger to pressure instead of flow, with a defining positive end-expiratory pressure (PEEP) of 8-10 cmH_2O. It is important to set to 'Off' both the reserve ventilation of the ventilator and the alarms to avoid wrong conclusions (ventilator self-cycling can be confused with brainstem-mediated respiratory effort as a phenomenon of auto triggering) [17].

3.3.2.2. *Spinal reflexes*

Since BD means loss of the encephalic function, neurologic activity depending on spinal cord may persist and be detectable, either clinically or in laboratory tests. In BD, complex withdrawal movements originated in the spine are possible, and must be differentiated from seizures, decortication and decerebration posturing movements, that 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 BD, and its presence does not indeed alter the reliability of BDD. In one prospective study of cases with the diagnosis of BD 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 [12]. 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 (only ipsilaterally, and cannot be elicited in patients who were not BD) 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' [9]. Consistent clinical documentation of BD and confirmation by electro-encephalography (EEG) or cerebral angiography will give the final evidence for BD.

American Academy of Neurology protocol list of occasional phenomena that should not be misinterpreted as evidence for brainstem function [13]

- spontaneous movements of limbs other than pathologic flexion or extension response;
- respiratory-like movements (shoulder elevation and adduction, back arching, intercostals expansion without significant tidal volumes);
- sweating, blushing and tachycardia;
- 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.

3.3.2.3. *Atropine test*

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, even if rarely needed, there is no such effect, so no heart rate increase of more than 10 % should be observed.

3.3.3. Observation period

Since the initial Harvard study, all protocols mention the need for an observation period to confirm the initial diagnosis of BD. Initially, a 7-h period was thought necessary to be sure that the patient was stabilised, but due to recent advances, this period is frequently shortened. Nevertheless, it is better to confirm BDD over a period of time, mainly if the irreversibility of the damage responsible for brainstem function loss is not obvious; for instance, a brainstem gunshot bullet lesion has a devastating effect more evident than an anoxia lesion. Additional observations can help conclusions about the irreversibility of the lesions.

Most protocols adopt the need for an additional physical exam, but the length of the observation period is not fixed, and mostly depends on the physician's judgment. Some recommend from 6 up to 24 h, depending on the clinical data of each case. Based on national consensus, guidelines in the different countries recommend either repeating the clinical examination after an observation period depending upon the type of devastating cerebral lesion and other characteristics of the patient, and/or replacing the observation period by an appropriate ancillary test.

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 (BD). Neurologic examination should be clearly consistent with a clinical BD state on the basis of a strict validation of all the required criteria (see sections 3.3.1 and 3.3.2) before performing any complementary test. The choice for an ancillary study is a function of factors such as local facilities and 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 BD (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 cerebral blood flow (CBF) investigation in brain-dead patients. 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 [18, 19]. 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 BD, 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.

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 BDD. 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 mainly in Canada and the United States [18, 19].

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 BDD.

With or without radionuclide angiography, planar imaging continues to be the pillar for the scintigraphic confirmation of BD. 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 BD confirmation when using planar imaging without the use of specific brain tracers [20]. 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 BD confirmation) is near 100 % [21].

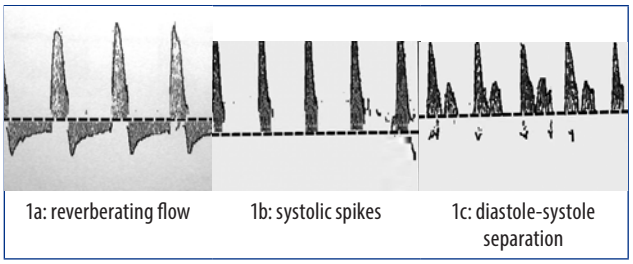
3.4.1.3. *Transcranial Doppler*

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 BD.

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). A complete TCD examination should include both the anterior (including internal carotid artery, middle cerebral artery and anterior cerebral arteries) and the posterior circulation. 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-h 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 different sonographic patterns compatible with a diagnosis of BD were considered: 1. a reverberant flow pattern; 2. a pattern of systolic

spikes; 3. a pattern of diastole–systole separation (see Figure 3.1) [22].

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



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.

The accuracy of TCD for the diagnosis of BD varies in the literature: in general, TCD sensitivity, according to the Subcommittee of the American Academy of Neurology, is between 91 % and 100 %, and specificity between 97 % and 100 %. In some studies, the non-exclusion of patients without air-tight cranium (external ventricular derivation, large craniotomies) probably contributes to a lower TCD accuracy: these patients are not suitable for TCD investigation [23]. 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 [24].

TCD is a non-invasive and easy-access technique at the bedside, which can be repeated. It has also the advantage of not being influenced by the effects of CNS-depressant agents. 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, is operator-dependent and is mainly performed by intensivists (unlike the other ancillary tests, performed by radiologists or electrophysiologists external to the ICU). 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 confirmative test. It is self-evident that, at a low blood pressure, 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 two-phase spiral (or helicoidal) computed tomographic angiography (CTA) could be useful in demonstrating a lack of intra-cerebral blood flow. This less invasive and more available test has progressively replaced the classic angiogram as a valuable alternative. According to the opacification or non-opacification of pericallosal arteries, cortical segments of the middle cerebral arteries, internal cerebral veins and the great cerebral vein, a 7-point CTA score was defined for this purpose [25]. A new 4-point score based on the lack of opacification of the middle cerebral arteries and internal cerebral veins has been recently recommended by the French Society of Neuroradiology. This score has been validated by a study showing a sensitivity of 85.7 %, a specificity of 100 % and a non-opacification of internal cerebral veins in 98.1 % of the 105 included patients [26]. This CT technique needs at least a multi-slice CT scanner with a strict method of image acquisition to be applied (specific parameters of the CT, modalities of the injection of the non-ionic contrast medium, control of the opacification of the superficial temporal arteries, acquisition times). However, a recent review of the technique concluded that the available evidence cannot support the use of CTA as a mandatory test for the diagnosis of BD (lack of evidence, small cohorts and false positive cases described, possibly due to inappropriate application of the technique). The conclusion was that 'CTA may be useful as a confirmatory or add-on test following a clinical diagnosis of death, assuming that clinicians are aware of the relatively low overall sensitivity' [27].

False negative results (opacification still present in clinically confirmed BD) 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 BD.

Both four-vessel angiography and CTA need the patient to be moved outside the ICU with a high risk during transfer when the haemodynamic conditions of the patient are unstable. As the cerebral perfusion loss is progressive, a delay of 4 to 6 h after the clinical diagnosis of BD is needed before confirming this state by a CBF test. When using a CTA, 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*

In the near future, magnetic resonance angiography could probably be a valuable test. The need for patient mobilisation and transfer to the radiology unit, along with the lack of proven superiority and

the technical constraints due to the material compatibility, limit its use for the purpose of BDD.

3.4.2. Electrophysiologic tests

3.4.2.1. *Electroencephalography*

Electroencephalography (EEG) is a conventional and valuable test for diagnosing BD 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 to perform EEG study for the diagnosis of BD were approved by the American Electroencephalographic Society [28]. It was 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), 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 low-frequency setting of 1 Hz. 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), can be pronounced 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 BD.

3.4.2.2. *Multimodal evoked potentials*

Using different techniques of evoked potentials, visual-auditory or somatosensory stimuli allows examination of the visual, auditory and somatosensory pathways at different levels of the CNS. Multimodal evoked potentials are able to attest to the pathway integrity, or otherwise, of its exclusive functional extension to the peripheral nervous system.

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. Evoked responses that demonstrate the spinal cord as the highest level of nerve-signal processing are compatible with BD

Table 3.2. **Advantages and disadvantages of ancillary tests available for the diagnosis of brain death**

	Advantages	Pitfalls and disadvantages
Electroencephalography	• Bedside	• Examination of supratentorial structures, but not infratentorial • Influenced by depressants of CNS
Transcranial Doppler	• Bedside • Can show cerebral circulatory arrest as a process • Can be repeated frequently • 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 • Appropriate blood pressure required
Angiography	• Not influenced by depressants of CNS	• 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 the ICU
Angio-scintigraphy	• 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 the ICU (except for portable gamma camera)
Computed Tomographic Angiography	• Not influenced by depressants of CNS	• False positive flow in cases of non-hermetic cranium (serious fractures of skull, decompressive craniectomy, cerebrospinal fluid drains) • Low sensitivity of this test for the diagnosis of BD • Need to move the patient out of the ICU (except for portable CT scan)
Multimodal evoked potentials	• Bedside • Less influenced by depressants of CNS than electro-encephalography	• Examination of few structures of CNS

(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. However, the accuracy of evoked potentials in the diagnosis of BD is still open to discussion, possibly due to lack of experience with the method outside of specialised centres.

3.4.3. Other tests

There are other instrumental tests (measurement of intracranial and cerebral perfusion pressure; decreases of cerebral consumption of oxygen etc.) described as useful add-on tools for BDD. However, their lack of accuracy makes them useless, since their role in BDD is not confirmed by appropriate studies.

3.4.4. Special circumstances

Ancillary tests, when used to confirm BD, 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 section 3.5).

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

The absence of cranial airtight skull induces changes in the normal balance of extra-cranial/intracranial pressure. As a consequence, tests exploring the CBF show a decrease in diagnostic accuracy, particularly in the following causes of persistent CBF in brain-dead patients [29]: a) infants with pliable skulls; b) decompressing fractures; c) ventricular shunts; d) ineffective deep brain flow; e) reperfusion; f) brain herniation; g) jugular reflux; h) emissary veins; and i) pressure injection artefacts. 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 BDD leads to false negative results. To avoid a delay in the diagnosis, the use of other tests such as EEG (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 [30]. Long-term infusion increases thiopental levels, which remain elevated for more than 6 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. Consequently, considering cases of isoelectric EEG due to the effect of drugs, the use of techniques such as those 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 BD. CBF studies are not influenced by confounders such as hypothermia or sedative agents, unlike EEG. In the case of non-airtight cranium, it is better to use an EEG to confirm the clinical diagnosis of BD. When available, four-vessel angiography, radionuclide CBF testing, TCD, CTA and EEG are currently the most widely used and recognised, with a legal value to confirm BD. Choosing one test over another requires a good knowledge of the advantages and limitations of each test and also of their technical requirements (see Table 3.2). 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 BDD process has been validated beyond doubt.

3.5. Brain death diagnosis in infants and children

Determination of BD 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 BD lack sufficient accuracy and confidence to be appropriately applied. In some countries, the BD concept is only considered after 2 months of life. Available recommendations refer mainly to the recently updated American Guidelines

for the Determination of Brain Death in Infants and Children from 2011 [31].

Where the clinical preconditions and conditions required in newborns, infants and children are different from adult care, specificities have to be considered according to the brain immaturity. More caution of the observational period is needed. There is a general consensus of the need for two clinical examinations including apnoea testing performed by two different attending physicians, with an inter-examination period ranging from 12-24 h to 24-48 h. This observation period is based upon the patient age:

a. 24 (to 48 h) for term newborns (37 weeks gestational age) to 1 month (to 2 months) of age;
b. 12 (to 24 h) for infants and children > 1 month (or 2 months) of age;
c. Depending on the country, after 1 month (United States) or 2 months (United Kingdom) or 1 year (France, Italy, Canada) or 2 years (Spain) of age, adult rules for BD diagnosis can be applied;
d. In case of hypoxic-ischaemic encephalopathy, this period should be longer;
e. Apnoea testing requires documentation of a 20 mmHg (2.67 kPa) increase of the baseline arterial $paCO_2$ and terminal $paCO_2 \geq 60$ mmHg (≥ 8.00 kPa)).

When ancillary tests, not legally required in the brainstem death concept, are performed, the observation period may be shortened, but this does not replace the need for repeated clinical tests. EEG and radionuclide CBF testing are the most frequently used ancillary tests. CTA is not validated in infants and children. In countries where whole-brain death concept is applied, EEG is the most frequently ancillary test used. In this case, two EEGs are often required together with 2 clinical examinations. A common waiting period of 24 h before repeating the EEG or radionuclide CBF (radiotracer clearance) is recommended. EEG should respect the standards established by the American Electroencephalographic Society [32]. Other ancillary tests (CTA, somatosensory evoked potential studies, MRI-magnetic resonance angiography, perfusion MRI) lack sufficient data for the purpose of BDD in infants and children.

The second clinical examination and apnoea test should be performed, and components that can be completed must remain consistent with BD.

Whereas the concept of BD is recognised worldwide, large differences exist between countries (even between regions in the same country) when considering BD in infants and children. An effort should be made in the near future to construct national/international guidelines of best practices by the paediatric scientific societies involved.

3.6. Implications of brain death diagnosis

Once a BD 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 BD. In most countries, an independent committee of specialists who perform the tests and finally sign the certificate is requested for BD 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 BD declaration, any legal and mourning procedures including autopsy and funeral can be performed and last wills can be probated.

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

This approach is of paramount importance for implications of BD declaration that cannot be influenced by the significant differences in procedures for death certification among European countries [33], particularly when BD 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 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 BD coming from relatives and professionals, taking into consideration the personal and psychological concerns of critical care personnel, and clarifying roles and responsibilities in BD determination and *post-mortem* procedures.

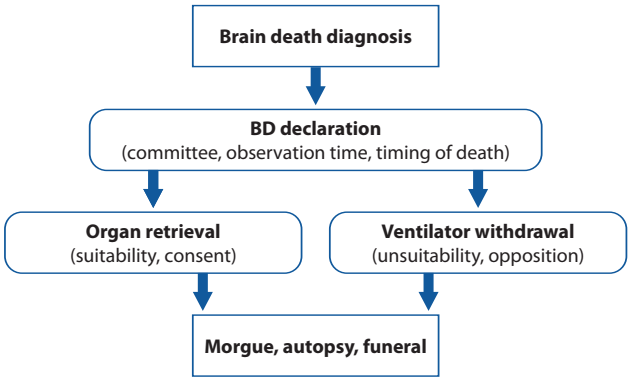
Nevertheless, some patients who fulfil BD criteria but present absolute contraindications or opposition to organ donation are not promptly disconnected from ventilation after BD declaration; death may thus follow by spontaneous circulatory arrest hours or days later. Surprisingly, this confusing situation is still seen, because of either family opposition or physicians' attitudes that reflect doubts about BD as real death [34]. In the case of donation refusal after BD 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 BD 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 BD implications: the public needs to fully understand that the declaration of death cannot be the family's decision and that BD 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 to integrate the concept of BD, 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 [35].

BD in a pregnant woman is an exception: intensive support can be prolonged after BD for days and weeks, after ethical approval and family request, to allow adequate foetal maturity prior to delivery and organ donation [36]. 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 [37].

Only a few national laws (in 7 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 BD 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 BD 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 BD. In these cases, brainstem reflexes or apnoea may not be tested or documented [38]. An audit of all deaths in British ICUs showed that brainstem tests had not been performed in more than 30 % of persons in a likely BD condition [39].

Figure 3.2. **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 support to death determination, unambiguous procedures regarding all the possible implications of BD declaration and a clear indication about the time of death (see Figure 3.2). 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 part of end-of-life care in ICUs [40].

Social confidence in BDD and family trust in the dead donor rule would benefit from BD declaration in all subjects who fulfil BD 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.

In conclusion, this chapter provides technical guidance on many aspects of death certified by neurologic criteria. Each donor co-ordinator 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, varying to some extent according to the specific situation in each country.

3.7. References

1. Machado C, Korein J, Ferrer Y *et al.* The Declaration of Sydney on human death. *J Med Ethics* 2007; (33): 699-703.
2. Diagnosis of brain death: statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 11 October 1976. *Br Med J* 1976; (2): 1187-8.
3. Dopki Guideline for quality programmes in organ donation [available from: www.ont.es/internacional/Documents/DOPKI.pdf, accessed: 30 January 2016].
4. Wesslau C, Grosse K, Krüger R *et al.* How large is the organ donor potential in Germany? Results of an analysis of data collected on deceased with primary and secondary brain damage in intensive care unit from 2002 to 2005. *Transpl Int* 2007;(20):147-55.
5. Kramer AH, Zygun DA, Doig CJ *et al.* Incidence of neurologic death among patients with brain injury: a cohort study in a Canadian health region. *CMAJ* 2013; (185): E838-E845.
6. Sprung CL, Cohen SL, Sjokvist P *et al.* The Ethicus Study. End-of-life practices in European intensive care units. *JAMA* 2003; (290): 790-7.
7. Achieving Comprehensive Coordination in Organ Donation throughout the European Union–Accord Joint Action [project website: www.accord-ja.eu, accessed: 30 January 2016].
8. Matesanz R, Coll E, Domínguez-Gil B *et al.* Benchmarking in the process of donation after brain death: a methodology to identify best performer hospitals. *Am J Transplant* 2012; (12): 2498-506.
9. Wijdicks EFM. The diagnosis of brain death. *N Engl J Med* 2001; 344 (16): 1215-21.
10. Gardiner D, Shemie S, Manara A *et al.* International perspective on the diagnosis of death. *Br J Anaesth* 2012; 108 (S1): i14-i28.
11. Domínguez-Roldán JM, Procaccio F, Villar-Gallardo J *et al.* Diagnosis of death by neurologic criteria (brain death). In: Valero R, editor, *Transplant coordination manual*. Barcelona: TPM-DTI Foundation; 2014: 155-80.
12. Setzer N. Brain death: physiologic definitions. *Crit Care Clin* 1985; (1): 375-96.
13. Practice parameters: determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1995; (45): 1012-14.
14. Rady MY, Verheijde JL. Determining brain death after therapeutic hypothermia on nonpulsatile continuous-flow mechanical circulatory support devices. *J Cardiothorac Vasc Anesth* 2013; (27): e8-e9.
15. Henry NR, Marshall SG. Apnea testing: the effects of insufflation catheter size and flow on pressure and volume in a test lung. *Respir Care* 2014; (59): 406-10.
16. Paries M, Boccheciampe N, Raux M *et al.* Benefit of a single recruitment maneuver after an apnea test for the diagnosis of brain death. *Crit Care* 2012; (16): R116.
17. Dodd-Sullivan R, Quirin J, Newhart J. Ventilator autotriggering: a caution in brain death diagnosis. *Prog Transplant* 2011; (21): 152-5.
18. Practice parameters: determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1995; (45): 1012-14.
19. Canadian Neurocritical Care Group. Guidelines for the diagnosis of brain death. *Can J Neurol Sci* 1999; (26): 64-6.
20. Flowers WM Jr, Patel BR. Radionuclide angiography as a confirmatory test for brain death: a review of 229 studies in 219 patients. *South Med J* 1997; (90): 1091-6.
21. Sinha P, Conrad GR. Scintigraphic confirmation of brain death. *Semin Nucl Med* 2012; (42): 27-32.
22. Ducrocq X, Hassler W, Moritake K *et al.* Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography: Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. *J Neurol Sci* 1998; (159): 145-50.
23. Poularas J, Karakitsos D, Kouraklis G *et al.* Comparison between transcranial color Doppler ultrasonography and angiography in the confirmation of brain death. *Transplant Proc* 2006; (38): 1213-17.
24. Domínguez-Roldán JM, Jiménez-González PI, García-Alfaro C *et al.* Diagnosis of brain death by transcranial Doppler sonography: solutions for cases of difficult sonic windows. *Transplant Proc* 2004; (36): 2896-7.
25. Dupas B, Gayet-Delacroix M, Villers D *et al.* Diagnosis of brain death using two-phase spiral CT. *AJNR Am J Neuroradiol* 1998; (19): 641-7.
26. Frampas E, Videcoq M, de Kerviler E *et al.* CT angiography for brain death diagnosis. *AJNR Am J Neuroradiol* 2009; (30): 1566-70.
27. Taylor T, Dineen RA, Gardiner DC *et al.* Computed tomography (CT) angiography for confirmation of

the clinical diagnosis of brain death. *Cochrane Database Syst Rev* 2014; (3): CD009694.

28. American Electroencephalographic Society. Minimum technical standards for EEG recording in suspected cerebral death. Guidelines in EEG. *J Clin Neurophysiol* 1994; (11): 10.
29. Flowers WM Jr, Patel BR. Persistence of cerebral blood flow after brain death. *South Med J* 2000; (93): 364-70.
30. Huynh F, Mabasa VH, Ensom MH. A critical review: does thiopental continuous infusion warrant therapeutic drug monitoring in the critical care population? *Ther Drug Monit* 2009; (31): 153-69.
31. Nakagawa TA, Ashwal S, Mathur M *et al;* Society of Critical Care Medicine, Section on Critical Care and Section on Neurology of American Academy of Pediatrics, Child Neurology Society. Clinical report – Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. *Pediatrics* 2011; (128): e720-e740.
32. American Electroencephalographic Society. Minimum technical standards for pediatric electroencephalography. Guidelines in EEG. *J Clin Neurophysiol* 1986; 3 (2): 139-43.
33. Haupt WF, Rudolf J. European brain death codes: a comparison of national guidelines. *J Neurol* 1999; (246): 432-7.
34. Escudero D, Valentin M, Escalante JL *et al.* Intensive care practices in brain death diagnosis and organ donation. *Anaesthesia* 2015; (70): 1130-9.
35. Magnus DC, Wilfond BS, Caplan AL. Accepting brain death. *N Engl J Med* 2014; (370): 891-4.
36. Shewmon DA. The brain and somatic integration: insights into the standard biological rationale for equating 'brain death' with death. *J Med Philos* 2001; (26): 457-78.
37. Lane A, Westbrook A, Grady D *et al.* Maternal brain death: medical, ethical and legal issues. *Intensive Care Med* 2004; (30): 1484-6.
38. Murphy PG, Smith M. Towards a framework for organ donation in the UK. *Br J Anaesth* 2012; 108 (Suppl 1): i56-i67.
39. Barber K, Falvey S, Hamilton C *et al.* Potential for organ donation in the UK: audit of intensive care records. *Br Med J* 2006; (332): 1124-7.
40. Sprung CL, Truog RD, Curtis JR *et al.* Seeking worldwide professional consensus on the principles of end-of-life care in critical ill (WELPICUS Study). *Am J Respir Crit Med* 2014; (190): 855-66.

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

4.1. Introduction

The deceased donation of organs and tissues saves lives, or significantly improves the quality of life, of patients on the transplant waiting list. However, before procurement can take place, consent to, or authorisation of, donation is needed, given either by the donor while alive (e.g. organ donor registry, organ donor card, 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 recovery 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 undertaken 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, in which consent to donation has to be obtained explicitly from the donor or an authorised individual (usually the next of kin); and an opting-out system, in which donation can take place if the prospective donor while still alive registered no objection to donation. In practice, operational variations exist with both systems, because the family still plays a prominent role in the decision-making process.

Table 4.1 gives an overview of the different national consent systems in Europe. The information is reproduced from a survey undertaken by the European Commission in August 2014 (Directive 2010/53/EU Implementation Survey). From the 29 answering countries, it appears that the majority (18 countries) have an 'opting-out' system, while seven countries reported an 'opting-in' system and four 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), while Wales introduced an 'opting-out' system from

December 2015. Other countries combine elements of both 'opting-in' and 'opting-out' systems.

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 to help make clear their willingness or refusal to donate organs after death. People who have donor cards are also often simultaneously recorded in the national donor consent registry. In the Netherlands for instance the most recent valid 'will' is written on a card or registered in the donor registry. In some countries, consent to donation recorded on a donor card contains detailed information, e.g. consent to various 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 after death.

There is no knowledge of donor cards being used to record an objection to donation. National legislation or operational policies will therefore need to be 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 in relation to organ donation. All national systems should

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

Country	National consent system	Donor registry	Non-donor registry
Austria	opting-out		✓
Belgium	opting-out	✓	✓
Bulgaria	opting-out		✓
Croatia	opting-out		✓
Cyprus	opting-in	✓	
Czech Republic	opting-out		✓
Denmark	opting-in	✓	✓
Germany	opting-in, other*		
Estonia	mixed system	✓	✓
Finland	opting-out		
France	opting-out		✓
Greece	opting-out		✓
Hungary	opting-out		✓
Ireland	opting-in		
Italy	mixed system	✓	✓
Latvia	opting-out	✓	✓
Lithuania	opting-in	✓	
Luxemburg	opting-out		
Malta	opting out		
The Netherlands	opting-in	✓	✓
Norway	opting-out		
Poland	opting-out		✓
Portugal	opting-out		✓
Romania	opting-in	✓	
Slovakia	opting-out		✓
Slovenia	opting-out	✓	✓
Spain	opting-out	✓**	✓**
Sweden	mixed system	✓	✓
United Kingdom	mixed system	✓	✓

Notes: *"other" in survey; –"opting-in" according to personal information. – **Advanced Directive registry allows for registering willingness to donate or not to donate organs after death.
European Commission's Implementation Survey regarding Directive 2010/53/EU, status: October 2015.

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 should an enquiry from a doctor or a donor co-ordinator involved in the donation process be received.

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 minors, 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 could 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 organ recovery needs to be given by a coroner, judge or family court, for example when death occurs in suspicious circumstances or as a result 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 may be absent or it is impossible to contact them, national procedures should enable organ and tissue recovery 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 *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 before the actual donation

Consent for organ donation should be documented [4]. The method of documenting and record-keeping should be described in a hospital quality system in accordance with national rules (see Chapter 15).

4.2.5. Consent to deceased donation from non-residents

With increasing global mobility, the number of deaths of persons not residing permanently or temporarily 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 and behavioural 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. However, where possible, the country of origin of the potential donor should be consulted – through, for example, the competent authority or embassy – in order to follow properly the rules that apply there and to establish 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), filled in 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.

4.3. Approaching the families of potential organ donors

4.3.1. Understanding family reactions to bad news

The death (or ominous prognosis) of a potential donor is often sudden and unexpected. Clinical staff need 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 [5, 6, 7].

4.3.2. Planning the approach

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. The

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 [7].

The team should determine:

a. The clinical issues to be clarified (discussed in further detail below).
b. Any evidence of consent – such as registration on the national registry.
c. The next of kin or key family members to be involved.
d. Specific family or faith issues to be taken into account.

4.3.3. Confirming understanding

Most intensive care clinicians will not have received specific training in approaching families of potential donors. Although the available evidence is conflicting, consent rates might be higher when donor co-ordinators are involved in family discussions [8].

The donor co-ordinator should first ensure that the family understands what is meant by death as determined by either neurological criteria or circulatory criteria. Where appropriate, donor co-ordinators will need to ensure that the family understands clearly the process of withdrawal of treatment when further treatment is deemed futile.

Only once the donor co-ordinator is certain that the family understands that the patient has died – or that death is inevitable – should organ donation be discussed.

4.3.3.1. *Family approach after brain death*

Irrespective of the consent system for organ donation, and practical differences across countries [9], a conversation with the family of the potential DBD donor is required to convey information about brain death and the potential for organ donation [5].

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

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 (the concept of 'brain death' and other aspects of death and donation) in a manner adapted to interlocutors;
d. inform relatives about the potential of donation;
e. establish the wishes of the deceased about organ donation;
f. obtain information from relatives on medical and social history (e.g. operations performed, addictions, etc.) and risk behaviour;
g. obtain family consent or support for organ donation.

4.3.3.2. *Family approach in controlled donation after circulatory death*

The decision to withdraw life-sustaining treatment 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 to discontinue futile therapy is undertaken in a transparent, consistent manner and independently of the intentions and plans for organ donation [10-13]. This eliminates any conflict of interest. No investigation focused on organ donation (including consent) can take place before a decision on cessation of treatment has been taken. However, it may not always be possible to completely separate discussions about treatment withdrawal and donation, when 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 the withdrawal of life-sustaining treatment must come first, before any discussion of organ donation.

Although cDCD cases naturally have to meet the same general donation principles with regard to consent, there are some differences and specificities of donation before death occurs. For example, some countries allow specific interventions to optimise the potential for organ donation, such as checking whether the potential donor was on a national organ donor registry or carried a donor card. Other countries accept maintainance of vital functions (circulation and ventilation) and delay withdrawal of therapy, providing it does not expose the patient to harm and distress, and regard this practice as in the best interest of the patient if he wished to be a donor [11]. On the same grounds, some countries allow *pre-mortem* interventions (cannulation of vessels, heparinisation) targeted to improve organ viability, provided that specific informed consent is granted and also that harm and distress is avoided to the potential donor and next of kin [10]. This will usually take place when the patient is unconscious and under artificial support. In many cases, the patient's will may not be known. Relevant information, such as whether the patient expressed his opinion on organ donation after death, should be obtained from registries or from the next of kin.

It is vital that the family be fully involved in discussions about the cDCD process including the following.

a. The location where the withdrawal of treatment will be carried out.

b. How organs are removed when the heart stops after withdrawal of mechanical ventilation and/or terminal extubation.

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

d. The possibility that the person will not die within a time frame consistent with organ recovery (the family should be assured that if that happens all the healthcare at the end of life will be provided and tissue donation will still be possible following death).

e. That the family can remain with the dying patient and privacy will be provided.

Table 4.2. **Information necessary in an enquiry form concerning the possibility of 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

4.3.3.3. *Family approach in uncontrolled donation after circulatory death*

General rules of consent for uDCD are similar to those of DBD, applied according to national regulations (see). 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 to DBD [14].

There are some interventions to optimise the potential for uDCD that are subject to legal, medical and ethical considerations in different countries. These include the cannulation of large vessels and the establishment of *in situ* preservation strategies that may need to be initiated before obtaining consent to donation. This procedure is allowed in some countries where there is an individual's consent record in the donor registry (the Netherlands) and in some countries where there is no record in the registry of an objection to donation – if such registry is the only way to express an objection (France). In other national systems, starting cannulation and body perfusion before consent to donation after death is considered lawful (Poland, Spain, United Kingdom). Obviously, cannulation is not acceptable where there is a known register of an individual's objection to organ donation. Organ recovery never proceeds before consent is established or obtained.

4.3.4. Family approach in tissue donation

Conversations with family on planned organ and tissue donation (DBD and DCD) do not generally differ from these related to organ donation described above (see *Guide to the quality and safety of tissues and cells for human application* for tissue-specific guidance). Therefore it is best practice to perform interviews about the donation of organs and tissues within one interview session with the family.

The experience of interviews with families suggests that some difficulties and possible opposition may occur in procurement of tissues from 'visible places' like skin, bone and, in particular, eyes when family members fear disfigurement of the body. In these situations, special emphasis should be put on the legal and medical obligations to respect the body appearance. If necessary, some technical aspects of procurement should be explained, for example the use of specific surgical incisions and sutures, or suitable prostheses or artificial eyes or bones.

Tissue donation could be carried out by interviewing the family by phone. Such phone interviews would need to ensure that the conversation takes place in the relative's private space, not in 'unfamiliar' hospital surroundings. Telephone conversations can make it more difficult to offer reassurance and support to family because there is no opportunity to demonstrate personal touch and this can increase emotional distance.

Authorisation for the recovery of tissues for research requires strict adherence to the research study protocol. Such considerations should not be in conflict with approaching the family about organ or tissue donation and it must be independent from conversations about donation for transplantation purposes.

4.4. Conversation with family members

Communication with family members of the deceased may require multiple conversations by professional staff. The strategy must be to avoid unnecessary harm or distress. It is best practice to establish a stable relationship between family members and medical staff before the subject of organ donation is introduced.

A Six-Step Protocol for Delivering Bad News (SPIKES) may be adapted from general medicine to approaching the family before donation [15]. It divides the task of breaking 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 Table 4.3).

Table 4.3. **A Six-Step Protocol for Delivering Bad News**

Breaking the bad news into steps	
S	Setting. Pick a private location.
P	Perception. Find out how the family views the (brain) death and the planned organ donation.
I	Invitation. Ask whether and how much the family wants to know.
K	Knowledge. Warn before disclosing bad news.
E	Emotions. Respond to the family's emotions using empathy and validation.
S	Strategy/Summary. Once they know, include family's acceptance of donation.

Source: SPIKES (adapted) [15].

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 or religious practices. This should be explained to the other family members.

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 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 champion a favourable attitude towards donation, not 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 [16-18]. The place of conversation should help facilitate 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 the family with a quiet room, where they can speak freely. It is also advisable to have resources that meet the minimum needs (telephone, handkerchiefs, water, some food).

Table 4.4. **Family and donor relatives' reactions to bad news in relation to grief**

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 of 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 to make decisions).
Denials and displacement	These reactions are associated with lack of acceptance of an irreversible loss. Observed statements include 'It's impossible', 'It is not true', 'How could he have died, as he is breathing?' or 'You've made a mistake'. Relatives use denial as 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 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 mourning, relatives intensively look for an explanation of the reasons of death and may accuse medical staff. These reactions of the family, especially claims or allegations against a doctor, are difficult to deal with. If the doctor perceives them as threatening and tries to defend himself, then it may be seen as confirmation of guilt. This should not be taken personally by the doctor 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 medical 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 one, it is necessary to find someone responsible for what has happened.

Grief reactions	Remarks
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 tend 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, so as 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 the medical staff. They ask only a few questions. In comparison with a reaction of denial or anger, such a 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.

The person conducting the conversation with the family can meet with different emotional reactions, which are characteristic of people in grief (see Table 4.4). It is very important to understand the possible reactions connected with mourning. For conversation about the potential organ donation, it is essential to establish good contact with the deceased's relatives. The donor co-ordinator is responsible for adjusting the conversation to the family's needs and expectations. This can be summarised by the term 'establishing a therapeutic relationship'.

The doctor or donor co-ordinator who is conducting the conversation with the relatives should respect their grieving. This type of conversation requires interpersonal skills, sensitivity and empathy. In situations when there is a huge pressure on medical staff, conversation with families can become difficult, rushed or insensitive.

Conversation about organ donation aims to fulfil the will of the deceased donor 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 to continue with the recovery without the support of the family and risk damaging the emotional health of the relatives, incurring possible bad publicity and a loss of public confidence in the organ donation programme, or to follow the wishes of the deceased and continue with the donation.

It might be helpful to use the following when discussing 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 concerning organ donation, discuss whether the deceased helped people generally e.g. as a blood donor or giver to charity, and how donation could help many people to benefit from a transplant.

c. Should families be concerned that the body will be disfigured, reassure them that the deceased's body will be fully respected.

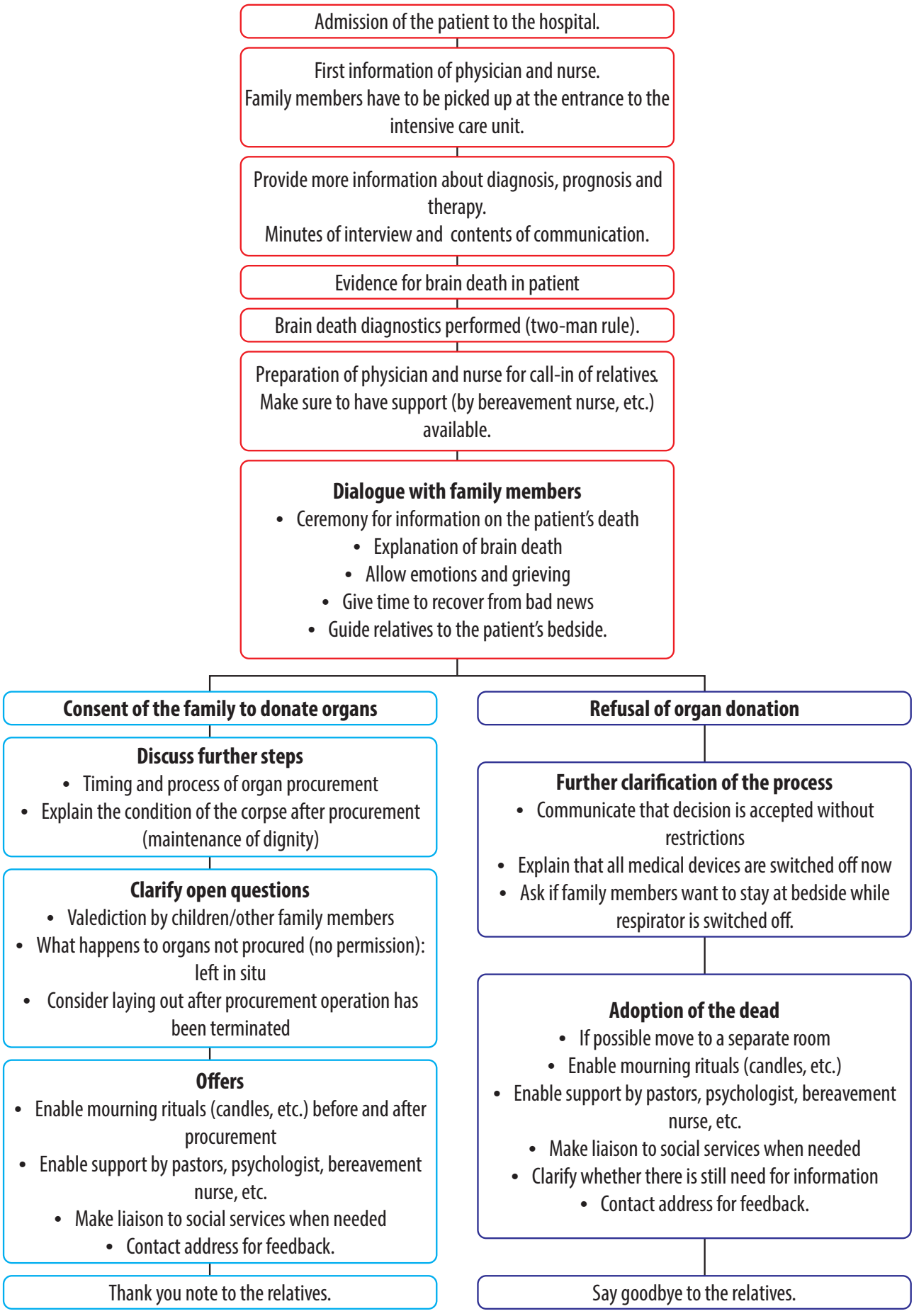
d. In a case of religious concerns, offer a consultation with a religious leader or representatives.

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 which come to light when a person has died. In this case, try to separate the conflict from the issue of organ donation.

Figure 4.1. **Standardised sequence of dialogue with family members**



Source: adapted from Swisstransplant: Family care and communication, Bern 2014 [19].

Table 4.5. **Aspects to consider in communication with the donor's family members**

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 are the leads in the family network. Explain clearly to the other family members that the intention is to talk first with the key persons responsible in order 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 persons 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 for saying farewell. It is important to provide the family with a quiet room, where they can speak freely and unobserved. They should be provided with the minimum needs (e.g. telephone, handkerchiefs, water, and food).
Establishing good contact	Persons conducting conversations with families will encounter different emotional reactions (see Table 4.4). 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 to donation	The conversation about organ donation aims to fulfil the will of the deceased donor and obtain acceptance of the family for donation. Regardless of the legal position, acceptance of organ donation by relatives has to be agreed, and this must not be achieved under pressure. Neither financial nor any material benefit can be offered, nor can donation be conditional on the deceased donation being directed to a particular recipient or group of recipients.
Family refusal	The family has the right to express its opinion about organ donation, but the will of the deceased, expressed during life, should be respected if possible. However, in certain circumstances it is better to stop the donation process than to cause conflict within the family.

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 handprints. 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 Swisstransplant [19].

Table 4.5 summarises some key aspects to consider during communication with donor family members.

4.5. Communication training for professionals

The training of professionals – doctors, nurses, co-ordinators and staff from the ICU: all those involved in family interviews, communication of bad news and organ donation – is essential. Their skills in verbal and non-verbal interpersonal communication are vital to establish a relationship with the family. It is also important for the professionals involved to receive specific training in order to avoid the emotional overload that this type of work may induce. It is recommended that hospital quality systems in organ donation should promote specific training of professionals in critical care units through continuing professional education (see Chapter 15).

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.

4.6. Conclusion

The sudden death of a family member is associated with profound sadness, insecurity and anxiety. This makes communication with the families difficult for doctors and nurses. In addition to medical expertise, key social and emotional skills are required. This chapter has set out the key mechanisms for establishing consent for organ and tissue donation and for communicating with families. It also recognises the specific skills required to address the issues raised by families.

4.7. References

1. WHO Guiding Principles On Human Cell, Tissue and Organ Transplantation. Available at: www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf. Accessed: 24 February 2016.

2. Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin. Available at: http://conventions.coe.int/treaty/en/Treaties/Html/186.htm. Accessed: 30 January 2016.
3. Rosenblum AM, Li AH, Roels L, Stewart B, Prakash V, Beitel J, et al. Worldwide variability in deceased organ donation registries. *Transpl Int* 2012; 25: 801-811.
4. Odequs. Project website: www.odequs.eu. Accessed: 30 January 2016.
5. Valero R, ed. Transplant Coordination Manual. 3rd edition. Aguiló grafic. Barcelona 2014. ISBN: 978-84-616-8840-1.
6. Good Practice Guidelines in the process of Organ Donation. Organización Nacional de Trasplantes. Madrid, 2011. Available at: www.ont.es/publicaciones/Paginas/Publicaciones.aspx. Accessed: 30 January 2016.
7. NICE. Organ donation for transplantation. Improving donor identification and consent rates for deceased organ donation. 2011. Available at: www.bts.org.uk/Documents/Publications. Accessed: 30 January 2016.
8. Danbury C, Barber V, Collett D, Jenkins B, Morgan K, Morgan L, et al. Effect of "collaborative requesting" on consent rate for organ donation: randomised controlled trial (ACRE trial). BMJ 2009; 339: 899–901.
9. Jansen NE, Mc Donald M, Haase-Kromwijk B, Sque M, Long-Sutehall T. When are bereaved family members approached for consent to donation? Commentary from ten European member states. Organs, Tissues & Cells 2014; 17: 101-112.
10. Donation after circulatory death in Spain: current situation and recommendations. National consensus document 2012 (in Spanish). Available at: www.ont.es/infesp/Paginas/DocumentosdeConsenso.aspx. Accessed: 30 January 2016.
11. Donation after Circulatory Death. British Transplant Society. Available at: www.bts.org.uk/Documents/Guidelines. Accessed: 30 January 2016.
12. National recommendations for donation after circulatory death in Canada. CMAJ 2006; 175: S1-S24.
13. Bernat JL, D'Alessandro AM, Port FK, Bleck TP, Heard SO, Medina J, et al. Report of a National Conference on Donation after cardiac death. Am J Transplant. 2006; 6: 281-291.
14. Andrés A, Morales E, Vázquez S, Cebrian MP, Nuño E, Ortuño T, et al. Lower rate of family refusal for organ donation in non-heart-beating versus brain-dead donors. Transplant Proc 2009; 41: 2304-2305.
15. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES - A Six-Step Protocol for Delivering Bad News. Oncologist 2000; 5: 302-311.
16. Haddow G. Donor and nondonor families' accounts of communication and relations with healthcare professionals. Prog Transplant 2004; 14:41-48.
17. Jacoby LH, Breitkopf CR, Pease EA. A qualitative examination of the needs of families faced with the option of organ donation. Dimens Crit Care Nurs 2005; 24: 183-189.
18. Sanner MA.Two perspectives on organ donation: experiences of potential donor families and intensive care physicians of the same event. J Crit Care 2007; 22: 296-304.
19. Swisstransplant and Comité National du don d'organes: The Swiss Donation Pathway, Modul V, Familienbetreuung und Kommunikation. Swisstransplant and Comité National du don d'organes, Berne, 2014. Available at www.swisstransplant.org/fileadmin/user_upload/Infos_und_Material/Swiss_Donation_Pathway/SDP_modul_5_Familie_Kommunikation_DE_2014.pdf (in German). Accessed: 24 February 2016.

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 which 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 BD. ADM protocols result in increased rates of organs recovered per donor [1]. Therefore ADM is an essential component of the process of donation after BD. 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 recovery, 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 BD, providing continuous protection to any tissue or organ.

5.2. Pathophysiological changes induced by brain death

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

BD 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 chemoreceptors and the hypothalamic-pituitary axis. The pathophysiological changes evolve in two successive phases:

a. The agonic phase occurring just before BD, a stage which is characterised by a catecholamine surge (autonomic storm) responsible for transient episodes of tachycardia-tachyarrhythmias and hypertension: a physiological response to maintain cerebral and coronary perfusion, associated with redistribution of regional blood flow, increased afterload, and visceral ischaemia/injury. This stage is followed by:

b. The cessation of central regulatory mechanisms as soon as residual brainstem 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 [9]:

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-resuscitated cardiac arrest shock 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.

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

Basic parameters	Target range (adults)
Central body temperature	35 °C to 38 °C
Mean arterial pressure (MAP)	60-110 mmHg
Heart rate*	70-100/min*
Urine output	> 0.5 to 1 mL/kg/h
Central venous pressure (CVP)	4-12 mmHg (4-8 mmHg in potential lung donors)
Peripheral arterial oxygen saturation (SaO_2)	> 95 %
Arterial blood gas, pH	7.3-7.5
Na	135-145 mmol/L
K	3.5-5 mmol/L
Blood glucose	< 150 mg/dL (8.3 mmol/L)
Calcium level	Normal range
Haemoglobin/Haematocrit	≥ 7-9 g/dL (≥ 4.4-5.6 mmol/L) / ≥ 20-30% (≥ 0.2-0.3)
Platelets	> 50 G/L
Prothrombin time/partial thromboplastin time	within acceptable range to avoiding bleeding†

Notes: *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.

These complications should be dealt with early and aggressively, as the number of organs recovered 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 BD 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 need 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 [9].

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.

Basic monitoring should include:

a. echocardiogram;
b. pulse oximetry.
c. invasive arterial pressure measurement;
d. central venous pressure measurement;
e. core temperature measurement;
f. urinary output.

Additional parameters (see Table 5.2) should also be monitored in haemodynamically unstable donors and in thoracic organ donors, 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.

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

5.4. Specific critical complications

5.4.1. Hypotension due to hypovolaemia and fluid replacement

Hypovolemia, absolute or relative, is frequent in BD because of cessation of central stimulation of the vascular bed and up-regulation of pro-inflammatory 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 BD, 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 acidosis 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 BD kidney donors. The European Society of Intensive Care Medicine recommends colloids not to be used in patients with head injury, and gelatins and hydroxyethyl starch not to be administered in organ donors [10-12]. This issue is currently the focus of considerable debate; several ongoing trials are likely to provide new data in the very near future.

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 a central venous pressure (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 [13]. Thus, implementing an intensive donor-treatment protocol focused on increasing lung retrieval does not have a negative impact on the retrieval rates of other grafts or on early survival of heart, liver, pancreas or kidney recipients.

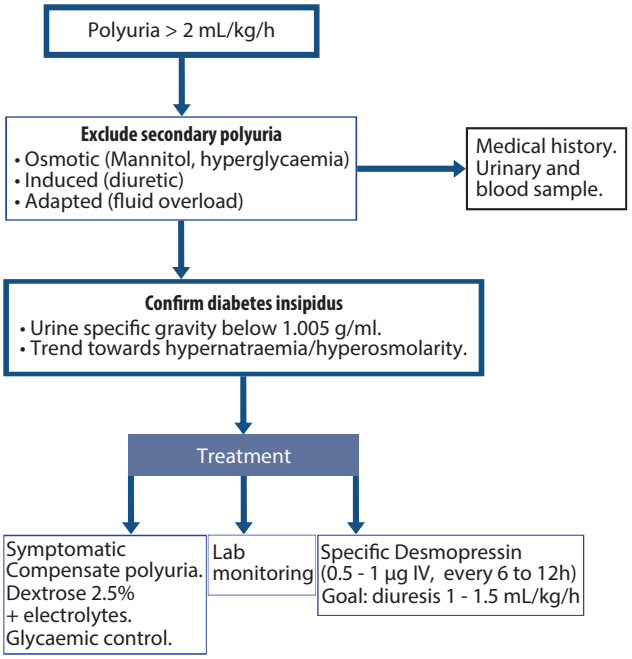
5.4.2. Central diabetes insipidus and endocrine management

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 [14]. 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, 15, 16].

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 [14].

Treatment of central diabetes insipidus (see also Figure 5.1) includes the following steps [15]:

a. ADH 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 through nasogastric tube and i.v. infusion. 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, 16].

Especially in haemodynamically unstable donors, methylprednisolone should be administered immediately after BD 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 BD 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) [17-20]. Early substitutive administration of glucocorticoids in a potential BD 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 [21]. 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 70-100 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 7-10 mmHg.

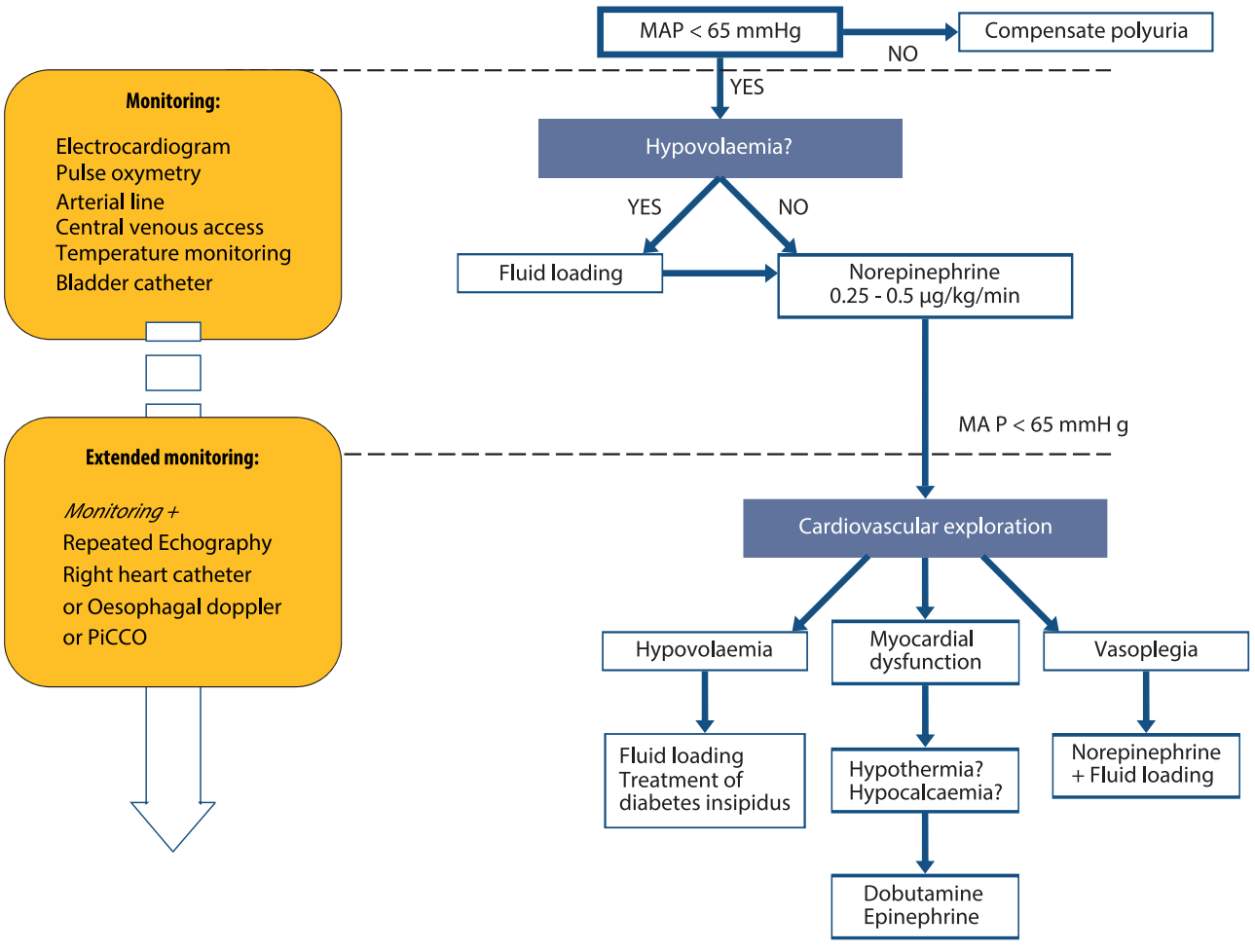
Administering fresh frozen plasma to replace fluid volume is only indicated for cases of simultaneous coagulation disorder. Erythrocyte concentrates should be maintained at 20-30 % haematocrit (see below). If adequate mean arterial pressure cannot be achieved by fluid replacement, then vasopressors are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

5.4.3.1. *Vasopressors*

Despite fluid replacement, administration of vasopressors frequently becomes essential. In cases of uncontrolled cardio-circulatory failure or persistent hypotension, extended haemodynamic monitoring by whatever means (e.g. echocardiography, PiCCO®, pulmonary catheter) is highly recommended. This will facilitate determination of the precise haemodynamic profile and causes of hypotension, whether caused by hypovolemia, vasoplegia or cardiogenic components (see Figure 5.2) [22-24]:

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.

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 [24].

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 % [22, 23].

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 [24, 25, 26]. 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 [27]. 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, the depletion of endogenous norepinephrine and of ATP reserves in the organs, and affect their function after transplantation, especially in the case of the heart.

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), a 5 % glucose solution may be administered as an infusion (always together with insulin). 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 over-hydration. In such cases, Furosemide should be administered and the volume of urine excreted hourly should be replaced with 5 % glucose solution.

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 recovery, 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.

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 FI_{02} possible • Maximal inspiratory plateau pressure < 300 mmHg (< 40.0 kPa), • Tidal volume 6-8 mL/Kg • PEEP 8-10 cm H_2O (a high PEEP prevents lung oedema and helps prevent atelectasis).
Recruitment manoeuvres	Once per hour and after every disconnection from the ventilator.
Bronchoscopy	With bilateral bronchoalveolar lavage, immediately after BD.
Close monitoring of haemodynamics [25-26]	• With PICCO • 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/FI_{02} > 300 mmHg (>40.0 kPa).

Note: CPAP: continuous positive airway pressure; CVP: central venous pressure; EVLW: extra-vascular lung water; FI_{02}: fraction of inspired oxygen; ICU: intensive care unit; PEEP: positive end expiratory pressure.

Source: [28, 29, 30, 31].

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 BD, 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 [28, 29] 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 [30], 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 continuous mucolysis, humidification of respiratory gases, aspiration of secretions, changes of body position and head of bed elevation (if no contraindications).

The targeted parameters, particularly if lung recovery 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. minimum 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 BD.

A lung-protective strategy aimed at improving lung function and protection in order to enable lung donation is summarised in Table 5.3 [28-31].

5.4.8. Haemostasis during organ transplantation

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

Platelets and haemostatic factors should be monitored and maintained 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.

5.5. Conclusion

To conclude, the period between BD and organ recovery is one in which organ function can deteriorate rapidly. Optimal management of the BD 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 recovery is still a question for debate along with consideration of, for example, 'spontaneous' heart recovery with time [32].

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

1. DuBose J, Salim A. Aggressive organ donor management protocol. *J Intensive Care Med* 2008; (23): 367-75.
2. Wood KE, Becker BN, McCartney JG *et al.* Care of the potential donor. *N Engl J Med* 2004; (351): 2730-9.
3. Kutsogiannis DJ, Pagliarello G, Doig C *et al.* Medical management to optimize donor organ potential: review of the literature. *Can J Anaesth* 2006; (53): 820-30.
4. Bugge JF. Brain death and its implications for management of the potential organ donor. *Acta Anaesthesiol Scand* 2009; (53): 1239-50.
5. Mascia L, Mastromauro I, Viberti S *et al.* Management to optimize organ procurement in brain-dead donors. *Minerva Anestesiol* 2009; (75): 125-33.
6. Reye JW, Ott T, Bösebeck D *et al.* Organ-protektive Intensivtherapie und Simulatortraining. *Anaesthesist* 2012; (61): 242-8.
7. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. *British J Anaesthesia* 2012; 108 (S1): i96–i107.
8. Patel MS, Zatarain J, De La Cruz S *et al.* The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor. A prospective study from the UNOS Region 5, Donor Management Goals Workgroup. *JAMA Surg* 2014; (149): 969-75.
9. Watts PR, Thom O, Fraser J. Inflammatory signalling associated with brain-dead organ donation: from brain injury to brain stem death and posttransplant ischaemia reperfusion injury. *J Transpl* 2013; DOI: 10.1155/521369.
10. Cittanova ML, Leblanc I, Legendre C *et al.* Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; (348): 1620-2.
11. Brunkhorst FM, Engel C, Bloos F *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Eng J Med* 2008; (358): 125-39.
12. Reinhart K, Perner A, Sprung CL *et al.* Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012; (38): 368-83.
13. Miñambres E, Pérez-Villares JM, Terceros-Almanza L *et al.* An intensive lung donor treatment protocol does not have negative influence on other grafts: a multicentre study. *Eur J Cardiothorac Surg.* 2016 June; 49(6): 1719-24. DOI: 10.1093/ejcts/ezv454 [epub 19 January 2016, pii: ezv454].
14. Cheisson G, Duranteau J. Modalités de la prise en charge hémodynamique. In: G Boulard, P Guiot, T Pottecher, A Tenaillon, editors. *Prise en charge des sujets en état de mort encéphalique dans l'optique du prélèvement d'organes et de tissus*. Paris: Elsevier, 2005; 135-48.
15. Benck U, Gottmann U, Hoeger S *et al.* Donor desmopressin is associated with superior graft survival after

kidney transplantation. *Transplantation* 2011; (92): 1252-8.

16. Venkateswaran RV, Steeds RP, Quinn DW *et al.* The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J* 2009; (30): 1771-80.
17. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. *J Heart Lung Transplant* 1998; (17): 423-9.
18. Kotsch K, Ulrich F, Reutzel-Selke A *et al.* Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg* 2008; (248): 1042-50.
19. Pinsard M, Ragot S, Mertes JM *et al.* Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. *Crit Care* 2014; (18): R158.
20. Dupuis S, Amiel JA, Desgroseilliers M *et al.* Corticosteroids in the management of brain-dead potential organ donors: a systematic review. *Br J Anaesth* 2014; (113): 346-59.
21. Novitzky D, Mi Z, Sun Q *et al.* Thyroid hormone in the management of 63,593 brain-dead organ donors: a retrospective analysis. *Transplantation* 2014; (98): 1119-27.
22. Pennefather SH, Bullock RE, Mantle D *et al.* Use of low dose arginine vasopressin to support brain-dead organ donors. *Transplantation* 1995; (59): 58-62.
23. Rosendale JD, Kaufmann HM, McBride M *et al.* Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation* 2003; (75): 482-7.
24. Charpentier J, Cariou A. Objectifs et moyens de la prise en charge hémo-dynamique. In: G Boulard, P Guiot, T Pottecher, A Tenaillon, editors. *Prise en charge des sujets en état de mort encéphalique dans l'optique du prélèvement d'organes et de tissus*. Paris: Elsevier, 2005; 125-35.
25. Vetel Ch, Hottenrott MC, Spindler R *et al.* Dopamin and lipophilic derivates protect cardiomyocytes against cold preservation injury. *J Pharmacol Exp Ther* 2014; (348): 77-85.
26. Schnuelle P, Gottmann U, Hoeger S *et al.* Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA* 2009; (302): 1067-75.
27. Benck U, Hoeger S, Brinkkoetter PT *et al.* Effects of donor pre-treatment with dopamine on survival after heart transplantation: a cohort study of heart transplant recipients nested in a randomized controlled multicenter trial. *J Am Coll Cardiol* 2011; (58): 1768-77.
28. Mascia L, Pasero D, Slutsky A *et al.* Effect of a lung-protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA* 2010; 304 (23): 2620-7.
29. Miñambres E, Coll E, Duerto J *et al.* Effect of an intensive lung donor management protocol on lung transplantation. *J Heart Lung Transplant* 2014; (33): 178-84.
30. Miñambres E, Pérez-Villares JM, Chico M *et al.* Lung donor treatment protocol in brain-dead-donor: a multicentre study. *J Heart Lung Transplant* 2015; (34): 773-80.
31. Venkateswaran RV, Dronavalli V, Patchell V *et al.* Measurement of extravascular lung water following human brain death; implications for lung donor assessment and transplantation. *Eur J Cardiothorac Surg* 2013; (43): 1227-32.
32. Borbely XI, Krishnamoorthy V, Modi S *et al.* Temporal changes in left ventricular systolic function and use of echocardiography in adult heart donors. *Neurocrit Care* 2015; (23): 66-71.

Chapter 6. Deceased donor and organ characterisation

6.1. Introduction

In order to maximise the benefits and minimise the risks of transplantation, the suitability of deceased organ donors should be assessed properly. Therefore, it is necessary that donors and all organs procured – or to be procured – are characterised before transplantation, i.e. that relevant information on the characteristics of the donor and each of the organs is collected from a variety of sources – which are extensively described in this chapter. Secondly, conclusions must be drawn about the risks of disease transmission and about the quality of each of the donated organs based on all data obtained during the characterisation process – this second step is covered in Chapter 7. Based on the conclusions extracted from characterisation of donor and organs, decisions can be made on whether a particular recipient will benefit from the transplantation of a specific organ or not. Moreover, any potential risks of disease transmission can be minimised and organ allocation can be optimised.

Identification of possible organ donors is the starting point for donor evaluation. This is one of the most critical phases of the whole deceased donation process because inappropriate exclusion criteria are often assumed by the treating physician, and otherwise suitable donors are not evaluated further. Therefore any patient who meets specific clinical triggers, e.g. a Glasgow coma scale ≤ 6 [1] or a Full Outline of UnResponsiveness score EoMoBoRo [2], should be referred by the treating physician or team to the donor co-ordinator for the start of the evaluation process and consideration of donation after brain death (DBD) [3] as indicated in the World Health Organization Critical Pathway for Deceased Donation (see Chapter 2). The same applies to any patient for whom withdrawal of life-sustaining therapy is planned because it is no longer in the best interests of the patient. In such cases, controlled Donation after Circulatory Death (cDCD) should be considered, when allowed within a given jurisdiction. Additionally, 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 vary from what is described in this chapter and as outlined in Chapter 12.

This chapter focuses on the principles of characterisation for deceased organ donors. 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.

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 so, several sources of information should be used:

a. interviews with the family and/or other relevant sources;
b. interview with the attending physician and nurse, as well as the healthcare provider, general practitioner etc.;
c. detailed review of the medical notes;
d. assessment of the donor's medical and behavioural history;
e. full physical examination;
f. autopsy (not possible before procurement), the results of which must be communicated;
g. laboratory tests, including all microbiologic testing (specific note should be made of assays with pending results and followed up post-procurement);
h. complementary investigations (e.g. ultrasound abdomen, echocardiography, ECG etc.) as outlined below.

The 'history' of an organ donor must be obtained with respect to all kinds of transmissible diseases and of diseases that may affect organ quality. An interview with relatives of deceased organ donors should be undertaken, bearing in mind that, under emotional stress, they might forget some details. However, adding any stress to grieving relatives should be avoided. Contact with the general practitioner of the donor may prove helpful, alongside a review of hospital archives for historic data or other sources of information (e.g. tumour registry).

The donor profile should document the donor's medical and behavioural history, including general data such as age, gender, body weight and height – which should be measured and not estimated [4] – as well as cause of death or intensive care unit (ICU) admission, signs of obvious medical interventions, scars, and skin or mucosal lesions. For organ donors, the clinical evaluation should also include their haemodynamic status, in particular, hypotensive episodes, need for mechanical cardiac resuscitation and use of inotropic and vaso-active drugs, as well as duration of mechanical ventilation and number of days in the ICU (see section 6.2.3).

Medical history and clinical, haemodynamic, biochemical and pharmacological parameters are all needed to assess the suitability of the deceased person as an organ donor in a first step and of a specific organ in a second step (see Chapter 7). This includes all diagnostic investigations performed, such as X-rays (especially thorax), CT-scans (especially head, thorax and abdomen), ultrasounds (especially abdomen), echocardiography, coronary angiography, bronchoscopy etc. according to the need for such investigations (see sections 6.2.1 to 6.2.5.9).

It is the responsibility of the person or team performing the procurement to document any suspicious anatomical findings observed during the procurement procedure (see section 6.3).

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 questionnaire see Appendix 7. In cases of abnormal findings, with further investigations having been undertaken, results must be included in the donor documentation according to sections 6.2.1 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.

Finally, verify the blood group and confirm the investigations for characterising the donor's infectious status. The points outlined in the following sections contribute to characterising the donor properly. There are three pitfalls to bear in mind:

a. Any uncertain encephalitis or neurologic/mental/psychiatric disorder, as well as fever, rash, discomfort, etc., should signal the risk of a transmissible disease (see Chapter 8). This should not be restricted to donors with a history of travel abroad.
b. Intra-cranial metastases should always be taken into account in donors diagnosed with intra-cranial haemorrhage, especially if no evidence of hypertension or arterio-venous malformation exists. Intra-cranial tumours have a different biologic behaviour compared to solid organ tumours or haematologic malignancies (see Chapter 8). When in doubt, a brain biopsy or autopsy could be performed.
c. After all data have been collected and cross-checked against the donor and 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 while 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).

6.2.1. Medical and behavioural history

Standardised questionnaires (for examples see appendices 4, 5 and 7) should be used to obtain the following information needed for characterisation of a donor or specific organ later on:

a. Age: while there may be no definitive maximum age for individual donations, with increasing age the presence of co-morbidities is likely to make donation less acceptable.

b. Cause of death, as ascertained from the medical notes, must be documented in the donor record in order to identify infectious and neoplastic diseases. Autopsy results are preferred when available.

c. Clinical history and pre-existing diseases: in particular, malignant disease, multi-system auto-immune disease, infectious disease, neuro-degenerative or neuro-psychiatric disease, intoxications or diseases of unknown aetiology.

Previous diseases or surgeries hint at potential disease transmission risks (infection, malignancy, etc.) as well as posing the risk of nosocomial infections. Hospital or nursing home admissions or consultations with a physician could have been disease-related, e.g. an infection or malignancy.

Records should be checked for any previously diagnosed neoplasms or tumours removed, with or without registration of the definitive diagnosis. All information on the malignancy should be obtained: date of first diagnosis, detailed histological report, staging, grading, type and date of surgery, chemotherapy and radiotherapy, as well as questions on the standard follow-up conducted, most recent follow-up, including the results, complete remission and tumour recurrence-free survival. Careful consideration should be given to details such as history of menstrual irregularities after pregnancies and/or miscarriages in women of fertile age (e.g. risk of a metastasised choriocarcinoma) or history of anaemia and rectal blood loss in elderly people (e.g. colon carcinoma). If the information is not available, the transplant team must be informed in order to assess the risks.

Information about congenital or inherited disorders should be obtained as well as other relevant family medical history

d. Behavioural risk and previous medical treatment: this can 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, i.e. not only men having sex with men), use of intravenous drugs or cocaine, lifestyle or imprisonment. Even if donor relatives trust the interviewer, they may neglect or not disclose this information or may not know the entire truth. For further details refer to section 8.2.

e. Travel history or residence abroad/overseas: this should be evaluated to rule out the risk of tropical or endemic infections, e.g. malaria or trypanosomiasis, as well as the subsequent risk of vertical transmissions. Emerging, non-tropical diseases also exist in some European regions, e.g. West Nile Virus, Chikungunya Virus.

i. Global climate change affects infectious diseases, specifically their incidence and spread from local/regional level to continental or even intercontinental outbreaks. For specific information, see Chapter 8, with special reference to the websites of the European Centre for Disease Prevention and Control (www.ecdc.europa.eu), the World Health Organization (www.who.int/ith/en) and the Centers for Disease Control and Prevention (the yellow book at wwwnc.cdc.gov/travel).

ii. The 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, and few are operational 24/7. Timely requests for these additional tests are necessary.

iii. The history of travel or residence abroad must be expanded to include information about living conditions, migration background, refugee status and work places (e.g. sewage plant, woodlands, farm, airport, hospital, foreign countries). This helps 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 also be obtained with the same intention.

iv. Asking about contact with fauna, especially bites from pets, domestic or wild animals, birds, etc., is essential, but it cannot rule out all infection risks.

f. History of recent immunisation: the transmission of a live vaccine from the donor into an immuno-suppressed recipient may be life-threatening (see section 8.4.1.4).

g. History of blood transfusions or transplant procedures: risk of blood-borne infections is increased if they occurred within the 180 days preceding death.

h. Body piercing or tattoos: these are very common nowadays. If they have not been applied professionally under sterile conditions, and not more than 180 days preceding death, then they carry the same risk as non-medical injections (see section 8.2).

i. Risk of transmitting prion disease: this includes a definite diagnosis or high suspicion of any transmissible spongiform encephalopathy in the donor, a family history of Creutzfeldt–Jakob Disease, and whether the donor was the recipient of human, but not recombinant, pituitary-derived hormones, *dura mater*, or corneal or scleral transplants.

j. History of chemical and/or radiation exposure, previous and current medication and/or immuno-suppression: elevated risk of organ damage, infection or transmission of malignancy.

k. Careful consideration of the risk of infections of the central nervous system (CNS): occasionally, a CNS-infection in a potential donor is obscured by other causes of death or by an overlap in imaging. If the diagnosis of CNS-infection is missed then fatal transmission of the pathogen occurs [5]. Any of the following conditions should raise concerns:

i. Cerebrovascular accident in donors without risk factors for stroke, etc.

ii. Fever or illness or altered mental status at presentation/admission without clear explanation

iii. Cerebrospinal fluid abnormalities (e.g. pleocytosis, low glucose, elevated protein)

iv. Immunosuppressed host (e.g. autoimmune disease, cirrhosis) and/or environmental exposure (e.g. animals)

The information obtained must be merged into the clinical data outlined in section 6.2.3. See Chapters 8-10 for further information.

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.

The information obtained through physical examination is complementary to the comprehensive summary of clinical data as outlined in section 6.2.3.

An international protocol of physical examination in tissue donation is shown in Appendix 6 of this guide and also in Appendix 6 of the *Guide to the quality and safety of tissues and cells for human application*. This was released by the American Association of Tissue Banks [6] 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 6.2.3 to 6.4).

6.2.3. Clinical data

For the comprehensive description of the donor and the quality and function of the organs, the clinical data shown in Table 6.1 should be collected, including the information already obtained in accordance with sections 6.2.1 and 6.2.2 and expanded with the data described in sections 6.2.4 and 6.2.5. Organ exchange can be performed once this information has been provided to the most complete extent enabling proper assessment and organ allocation. 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.

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 which has to 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 also be added that, while the EU Directive gathers 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.

Table 6.1. **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 (**).

Data		Comment, informative value and background
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. Relevant for further contact, double-checks or possible follow-up questions from the different transplant teams, as well as for vigilance. Other general data can be indications about the procurement team in charge.
	Age*, gender*, height*, weight*, and other demographic and anthropometrical data**	Needed to assess the physical condition of the donor (e.g. obesity as cardiovascular risk factor). Advanced age is indicative for additional morbidities. Data may determine allocation of organs (size-match, age-match). The compatibility itself between donor and recipients does not influence the process of donor evaluation. For heart, lung, liver and intestinal transplantation, the size/weight match between donor and recipient is important. These demographic and anthropometrical data are required to support appropriate matching between donor/organ and recipient.
	Blood-group*, HLA-typing	Relevant for organ allocation (e.g. blood group compatibility). The compatibility tests between donor and recipients do not influence the process of donor evaluation (e.g. HLA- cross match virtual or direct). The correctness of blood group should be ensured when determined and every time when data are transmitted. It should be ensured that specimens for determination have been drawn properly and in time.
	Virology/Microbiology	All details must be known about the risk of transmissible pathogens (see Chapter 7). The variables may further determine allocation of organs (e.g. D+/R match in cases of donor-HCV-infection). Section 6.2.4 describes the principles of basic donor screening. Before any graft is transplanted, anti-HIV1/2 (including HIV-1-Ag)*, anti-HCV*, anti-HBc* and HBsAg* must have been determined. In addition, anti-CMV, anti-EBV, anti-Toxoplasma, TPHA or equivalent anti-Treponema pallidum testing should be available as soon as possible (see sections 6.2.4 and 8.4.1). Ensure the donor's infection status is correct when determined and each time that data are transmitted. Ensure that specimens for determination have been drawn properly and in time.
General data, medical history of acute event	Cause of death* Date/time of death*	It is imperative to know exact cause of death. A precise description helps to exclude or identify additional risks (traumatic or non-traumatic and primary or secondary brain injury).
	Timeline of admission to hospital, admission to ICU, start of ventilation and 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.
	Episodes of cardiac arrests/ resuscitation	For each episode of cardiac arrest, information on its duration, duration of CPR and treatment provided should be collected, as well as about the haemodynamic status afterwards. The kind of techniques should be mentioned (e.g. mechanical, defibrillation, medication).
	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.

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.

Data		Comment, informative value and background
General data, medical history before hospital admission	History of arterial hypertension	Duration and kind as well as 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. Valuable information may be obtained by contacting the family physician or relatives or other sources.
	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, but is often not detected because patient did not seek medical advice. Insulin demand of a donor in an ICU is not necessarily indicative of an active diabetes.
	History of smoking	Duration and quantity of smoking (pack-years) may be indicative for organ damage (heart, coronary artery disease, risk of arteriosclerosis) and risk of smoking-related malignancies.
	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 alcohol abuse combined with malnutrition and/or smoking is a risk factor for other diseases.
	History of drug abuse* (IV-drug abuse)	It should cover past and present 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.
	History of malignancies*	It should cover past and present history of (malignant) neoplasia. It should cover the detailed past and current history of malignancies (for details see section 8.2 and 8.4.1.4)
	History of transmissible diseases*, HIV*, HCV*, HBV*	For transmissible diseases, the present history is particularly relevant. For the principles of basic donor screening, see 6.2.4 and 8.4.1. HBV/HCV: pattern of infection, treatment (medication) and virologic response to treatment (NAT viral load, genotype) are informative in concert with the medical history.
	History of other diseases or risk factors for potential malfunction of an organ*	This information is needed to assess the side-effects of these diseases: duration, treatment, quality of treatment. Co-existing laboratory data are helpful.
	Medications before hospital admission (long-term use)	Some kinds of chronic medication may be indicative of organ damage.
	Living conditions, social contacts, job description, travelling, immigration, living abroad, private hobbies, pets, imprisonment, commercial sex worker, sexual contacts.	Information about social environment and behavioural history is helpful to assess possible risks. However it is sometimes difficult to obtain because the next of kin might not know everything.
	Basic organ-specific information*	When/if already available before procurement. Such information will help to evaluate the function of the organ once donated.
	Uniform donor health questionnaire	This is a complementary checklist that can help to avoid missing important topics.

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.

Data		Comment, informative value and background
Haemodynamic parameters and further monitoring	Body temperature	Decreased body temperature is common in DBD. Sometimes, fever occurs due to SIRS but increased temperature due to infection must be excluded. Low body temperature can make BD determination difficult. In cases of fever, taking cultures for exclusion of bacterial infections should be considered.
	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 brain stem coning.
	Arterial blood pressure	Surrogate for quality of organ perfusion; to be considered in association with demand of vasopressors and diuresis. Consider age adjustment in children and the need for elevated organ perfusion pressure in cases of pre-existing arterial hypertension without proper treatment.
	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 appropriate fluid balance exists. Polyuria may be due to diabetes insipidus, elevated serum glucose or recovery from acute kidney injury. Oligoanuria or anuria may occur due to haemodynamic unstable conditions, volume depletion or acute kidney injury.
	Central venous pressure	Correction for PEEP is mandatory. Surrogate marker for venous filling and right cardiac function. Before any conclusions are drawn, quality of measurement must be assured. In cases of maintenance problems, invasive monitoring is preferred and is more informative (PICCO®, echocardiography, Pulmonalis catheter).
	Pulmonary artery pressure	May be estimated via echocardiography when no invasive measurement is available.
	Physical and clinical data**	Data from clinical examination which are necessary for evaluation of physiological maintenance of the potential donor as well as any finding revealing conditions which remained undetected during examination of the donor's medical history and which might affect the suitability of organs for transplantation, or might imply the risk of disease transmission. See also sections 6.3 and 6.5 for examination during and after procurement.
Medication during current stay at ICU** (for any kind of medication, timeline and dose should be known)	Adrenaline, noradrenaline, dopamine, dobutamine, vasopressin, other vasopressor or inotropic drugs**	Indicative for the kind of haemodynamic achieved. The dose over the time-line is of interest in terms of haemodynamic parameters. Medications used during cardiac resuscitation should be documented separately.
	Blood transfusions**	Erythrocyte concentrate, fresh frozen plasma and thrombocyte concentrate. Units over time-line 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 often be provided.
	Plasma expanders**	Type, dose and duration of substitute may be informative about haemodynamic stabilisation and damage to kidneys.
	Other blood products**	Medication for correction of coagulation status.
	Antibiotics**	Indication, type and duration of antibiotic or anti-fungal or anti-viral medication and success in treatment of infections. Treatment according to antibiogram and resistance patterns should be confirmed.
	Anti-diuretics**	Treatment of diabetes insipidus in the context of diuresis and serum-sodium level.
	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.
	Insulin**	Glucose metabolism is frequently deranged after admission to ICU.
	Steroids**	Treatment of SIRS.
	Other medication**	Document of other relevant medication.
Ventilation and pulmonary function	Respirator settings, blood gas analysis	Conclusive for protective ventilation and achieved gas exchange. For standardised interpretation of blood gas analysis, the following procedure is recommended for lung donation: Suction the airway. Perform lung recruitment. Ventilate at PEEP $\geq$ 5 cm H_2O at $FIO_2 = 1.0$ for 10 minutes.
	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.
Others	Laboratory parameters**, image tests ** and other complementary tests	This information is complementary to the clinical data and explains, clarifies and verifies the data set in detail (see sections 6.2.4 and 6.2.5). Laboratory parameters are needed for assessment of organ function and to detect potentially transmissible diseases and possible contraindications with respect to organ donation; image explorations are also necessary for assessment of the anatomical status of the organs for transplant.

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.

Data		Comment, informative value and background
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 pre of hypoperfusion of the kidney and other organs.
	Electrolyte	Monitoring and correction of hypokalaemia, hyperkalaemia, hyponatremia and hypernatremia.
	Body temperature	Kept within a physiological range (> 34 °C).
	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.
	Coagulation	Monitoring and correction of major coagulopathies.
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	Details must be described as outlined in Chapter 12. 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.
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	Details must be described as outlined in Chapter 12. 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.

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.

6.2.4. Laboratory tests

All laboratory (lab) tests should be carried out before cessation of circulation in DBD. 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 during the actual course of disease, see section 6.2.3.

All data collected since ICU admission, before cessation of circulation, should be reported carefully and 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 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 CPR).

In the case of lab parameters, the units of measurement should be clearly communicated, as well as the reference range for healthy individuals used in the particular donor hospital. Although many parameters are standardised in their measurement, deviations from assumed reference ranges in general exist even between hospitals within one region, and thus more probably also between countries. Furthermore, the range of normal 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.

The informative value and clinical relevance of lab parameters are summarised in Table 6.2. 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:

i. It is important to note that some trauma victims arrive at hospital in an already haemodiluted or exsanguinated state. In the course of subsequent intensive care therapy, a certain and significant degree of haemodilution by crystalloids is standard. Replacement of a relevant acute blood loss should be considered in the context of its effect on haemodilution. Nevertheless, haemodilution should never be used as an excuse to discard a donor unless there are other risk factors, as outlined in Chapter 8.

ii. If no qualified specimen without acceptable dilution is available, then an algorithm incorporating the timing, nature and volume of the fluids infused, the donor's own blood volume and any blood loss from the intra-vascular space can be employed to assess any resultant

plasma dilution (see section 8.10.2) in the processed specimen in order to add some further information to the risk–benefit assessment during allocation for a donor-recipient-matching.

iii. If testing is done using haemodiluted specimens, it is necessary to evaluate if the percentage of haemodilution may result in false negative results according to the sensitivity of the method used, and to inform all potential recipient centres about thisin detail. If there is a limited supply of qualified blood for testing, human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) testing should be carried out on the sample in this sequence before using it for other assays.

iv. In some cases, nucleic acid amplification (NAT) technique for HIV, HCV and HBV may be helpful (see section 8.4.1). Again in diluted samples the probability of detecting pathogens by NAT is reduced too.

v. Antibody reactivity may be acquired by blood products post-transfusion. Not all tests used in donor screening are required for blood donation, so reactivity may exist in a blood donor (e.g. anti-CMV, anti-EBV, anti-Toxoplasma and, if not screened, anti-HBc). For safety reasons, reactivity must be assumed to be donor-associated.

vi. For other lab blood tests, the interaction of haemodilution should also be considered.

Screening and confirmatory microbiological tests should be performed in nationally accredited laboratories using appropriately validated testing techniques, i.e. certified by responsible authorities. These tests are performed to minimise the risk of donor-derived infectious diseases.

b. If samples for microbiological cultures are obtained at the time of procurement, samples of each recovered tissue should be taken prior to exposure of the tissue to antibiotic- or antiseptic-containing solutions. The culture technique should allow for the growth of both aerobic and anaerobic bacteria and fungi. The results should be documented in the donor record and must be communicated to the relevant organ procurement organisation and recipient centres immediately upon arrival.

Blood culture, if procurement is performed on a deceased donor, may be useful in evaluating the donor and interpreting the cultures performed on individual grafts. Especially in cases of fever, cultures from various sites may help to explain or exclude bacterial or fungal infections.

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 section 8.3). The newest-generation tests available should be used in each case:

i. HIV-1/2 antibody (combined with HIV-1 p24 antigen in the newest-generation tests)

ii. HBsAg and anti-HBc

iii. HCV antibody (combined with antigen test if available in future).

Additional tests can be mandated according to national regulations and depending on the type of transplantation. 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.

In order to maximise donor availability and ensure an acceptable level of safety, a thorough evaluation is required in donors with reactive HBV/HCV markers, using appropriate algorithms for matching donors and recipients.

Other tests may be required in specific situations or according to national provisions. Based on current experience, minimum testing on donors should be extended to:

iv. Syphilis (see section 8.3 with the side-effect of further assessment of infectious risks).

v. CMV-, Toxoplasma- and EBV-antibody testing in grafts to be used in immuno-suppressed patients so that adequate prophylaxis can be initiated in recipients as soon as possible. The test can be provided retrospectively in cases where it is not available prospectively.

vi. Herpes simplex virus 1 and 2 or varicella-zoster virus or human herpes virus HHV-8 for sero-negative recipients retrospectively at the recipient centre so that adequate prophylaxis can be provided if necessary.

vii. Human T-lymphotrophic virus 1 antibody, Chagas disease, malaria, HHV-8, West Nile Virus, etc. for donors living in, or coming from, high-prevalence areas (see sections 8.3, 8.4.2 and 8.4.2.12 for further details).

d. 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 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 the best practice of donor screening, see Chapter 8.

e. Other tests depend upon the organs or grafts to be transplanted. These may include some non-microbiological tests such as:

i. 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;

ii. other laboratory parameters as outlined in Table 6.2.

f. The routine determination of tumour markers is not recommended (see Chapter 9), since false positive determinations may lead to suitable organs being unnecessarily rejected. However, in cases of a confirmed prior malignancy in the donor's history, specific tumour markers should be tested to gain information about the current tumour status. In women of fertile age with unexplained intracranial bleeding, βHCG can be determined in the case of a history of menstrual irregularities or miscarriages to detect a chorio-carcinoma.

Table 6.2. **Informative value and clinical relevance of laboratory parameters in donor and organ characterisation**

Laboratory values are only informative 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 laboratory reference ranges adjusted to their local environment. Also, 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 occ(multiple causes).
Platelets	+++							Elevated after brain damage, decreased due to bleeding or coagulation disorders or sepsis. Substitution indication exists only in cases of bleeding due to thrombocytopenia.
Erythrocytes								
Na+ *	+++							Consider diabetes insipidus.
K+ *	+++							Consider kidney function.
Ca2+								
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) (see also Urea).
Urea	+++	+++						See Creatinine.
LDH (IFCC 37 °C)	+++	+	+	+	+	+		Tissue damage.
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 due to brain damage and not informative for heart quality.
Troponine						+++		
ASAT/SGOT(IFCC 37 °C)			+++	+++	+++	+++		Myocardial damage or liver damage >(see ALAT).

IFCC 37 °C: measurement according to methods of international federation of clinical chemistry and laboratory medicine at 37 °C; BAL: broncho alveolar lavage; KDIGO: Kidney disease improving global outcomes.

Laboratory values are only informative 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 laboratory reference ranges adjusted to their local environment. Also, age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
ALAT/SGPT(IFCC 37 °C)			+++	+++	+++			Liver damage may also be indicative of pancreas or intestine damage.
γGT(IFCC 37 °C)			+++	+++	+++			Liver damage.
Bilirubin tot.			+++					Consider if increased in cases of trauma and poly-transfusion due to bleeding or liver damage.
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.
Fibrinogen	+							Increased due to brain damage or inflammation.
Quick/PT	+++							Distorted by bleeding and coagulation disorders due to brain damage or therapeutic anticoagulation after correction by FFP transfusion.
INR	+							Measurement not adjusted to liver function. Used in anti-coagulation therapy in people with normal liver function.
APTT	+++							Distorted by bleeding and coagulation disorders due to brain damage or therapeutic anti-coagulation after correction by FFP transfusion.
AT III	+		+					Must be viewed in the context of bleeding disorders as well as liver function.
CRP	+++					+	+	Acute elevation due to brain stem coning, not representative for monitoring of infection.
FIO_2	+++						+	Must be viewed in the context of respiration therapy.
PEEP	+++					+	+++	Must be viewed in the context of respiration therapy.
pH	+++							Must be viewed in the context of respiration therapy as well as other acute events.
$paCO_2$	+++						+	Must be viewed in the context of respiration therapy.
paO_2	+++	+	+	+	+	+	+	Must be viewed in the context of respiration therapy.
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	+++							Must be viewed in the context of respiration therapy as well as other acute events.
O_2 saturation	+++							Must be viewed in the context of respiration therapy.
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.

IFCC 37 °C: measurement according to methods of international federation of clinical chemistry and laboratory medicine at 37 °C; BAL: broncho alveolar lavage; KDIGO: Kidney disease improving global outcomes.

Laboratory values are only informative 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 laboratory reference ranges adjusted to their local environment. Also, age and gender adjustment must be considered. Acceptable reference ranges for DBD and DCD have not yet been published.**
Urine protein		+	Slight proteinuria possible due to urethral-catheter; kidney damage. Only data of pre-hospital time during a steady state care can be informative. According to KDIGO Guidelines albuminuria should be investigated instead of total proteinuria [7]. Also the ratio urine protein/urine creatinine is a simple parameter resistant against sampling errors compared to collecting urine for 12 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 [7].
Urine albumin		+++	For assessment of glomerular function more indicative than protein (KDIGO Guidelines) [7].
Ratio urine-albumin/ urine-creatinine		+++	<30mg albumin/g Creatinine normal; >300mg albumin/g Creatinine indicative of kidney damage if measured in a steady state outside ICU [7].
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 out-clinic patients 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 [7].
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).
Anti-HIV-1/2	+++		Test should cover all subtypes of HIV virus and include HIV-1p24 Ag. In cases of true positive result, HIV will be transmitted with any organ.
HIV-NAT			See Chapter 8.
Anti-HCV	+++		In cases of true positive result, HCV will be transmitted with any organ when viraemia exists (if HCV-RNA reactive). Depending on the country, reactive results may occur as HCVinfection may be endemic.
HCV-NAT			See Chapter 8.
HBsAg	+++		In cases of true positive result, HBV will be transmitted with any organ when viraemia exists (if HBV-DNA reactive).
Anti-HBc	+++		In cases of true positive result, HBV will be transmitted with the liver. Viraemia rarely exists (if HBV-DNA reactive). Depending on the country, reactive results may occur as HBVinfection may be endemic.
Anti-CMV; Anti-EBV; Anti-Toxoplasma	+++		Depending on the country and age, reactive results may occur as infection may be endemic. IgG determination will be appropriate for CMV. Test results determine organ allocation or need for chemoprophylaxis in recipients.
Syphilis test	+++		Consider co-infection by other sexually-transmittable diseases. An initial reactive result for screening (e.g. TPHA-test) should be verified by confirmative testing.
Further tests for infections	+		Indication exists according to incidence of disease in the population. This may cover infections like malaria disease, etc.
Microbiological cultures	+		Microbiological cultures (blood, urine, BAL, other sites or wounds) must be tested for bacteria or fungi with a drug-resistance pattern whenever pathogens are detected.

IFCC 37 °C: measurement according to methods of international federation of clinical chemistry and laboratory medicine at 37 °C; BAL: broncho alveolar lavage; KDIGO: Kidney disease improving global outcomes.

6.2.5. Other complementary tests

Complementary tests contribute further to characterising the donor when standardised questionnaires are used as outlined below. One common language should be used by the investigator performing the test and the recipient centres interpreting the result within their risk–benefit assessment.

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 might be helpful.

For thoracic organs a specific indication should exist for performing the investigation (e.g. coronary angiography in a donor with relevant risk for coronary artery disease). For any organ procurement, as a minimum abdominal imaging is strongly suggested. 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 history of malignancy).

The next sections give a basic description for each test along with the facts to be investigated by the specific complementary test, and a list of values to achieve the goal of one common language in interpreting the test.

In cases of cDCD as well as DBD, these tests can be performed *ante mortem* as long as they are not invasive and are without harm to the patient and part of the repertoire of high-quality intensive care medicine. 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 represent the needs of investigations required to decide on further therapy and they do not represent a more detailed and qualified examination applied in cDCD or DBD.

6.2.5.1. *X-Ray thorax*

Figure 6.1. **Reporting workflow for minimum dataset to be communicated for X-ray of chest/thorax or CT-thorax**

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		

n.a. = not assessable; ET = endo-tracheal.

Source: Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization [8].

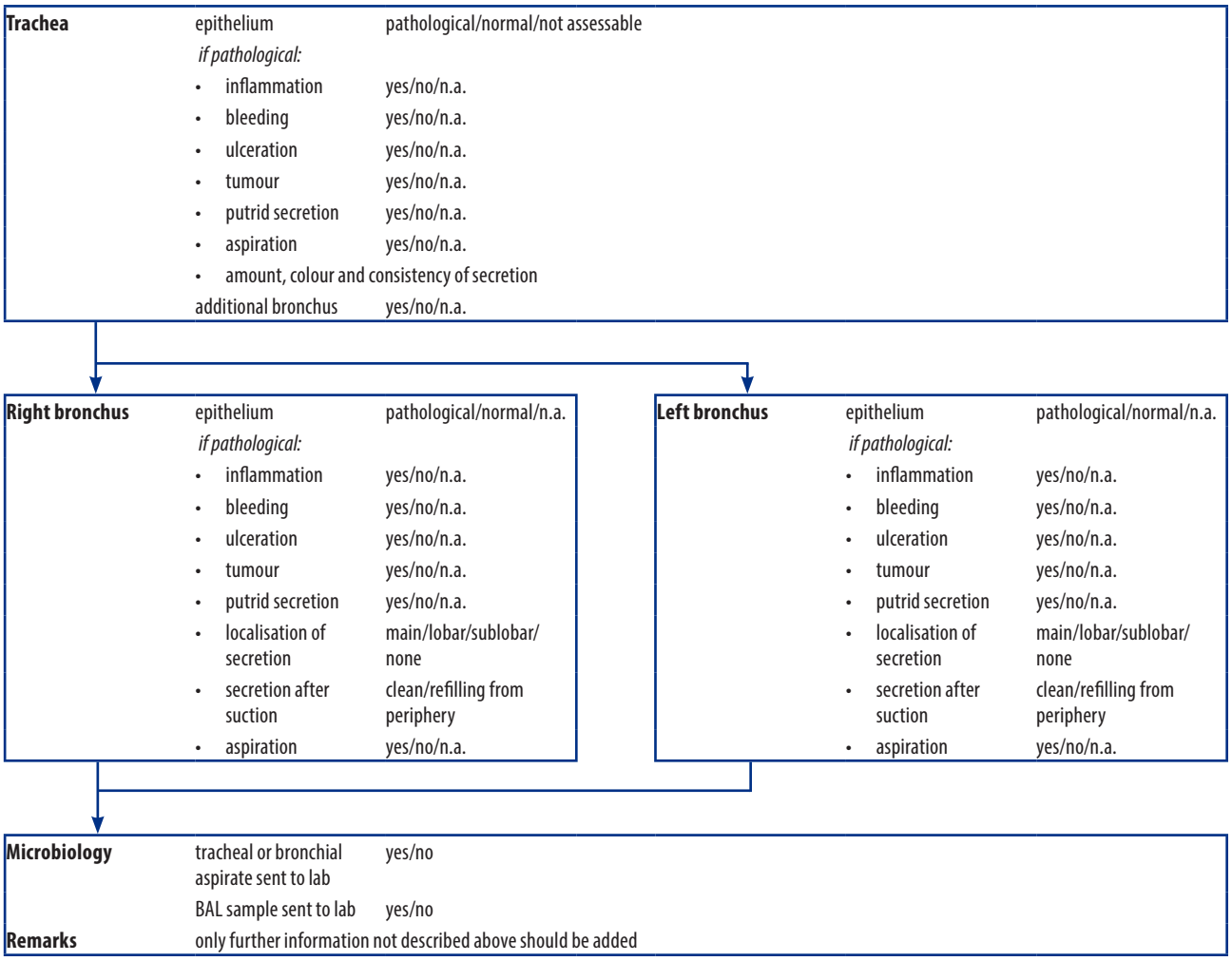
Chest X-ray can be performed as a bedside method in the ICU with the known limitations of the sensitivity and specificity of the investigation (see Table 6.1). In the case of a whole-body CT-scan or thoracic CT-scan, the information provided should be structured in the same way as described here. A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 6.1; an example questionnaire can be found in Appendix 8.

Table 6.3. **X-Ray thorax parameters to be investigated and standard data list**

X-Ray thorax	Comment, informative value
Indication	Rough assessment of lung and thorax.
Safety warning	Bedside measurement may not rule out small lesions or space-occupying lesions as well as minor changes of the parenchymal structure.
Standard evaluation	Bedside X-rays cannot exclude small tumours or minor changes of lung parenchyma.
Lung size measurement	Not necessary for standard matching of donor and recipient, but helpful in cases of malformations of the thoracic cavity of the potential recipient or in extremely adipose donors (small lungs compared to body mass).

6.2.5.2. *Bronchoscopy*

Figure 6.2. **Reporting workflow for minimum dataset to be communicated for bronchoscopy**



BAL: broncho-alveolar lavage; n.a. = not assessable.

Source: Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization [8].

Bronchoscopy can be performed in any donor as a bedside method especially for assessing the status of the bronchial system (see Table 6.4). A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 6.2 and an example questionnaire can be found in Appendix 8. 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.

Table 6.4. **Bronchoscopy parameters to be investigated and standard data list**

Bronchoscopy	Comment, informative value, background
Indication	In a lung donor before procurement or for exclusion of bronchial malignancy if suspected.
Safety warning	Ensure appropriate oxygenation.
Status of bronchus and trachea	Blocked peripheral orifices or purulent secretions may indicate infection. 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.
Signs of aspiration or pneumonia	Aspiration is a leading cause of pneumonia. Uncontrolled loss of consciousness or any emergency intubation is associated with the risk of aspiration (stomach contents). This justifies explorative bronchoscopy. Cleaning airways may give the lung a chance to recover.
Localised secretions and descriptions of them	Secretions originating from the peripheral bronchial orifice indicate infection in peripheral tissue of the lung (purulent, blood, clean).
Secretion or broncho-alveolar lavage sent to microbiology	Identification of colonisation or infection (e.g. bacteria or fungi and their resistance pattern against anti-microbiological agents).

6.2.5.3. *Echocardiography*

Figure 6.3. **Reporting workflow for minimum dataset to be communicated for echocardiography**

At time of echo	Haemodynamics:	MAP (mmHg), CVP (mmHg), heart rate (BPM)
	Inotropes, catecholamines:	yes/no ? if yes: kind and dosage (µg/kg/min)
Basic	Type of examination:	TTE (trans-thoracic)/TEE (trans-oesophagal)
	Visualisation:	normal/limited/severely limited
Left heart morphology	measurements:	LV-EDD & LV-ESD (mm), LV-PWd & LV-PWs (mm), IVSd & IVSs (mm), LA (diameter, mm)
	left ventricular hypertrophy (LVH):	normal/moderate/severe/n.a.
Left ventricular function (LVF)	measurements:	LV-EF (%, Simpson/ Teichholz/estimated) or LV-FS (%)
	systolic LVF:	normal/moderately reduced/severely reduced/n.a.
	diastolic LVF:	normal/abnormal relaxation/pseudo-normalisation/restrictive filling/n.a.
Wall motion disorders	any wall motion disorders:	yes/no/n.a.
	if yes, description:	regional akinesia/hypokinesia/n.a. & location
Right heart	measurements:	RV-EDD & RV-ESD (mm) , RV-TAPSE (mm), RA (diameter, mm)
	right ventricle function (RFV):	normal/reduced/n.a.
	right ventricle morphology:	normal/hypertrophy (wall > 5mm)/n.a.
	right ventricle dimension:	normal/moderately dilated/dilated/n.a.
Aorta	measurements:	Aortic anulus (diameter, mm), Ascending aorta (diameter, mm).
	morphology:	description if abnormal
Heart valves	aortic valva	obtain following data for each valve:
	mitral valve	• insufficiency: none/1°/2°/≥ 3°/n.a.
	tricuspidal valve	• stenosis: normal/mild/moderate/ server/n.a.
	pulmonary valve	• morphology: normal/thickened/calcification/n.a.
Other	QTC-Time:	normal/prolonged/n.a.
		if prolonged: QTc-time in ms
Remarks	only further information not described above should be added	

n.a. = not assessable

Source: Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization [8].

Table 6.5. **Echocardiographic parameters to be investigated and standard data list**

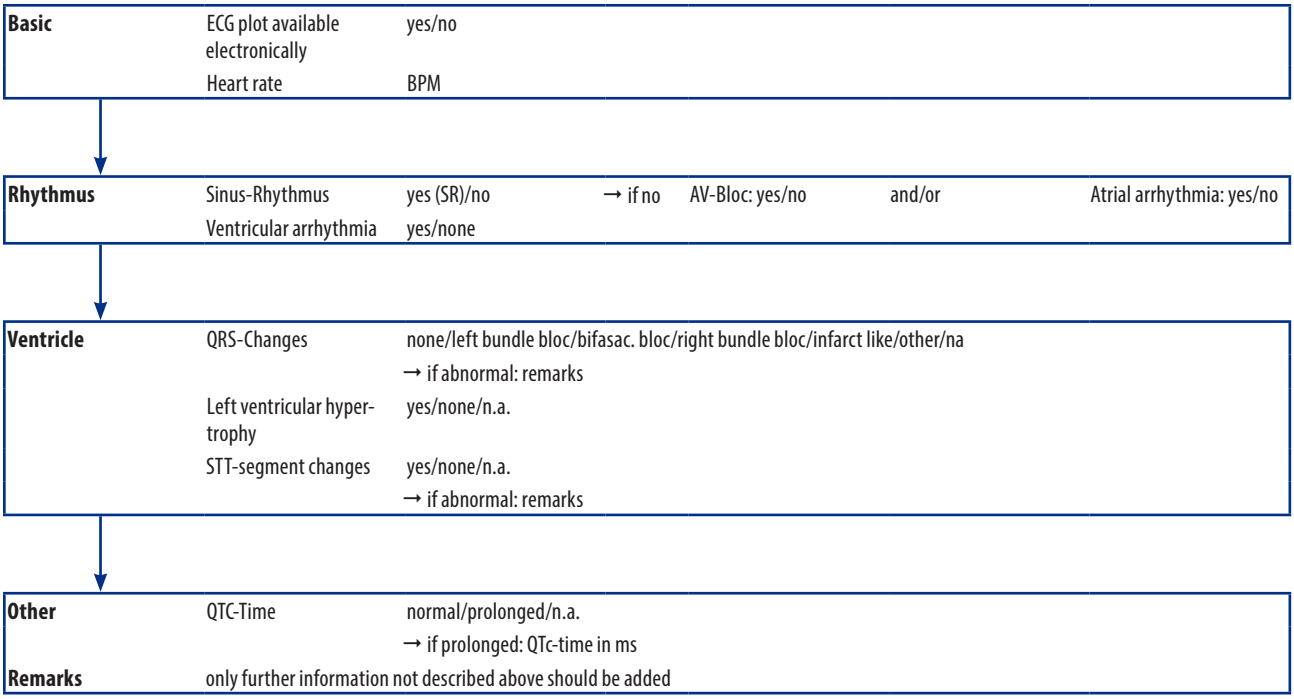
Echocardiography	Informative value
Indication in donor evaluation	In donors with a heart clinically suitable for transplantation (or for assessment of history of arterial hypertension as well as haemodynamic status). TTE may be acceptable, TEE may be performed if helpful.
Safety warning:	Echocardiography is suitable in donors with haemodynamic instability for assessing the current status. Only after appropriate haemodynamic maintenance may an assessment become possible of whether the heart may be suitable for transplantation or not. Especially in cases of cerebral vascular events or brain-stem coning, the neuro-cardiac damage with temporarily decreased cardiac output and wall motion disorders may require time and serial evaluations for final conclusions. In donors with tachycardia the heart rate should not be lowered for diagnostic purposes and calculation of certain parameters becomes questionable. Sometimes conditions for measurements are limited at bedside at ICU.
Haemodynamic parameter during investigation	HF, MAP, CVP, etc. and type of therapy (vasopressors, inotropic medications) should be known. 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.
Global ventricular function and morphology (right/left) Atrial status (right/left)	The functional status of the left and right ventricle should be described (systolic function, diastolic function). Precise measurement of the ejection fraction (EF) or shortening fraction (FS) is important. The status of all four segments of the heart should be described (e.g. hypertrophy, dilatation). Measurement should be made of the: • inter-ventricular septum (thickness diastolic and systolic: IVSd, IVSs); • left ventricular posterior wall (thickness diastolic and systolic); • diameter of left ventricle (diastolic and systolic: LVEDD, LVEDS); • diameter of right ventricle (diastolic and systolic: RVEDD, RVEDS); • diameter of left atrium (LA); • left ventricular ejection fraction (LVEF) or shortening fraction (LVFS); • function and morphology of the right ventricle: description and/or measurement of tricuspidal annular plane systolic excursion (TAPSE) 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 movement disorders of the ventricular wall	Exact descriptions of movement disorders are helpful to distinguish between temporary neuro-cardiac injury and other irreversible damage. Minor movement disorders may not exclude the heart from transplantation – especially if improvement was observed in serial evaluation.
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) are critical and must be described properly (pressure- or flow-velocity measurements over the valves will be helpful but can often not be performed well due to impaired conditions for investigation at ICU).
Aortic root and ascending aorta	Diameters should be measured. 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.
Pericardial effusion	A precise description is helpful to explain the haemodynamic situation.
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.

Beside basic assessment of the heart and heart function (see Table 6.5) this bedside method can be used for complementary haemodynamic monitoring. It is imperative to assure that the donor is in the best haemodynamic management condition before assessment by echocardiography becomes 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 [9]. A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 6.3 and an example questionnaire can be found in Appendix 8.

In cases of valve stenosis, further measurements should be provided. The determination of E/E′ or E/A is not requested since most donors have tachycardia and echocardiographic measurement will be difficult.

6.2.5.4. *Electrocardiogram*

Figure 6.4. **Reporting workflow for minimum dataset to be communicated for electrocardiogram**



n.a. = not assessable.

Source: Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization [8].

Table 6.6. **Electrocardiogram parameters to be investigated and standard data list**

Electrocardiogram	Comment, informative value
Indication	In any donor suitable for heart donation or for assessment of arrhythmias as well as history of arterial hypertension (left hypertrophy).
Safety warning	Misinterpretation should be avoided of temporary T-Wave and ST-segment changes due to neurocardiac damage in direct timely association.
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. 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.

A 12-lead measurement at the bedside will be helpful for exclusion of severe heart damage, arrhythmias or hypertrophy (see Table 6.6). A proposal for a standardised dataset to be communicated within the investigation is shown in Figure 6.4 and an example questionnaire can be found in Appendix 8.

6.2.5.5. *Coronary angiography*

Figure 6.5. **Reporting workflow for minimum dataset to be communicated for coronary-angiography**

RCA & branches	degree of stenosis:	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	→ *if not normal*	
	• type of stenosis:	none/luminal irregularities/A (≤ 1cm, concentric) /B (1-2cm, excentric)/C (>2cm, diffuse lesion)/n.a.
	– proximal RCA (1):	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– middle RCA (2):	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– distal RCA (3)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– posterior-descending RCA (4)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
LCA (5)	degree of stenosis:	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	→ *if not normal*	
	• type of stenosis:	none/luminal irregularities/A (≤ 1cm, concentric) /B (1-2cm, excentric)/C (>2cm, diffuse lesion)/n.a.
RIVA & branches	degree of stenosis:	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	→ *if not normal*	
	• type of stenosis:	none/luminal irregularities/A (≤ 1cm, concentric) /B (1-2cm, excentric)/C (>2cm, diffuse lesion)/n.a.
	– proximal RIVA/LAD (6):	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– middle RIVA/LAD (7):	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– distal RIVA/LAD (8)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– 1st diagonal branch/D1 (9)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– 2nd diagonal branch/D2 (10)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
RCX & branches	degree of stenosis:	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	if not normal	
	• type of stenosis:	none/luminal irregularities/A (≤ 1cm, concentric) /B (1-2cm, excentric)/C (>2cm, diffuse lesion)/n.a.
	– proximal RCX/LCX (11)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– 1st marginal branch/OM (12)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– distal RCX/LCX (13)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– posterolat. marginal branch (14)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
	– posterio-desc. RCX/PD (15)	normal/luminal irregularities or < 25%/26-50%/51-75%/76-90%/91-99%/occlusion/not existent/n.a.
Other	major supply	left/right/n.a.
	vessel variant	normal/variants
Remarks	only further information not described above should be added	
	if laevocardiography was performed please provide data	

n.a: not assessable; RCA: right coronary artery, LCA: left coronary artery main stem; RIVA: ramus interventricularis; RCX: ramus circumflexus.

Source: Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization [8].

Table 6.7. **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 (see section 7.3.5) 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, as well as in the case of donors of either sex aged between 45 and 55 years if more than one risk factor for CAD exists. However, the absence of coronary angiogram data is not necessarily a cause for exclusion of a potential donor.
Safety warning	Invasive investigation: requires death certification and consent when exclusively performed for donor characterisation. Typical complications may occur during transfer and investigation (e.g. donor instability, worsening of lung function, vasospasm with cardiac arrest, rupture of vessel) and must be considered before transfer. In cases of stenosis detected during investigation, interventions like PTCA or stenting may only be upon agreement by the recipient centre.
Coronary sclerosis and stenosis	The narrowing and shape of stenosis (diameter and length), its location and affection of vessel should be described, as well as the shape of the intravascular structure (RCX, LCX, LCA, RIVA and their branches).
Functional parameters (Laevo-cardiography)	Functional parameters should be obtained only 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).

The donor must be transferred to a coronary angiography laboratory for investigation. 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 [9] and there should be an indication that justifies investigation (see Table 6.6). Also, it should not be assumed that coronary angiography mitigates donor-age-related cardiac risk factors [10]. This investigation assesses the intraluminal status of the coronary vessels (see Table 6.6) 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 6.5 and an example questionnaire can be found in Appendix 8.

Coronary arteries may be graded according to the 15-vessel model of the American College of Cardiology/American Heart Association classification [11]. This is used by many institutions and is also compatible with CT-angiography. The grading reflects the questions of cardiac transplant teams and the point of view of cardiologists.

6.2.5.6. *Abdominal ultrasound*

Table 6.8. **Parameters to be investigated through abdominal ultrasound and standard data list**

Abdominal ultrasound sonography	Comment, informative value
Indication in donor evaluation	Screening for abdominal pathologies and rough assessment of the quality of abdominal organs
Safety warning	Conditions of investigations might be limited due to obesity, intestinal overlay (intraluminal gas) or inability to position for investigation properly. In any case of a space-occupying lesion, it can be assessed to identify whether it is a cyst, tumour, haemangioma, trauma lesion, haematoma, etc. This must be verified by intra-operative inspection and histopathology when indicated. A CT-scan might be helpful to verify the kind and seriousness of the space-occupying lesion further but also without final conclusion.
Aorta	Aneurysm and arteriosclerotic plaques indicative of systemic arteriosclerosis (i.e. coronary arteries may also be affected). Check for para-aortic space-occupying lesions (e.g. lymphoma)
Kidney	Standard description plus quantitative measurement of length, width and parenchyma mass (thickness). Watch for: tumour and cysts, space occupying lesions, hydronephrosis, renal calculi, scars of parenchyma.
Liver	Standard description – i.e. size in medio-calvicular line (MCL), liver edge – plus comparison of echogenicity of liver to kidney parenchyma (probability of macro-vesicular steatosis elevated in cases of non-homogenous or enhanced echogenicity liver parenchyma). Watch for cysts, tumour, cholestasis, space-occupying lesions, flow in portal vein, status of vena cava, status of gall-bladder and bile ducts.
Pancreas	Standard description should include statement about intraparenchymal 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 spleen	Should be investigated. This information is very relevant for the general assessment of donors but not directly for description of organ specific selection criteria (e.g. liver, pancreas, and kidney). In general it is assumed that it is screened for all of these pathologies and when nothing is mentioned that they do not exist.
Vena cava inferior	Information about fluid status of the donor (donor maintenance).

Figure 6.6. **Reporting workflow for minimum dataset to be communicated for investigation of the abdomen by ultrasound, CT or MRI**

Liver	size MCL (cm)	only if not measured: size in relation to MCL: normal/small/large/enlarged/n.a.			
	parenchyma	normal/slightly hyperechogenous/severly 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/cholecytectomy/choelcystitis/cholecystolithiasis/choelcystitis & 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/edema/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), 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), 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.

Source: Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization [8].

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 6.7). In the cases where a whole-body CT-scan or abdominal CT-scan or MRI is performed, the information provided should be structured in the same way as described here. A proposal for a standardised dataset to be communicated within the investigation is in Figure 6.6 and an example questionnaire can be found in Appendix 8.

Table 6.9. **Computer tomography or magnetic resonance imaging parameters to be investigated and standard data list**

CT-thorax/abdomen/ head	Comment, informative value
Indication in donor evaluation	Screening for thoracic and abdominal pathologies and further assessment of the quality of abdominal organs as well as exclusion of malignancies or further verification of space-occupying lesions.
Safety warning	The donor has to be transferred to the CT-machine which is time-consuming and a risk for suboptimal donor maintenance. In any case of space occupying lesions it can be assumed whether it is a cyst, tumour, haemangioma, trauma lesion, haematoma, etc. This must be verified by intraoperative inspection and histopathology when indicated. A CT-scan might be helpful to further verify the nature of the space occupying lesion but also without final conclusion.
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).
Organ description	Check for smaller tumours and abnormal lymph nodes to exclude malignancies, trauma lesions, description of mesenteric root and calcification of aorta. Abdominal CT equivalent to abdominal ultrasound.
Space occupying lesion	Indicative for malignancies, abscess, haematoma, etc.
Head	Describes devastating cerebral lesion

Note: CT = computer tomography.

6.2.5.7. *Computer tomography or magnetic resonance imaging of thorax, abdomen, whole body or head*

Abdominal ultrasound and X-Ray-thorax are preferred as bedside methods in ICU despite the known limitations of the sensitivity and specificity (see Table 6.8). In cases where a whole body computer tomography (CT)-scan or abdominal CT-scan or magnetic resonance imaging (MRI) is performed, the information provided should be structured in the same way as described for these methods (see sections 6.2.5.1 and 6.2.5.6) and may replace these investigations when appropriate.

Whenever a CT-scan of the body has been performed re-evaluation should be attempted. Especially 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.

For dataset to be communicated, refer to ultrasound abdomen and/or X-Ray thorax (see sections 6.2.5.1 and 6.2.5.6).

6.2.5.8. *Biopsy of liver and kidney*

Frequently, morphologic changes of organs exist which require histopathologic examination for final determination of suitability for transplantation (see Table 6.9). The pathologist should be informed about all donor data and the macroscopy of the organ. Biopsy before procurement can be done when death has been certified and consent exists as well as where there are no coagulation disorders and the physician performing the biopsy is very experienced (because of bleeding risks) [12].

Table 6.10. **Parameters to be considered in liver or kidney biopsy**

Liver and kidney biopsy	Comment, informative value
Indication	Suspected abnormality of organ.
Liver	Differentiate between macro-vesicular steatosis (risk factor for primary malfunction) and micro-vesicular steatosis. The percentage of cells affected should be documented. Extent of fibrosis, inflammation, cholestasis and any other findings should be reported. Consider sampling error (e.g. nodular cirrhosis), as well as non-representative findings from biopsy taken from sub-capsular liver edge.
Kidney	It is inappropriate to discard kidney grafts for transplantation based exclusively on biopsy results. In case 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 [13].
Transport medium of specimen	This should be discussed with the pathologist performing the investigation.

6.2.5.9. *Histopathological examination of any other suspect mass*

Any suspect mass (e.g. lymph node, cyst wall of solid organ) should be investigated by histopathology (see Table 6.10). Since a biopsy may be representa-

tive only of the sample sent in, the mass should be resected in toto to rule out malignancy 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 9). In cases of suspected tumours, the whole tumour mass with a surrounding safety edge (according to an R0-resection) must always be sent to the pathologist. Isolated biopsy or segments may not be representative.

Table 6.11. **Data to be provided in cases of other examinations**

Pathologic examination	Comment, informative value
Indication	Suspected abnormality of organ.
Any organ (whole tumour excision)	Exclude malignancy, confirm other suspected lesion.
Transport medium of specimen	This should be discussed with the pathologist performing the investigation.

A frequent question 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. brain can be procured for autopsy right away during or after organ procurement).

6.2.5.10. *Other complementary tests*

Beyond the above-mentioned investigations, further specific investigations may be performed when clearly indicated according to the knowledge of medical science. Since resources are limited in all hospitals, evidence-based indications should exist according to the diagnostic pathways applied in any other patient.

6.3. Examination during procurement

Prior to the procurement of any graft from a potential donor, a detailed medical examination should be performed and documented. It is the responsibility of the professional performing the procurement to document any suspicious anatomical findings observed during the 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.

At least in cases of abnormal findings, further investigations should be provided and the results must be included in the donor documentation according to sections 6.2.3 to 6.2.5.9.

Any space-occupying lesion detected either during pre-procurement investigations or during procurement should be verified. Histopathologic examination of the whole lesion is best practice.

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 (see section 6.2).

6.4. Examinations after procurement

Performing an autopsy after procurement for final exclusion of undetected diseases could 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 autopsy. Therefore it is recommended to carry out an inspection at least at procurement (see section 6.3).

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 investigated by standard methods) and must be forwarded immediately to all relevant institutions (e.g. organ procurement organisation, transplant centres, tissue establishment, as outlined in Chapter 14). 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 one or several potential recipients. In cases where results are pending, grafts can be offered to centres and recipients willing to accept the risks associated with unknown data. Indeed, the transplant team might assess the risks posed by non-transplantation as outweighing the risks associated with data partly unknown, and might choose to monitor the situation before and when results become available.

Whenever a graft is 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 procurement organisation 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 [14], 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 Europe 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.

6.5. 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 although their purpose is recipient-oriented (but the data concern the donor and their organs). 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 starting from end of death certification and final consent until the start of procurement and cross-clamp.

It is especially important that the extent of immunisation in recipients against HLA-antigens or -epitopes is properly identified and monitored. Then proper prospective HLA-typing of the donor by molecular-biologic methods – i.e. polymerase chain reaction (PCR-SSO or PCR-SSP) in low or high resolution as indicative of at least HLA-A, -B, -C, -DR, -DQ, -DP alleles in sensitised kidney recipients [13] – enables transplant centres to perform virtual cross-match and compatibility evaluation without risk of organ wastage. 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.

6.6. Conclusion

Appropriate donor characterisation contributes to the safety and quality of organs. It has to be remembered that certain medical findings are indicative for using or not using an organ for transplant, e.g. severe macro-vesicular steatosis of the liver is a known risk factor for initial graft failure and therefore transplantation of such grafts can be avoided by proper donor characterisation [15]. Other fixed factors cannot be eliminated by donor characterisation and therefore persist as expected risk factors after transplantation (e.g. donor age). But all the information obtained is needed for donor and organ assessment (see Chapter 7). The aim is to perform 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 of donor evaluation and characterisation.

6.7. References

1. Teasdale G, Jennet B. Assessment of coma and impaired consciousness. *Lancet*, 1974; (304): 81-4.
2. Wijdicks E, Bamlet W, Maramatton B *et al.* Validation of a new coma scale. *Ann Neurol* 2005 (58): 585-93.
3. Valero R, editor. *Transplant coordination manual.* 3rd edition. Also: Escalant Cobo JL, Fernández García A. Chapter 2: Donor detection, clinical assessment and expanded criteria: 31-74; and Andrés Belmonte A, Fischer-Fröhlich CL. Chapter 4: Organ viability: 99-154; In: Valero R, editor. *Transplant coordination manual.* 3rd edition. Barcelona: Aguilógrafic, 2014. ISBN: 978-84-616-8840-1.
4. Li J, Kaiser G, Schaffer R *et al.* Inaccurate estimation of donor body weight, height and consequent assessment of body mass index may affect allocation of liver grafts from deceased donors. *Transpl Int* 2009; (22): 356-7.
5. Kaul DR, Covington S, Taranto S *et al.* Solid organ transplant donors with central nervous system

infection. *Transplantation* 2014; (98): 666-70. DOI: 10.1097/TP.0000000000000117.

6. American Association of Tissue Banks. AATB Guidance Document No. 1, v.2. Tissue donor physical assessment form (27 June 2005). American Association of Tissue Banks: McLean, Virginia, USA, 2005 [available from: www.aatb.org].
7. CKD Work Group. Kidney disease: improving global outcomes. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter.* 2013; (3) Suppl: 1-150.
8. Technical Working Group of Organ Procurement Committee of Eurotransplant: The ET-future of donor characterization: Step 1: Structured documentation of technical investigations for improved quality and safety. Annual Meeting of Eurotransplant Foundation, Leiden, The Netherlands, 2015. Available at https://members.eurotransplant.org/cms/index.php?page=meeting_2015 (restricted access).
9. Zaroff JG, Babcock WD, Shiboski SC *et al.* Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. *J Heart Lung Transplant*. 2003; (22): 383-8.
10. Kutschmann M, Fischer-Fröhlich CL, Schmidtmann I *et al.* Outcome of heart transplantation in Germany: details to be considered beyond multivariate analysis to improve the quality of graft allocation. *Organs, Tissues and Cells* 2014; (17): 53-61.
11. Smith SC Jr, Feldman TE, Hirshfeld JW Jr *et al.* Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 1988; (78): 486-502.
12. Clinicaltrials.gov NCT01810640: Rutgers, The State University of New Jersey, March 2013: Pre-recovery bedside liver biopsy in brain death organ donors (PPB). Biopsy liver pretransplantation [available from: http://clinicaltrials.gov/show/NCT01810640, accessed 10 July 2014].
13. Abramowicz D, Cochat P, Claas F *et al.* European renal best practice guideline in kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant* 2013; (28): ii1–ii71.
14. Foedus (Facilitating Exchange of Organs Donated in EU Member States, EU-funded project). [project website: www.foedus-ja.eu, accessed: 30 January 2016].
15. Fischer-Fröhlich CL, Frühauf NR, Schleicher C *et al.* Analysis of competing failure risks reveals proper liver assessment at recovery excluding severe steatosis as crucial compared to other cumulative extended donor criteria. *Organs, Tissues and Cells* 2012; (15): 115-21.

Related documents: Appendix 4. Patient assessment rationale (United Kingdom); Appendix 5. Donor patient history questionnaire (Germany, English language version); Appendix 6. Physical examination of an organ donor (American Association of Tissue Banks); Appendix 7. Donor information form (Eurotransplant, English language version); Appendix 8. Donor examination by various means.

Chapter 7. Donor and organ assessment and selection criteria

7.1. Introduction

Donor and organ assessment is intended to support the decision on which organs of a donor can be transplanted without unnecessary harm to a recipient. For this purpose, a set of clinical, analytical, morphological and functional data is obtained during donor and organ characterisation (see Chapter 6). This data set allows a global prediction on whether transplantation of a particular graft will be of harm to any recipient or not. Only after this risk–benefit assessment can the transplantation of a particular organ into a particular recipient be considered. The health status of patients on the waiting list during the waiting period deteriorates and the urgency of a transplant 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 selection criteria of donors and organs for transplantation have significantly changed during the last few decades. This is based on growing experience that rigid selection criteria limit the transplantation of organs that may not be beneficial for one particular recipient while being life-saving for another. It is difficult to determine where the absolute limits are. Still selection criteria should be considered as minimum inclusion criteria for an organ to be considered for transplantation.

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), some additional specific criteria exist on donor evaluation and selection. For details of these, see Chapter 12. There are additional specific selection criteria for living donors (LD), as 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 specific issues of donor disease transmission risks are covered in Chapters 8-10.

There are two major categories in the risk factors limiting the outcome of transplantation:

a. There is a risk of donor disease transmission (e.g. infections or malignancies) to the recipient. In cases where such risk is identified, the donor is classified as a non-standard risk – in contrast to standard-risk donors, where after careful evaluation, no evidence of risk of disease transmission has been detected currently, although some risks for unexpected and undetected diseases remain (see section 7.1.1).

b. There are donor or organ characteristics which increase the likelihood of limited outcome after transplantation. These factors, associated with organ quality, help define the expanded criteria donor (ECD) in contrast to a standard criteria donor (SCD); see section 7.1.2.

7.1.1. Risk assessment and risk levels related to donor disease transmission risks

Based on data from seven different countries and inspired by the Italian experience, 'non-standard risk donors' are defined by the EU-funded Alliance-O project as those in whom the risk of disease transmission to the recipient is estimated to be in one of four categories: unacceptable, increased but acceptable, calculated, not assessable [1]. Based on data collected in 11 different European countries, another EU-funded project, Dopki, showed that non-standard risk donors were not uniformly considered throughout the EU [2]. Some member states systematically prevented the transplant of organs from such donors by means of legal or technical provisions, whereas others followed specific protocols for using organs from these donors. Based on these conclusions and on knowledge gathered in countries where such donors were considered, it appeared that more organs from non-standard risk donors could be used and this is crucial to cope with the increasing transplantation needs of patients.

The vast majority of deceased donors nowadays suffer from severe cerebral damage due to different kinds of cerebro-vascular diseases while death due to cerebral traumas such as road traffic accidents has become the exception. In many countries, more than 50 % of deceased organ donors are above the age of 55. There is an increased risk of transmission of non-detected and untreated malignancies in this older donor group.

The risk of transmission of rare infections is also increasing with climate change and with higher global mobility of both people and goods. For instance, some infections have spread rapidly from localised regions to more or less worldwide, for example West Nile virus.

Careful assessment of donors is necessary in order to minimise the risk of transmission of infections or malignancies to the recipient. Transplant physicians have to weigh the risk of disease transmission against the risk of the patient dying while on the waiting list. By refusing an allocated organ, the patient might die or his/her clinical condition might deteriorate to the extent that a transplant is no longer feasible.

This risk–benefit analysis is not possible without thorough knowledge of the donor. Careful evaluation of the medical history, travel history, behavioural risks and history of malignancies is necessary. Of course, every donor needs careful medical evaluation.

The following Alliance-O classification of risk levels (RL) regarding disease transmission is widely accepted (except for malignancies) [3]. Note that this is not an assessment in relation to organ function, but only considering the donor:

a. Standard risk donor or Standard risk (RL 5)
Includes cases where the evaluation process did not identify a transmissible disease.

b. Non-standard risk donor with 'Not assessable risk' (RL 4)
Includes cases where the evaluation process does not allow an appropriate risk assessment for transmissible diseases.

c. Non-standard risk donor with 'calculated risk' (RL 3)
This criterion refers to protocols for elective transplants. It includes all cases where, even in the presence of transmissible diseases, transplantation is allowed for recipients with the same disease or with a protective serological status. It also includes donors with broad spectrum antibiotic therapy of a minimum duration (24 h) and those with documented bacteraemia who have started targeted antibiotic therapy.

d. Non-standard risk donor with 'increased but acceptable risk' (RL 2)
Includes cases where transmissible organisms or diseases are identified during the evaluation process of the donor, but organ utilisation is justified by the specific health situation of the recipient or the severity of her/his clinical condition.

e. Non-standard risk donor with 'unacceptable risk' (RL 1)
Absolute contraindication to organ donation, with the exception of some life-saving transplant procedures in the absence of other therapeutic options on a case-by-case basis.

In donors with previous malignancies, the following classification should be used in order to maintain consistency with international studies:

a. Minimal risk
Donor acceptable for all organs and all recipients.

b. Low to Intermediate risk
Donor acceptable, justified by the specific health situation of the recipient or the severity of his/her clinical condition, based on a risk–benefit analysis.

c. 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 recipient.

d. Unacceptable risk
Absolute contraindication due to active malignancy and/or metastatic disease.

7.1.2. Risk assessment due to assumed reduced graft quality

The concept of ECD was developed by the United Network for Organ Sharing to recognise the fact that not all deceased donor organs provide a similar outcome for transplant recipients. Efforts to define ECD in Europe have, so far, been inconclusive, specifically because there are no complete follow-up data available.

Due to different pre-conditions, data from the US may not be transferable to the European context, for example regarding donor risk index calculations [4, 5]. However, one recent German study on expanded donor criteria concluded that only donor age was a risk factor for graft survival in liver transplantation [6].

A programme initiated in Europe which matches kidneys from donors above the age of 65 to recipients above the age of 65 (the Eurotransplant Senior Program) has been successful [7, 8]. As noted by the Dopki project, donors aged 60 years or over represent more than 30 % of all deceased donors in Italy, France or Spain, but less than 10 % in some other countries, while everywhere the general tendency is a growing age of donors [9].

7.1.3. Risks not associated with the donor or organ assessment

Further risks for transplant recipients are those associated with the transplantation procedure (including 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. There are risks to the recipient of a new outbreak of latent infectious diseases under immuno-suppression, such as re-activation 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 such as re-activation of CMV as well as pre-existing (and presumably cured) malignancies.

Little is known about the frequency and 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.

7.2. General donor selection criteria

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 so-called 'critical donors' become actual donors. Thanks to this experience, knowledge of transmission risks is expanding. However, according to national regulations, 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 general exclusion criteria (associated risk levels are shown in brackets according to section 7.1.1):

a. Rabies (RL 1).

b. Active tuberculosis, except in some cases of concomitant infection in recipients (RL 1-2)

c. Symptomatic HIV disease like Aids (RL 1).

d. HIV-positive or hepatitis-positive donors can be considered suitable under experimental or specific conditions. Flowcharts on HIV- and HBV/HCV testing are provided in section 8.4.1.1 for donors with a standard risk, as well as donors at increased risk of having acquired one of these specific infections, for example, through behavioural risks especially during window period (RL 1 or 4, depending on experimental protocols in special cases according to section 8.4.2.11).

e. Viral hepatitis (RL 2): depending on national regulations, organs from HBsAg- or HCV-positive donors may be used for HBsAg- or HCV-positive recipients, respectively. Furthermore, a donor who is HBsAg non-reactive but HBc-antibody reactive is acceptable as a donor (RL 2-3), but it must be considered that HBV can be hidden in the liver while all other organs may be free of HBV. For donors who are anti-HCV reactive and without viraemia confirmed, actually allocation of organs to recipients without HCV viraemia can be considered as outlined in section 8.4.2.7.

f. A long list exists of infectious diseases that have been transmitted with organs, as out-

lined in Chapter 8. There is no reason to believe that a disease could not be transmitted with an organ, independently of how well the graft has been perfused during preservation. For the occurrence and/or prevalence of significant transmissible infectious diseases, see the WHO website (www.who.int/ith), the European Centre for Disease Prevention and Control (www.ecdc.europa.eu) or the Centers for Disease Control (wwwnc.cdc.gov/travel) in Atlanta (see Chapter 8).

g. Active malignant neoplasia (with some exceptions: see section 9.4).

h. Severe systemic infections that are untreated or of unknown origin (RL 1). This includes any case of uncertain encephalitis especially of viral origin or febrile meningoencephalitis of unknown origin (see 8.9), as well as sepsis or disseminated, uncontrolled infection (bacterial, viral, fungal, parasitic, active tuberculosis, acute Chagas disease) or infections without option of treatment in a recipient (e.g. rabies).

i. Prion risk: careful consideration should be given to donors treated with extracts derived from human pituitary glands (growth hormone, etc.) (RL 1-2), a family history of Creutzfeldt–Jakob disease or similar transmissible spongiform encephalopathies (RL 1) or donors who have received human *dura mater* (RL 1), corneal or scleral grafts (RL 1-2). Elevated risk for prion disease requires a case-by-case decision (see section 8.8).

j. The use of live vaccines (e.g. varicella–zoster virus) within the 4 weeks before death (or living organ donation) is not an absolute contraindication, but it requires special consideration in terms of transmission risks (RL 1-5).

k. Depending on guidelines of death determined by neurologic criteria, in some countries anencephaly is an exclusion criterion for DBD while other countries follow a protocol of controlled DCD.

Where recipients are already infected with a transmissible disease, specific risk assessments become necessary, with an associated revision of individual risk levels.

Behavioural risks for HIV, HCV, HBV and other transmissible infectious diseases (see section 8.2) should be evaluated according to the type of graft and urgency required.

The factor of age and its associated co-morbidities should be evaluated according to the organ specific selection criteria.

For any other systemic disease, the pragmatic pathway shown in Table 7.1 can be used as a checklist on how to handle the case when a rare disease is not covered within the scope of Chapters 8-10.

Table 7.1. **Checklist of a pragmatic pathway for the assessment of donors and grafts concerning suitability for transplantation in cases of a rare disease where insufficient data are available**

Question 1: Has a successful transplant already been carried out where the donor was known to have had such a disease? What was the outcome and how were other organs affected in this recipient (e.g. www.notifylibrary.org)?
Question 2: Were all additional resources/sources of information checked (e.g. www.orpha.net for rare diseases)?
Question 3: 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 4: 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?
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.

Infections, malignancies and other diseases transmitted with a graft expose the recipient to unexpected 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 7.2 provides a summary of risk factors limiting successful donation. These should be considered in order to make final conclusions about donor suitability.

Table 7.2. **Summary of general conditions in the donor which can be risk factors for successful transplantation**

Condition	Conditions that might be limiting for successful donation
Acute	*Unfavourable – but avoidable* Prolonged hypoxia + hypotension (except for initial shock, resuscitation or intervention), prolonged + excessive catecholamine application before procurement without volume-resuscitation, untreated diabetes insipidus (hypernatremia). For prevention and care of such conditions see Chapter 5. *Irreversible* Acute multiple organ failure without chance of recovery as well as chronic organ insufficiency with structural damage or irreversible organ failure requires a case by case decision.
Infections	Bacterial infections: 48h definitively effective antibiotic therapy sufficient (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. Usually these infections must be cured but, after a case-by-case decision, selected recipients can have an organ transplanted successfully because either treatment is available or recipient-related infection treatment is mandatory (e.g. hepatitis B- and hepatitis C-matched recipients can receive a transplant). CMV, EBV and toxoplasmosis: chemoprophylaxis in recipient is mandatory if D+/R–. HIV: in the future, in countries with high HIV prevalence, in controlled studies, transplant of HIV-matched organs will be considered (D+/R+) from donors without viraemia. Until final results of such transplantation procedures become available, in most countries HIV reactive tests (serology or PCR) preclude organ donation. Special consideration should be given to appropriate diagnostics for exclusion of asymptomatic infection by HIV, HBV or HCV as well as HTLV I/II virus, *Trypanosoma cruzi*, etc. in donors who originate from endemic areas for these infections or at risk for vertical transmission. In donor populations at an increased risk for HCV or HIV-infection, besides serology testing, NAT is recommended in order to rule out window period infections. In some infections, the combination of D+/R+ can be considered after exclusion of additional risk factors (e.g. HCV). Further details: see Chapter 8.
(Previous) Malignancies	Depends on tumour: Individual decisions on a case-by-case basis. • Primary brain tumour according to WHO grading (with additional risk factors in cases of destruction of the blood-brain barrier by resection, shunting, chemo- and/or radiotherapy) • Other malignancies according to kind of tumour, stage, grade, time of diagnosis and performed therapy • Further details: see Chapter 9.
Poisoning	For appropriate determination of brain death, detoxification usually becomes mandatory. After recovery from poisoning, each organ should be individually evaluated. Further details: see Chapter 10.
Inherited or rare diseases	Individual decisions on a case-by-case basis: systematic reports are not available. For further information, visit www.orpha.net to see emergency guidelines for each disease. Systemic diseases with possible effects on graft quality (e.g. collagen disease or systemic vasculitis) require additional considerations or examinations. Further details: see Chapter 10.
Age-related co-morbidities	With advanced age the frequency of arterial hypertension, diabetes, obesity and side effects of chronic alcohol abuse and smoking increases. Finally, beyond cardiovascular risks including progressive arteriosclerosis, irreversible organ damage may occur to different degrees which require an individual assessment for each organ. Further, properly treated arterial hypertension and diabetes as well as a lifestyle including enough physical activity may compensate 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 after donation.

CMV: Cytomegalovirus; D/R: Donor/Recipient; EBV: Epstein–Barr virus; HBV; Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HTLV: Human T-lymphotrophic virus. NAT: Nucleic acid test.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

7.3. Organ-specific selection criteria

Acceptance criteria for organs are mainly based on an assessment of the functioning 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 surgical technique 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 donor selection criteria and management is to avoid this condition of non-function, although these events are often not donor-related. The second priority is to avoid transmission of a damaged organ becoming long-term harm. Daily clinical practice demonstrates that many transplanted organs function well although originally they did not seem to fulfil selection criteria published previously [10]. 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 [10].

Despite the well-documented risks of disease transmission, malignancy, toxicity or inherited diseases (see Chapters 8-10), no evidence-based studies exist in Europe to assist the definition of ECD. In the US, liver- and kidney-specific donor risk indices were derived from the national transplantation registry (UNOS/SRTR) [4-5]. Whether these indices are applicable in a European context has yet to be determined. One German multi-centre study could not confirm a monotonic relationship between increasing donor risk index values and the risk of graft failure in liver transplantation [6]. Furthermore, prevalence of risk factors like arterial hypertension or diabetes varies in the donor populations – especially after adjustment for age. This requires careful analysis of all studies used in order to identify the relevant criteria for classifying a graft as ECD-graft or not. Tables 7.3 to 7.8 summarise risk factors justifying the use of the term ECD as 'Conditions that might be limiting for successful donation'.

Beyond the general acceptance criteria as outlined in the previous section 7.2, specific acceptability criteria for different organs are discussed in the following sections with a focus on DBD. They can be used for DCD when the additional risks due to the agonal period and/or warm ischaemia time prior to organ preservation are considered as outlined in Chapter 12. For living donors, the data here show a minimum set of selection criteria, which are further verified in Chapter 13.

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. By contrast, for living donation it is a safe procedure to evaluate whether ABO incompatibility can be overcome by desensitisation protocols [12].

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 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, then transplantation can be considered with informed consent of the recipient [10, 13-15]. Re-use of previously transplanted grafts is possible [10, 16-18] although after many years of a graft *in situ*, adhesions or complications due to chronic or subclinical rejection may limit successful procurement and transplantation, which requires a case-by-case decision [17].

In any donor, as a result of previous surgeries, adhesions might be a challenge or a limitation for successful procurement but should not be considered as an exclusion criterion. The same can be said for previous trauma, where without inspection during procurement, no final assessment is possible.

In the case of damage to the central vessels (e.g. aorta, vena cava), in a first step procurement, techniques should be considered equivalent to procurement of a graft for living donation and in a second step the vessels supplying the organ must be carefully inspected at procurement.

7.3.1. Renal-specific selection criteria

a. Age

Generally no age limit applies [19] although grafts procured from elderly or advanced age donors should be used in elderly recipients due to the limited duration of graft function (e.g. Eurostransplant Senior Program) [7-8]. Many studies have concluded that increasing donor age is associated with an increased risk of graft failure, especially in cases where donor age exceeds the seventh decade of life [19, 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 [24-25]. Usually, local protocols taking into account the recipient's condition, exist for handling this issue.

b. Clinical history

Chronic hypertension, diabetes mellitus, albuminuria and chronic kidney disease are typically considered as risk factors for inferior outcome after kidney transplantation, after adjustment for donor age and quality of care and treatment for the aforementioned problems [26-29].

c. Renal function and morphology

Consideration should be given to urine output, current and previous serum creatinine levels, estimated glomerular filtration rate or creatinine clearance in living donors or obtained from a stable period of life before hospital admission, urea, albuminuria or proteinuria, urinary sediment, ultrasound of the kidneys and urinary tracts.

In case 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 should be

assumed when, during the previous 3 months, either severely decreased kidney function or severely increased albuminuria, or both moderately decreased kidney function and moderately increased albuminuria, existed according to the KDIGO-Guidelines [30]. Unfortunately, this cannot be concluded when only the data of the most recent hospital stay are available.

Acute impairment in donor renal function may not necessarily be a contraindication, since it may be reversible (RL 2-3). In case of acute tubular necrosis without cortical necrosis, results are good [31-33].

d. Macroscopic appearance and perfusion

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). Depending on local regulations, limited warm ischaemia may be acceptable for kidneys. In every solid mass not equivalent to renal parenchyma or cysts, malignancy should be ruled out; the mass should be removed as Ro resection with appropriate preservation of the rest of the graft in order to permit later transplantation and investigation by histopathology.

e. Biopsy

Biopsy of organs is helpful for assessment of older donors and donors with vascular pathology, a history of hypertension, diabetes or a brain haemorrhage of unknown cause. 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]. Other groups prefer the Banff grading used for kidney biopsies after transplantation, in order to assure compatibility with subsequent biopsies. Pre-implantation biopsies are not done systematically in all Eurotransplant countries because there is general agreement in the Eurotransplant community that the added value of routine biopsy is limited when it comes to predicting intermediate or long-term function of donated kidneys. Therefore kidney should not be discarded based on biopsy results.

Table 7.3. **General conditions in the donor that can be risk factors for successful kidney transplantation**

Kidney	Conditions that might be limiting for successful donation
Acute changes	Abdominal trauma, acute kidney injury (reversible or irreversible with/without anuria due to hypo-perfusion/shock or other reasons). Acute kidney injury may occur as complication of the acute illness independently of chronic damage. Acute changes are often reversible and final determination should be done during procurement.
Previous diseases	Arterial hypertension + arteriosclerosis, systemic diseases or chronic kidney disease with albuminuria (> 30mg albumin/g creatinine in the urine) or proteinuria (> 1g protein/g creatinine in the urine), diabetes or age-related co-morbidities: always, the quality and success of treatment determines whether irreversible damage to the organ exists or not, which can only be seen by macroscopic (and histologic) assessment at procurement. In the case of diabetes, contact with the family physician may provide information about renal damage such as albuminuria or renal function (obtaining these parameters during acute stay at intensive care unit might be misleading). Grafts without increased proteinuria can be used successfully Kidneys of donors with weight > 2.7kg can be transplanted (*en bloc*, if body weight > 5-10kg single). Beyond 80 years of age, functional impairment might be compensated by double transplantation since advanced donor age (> 70-80 years) is associated with a reduction of nephron mass which may not become evident through measurement of creatinine levels. Creatinine levels are not always representative of renal function, due to haemodynamic deterioration or volume depletion during the acute process of donor maintenance.
Intraoperative decision	Morphology, arteriosclerosis of arteria renalis (orifice from aorta and branches). In case of acute kidney injury, grafts without obvious necrosis can be used for transplant.
Helpful diagnostics	General + kidney-function parameters, urine-status/sediment; optional: exclude albumin-/proteinuria, urine-culture. Precise description of kidney morphology (quantitative: length × width × parenchyma thickness + structure)
Non-renal diseases	It should be checked whether these diseases affect the kidney or not. In the case of transmissible diseases, the principles outlined in Chapters 8-10 should be respected. Opinions on the lifesaving importance of kidney transplantation vary from centre to centre despite the known risks of morbidity or mortality when remaining on dialysis.
Remarks	Risk scores: scoring systems for expanded donor criteria developed in other countries (e.g. US) require adjustment to the population of the donor country. Allocation of kidneys from donors older than 65 years to recipients older than 65 years is established in many countries (in many studies, with increasing donor age the risk of kidney function loss is increased in midterm).
DCD	In controlled and uncontrolled DCD, despite exposure to prolonged ischaemic episodes, functional recovery of the kidney is possible without impairment of long-term function [38-43] although DGF may occur and a left-over risk of PNF exists.

DCD: donation after circulatory death; DGF: delayed graft function; PNF: primary non-function.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

En bloc and single kidney transplantation from small paediatric donors (e.g. < 10 kg) has been demonstrated to be possible and successful [34-37].

Such kidneys may be allocated to two different appropriate recipients. 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. It is inappropriate to separate kidneys removed *en bloc* and then to use one just to generate a vascular patch for the contra-lateral graft.

Table 7.3 summarises conditions in the donor that can limit successful outcomes after kidney transplantation.

7.3.2. Hepatic-specific selection criteria

a. Age
Generally there is no age limit although with increasing age the risk of failure may be elevated due to arteriosclerosis of the small vessels of the biliary tract [44-60].

b. Clinical history
Prior viral, alcoholic or fatty liver disease, previous hepato-biliary surgery, uncontrolled abdominal infections, intoxication affecting liver function and liver trauma are typically considered as risk factors for inferior outcomes after liver transplantation.

c. Hepatic function
Consideration should be given to liver transaminases (alanine aminotransferase [AST] or aspartate aminotransferase [ALT]), serum bilirubin, alkaline phosphatase, LDH, albumin and coagulation tests. Evaluation of liver enzymes should take clinical history into account with respect to hepatic and non-hepatic causes of deviation.

d. Hepatic morphology
Liver ultrasonography may be used to exclude obvious fatty liver degeneration, cirrhosis and fibrosis or any morphological abnormality. It is recommended to confirm the result intraoperatively.

e. Macroscopic appearance and perfusion
It is important to evaluate 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 fatty degeneration can be evaluated using peri-operative biopsies [44, 46-48, 59, 61-65]. 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 [66-67].

Table 7.4. **General conditions in the donor that can be risk factors for successful liver transplantation**

Liver	Conditions that might be limiting for successful donation
Acute changes	Trauma, reduced synthesis, coagulation, CVP elevated, acute v. chronic right heart failure. Historic data for the following – cardiac arrest or hypotensive periods, ICU Stay > 7 days, use of vasopressors, acute kidney failure, etc. – do not preclude liver donation [10].
Previous diseases and/or hepatotoxic medication	Viral infection, malnutrition (e.g. alcohol), confirmed macro-vesicular steatosis (~elevated BMI), fibrosis, cirrhosis. Without steatosis, no age-limit (0-100 years).
Intraoperative decision	In livers without morphologic changes the only limitation for a liver split is the vascular anatomy. Assessment of steatosis and fibrosis in correlation with biopsy result (see Appendix 9). A subcapsular biopsy may not be representative for the whole organ due to localised lobular changes. In case of steatosis, only the macro-vesicular steatosis is important (30 %-60 % of the hepatocytes are affected = increased risk for primary non function; >60 % of the hepatocytes are affected = primary non-function very likely). Severe arteriosclerosis may not harm the hepatocytes but is a risk factor for damage to arterioles of the bile ducts. In this case, an appropriate flush with preservation solution during procurement must be carried out.
Helpful diagnostics	General + liver and kidney-function parameters, coagulation, protein. Ultrasound abdomen should describe size in MCL, edge and echogenity of parenchyma compared to kidney parenchyma. If stable coagulation and experienced team, biopsy before procurement can be considered if safely possible.
Remarks	Risk scores: scoring systems for ECDs developed in other countries (e.g. Donor Risk Index in the US) require adjustment to the population of the donor country. Many studies confirm that ECDs do not limit the outcome of liver transplantation especially after proper recipient selection [10, 44]. Proper matching of donor and recipient after critical risk–benefit assessment may result in different utilisation rates for specific cases.
DCD	In uncontrolled as well as controlled DCD, liver can be recovered and transplanted. Depending on the study compared to DBD there is a more or less higher risk for DGF, PNF or ischaemic type biliary tract lesions [10, 73-77].

BMI: body mass index; CVP: central venous pressure; DBD: donation after brain death; DCD: donation after circulatory death; DGF: delayed graft function; ECD: expanded criteria donor; ICU: intensive care unit; PNF: primary non-function.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

Unfortunately, there are no internationally agreed 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, macro-vesicular fatty degeneration is associated with a high risk of primary non-function or dysfunction of the graft after transplantation, whereas micro-vesicular degeneration is not. Moreover, allocation of a liver with some fatty degeneration might not be advisable for a recipient with a high model of end-stage liver disease (MELD) score, whereas allocation to another specifically selected recipient with a better clinical

status, or with a malignancy as the underlying disease, can be helpful in particular cases (with the risk of initial dysfunction or the need for re-transplantation). There is no consensus on the use of critical grafts and selection of the appropriate recipient at different MELD scores. Many surgeons do not transplant liver grafts with a macro-vesicular steatosis affecting more than 60 % of the hepatocytes. A level of more than 30 % is assumed to be critical for primary non-function [68-72]. The degree of micro-vesicular steatosis does not affect the outcome of liver transplantation [64-65, 72].

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.

Table 7.4 summarises donor conditions that may limit the outcome of liver transplantation.

7.3.2.1. *Remarks about initial donor and organ assessment*

ECDs are assumed to be associated with an increased risk of PNF or DGF [78-79] since compromised liver grafts have a poor tolerance to ischaemia/reperfusion injury (IRI) [80] due to complex pathophysiological interactions [81]. From clinical experience, ECD criteria associated with increased graft failure rates are donor age > 65 years, serum sodium > 155 mmol/L, macro-vesicular steatosis > 40 %, cold ischaemic time > 12h [82], split-liver grafts [83], DCD grafts [84] or haemodynamically compromised donors. Nonetheless, experienced transplant centres overcome such restriction and they successfully use grafts from donors with a hospital stay > 7 days, body mass index (BMI) > 34.9 kg/m^2, maximum AST or ALT > 500 IU/l and maximum bilirubin > 2.0 mg/dl [85].

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 hyperlipidemia. Literature supports the use of liver grafts from upper extremes of age [86-87] when routine biopsy excludes relevant fibrosis, macro-vesicular steatosis etc. With advanced age the prevalence of obesity increases [88] as well as the risk of macro-vesicular steatosis of the hepatocyte – which is observed in 9 % to 26 % of the procured livers [89]. 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 upregulation [90, 91]. This causes poor outcomes when grafts are used with such moderate or severe steatosis in addition to the above mentioned IRI [92]. The macroscopic view of the liver combined with its histology is of crucial importance. The biopsy is mandatory to exclude hepatic ischaemia with necrosis of hepatocytes, inflammation, fibrosis and the percentage of steatosis.

Hypernatremia as a complication of diabetes insipidus is known to be associated with a high probability of PNF. The critical effect on the graft is thought to be the result of cell swelling, increased osmolality during IRI. Thereby 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 [93].

Abnormal liver biochemistry *per se* does not exclude the use of these organs for transplantation. 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 this event allowing recovery from dysfunction especially in younger donors [94]. 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 from each other. It is possible that with novel preservation techniques available, grafts with severe dysfunction prior to procurement can be resuscitated *ex situ*.

7.3.3. Cardiac-specific selection criteria

a. Age

This depends on local protocols and the condition of the recipient. 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 [95-105], although some successful transplants have nevertheless been reported [95, 98-100].

Table 7.5. **General conditions in the donor that can be risk factors for successful heart transplantation**

Heart	Conditions that might be limiting for successful donation
Acute changes	Recovery from trauma, cardiac resuscitation, temporary arrhythmias or 'broken heart syndrome' due to neuro-cardiac lesions (reduced left ventricular function, wall motion disorders). Use of inotropic catecholamines with indication due to decreased cardiac output. Temporarily stunned myocardium due to neuro-cardiac disease should be given time to recover – then the heart can be used safely. Temporarily impaired right ventricular function should be given time to recover – then the heart might be used for a recipient without risks due to pulmonary hypertension. Poisoning from carbon monoxide or other agents requires a critical assessment of recovery from intoxication and successful detoxification.
Previous diseases	Exclusion if infarct, severe valve abnormality (stenosis, insufficiency > 1 °), coronary heart disease with diffuse sclerosis or severe stenosis of multiple vessels or critical location of stenosis, dilative cardiomyopathy, endocarditis without option for intervention etc., chronic right and left ventricular dysfunction. Minor morphologic abnormalities (e.g. open foramen ovale, atypical venous drainage of coronary vessel, previous correcting heart surgery etc.) require a case-by-case decision. The risk of coronary sclerosis starts to increase at an age beyond 44-55 years in cases wherew there are other risk-factors (high blood pressure, diabetes, tobacco use, even in combination with alcohol abuse, age, hyperlipidaemia, cocaine abuse): to be verified by donor evaluation; minor stenosis or wall sclerosis detected by coronary angiography require a case-by-case decision. Severe left ventricular hypertrophy is a risk factor (IVSd > 16 mm in adults), moderate hypertrophy a minor risk (IVSd12-16 mm in adults). 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. Arrythmogenic hearts may not be used for every recipient since the risk of 'arrhythmia transmission' still exists even when morphologic reasons have been excluded and implantation of automated implantable cardioverter-defibrillator is considered.
Intraoperative decision	Pumping function and wall motion, coronary sclerosis, aorta and heart valve morphology, contusion marks, anatomic variants. Cold ischaemia time foreseen > 4-5 h (net transport time > 2-3 h) in case of hypothermic preservation.
Helpful diagnostics	General + electrolytes + Troponin (CPK/CPK-MB outdated), echocardiography, coronary-angiography if indicated and possible. Important: precise description of the heart morphology and function.
DCD	Currently under development in Europe.

DCD: donation after circulatory death; CPK: creatine phosphokinase.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

b. Clinical history

Prior cardiac diseases (e.g. pathologies at the heart valves, ischaemic heart disease), left ventricular hypertrophy (e.g. caused by hypertension), risk factors for CAD or cardiomyopathy (e.g. diabetes mellitus, history of smoking, high alcohol consumption, arteriosclerosis, hyperlipidaemia, abuse of substances such as cocaine), thoracic trauma, time spent in an ICU during recovery from neuro-cardiac injury after major cerebral lesions, cardio-respiratory arrest and body surface area measurements are typically considered as risk factors for inferior outcome after heart transplantation.

c. Investigation for acute myocardial ischaemia

This should include tests for enzymatic changes such as troponin (either I or T), creatine phosphokinase (CPK) and CPK-MB fractions (with due consideration of all causes for elevation due to non-cardiac tissue damage [104-105]), which should take clinical history and evolution into account. Electrocardiograms should be (or have been) normal. Atypical re-polarisation can be accepted under certain conditions, especially when clearly related to cerebral complications. Arrhythmia or diseases with arrhythmogenic potential (e.g. long QT-syndrome) limit the success of transplantation.

d. Morphological examinations

Echocardiography should evaluate contractility, 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 [4, 106-107]. Chest X-rays are required. 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 [103, 106, 107-111]. 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.

e. Haemodynamics 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 and perfusion

Consideration should be given to macroscopic appearance, contractility, coronary artery palpation and morphology of valves or aorta.

Table 7.5 summarises donor conditions that may limit the outcome of heart transplantation.

7.3.3.1. *Remarks about initial donor and organ assessment*

The complications of temporary neurocardiac injury after devastating cerebral injuries with or without cardiac arrest must be taken into account as one reason for reversible increase in heart enzymes. As the level of 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) [112] but increased donor Troponin levels themselves should not preclude heart transplantation as experienced centres achieve acceptable results after appropriate recipient selection and short ischaemia times [105].

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) [113]. 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 [114-116]. 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 [117]. Methylprednisolone i.v. remains beneficial [118].

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 [95]. Although echocardiography is very effective as a snapshot assessment of function, assessment can also be achieved by invasive haemodynamic investigations (see Tables 5.1 and 5.2) which may contribute to 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 [104].

Careful donor and recipient selection should be carried out, especially in donors with recovery from cardiocirculatory instability while adhering to recommendations [119]. 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.

7.3.4. Pulmonary-specific selection criteria

a. Age

This 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 [10, 120].

b. Clinical history

A history of pulmonary disease or smoking, active pulmonary infection, aspiration, purulent secretions, thoracic trauma and previous thoracic surgery are typically considered as risk factors for inferior outcomes after transplantation.

c. Lung function

This should be assessed in order to exclude organs with inadequate gas exchange. Functional data about gas exchange measured at a minimum Positive End Expiratory Pressure (PEEP) of 5.0 cm H_2O, and temporarily at 1.0 FI_{O_2} (10 minutes), allow easier exchange of information between transplant personnel. For this measurement, bronchial cleaning and recruitment of atelectasis must be performed in advance. At least in every donor younger than 80 years with a paO_2/FIO_2 of > 250 mmHg, lung donation should be considered after proper assessment and recruitment of atelectasis. Donors with reduced lung function can still be considered for single lung donation. See Appendix 8.

d. Morphological examinations

Chest X-ray is mandatory and, if indicated, a CT-scan. Bronchoscopy is performed by most procurement teams 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.

e. Macroscopic appearance and perfusion

Consideration should be given to the colour of the lungs, presence of atelectasis, tumours, water content of the tissue and appropriate

insufflations. Single lung transplantation is possible for selected recipients in the case of one lung being unsuitable. Some cases of pneumonia may not be detected until procurement of the lung.

Table 7.6 summarises donor conditions that may limit the outcome of lung transplantation.

Table 7.6. **General conditions in the donor that can be risk factors for successful lung transplantation**

Lung	Conditions that might be limiting for successful donation
Acute changes	Deterioration of gas exchange with $paO_2/FI_{02} < 250$ mmHg (< 33.3 kPa) with PEEP = 5 cmH_20, kind of recovery from trauma/contusion, aspiration, inappropriate ventilation, fever, fluid overload, transfusion associated lung injury. absolute exclusion criteria: acute pneumonia, intra-parenchymal bleedings due to contusion.
Previous diseases	Case-by-case: asthma, other parenchyma changes (e.g. micro-emphysema), Absolute exclusion criteria: COPD, irreversible structural damage to the lung parenchyma
Intraoperative decision	Inflammation (consider early pneumonia), parenchyma (water content: consider neurogenic lung oedema), contusion, recruitment of atelectasis, pleural adhesions.
Helpful diagnostics	Ventilator setting + blood gases after proper recruitment of atelectasis (< 4h) + X-ray-thorax (<8h), bronchoscopy with BAL (culture, staining).
Remarks	Single lung donation should always be considered when one lung is deemed unsuitable. Lung donation should be considered in every donor with PaO_2/F_iO_2 >250 mmHg (>33.3 kPa) and age below 80 years and no evidence of pneumonia. In case of $PaO_2/F_iO_2 < 250$ mmHg (< 33.3 kPa), blood gas samples drawn intra-operatively from the pulmonary veins help to identify which segment and lobes perform an appropriate or a poor gas exchange. This allows decisions about using a single lung or certain segments of the lung lobe (size reduction). Donor/recipient over-sized ratio can be overcome by resection of segments.
DCD	Lungs can be successfully transplanted from both uncontrolled and controlled DCD donors [10, 121-122]. See Chapter 12.

BAL: broncho-alveolar lavage; COPD: chronic obstructive pulmonary disease; DCD: donation after circulatory death; PEEP: positive end-expiratory pressure.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

7.3.4.1. *Remarks about initial donor and organ assessment*

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 [123-125]. 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 [126-127]. In some studies smoking history in lung donors is associated with decreased recipient survival, [128] but this is still higher than when remaining on the waiting list [129]. Other studies could not confirm a relevant impact on long-term survival [125, 130-132]. 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 % of cases [133]. All patients transplanted with such infiltrates were alive at one year of follow-up. Plain chest X-rays taken at the bedside are of low sensitivity and only CT scans may properly estimate structural abnormalities like minor contusions or small infiltrates. Donors with strong unilateral abnormalities should not be excluded for donation of the contralateral lung [134]. Finally evaluation of a donor chest X-ray is highly subjective, which limits its value for determining organ suitability [135]. 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 [136-136]. Positive donor gram stain did not predict post-transplant pneumonia, oxygenation, or duration of post-transplant mechanical ventilation [139-141]. The Newcastle group reported decreased survival in a group of patients with positive cultures of donor broncho-alveolar lavage (BAL), suggesting that lower airway colonisation may be indicative of an increased risk for post-operative graft infection and dysfunction [142]. 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 [143]. 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 [144]. 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. Donor management for improving initially poor gas exchange is important (see section Table 5.3). Steroid administration after brain death is associated with an increase in paO_2/FIO_2 [117-118].

7.3.5. Pancreatic-specific selection criteria

a. Age
This depends on local protocols. Traditionally many centres are reluctant to use pancreases from donors older than 50 years despite some good results after a careful donor selection [145-147]. 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 [145].

b. Clinical history
Prior pancreatic disease, alcoholism, diabetes mellitus, history of arterial hypertension, active abdominal infection, abdominal trauma (especially deceleration trauma of the mesenteric root), significant number of days spent in the ICU (due to the development of pancreatic oedema), cardio-respiratory arrest and resuscitation manoeuvres are all typically considered as risk factors for inferior outcomes after pancreas transplantation.

c. Pancreatic function
This may be assessed by factors other than glucose and insulin requirements, pancreatic enzymes and calcium levels. Evaluation of pancreatic enzymes should take clinical history and previous trauma into account. Some donor maintenance protocols recommend insulin treatment, among other hormones. Many patients with severe head trauma become hyper-glycaemic and require insulin therapy, despite normal pancreatic function and no history of diabetes.

d. Morphological study
This can be assessed by pancreatic ultrasonography, magnetic resonance imaging (MRI) or other imaging (e.g. trauma CT on admission).

e. Haemodynamics
Uncontrolled severe hypotension and cardiac/pulmonary arrest profoundly compromise the quality of pancreatic organs outside the issue of DCD.

f. Macroscopic appearance and perfusion
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 or bleeding. Peri-pancreatic haematomas or capsular tears are risk factors for graft pancreatitis. Elevated intra-capsular fat content is an additional risk factor for post-transplantation-pancreatitis.

Table 7.7 summarises donor conditions that may limit the outcome of pancreas transplant.

Table 7.7. **General conditions in the donor that can be risk factors for successful pancreas transplantation**

Pancreas	Conditions that might be limiting for successful donation
Acute changes	See liver: glucose-metabolism is frequently deregulated during stay at ICU. Critical are abdominal trauma (e.g. deceleration of mesenteric root).
Previous diseases	See liver and arterial hypertension, arteriosclerosis, risk for pancreatitis, risk of intracapsular lipomatosis with increased BMI, overlap with manifestation of diabetes mellitus type II possible in ages over 50-65 years, alcoholism (independent of age as risk factor for chronic pancreatitis).
Intraoperative decision	Assessment by experienced pancreas surgeon essential: intra-parenchymal/-capsular fat, fibrosis, induration, trauma, pancreatitis (despite toxic causes and without evidence in imaging or laboratory parameter), induration. Abnormalities of vascular in- and outflow often exist. This may compromise pancreas procurement in case of intestinal and liver procurement for other recipients (branches of A./V. mesenterica superior and Truncus coeliacus).
Helpful diagnostics	See liver, amylase=unspecific (prefer to use only pancreas-specific-amylase or lipase), history of diabetes, hypertension or alcohol consumption. Imaging studies for acute trauma.
Remarks	Prediction of graft quality by risk scores, e.g. P-PASS, does not correlate with situs found at procurement. Therefore an experienced pancreas surgeon should inspect the graft.
DCD	Currently under development. Successful results with pancreas transplanted from selected controlled DCD donors have been reported.

BMI: body mass index; DCD: donation after circulatory death.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

7.3.6. Intestinal-specific selection criteria

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.

a. Age
Depends upon local protocols. Some centres have successfully used grafts from donors older than 50 years [148-151]. In any donor aged 0-50 years, intestinal donation must be considered [10, 148-149].

b. Body weight and donor size
Donor weight should preferably be lower than recipient weight. The major obstacle in intestinal transplantation is the size match, in terms of both weight and length, between donors and recipients. Typically, recipients have retracted abdominal cavities [149].

c. Clinical 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, abdominal trauma (especially deceleration trauma to the mesenteric root), previous intestinal illness or unexplained diarrhoea. Enteral nutrition is essential for preserving intestinal function (if possible after failure of vagal nodes in DBD). There is no evidence for other specific pre-treatment requirements [149].

d. Gastro-intestinal and liver evaluation
Serum electrolytes, liver function tests and liver enzymes should be considered. Evaluation should be undertaken of intestinal motility, and the use of vaso-active drugs with a vaso-constricting effect.
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 [149-151].

e. Intestinal morphology
This can be assessed by abdominal ultrasonography to exclude ascites, other lesions and tumours. Abdominal X-ray or CT-scan may be used when appropriate.

f. Macroscopic appearance and perfusion
Macroscopic appearance, intestinal peristalsis, 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.

Table 7.8 summarises donor conditions that may limit the outcome of small bowel transplant.

Table 7.8. **General conditions in the donor which can be risk factors for successful intestinal transplantation**

Intestine	Conditions that might be limiting for successful donation
Acute changes	See liver and pancreas. Hospital stay >5-7 days without enteral nutrition.
Previous diseases	See liver and pancreas, arterial hypertension, alcoholism, arteriosclerosis, increased BMI>28 kg/m^2, age >50-65 years due to overlap with manifestations of other chronic diseases.
Intraoperative decision	Assessment by experienced intestinal transplant pancreas surgeon mandatory from start until end of procurement (e.g. procurement procedure is different if colon is included in the graft). Prolonged hospital stay (> 1 week) increases the probability of intestinal oedema.
Helpful diagnostics	See liver and pancreas. History, all details about abdominal trauma or previous surgery.
Remarks	Intestinal grafts will be often transplanted as a package including more than the small intestine +/- 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).
DCD	Currently no reports about DCD and intestinal donations exist. It is probably not practiced due to the limited data about the effects of acute hypo-perfusion and hypo-oxygenation right before procurement.

DCD: donation after circulatory death.

Source: Andrés A, Fischer-Fröhlich CL. Oran Viability [10]; Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz [11].

Remarks about initial donor and organ assessment

There is widespread confusion over what is an ideal intestinal donor [149]. Current 'ideal donor criteria' are [149-151]: 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 [149]. For donor management, it is important to consider enteral nutrition if possible. The limitation is that intestinal paralysis occurs in many donors due to the lack of vagal stimulation.

7.3.7. 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.

Notably, the donation and transplant process applied to VCAs has important similarities with that of whole organs. The main consideration is their essential vascularisation, in contrast with 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. Morphological matching, skin phototype and ideal donor conditions are important factors. As graft procurement is atypical, reconstruction of the donor body is mandatory. Therefore, it is recommended to fully inform, and obtain specific consent from the relevant parties for these special procedures, beyond the requirements under national regulations.

Owing to the currently limited experience, it is recommended to discuss each potential case with an experienced centre performing VCA transplants.

7.3.8. 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 amongst 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.

7.4. Donor and organ documentation

A database of donor information should be maintained that protects anonymity. In the European Union, 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 following forms (see sections 7.4.1 and 7.4.2) are recommended. Storing of data must be carried out according to the legislation within the member states for at least 30 years (see 7.4.3). Directive 2010/53/EU 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).

7.4.1. Donor information form

The donor information form should contain relevant and sufficient information about the donor to allow evaluation of eligibility for organ donation and to support the allocation process. 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 procurement organisation. The donor records should include the donor information form and the documents as proposed in Chapter 6, as well as the records allowing reproducibility of consent/authorisations and death certificates. This must not be in paper form when an appropriate electronic database exists.

The EU-funded project Foedus [152] is aimed at facilitating exchange of organs donated in EU member states, in particular, through cross-border exchange in the case 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, it has not only mapped barriers to organ exchange and developed an IT tool (to launch quick offers), but it has proposed a short form including donor and organ-specific information enabling potentially interested countries to check within the national waiting lists and so to confirm (or not) their interest in the organs proposed.

7.4.2. Organs report form

This form should contain data concerning donor organs at the time of procurement. It should

be completed by the procuring personnel and verified by the person responsible for procurement or his/her assignee. The time of aortic cross-clamping and the start of cold perfusion, quality of perfusion, anatomical findings and time of organ removal should be detailed. Separate forms should be filled out for each organ to be transplanted.

7.4.3. Donor sample archive

Samples of relevant donor material should be stored for reasons of traceability according to local regulations. A 10-year period is recommended. The samples must be linked to the donor. It is preferable to archive at least serum as well as material containing DNA or RNA for further analysis.

When new or improved mandatory tests are introduced, a decision should be made and recorded regarding the need to re-test archived samples. When no archive samples are available, a risk assessment must be performed.

7.5. Conclusion

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 time as short as possible.

Risk evaluation of 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 life-saving for another recipient. 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 also from these findings and ensure optimised organ use for the future.

A 'customised' donor/organ profile should be produced for each patient enrolled on a transplant waiting list. This approach facilitates planning of adequate donor/recipient risk assessments and the best use of all suitable organs.

The physician performing the transplantation of a graft has overall responsibility for its use in a particular recipient, regardless of the risks present according to the above grading system.

7.6. References

1. Alliance-O (European Group for Co-ordination of National Research Programmes on Organ Donation and Transplantation) [available from: http://ec.europa.eu/research/fp7/pdf/era-net/fact_sheets/fp6/alliance-o_en.pdf, accessed: 30 January 2016].
2. Project Dopki (Improving the knowledge and practices in organ donation): Guide of recommendations for quality assurance programmes in the deceased donation process [available from: www.ont.es/publicaciones/Documents/DOPKI%20GUIA.pdf, accessed: 30 January 2016].
3. Nanni Costa A, Grossi P, Gianelli Castiglione A *et al.* Quality and safety in the Italian donor evaluation process. *Transplantation* 2008; (85): S52-S56.
4. Feng S, Goodrich NP, Bragg-Gresham JL *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; (6): 783-90.
5. Rao PS, Schaubel DE, Guidinger MK *et al.* A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009; (88): 231-6.
6. Frühauf NR, Fischer-Fröhlich CL, Kutschmann M *et al.* Joint impact of donor and recipient parameters on the outcome of liver transplantation in Germany. *Transplantation* 2011; (92): 1378-84.
7. Giessing M. Ten years of the Eurotransplant senior program: are there still age limits for kidney transplantation? *Urologe* A 2009; (48): 1429-37.
8. Giessing M, Fuller TF, Friedersdorff F *et al.* Outcomes of transplanting deceased-donor kidneys between elderly donors and recipients. *J Am SocNephrol* 2009; (20): 37-40.
9. Dopki (Improving the knowledge and practices in organ donation) [available from: http://ec.europa.eu/research/fp6/ssp/dopki_en.htm, accessed: 30 January 2016; and from www.ont.es/internacional/Documents/DOPKI.pdf, accessed: 30 January 2016].
10. Andrés A, Fischer-Fröhlich CL. Chapter 4: Oran Viability: 99-154. In: Valero R, editor. *Transplant coordination manual.* 3rd edition. Barcelona: Aguilógrafic, 2014. ISBN: 978-84-616-8840-1.
11. Fischer-Fröhlich CL, Königsrainer A, Nadalin S. Spenderselektion und neues Transplantationsgesetz. *Allgemein und Viszeralchirurgie up2date* 2012; (5): 339-56.
12. Shin M, Kim SJ. ABO incompatible kidney transplantation – current status and uncertainties. *J Transplant* 2011; 970421.

13. Panis Y, Massault P, Sarfati P *et al.* Emergency liver retransplantation using a polycystic donor liver. *Transplantation* 1994; (57): 1672-3.
14. Jiménez C, Moreno E, García I *et al.* Successful transplantation of a liver graft with a calcified hydatid cyst after back-table resection. *Transplantation* 1995; (60): 883-4.
15. Mor E, Bozzagni P, Thung SN *et al.* Backtable resection of a giant cavernous hemangioma in a donor liver. *Transplantation* 1995; (60): 616-17.
16. Moreno E, García I, González-Pinto I *et al.* Succesful reuse of a liver graft. *Br J Surg* 1991; (78): 813-14.
17. Rentsch M, Meyer J, Andrassy J *et al.* Late reuse of liver allografts from brain-dead graft recipients: the Munich experience and a review of the literature. *Liver Transpl* 2010; (16): 701-4.
18. Pasic M, Gallino A, Carrel T *et al.* Reuse of a transplanted heart. *N Engl J Med* 1993; (328): 319-20.
19. Andrés A, Morales JM, Herrero JC *et al.* Double versus single renal allograft from aged donors. *Transplantation* 2000; (69): 2060-6.
20. Cecka JM, Terasaki PI. Optimal use for older donor kidneys: older recipients. *Transplant Proc* 1995; (27): 801-2.
21. Herrero JC, Gutiérrez E, Martínez A *et al.* Results of kidney transplantation in recipients over 70 years of age: experience at a single center. *Transplant Proc* 2003; (35): 1675-6.
22. Remuzzi G, Cravedi P, Perna A *et al.* Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006; (354): 343-52.
23. Andrés A, Hernandez A, Herrero JC *et al.* Kidney transplant in extremely aged recipients using extremely aged deceased donors [abstract] *Am J Transplant* 2008; 8 (Suppl 2): 455.
24. Lim WH, Chang S, Chadban S *et al.* Donor–recipient age matching improves years of graft function in deceased-donor kidney transplantation. *Nephrol Dial Transplant* 2010; (25): 3082–9.
25. The Canadian Council for Donation and Transplantation: *Kidney allocation in Canada: A Canadian Forum, Report and Recommendations (Toronto, ONT, Canada, 2006).* Edmonton, AB, Canada: The Canadian Council for Donation and Transplantation, 2007 [available from: www.organsandtissues.ca/s/wp-content/uploads/2011/11/Kidney_Allocation_FINAL.pdf, accessed 30 January 2016].
26. Port FK, Bragg-Gresham JL, Metzger RA *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation 2002; (74): 1281-6.
27. Metzger RA, Delmonico FL, Feng S *et al.* Expanded criteria donors for kidney transplantation. *Am J Transplant* 2003; 3(Suppl 4): 114-25.
28. Becker YT, Leverson GE, D'Alessandro AM *et al.* Diabetic kidneys can safely expand the donor pool. *Transplantation* 2002; (74): 141-5.
29. Ojo AO, Leichtman AB, Punch JD *et al.* Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. *Am J Kidney Dis* 2000; (36): 153-9.
30. CKD Work Group. Kidney disease: improving global outcomes. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter.* 2013; (3) Suppl: 1-150.
31. Gutiérrez E, González E, Martínez A *et al.* Resultados del trasplanterenal con riñones de donantes en muertecerebral y deterioroagudo de función renal [abstract] *Nefrología* 2002; 22 (Suppl 6): 83.
32. Anil Kumar MS, Khan SM, Jaglan S *et al.* Successful transplantation of kidneys from deceased donors with acute renal failure: three-year results. *Transplantation* 2006; (82): 1640-5.
33. Rodrigo E, Miñambres E, Piñeera C *et al.* Using RIFLE criteria to evaluate acute kidney injury in brain-deceased kidney donors. *Nephrol Dial Transplant.* 2010; (25): 1531-7.
34. Portolés J, Marañes A, Marrón B *et al.* Double renal transplant from infant donor. *Transplantation* 1996; (61): 37-40.
35. Kirste G, Blumke M, Krumme B. A new operative technique of paratopic positioning of paediatric *en bloc* kidneys for transplantation. *Clin Transplant* 1914; (8): 139-43.
36. Kayler LK, Magliocca J, Kim RD *et al.* Single kidney transplantation from young paediatric donors in the United States. *Am J Transplant* 2009; (9): 2745-51.
37. Gallinat A, Sotiropoulos GC, Witzke O *et al.* Kidney grafts from donors ≤ 5 yrs of age: single kidney transplantation for paediatric recipients or *en bloc* transplantation for adults? *Pediatr Transplant* 2013; (17): 179-84.
38. Booster MH, Wijnem RM, Vroemen AM *et al.* In situ preservation of kidneys from non-heart-beating donors – a proposal for a standardized protocol. *Transplantation* 1993; (56): 613-17.
39. Weber M, Dindo D, Demartines N *et al.* Kidney transplantation from donors without a heartbeat. *N Engl J Med* 2002; (347): 248-55.
40. Alonso A, Fernández-Rivera C, Villaverde P *et al.* Renal transplantation from non-heart-beating donors: a single-center 10-year experience. *Transplant Proc* 2005; (37): 3658-60.
41. Valero R, Cabrer C, Oppenheimer F *et al.* Normothermic recirculation reduces primary graft dysfunction of kidneys obtained from non-heart-beating donors. *Transpl Int* 2000; (13): 303-10.

42. Sánchez-Fructuoso AI, Prats D, Torrente J *et al.* Renal transplantation from non-heart-beating donors: a promising alternative to enlarge the donor pool. *J Am Soc Nephrol* 2000; (11): 350-8.
43. Andrés A, Gutiérrez E, Dipalma T *et al.* Successful kidney transplantation from helicopter transported deceased after cardiac death (DCD) donors with irreversible cardiac arrest in the street or at home far from the hospital [abstract] *Am J Transplant* 2011; 11 (Suppl 2): 224.
44. Frühauf NR, Fischer-Fröhlich CL, Kutschmann M *et al.* Joint impact of donor and recipient parameters on the outcome of liver transplantation in Germany. *Transplantation* 2011; (92): 1378-84.
45. Cuende N, Grande L, Sanjuan F *et al.* Liver transplant with organs from elderly donors: Spanish experience with more than 300 liver donors over 70 years of age. *Transplantation* 2002; (73): 1360.
46. Cescon M, Grazi GL, Cucchetti A *et al.* Improving the outcome of liver transplantation with very old donors with updated selection and management criteria. *Liver Transpl* 2008; (14): 672-9.
47. Yersiz H, Shaked A, Olthoff K *et al.* Correlation between donor age and the pattern of liver graft recovery after transplantation. *Transplantation* 1995; (60): 790-4.
48. Emre S, Schwartz ME, Altaca G *et al.* Safe use of hepatic allografts from donors older than 70 years. *Transplantation* 1996; (62): 62-5.
49. Jiménez C, Moreno E, Colina F *et al.* Use of octogenarian livers safely expands the donor pool. *Transplantation* 1999; (68): 572-5.
50. Cescon M, Grazi GL, Ercolani G *et al.* Long-term survival of recipients of liver grafts from donors older than 80 years: is it achievable? *Liver Transpl* 2003; (9): 1174-80.
51. Nardo B, Masetti M, Urbani L *et al.* Liver transplantation from donors aged 80 years and over: pushing the limit. *Am J Transplant* 2004; (4): 1139-47.
52. Kim DY, Cauduro SP, Bohorquez HE *et al.* Routine use of livers from deceased donors older than 70: is it justified? *Transpl Int* 2005; (18): 73-7.
53. Singhal A, Sezginsoy B, Ghuloom AE *et al.* Orthotopic liver transplant using allografts from geriatric population in the United States: is there any age limit? *Exp Clin Transplant* 2010; (8): 196-201.
54. Faber W, Seehofer D, Puhl G *et al.* Donor age does not influence 12-month outcome after orthotopic liver transplantation. *Transplant Proc* 2011; (43): 3789-95.
55. Kim DY, Moon J, Island ER *et al.* Liver transplantation using elderly donors: a risk factor analysis. *Clin Transplant* 2011; (25): 270-6.
56. Lai Q, Melandro F, Levi Sandri GB *et al.* Use of elderly donors for liver transplantation: has the limit been reached? *J Gastrointestin Liver Dis* 2011; (20): 383-7.
57. Sampedro B, Cabezas J, Fábrega E *et al.* Liver transplantation with donors older than 75 years. *Transplant Proc* 2011; (43): 679-82.
58. Akkina SK, Asrani SK, Peng Y *et al.* Development of organ-specific donor risk indices. *Liver Transpl* 2012; (18): 395-404.
59. Ploeg R, D'Alessandro A, Knechtle SJ *et al.* Risk factors for primary dysfunction after liver transplantation – a multivariate analysis. *Transplantation* 1993; (55): 807-13.
60. Cescon M, Grazi GL, Cucchetti A *et al.* Improving the outcome of liver transplantation with very old donors with updated selection and management criteria. *Liver Transpl* 2008; (14): 672-9.
61. Fischer-Fröhlich CL, Frühauf NR *et al.* Analysis of competing failure risks reveals proper liver assessment at recovery excluding severe steatosis as crucial compared to other cumulative extended donor criteria. *Organs, Tissues and Cells* 2012; (15): 115-21.
62. Rey JW, Wirges U, Dienes HP *et al.* Hepatic steatosis in organ donors: disparity between surgery and histology? *Transplant Proc* 2009; (41): 2557-60.
63. D'Alessandro A, Kalayoglu M, Sollinguer H *et al.* The predictive value of donor liver biopsies for the development of primary nonfunction after orthotopic liver transplantation. *Transplantation* 1991; (51): 157-63.
64. Urena MA, Moreno E, Romero CJ *et al.* An approach to the rational use of steatotic donor livers in liver transplantation. *Hepatogastroenterology* 1999; (46): 1164-73.
65. de Graaf EL, Kench J, Dilworth P *et al.* Grade of deceased donor liver macrovesicular steatosis impacts graft and recipient outcomes more than the donor risk index. *J Gastroenterol Hepatol* 2012; (27): 422-4.
66. Avolio AW, Frongillo F, Nicolotti N *et al.* Successful use of extended criteria donor grafts with low to moderate steatosis in patients with model for end-stage liver disease scores below 27. *Transplant Proc* 2009 Jan-Feb; 41 (1): 208-12.
67. Briceño J, Ciria R, Pleguezuelo M *et al.* Impact of donor graft steatosis on overall outcome and viral recurrence after liver transplantation for hepatitis C virus cirrhosis. Liver Transpl 2009; (15): 37-48.
68. Cucchetti A, Vivarelli M, Ravaioli M *et al.* Assessment of donor steatosis in liver transplantation: is it possible without liver biopsy? *Clin Transplant* 2009; (23): 519-24.
69. de Graaf EL, Kench J, Dilworth P *et al.* Grade of deceased donor liver macrovesicularsteatosis impacts graft and recipient outcomes more than the donor risk index. *J Gastroenterol Hepatol* 2012; (27): 422-4.

70. Noujaim HM, de Ville de Goyet J, Montero EF *et al.* Expanding post mortem donor pool using steatotic liver grafts: a new look. *Transplantation* 2009; (87): 919-25.
71. Verran D, Kusyk T, Painter D *et al.* Use of 120 steatotic donor livers for orthotopic liver transplantation. *Liver Transpl* 2003; (9): 500-5.
72. Sharkey FE, Lytvak I, Prihoda TJ *et al.* High-grade microsteatosis and delay in hepatic function after orthotopic liver transplantation. *Hum Pathol* 2011; (42): 1337-42.
73. Foley DP, Fernández LA, Leverson G *et al.* Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. *Ann Surg* 2011; (253): 817-25.
74. Taner CB, Bulatao IG, Perry DK *et al.* Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. *Transpl Int* 2012; (25): 838-46.
75. Taner CB, Bulatao IG, Willingham DL *et al.* Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transpl* 2012; (18): 100-11.
76. Abt P, Crawford M, Desai N *et al.* Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. *Transplantation* 2003; (75): 1659-63.
77. Fondevila C, Hessheimer AJ, Flores E *et al.* Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. *Am J Transplant* 2012; (12): 162-70.
78. Thuluvath PJ, Guidinger MK, Fung JJ *et al.* Liver transplantation in the United States, 1999–2008. *Am J Transplant* 2010; (10): 1003-19.
79. Kim WR, Therneau TM, Benson JT *et al.* Deaths on the liver transplant waiting list: an analysis of competing risks. *Hepatology* 2006; (43): 345-51.
80. Peralta C, Jiménez-Castro MB, Gracia-Sancho J. Hepatic ischemia and reperfusion injury: effects on the liver sinusoidal milieu. *J Hepatol* 2013; (59): 1094-1106.
81. Van Golen RF, van Gulik TM, Heger M. The sterile immune response during hepatic ischemia/reperfusion. *Cytokine Growth Factor Rev* 2012; (23): 69-84.
82. Adam R, Sanchez C, Astarcioglu I *et al.* Deleterious effect of extended cold ischemia time on the post-transplant outcome of aged livers. *Transplant Proc* 1995; (27): 1181-3.
83. Yersiz H, Renz JF, Farmer DG *et al.* One hundred *in situ* split-liver transplantations: a single-center experience. *Ann Surg* 2003; (238): 496-505.
84. Reich DJ, Muñoz SJ, Rothstein KD *et al.* Controlled non-heart-beating donor liver transplantation: a successful single center experience, with topic update. *Transplantation* 2000; (70): 1159-66.
85. Cameron A, Busuttil RW. AASLD/ILTS transplant course: is there an extended donor suitable for everyone? *Liver Transpl* 2005 November: 11 (Suppl 2): S2-5.
86. Rauchfuss F, Voigt R, Dittmar Y *et al.* Liver transplantation utilizing old donor organs: a German single-center experience. *Transplant Proc* 2010; (42): 175-7.
87. Fouzas I, Sgourakis G, Nowak KM *et al.* Liver transplantation with grafts from septuagenarians. *Transplant Proc* 2008; (40): 3198-200.
88. Saidi RF. Change in pattern of organ donation and utilization in US. *Int J Organ Transplant Med* 2012; (3): 149-56.
89. Loinaz C, González EM. Marginal donors in liver transplantation. *Hepatogastroenterology* 2000; (47): 256-63.
90. Verran D, Kusyk T, Painter D *et al.* Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. *Liver Transpl* 2003; (9): 500-5.
91. George J, Pera N, Phung N *et al.* Lipid peroxidation, stellate cell activation and hepatic fibrogenesis in a rat model of chronic steatohepatitis. *J Hepatol* 2003; (39): 756-64.
92. Gabrielli M, Moisan F, Vidal M *et al.* Steatotic livers. Can we use them in OLTX? Outcome data from a prospective baseline liver biopsy study. *Ann Hepatol* 2012; (11): 891-8.
93. Cywinski JB, Mascha E, Miller C *et al.* Association between donor–recipient serum sodium differences and orthotopic liver transplant graft function. *Liver Transpl* 2008; (14): 59-85.
94. Powner DJ. Factors during donor care that may affect liver transplantation outcome. *Prog Transplant* 2004; (14): 241-7; quiz 248-9.
95. Forni A, Luciani GB, Chiominto B *et al.* Results with expanded donor acceptance criteria in heart transplantation. *Transplant Proc* 2011; (43): 953-9.
96. Forni A, Luciani GB, Chiominto B *et al.* Impact of donor quality on outcome of heart transplantation. *Eur J Cardiothorac Surg* 2010; (38): 788-94.
97. Shöler S, Matsahke K, Loebe M *et al.* Coronary artery disease in patients with hearts from older donors: morphologic features and therapeutics implications. *J Heart Lung Transplant* 1993; (12): 100-9.
98. Luciani G, Levi H, Faggian G *et al.* Clinical results of heart transplantation in recipients over 55 years of age with donors over 40 years of age. *J Heart Lung Transplant* 1992; (11): 1177-83.

99. Potapov EV, Loebe M, Hubler M *et al.* Medium-term results of heart transplantation using donors over 63 years of age. Transplantation 1999; (68): 1834-8.
100. Lietz K, John R, Mancini DM *et al.* Outcomes in cardiac transplant recipients using allografts from older donors versus mortality on the transplant waiting list; implications for donor selection criteria. *J Am Coll* Cardiol 2004; (43): 1553-61.
101. Bruschi G, Colombo T, Oliva F *et al.* Orthotopic heart transplantation with donors greater than or equal to 60 years of age: a single-center experience. *Eur J Cardiothorac Surg* 2011; (40): 55-61.
102. Mancini DM, Schulze PC, Jiang J *et al.* Cardiac transplantation in over 2000 patients: a single-institution experience from Columbia University. *Clin Transpl* 2011; (25): 157-75.
103. Zeissig SR, Fischer-Froehlich CL, Polster F *et al.* Current practice of heart donor evaluation in Germany: multivariable risk factor analysis confirms practicability of guidelines. *J Transplant*. 2013; 2013: 701854. Published online 30 September 2013. DOI: 10.1155/2013/701854.
104. Kutschmann M, Fischer-Fröhlich CL, Schmidtmann I *et al.* The joint impact of donor and recipient parameters on the outcome of heart transplantation in Germany after graft allocation. *Transpl Int* 2014; (27): 152-61.
105. Kutschmann M, Fischer-Fröhlich CL, Schmidtmann I. Outcome of heart transplantation in Germany: details to be considered beyond multivariate analysis to improve the quality of graft allocation. *Organs, Tissues and Cells* 2014; (17): 53-61.
106. Simion D, Casartelli ML, Procaccio F. Early targeted treatment may facilitate complete weaning from vasopressors and recovery of stunned hearts in unstable potential donors: a new golden time for organ retrieval? *Organs, Tissues and Cells* 2014; (17): 49-52.
107. Fischer-Fröhlich CL, Lauchart W. Evaluation of heart function in organ donors. *Organs Tissues and Cells* 2008; (11): 101.
108. Grauhan O, Siniawski H, Dandel M *et al.* Coronary atherosclerosis of the donor heart – impact on early graft failure. *Eur J Cardiothorac Surg* 2007; (32): 634-8.
109. Grauhan O, Wesslau C, Hetzer R. Routine screening of donor hearts by coronary angiography is feasible. *Transplant Proc* 2006; (38): 666-7.
110. Bombardini T, Gherardi S, Arpesella G *et al.* Favorable short-term outcome of transplanted hearts selected from marginal donors by pharmacological stress echocardiography. *J Am Soc Echocardiogr* 2011; (24): 353-62.
111. Costanzo MR, Dipchand A, Starling R *et al.* The International Society of Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; (29): 914-56.
112. Shemie SD, Ross H, Pagliarello J *et al.* Organ donor management in Canada: recommendations of the forum on medical management to optimize donor organ potential. *CMAJ* 2006; (174): S13-32.
113. Wood KE, Becker BN, McCartney JG *et al.* Current concepts: care of potential organ donor. *N Engl J Med* 2004; (351): 2730-9.
114. Audibert G, Charpentier C, Seguin-Devaux C *et al.* Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation* 2006; (82): 1031-6.
115. Ryan JB, Hicks M, Cropper JR *et al.* Functional evidence of reversible ischemic injury immediately after the sympathetic storm associated with experimental brain death. *J Heart Lung Transplant* 2003; (22): 922-8.
116. Rosendale JD, Kauffman HM, McBride MA *et al.* Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation* 2003; 5 (8): 1336-1441.
117. Novitzky D, Cooper DK, Rosendale JD *et al.* Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation* 2006; 82 (11): 1396-1401.
118. Rosendale JD, Kauffman HM, McBride MA *et al.* Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation* 2003; 5 (8): 1336-41.
119. Wittwer T, Wahlers T. Marginal donor grafts in heart transplantation: lessons learned from 25 years of experience. *Transpl Int* 2008; (21): 113-25.
120. Warnecke G, Moradiellos J, Tudorache I *et al.* Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. *Lancet* 2012; (380): 1851-8.
121. Núñez JR, Varela A, del Rio F *et al.* Bipulmonary transplants with lungs obtained from two non-heart-beating donors who died out of hospital. *J Thorac Cardiovasc Surg* 2004; (127): 297-9.
122. Gómez-de-Antonio D, Campo-Cañaveral JL, Crowley S *et al.* Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. *J Heart Lung Transplant* 2012; (31): 349-53.
123. de Perrot M, Liu M, Waddell TK *et al.* Ischemia-reperfusion induced lung injury. *Am J Respir Crit Care Med* 2003; (167): 490-511.
124. Christie JD, Van Raemdonck D, de Perrot M *et al;* Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on primary lung graft dysfunction, Part I: introduction and methods. *J Heart Lung Transplant* 2005; (24): 1451-3.

125. Bhorade S, Vigneswaran W, McCabe M *et al.* Liberalization of donor criteria may expand the donor pool without adverse consequence in lung transplantation. *J Heart Lung Transplant* 2000; (19): 1200-4.
126. De Soyza AG, Dark JH, Parums DV *et al.* Donor acquired small cell lung cancer following pulmonary transplantation. *Chest* 2001; (120): 1030-1.
127. de Perrot M, Wigle DA, Pierre AF *et al.* Bronchogenic carcinoma after solid organ transplantation. *Ann Thorac Surg* 2003; (75): 367-71.
128. Diamond JM, Lee JC, Kawut SM *et al.* Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013; (187): 527-34.
129. Bonser RS, Taylor R, Collett D *et al;* Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK). Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. *Lancet* 2012; (380): 747-55.
130. Taghavi S, Jayarajan S, Komaroff E *et al.* Double-lung transplantation can be safely performed using donors with heavy smoking history. *Ann Thorac Surg* 2013; (95): 1912-17.
131. Berman M, Goldsmith K, Jenkins D *et al.* Comparison of outcomes from smoking and nonsmoking donors: thirteen-year experience. *Ann Thorac Surg* 2010; (90): 1786-92.
132. Oto T, Griffiths AP, Levvey B *et al.* A donor history of smoking affects early but not late outcome in lung transplantation. *Transplantation* 2004; (78): 599-606.
133. McCowin MJ, Hall TS, Babcock WD *et al.* Changes in radiographic abnormalities in organ donors: associations with lung transplantation. *J Heart Lung Transplant* 2005; (24): 323-30.
134. Puskas JD, Winton TL, Miller DJ *et al.* Unilateral donor lung dysfunction does not preclude successful contralateral single-lung transplantation. *J Thorac Cardiovasc Surg* 1992; (103): 1015-17.
135. Bolton JS, Padia SA, Borja MC *et al.* The predictive value and inter-observer variability of donor chest radiograph interpretation in lung transplantation. *Eur J Cardiothorac Surg* 2003; (23): 484-7.
136. Mattner F, Kola A, Fischer S *et al.* Impact of bacterial and fungal donor organ contamination in lung, heart-lung, heart and liver transplantation. *Infection* 2008; (36): 207-12.
137. Campos S, Caramori M, Teixeira R *et al.* Bacterial and fungal pneumonias after lung transplantation. *Transplant Proc* 2008; (40): 822-4.
138. Bonde PN, Patel ND, Borja MC *et al.* Impact of donor lung organisms on post-lung transplant pneumonia. *J Heart Lung Transplant* 2006; (25): 99-105.
139. Weill D, Dey GC, Young KR *et al.* A positive donor Gram stain does not predict the development of pneumonia, oxygenation or duration of mechanical ventilation following lung transplantation [abstract]. J *Heart Lung Transplant* 2001; (20): 255.
140. Zenati M, Dowling RD, Dummer JS *et al.* Influence of the donor lung on development of early infections in lung transplant recipients. *J Heart Lung Transplant* 1990; (9): 502-9.
141. Avlonitis VS, Krause A, Luzzi L *et al.* Bacterial colonization of the donor lower airways is a predictor of poor outcome in lung transplantation. *Eur J Cardiothorac Surg* 2003; (24): 601-7.
142. Zafar F, Khan MS, Heinle JS *et al.* Does donor arterial partial pressure of oxygen affect outcomes after lung transplantation? A review of more than 12 000 lung transplants. *J Thorac Cardiovasc Surg* 2012; (143): 919-25.
143. Ruiz I, Gavaldá J, Monforte V *et al.* Donor-to-host transmission of bacterial and fungal infections in lung transplantation. *Am J Transplant* 2006; (6): 178-82.
144. Ciulli F, Tamm M, Dennis CM *et al.* Donor-transmitted bacterial infection in heart–lung transplantation. *Transplant Proc* 1993; (25): 1155-6.
145. Eurotransplant Foundation: *Eurotransplant manual*, chapter 7: ET-Pancreas allocation system (EPAS). Leiden, Netherlands: Eurotransplant Foundation, 2013 [available from: www.eurotransplant.org/cms/mediaobject.php?file=H7+EPAS+september+2013+v2.pdf, accessed: 24 February 2016].
146. Neidlinger NA, Odorico JS, Sollinger HW *et al.* Can 'extreme' pancreas donors expand the donor pool? *Curr Opin Organ Transplant* 2008; (13): 67-71.
147. Singh RP, Rogers J, Farney AC *et al.* Outcomes of extended donors in pancreatic transplantation with portal-enteric drainage. *Transplant Proc* 2008; (40): 502-5.
148. Vianna RM, Mangus RS, Tector AJ. Current status of small bowel and multivisceral transplantation. *Adv Surg* 2008; (42): 129-50.
149. Fischer-Fröhlich CL, Königsrainer A, Schaffer R *et al.* Organ donation: when should we consider intestinal donation. *Transpl Int* 2012; (25): 1229-40.
150. Rushton SN, Hudson AJ, Collett D *et al.* Strategies for expanding the UK pool of potential intestinal transplant donors. *Transplantation* 2013; (95): 234-9.
151. Matsumoto CS, Kaufman SS, Girlanda R *et al.* Utilization of donors who have suffered cardiopulmonary arrest and resuscitation in intestinal transplantation. *Transplantation* 2008; (86): 941-6.
152. Foedus (Facilitating Exchange of Organs Donated in EU Member States, EU-funded project) [project website: www.foedus-ja.eu, accessed: 30 January 2016].

Related documents: Appendix 7. Donor information form (Eurotransplant, English language version); Appendix 9. Grading for biopsies at histo-pathological 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]. Intended use of donors with certain infections – e.g. cytomegalovirus (CMV), hepatitis B virus (HBV) or hepatitis C virus (HCV) – 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].

The classification of disease transmission according to risk levels (RL) as outlined in Chapter 7, section 7.1.1, may be helpful, but it should only be regarded as a guide. Ultimately, each donor and recipient combination must be assessed individually, based on their respective risks for infections and those related to spending a prolonged time on the waiting list. The information available on donor-transmitted (or derived) infections consists of individual case reports on fatal outcomes or cases treated successfully, in addition to critical reviews by national institutions or experts [1, 4-7].

In the context of deceased donation, there is not sufficient time for an exhaustive epidemiological investigation, except for tests for which results are likely to be available within a few hours [3, 5]. In donation procedures without such time constraints, more extensive diagnostic procedures should be attempted for safer risk assessments – e.g. nucleic acid amplifying technique (NAT) for tissue grafts requiring time-consuming processing and storage for more than 1 week.

In addition to national guidelines, the current and updated epidemiology of infectious diseases should be taken into account [8, 9]. Recent experience with emerging local or geographically restricted and pandemic infections highlights the changing nature of risk and this is best addressed by *ad hoc* action plans on a national or international level – e.g. Chikungunya virus, West Nile virus (WNV) or the pandemic influenza H1N1 virus in 2009 [10-14].

Infectious agents transmissible by organs or tissues belong to five groups of pathogens:

- Viruses: by infection in the tissue of donors with or without current viraemia. Thereby DNA-virus may persist latently in the tissues without detectable viraemia; RNA-viruses usually cause direct infection and disease.
- 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 usually made by detection of an immunological response (e.g. through serologic testing) or, if present, by other clinical signs or symptoms in the donor. Serological screening

methodologies cannot adequately differentiate whether a donor has cleared an infection or if latent infection prevails in tissues or organs. Such latent infections in the donor can be transmitted by a graft and may be re-activated 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.

Table 8.1. **Acronyms used for the reporting of viral screening results**

Acronym (standardised)	Other acronyms still in use	Explanation
anti-HBs	HBs-Ab	Antibodies against surface antigen of hepatitis B virus
Anti-HBe		Antibodies against E antigen of hepatitis B
anti-HCV	HCV-Ab	Antibodies against hepatitis C virus
HBeAg		E antigen of hepatitis B virus
HBsAg		Surface antigen of hepatitis B virus
anti-HBc	HBc-Ab	Antibodies against the core antigen of the hepatitis B virus
anti-HBc-IgM	HBc-AbIgM	IgM-antibodies against the core antigen of the hepatitis B virus
anti-HIV	HIV-Ab	Antibodies against HIV without definition of the subtype
anti-HIV-1/2	HIV-1/2-Ab	Antibodies against human immunodeficiency virus subtype 1 or 2
anti-HIV-1	HIV-1-Ab	Antibodies against human immunodeficiency virus-1 subtype only
anti-HIV-2	HIV-2-Ab	Antibodies against human immunodeficiency virus-2 subtype only
HIV-1-p24-Ag	HIV-p24-Ag	p24-Antigen of human immunodeficiency virus-1 subtype
anti-CMV	CMV-Ab	Antibodies against cytomegalovirus [CMV] (total antibodies of IgG and IgM)
anti-EBV	EBV-Ab	Antibodies against Epstein-Barr virus (anti-EBV-VCA-IgG is usually tested in donors)
D+/R–		The donor has been infected by the pathogen and the recipient is naïve (i.e. has not been infected)
D+/R+		Both the donor and the recipient have been infected by the pathogen
D–/R+		The donor is naïve (i.e. has not been infected) and the recipient has been infected by the pathogen
D–/R–		Both the donor and recipient are naïve (i.e. have not been infected) by the pathogen

b. The infection may have been acquired shortly before hospital admission – e.g. human immunodeficiency virus (HIV), HBV, HCV or WNV – and the donor has not yet presented clinical symptoms of the infection or a serologic response to it.

The time frame between exposure to a pathogen and the ability to detect antibodies against the pathogen is known as the window period. The window period consists of two phases. In the first phase, specific target tissues, such as lymph nodes or the liver, can be infected, while a systemic spread has not yet occurred and the pathogen cannot be detected in the blood. In such settings, use of infected organs may transfer the infection from the donor to the recipient. This phase of the window period is known as the eclipse phase, since the circulating pathogen cannot be demonstrated. In the second phase of the window period, the pathogen is present in the circulation, but antibodies are not detectable since proper reaction of the immune system has not yet occurred.

Since serologic assays may be not reactive during the window period, and clinical signs may be absent, assessment of the pathogen in the blood by 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, during the early days when even NAT testing is not sensitive enough to detect the pathogen in the blood or plasma (≈ 5-7 days for HIV and HCV, and ≈ 20 days for HBV), infection may be transmitted even with a non-reactive NAT.

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 sero-conversion occurs, but this is not always available. Furthermore, even with NAT testing, the risk can never be completely eliminated [15].

c. The infection may have been acquired during the terminal hospital stay or during the procurement and transportation 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. 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 results at the time

of procurement need to be carefully recorded, and follow-up of all results (e.g. microbiological tests) 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 (RL 1-5).

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. However, it is impossible to completely exclude all risks for unexpected disease transmission. Some pitfalls or limitations exist in screening for infectious diseases in organ donors:

- Because of changing epidemiology and the globalisation of atypical 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 and transplant centres. Also the appropriateness, sensitivity and specificity of screening assays should be reviewed periodically. False positive screening results, or turning down organs because of an inability to screen for all suspected pathogens, must be minimised in order to avoid organ loss [8].
- Basic screening results must be available 3-6 h before organ recovery (see section 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 [16].
- 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 [17]. 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 [18].

The following two principles should be considered when communicating screening results:

a. Any 'reactive' test result indicates either a current or past exposure of infection. The medical community documents this as 'positive'.
Any 'non-reactive' test result only indicates that the test did not detect evidence of the pathogen in the specimen investigated. The medical community documents this as 'negative', without knowing whether the pathogen was missed or whether it did not exist.
In order to avoid misinterpretation, test results should be communicated as 'non-reactive' and 'reactive' only. Then the limitations of screening test as outlined above are properly considered (see section 8.10.3).

b. Abbreviations used in viral screening and interpretation of results should be standardised as summarised in Table 8.1. They are used in this form throughout the chapter.

8.2. Medical history and behavioural risk evaluation

The guidelines for excluding or including donors presenting certain risk behaviours vary between countries and regions, and are determined by local disease prevalence and risk assessments. This catalogue of risk criteria should be regularly reviewed, as epidemiological changes and future developments in diagnostics occur.

Data to be obtained for detecting potential infectious disease transmission risks have previously been outlined in Chapter 6, section 6.2.1.

One major concern is the risk of unintended transmission of HIV, HCV or HBV infection [19]. The incidence and prevalence of HIV and HCV infection varies depending on different risk factors [20-21], and the causes of *de novo* infections vary between European regions [22]. Unfortunately there are only a few studies based on adequate evidence that identify the risks of window period infections [15, 19].

In spite of these limitations, the guidelines issued by the United States Public Health Service (PHS) and the American Centers for Disease Control and Prevention (CDC), as updated in 2013 and evidence-based, are recommended for assessing individuals at increased or non-standard risk for HIV, HCV or HBV infections [19]. 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 nonmedical reasons in the preceding 12 months (intranasal 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 the 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 nonmedical 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, gonorrhea, 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 high-risk donors, extended screening by NAT for HIV and HCV is highly recommended to reduce the diagnostic window period [3, 19] (see section 8.4.1.1).

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.

Table 8.2. **Additional tests which should be considered for screening of donors who have lived in geographically restricted areas or are at risk for vertical transmission due to ancestors having lived there**

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 stercolaris 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
Histoplasma capsulatum and *Coccidioides immitis* serology	Always	No	Western Africa (*Histoplasmosis*)	No	No

*NAT is more sensitive as a test to rule out parasitemia than other tests.

***Entamoeba histolytica*, *Clonorchis* spp. *Opistorchis* spp., *Schistosoma* spp., *Strongyloides* spp.

****S. hameatobium*, *Blastomyces dermatitidis*.

Modified according to [23].

b. In the annual epidemiological report of the European Centre for Disease Control (ECDC) [20], 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 high risk donors according to the PHS-guidelines may be shortened to the duration of two incubation periods.

Any recipient, particularly those having received organs from high risk donors, should be followed up regularly for an early detection of donor-derived infections [4]. Both post-transplant serology and NAT assessment of the recipients should be carried out, as they may not adequately seroconvert.

Screening for some parasitic and bacterial infections in particular (e.g. Chagas disease, malaria, toxoplasmosis) should be considered, according to their prevalence in the region or in the specific subpopulation of the donor. Insanitary living conditions (especially with respect to water) and outdoor conditions may expose people to pathogens at different situations – e.g. Chagas disease, tick-borne encephalitis (TBE), 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 in areas with endemic transmissible diseases such as malaria, trypanosomiasis, rabies, WNV, etc. requires further consideration. The history of recent immunisations with live vaccines should also be evaluated (see section 8.4.1.4). If the donor has been deferred from blood donation, then the reason for deferral should be evaluated.

8.3. Basic screening for infections in organ donors

The basic screening for infections in deceased organ donors must include the following serological tests, with results being provided within the time-frame specified in the box:

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 • anti-EBV-VCA-IgG • anti-*Treponema pallidum* ELISA (enzyme-linked immunosorbent assay) • anti-Toxoplasma	Additional tests can be performed according to the recipient profile for targeting specific prophylaxis.

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 8.2 should be considered in donor screening [23]. Further, the risk of vertical transmission from mother to child should be considered too.

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 8.4.1.1.

In the event of an anti-HCV reactive result, HCV-NAT should be performed as a complementary test to assess whether clearance of viraemia exists (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.

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 recovery, as indicated. Always a critical review should be provided about considerations of all pathogens as outlined in the following sections and results available currently – e.g. include all results of blood cultures, broncho-alveolar lavage (BAL), urine cultures, etc.

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.

Screening should be extended to NAT for donors with an increased risk of HIV-1, HBV or HCV infection [24] (see sections 8.2 and 8.4.1.1). 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.

Screening should be performed with the latest generation assay available, according to the manufacturer's instructions and as licensed by the national health authorities [9]. Each centre should have a plan on how to handle reactive or unexpected results (sections 8.4.1.1 and 8.10.1) [9]. For basic screening, serologic tests should detect IgG antibodies. Only in special cases is IgM detection necessary. Donor sera or plasma samples should be stored for at least 10 years by the organ procurement organisation, according to the methods available and national recommendations [8]. 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 2015 in most 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-around time must be ensured when using NAT testing under the specific circumstances of organ donation, i.e. as single-probe runs outside standard working hours and without routine staff availability.

Serologic markers may require weeks before achieving detection limits, and viraemia does not always exist. Viral diseases may not be detected by NAT unless a specimen has been recovered from the appropriate tissue, e.g. rabies from specific areas of the brain, cardio-tropic 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 (or only problematic) 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 [9]. For example, prevalence of HTLV, HBV, hepatitis D or hepatitis E varies regionally, due to different immigration patterns from endemic areas and environmental 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 [4, 5]. Up-to-date information about new and emerging, seasonally occurring or regionally endemic virus infections (e.g. WNV, Usutu virus, chikungunya virus, dengue, influenza) 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.

More specific information about infections can be obtained from the following websites:

- World Health Organization (WHO): manual 'International Travel and Health' 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. Germany, see www.rki.de)

8.4.1.1. *Screening algorithms in organ donors*

Criteria defining 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. In contrast, for donors at standard risk for such infections a controversy exists about the risk of false positive results increasing the rate of organ wastage versus the benefits of increasing safety by systematically performing further tests to reduce the diagnostic window period [25, 26]. Therefore, different screening algorithms should be used based on the recognised risk of the donor, as appropriate (see Figures 8.1, 8.2 and 8.3).

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. This might be associated with a low risk for HCV transmission when viraemia can be ruled out properly by NAT (see section 8.4.2.7) [27].

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 8.1, 8.2 and 8.3). Any initially reactive result in tissue or cell donors without time constraints should be carefully verified.

Screening algorithms for donors at standard risk for HIV-, HCV- and HBV-infection are shown in the left diagrams of Figures 8.1, 8.2 and 8.3.

Screening algorithms for donors at increased risk for such infections are shown in the right diagrams of Figures 8.1, 8.2 and 8.3.

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 hidden occult HBV-infection.

The utility of NAT-screening in donors lacking identified risk factors is to decrease the diagnostic window period further, but the limitation is that access to NAT for prospective single donor screening is limited in many European countries while the transmission risk has been assumed to be negligible.

Donors that do not present elevated risks for infection as outlined in section 8.2, but are HBsAg non-reactive and anti-HBc reactive, should be considered as a calculated risk for HBV-transmission for liver grafts (see section 8.4.2.6).

In donors with anti-HCV reactive results, HCV-NAT or equivalent measurements clarify whether the donor is viraemic or not with relevant consequences regarding the use of organs (see section 8.4.2.7).

8.4.1.2. *Basic screening for viral 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. 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 [18]. Therefore, transmission risks still exist despite reasonable screening since such transmission has occurred. This requires education about avoiding infections like HIV, HCV and HBV, etc., which may help to reduce risks. For further details see Chapter 13.

8.4.1.3. *Basic screening for viral 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*.

8.4.1.4. *Previous vaccinations of the donor*

Vaccinations with live vaccines may result in transmission of a vaccine-derived pathogen to an immuno-suppressed recipient. This may give rise to a life-threatening disease (RL 1-2). In contrast, inactivated vaccine or passive immunisation of the donor is unlikely to pose harm to the recipient, but may confound screening testing (i.e. recent HBV vaccination may yield a positive HBsAg test).

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, rotavirus, measles, mumps, rubella, Bacillus Calmette-Guérin (BCG), smallpox, oral cholera (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.

Live vaccines are equivalent to transmission of acute infection, requiring individual risk assessment of potential recipients for 4 weeks after vaccination (RL 1-2).

Live vaccines include vaccination against the following pathogens:
- Influenza (inhaled = live, injectable = inactivated)
- Varicella/zoster
- 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 some specific organs:
- Inhaled Influenza vaccine: Lung, Face
- Rotavirus: Intestine
- Cholera: Intestine
- Salmonella: Intestine

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 the areas surrounding the Indian Ocean, tropical Africa and areas surrounding the Caribbean. Transmission occurs by bites of infected *Aedes* species mosquitoes (*aegypti* or *albopticus*), 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 albopticus* 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 [20].

Infection may manifest through fever, arthralgia, exanthema and rarely as meningoencephalitis, uveitis, retinitis, myocarditis, hepatitis, nephritis, haemorrhage, myelitis or Guillain–Barre 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.

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 prophylactic 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 *Chikungunya virus* should not be used without consulting with a transplant infectious disease expert.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information can be obtained.

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, *Herpes viridae* 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 (RL 3) [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 prophylactic anti-viral agents are, at least partially, effective in preventing/treating other herpes viruses including Epstein–Barr virus (EBV), herpes simplex virus (HSV) and varicella–zoster virus (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 *albopticus*). Distribution of *Aedes aegypti* or *Aedes albopticus* 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 through migration of infected humans or through importing 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.

Infection may be asymptomatic or of 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 [28].

One case of transmission with a manifestation of haemorrhagic fever in living kidney transplantation has been reported [29].

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 prophylactic 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 dengue virus should not be used without consulting with a transplant infectious disease expert.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information can be obtained.

8.4.2.4. *Epstein–Barr virus*

In Europe, more than 90 % of all adults are infected with Epstein–Barr virus (EBV: DNA-virus, *Herpes viridae* family). After primary infection with or without disease, people may remain asymptomatic if not immuno-compromised.

EBV transmission to naïve transplant recipients increases the risk of post-transplant Lympho-Proliferative Disorders (PTLD). This risk requires regular follow-up of all transplant recipients (RL 3) and consideration of specific therapies if viraemia or malignancy is identified.

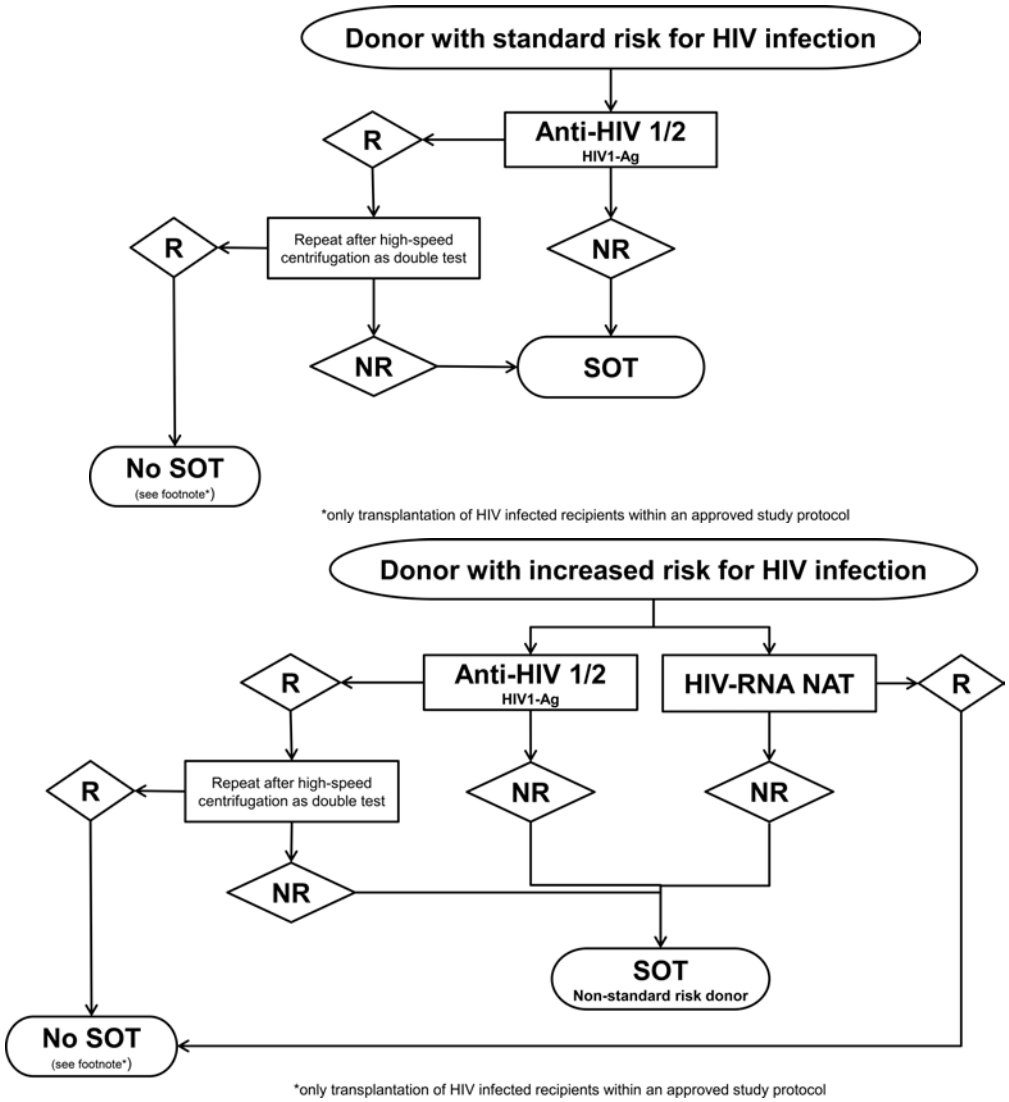
In the case of EBV D+/R– (for instance, most paediatric transplant recipients), protocols for close monitoring of such recipients contribute to reducing the fatal complications of PTLD by earlier diagnosis.

For chemo-prophylactic protocols it should be considered that there is no prophylactic treatment which can prevent primary EBV infection. EBV-DNA monitoring and early treatment should be adopted for all D+/R– recipients.

In case of suspected acute mononucleosis, EBV-infection can be ruled out by investigation of EBV-DNA in peripheral blood and EBV nuclear antigen.

Organs can be accepted independently of the anti-EBV IgG status of the donor. Proper follow-up/surveillance regarding PTLD is required particularly in children and D+/R– cases.

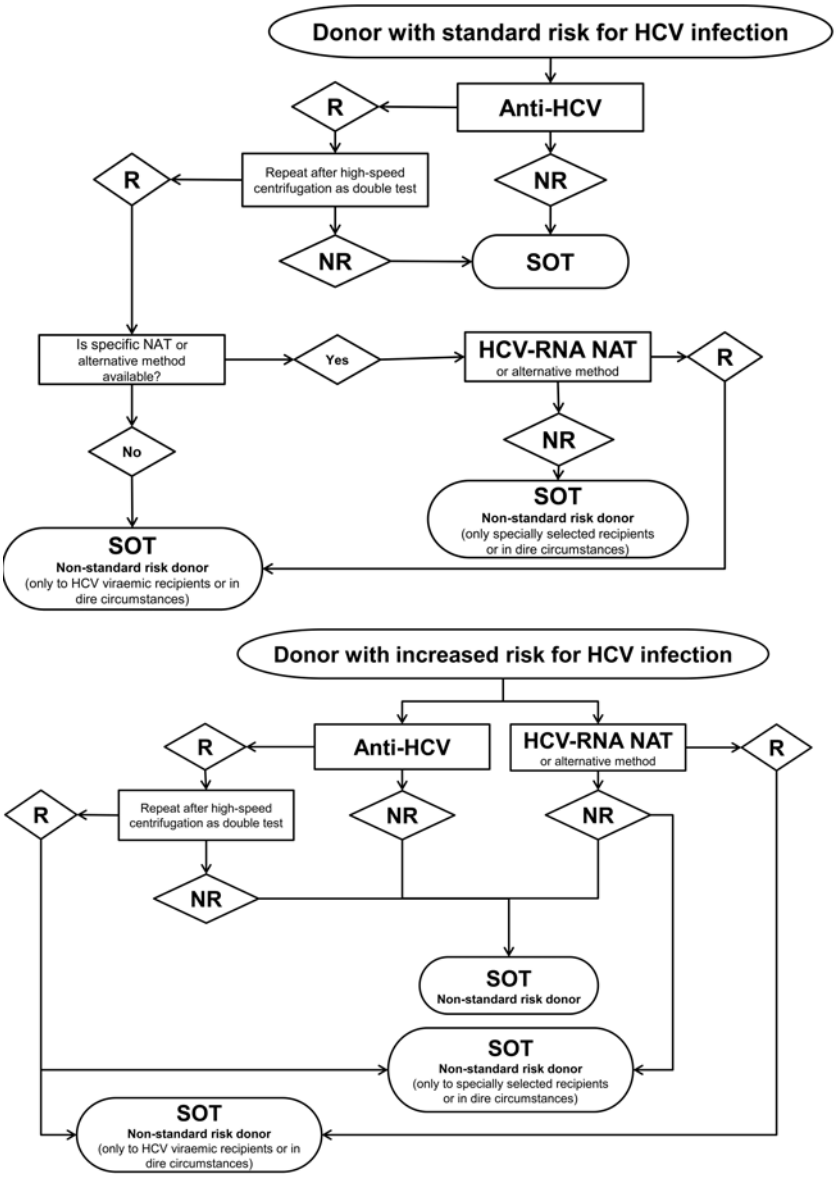
Figure 8.1. **Screening algorithms for HIV infection in organ donors**



R=reactive, NR=not reactive, SOT=solid organ transplantation.

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 based on a result obtained through this screening algorithm. As this process is time-consuming, 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. For further consideration about protocols of HIV-to-HIV-transplantation (D+/R+), see section 8.4.2.11.

Figure 8.2. **Screening algorithms for HCV infection in organ donors**

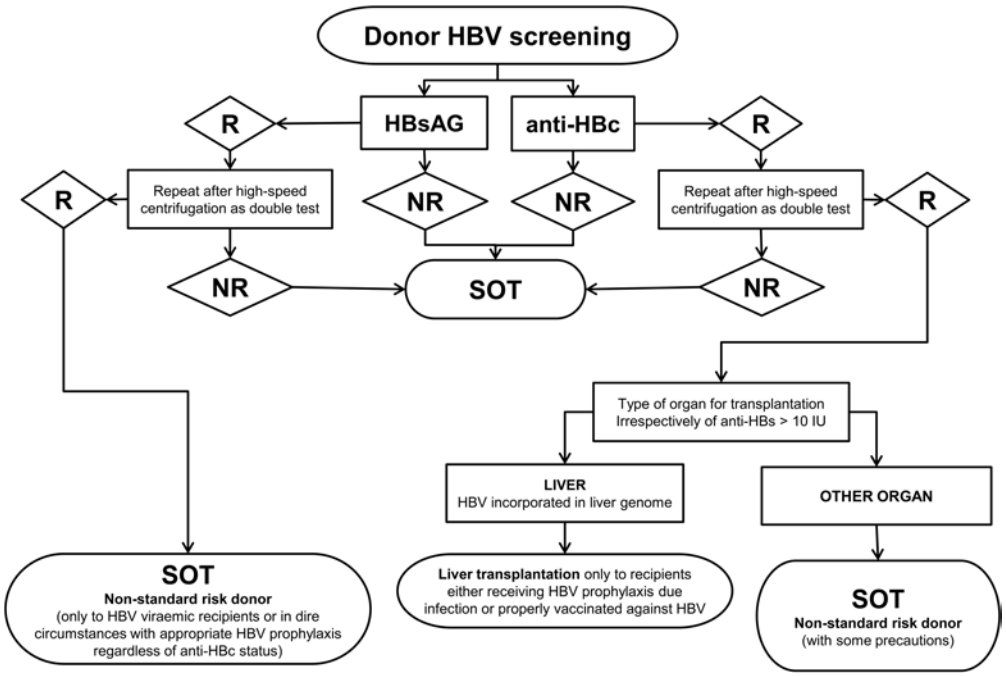


R=reactive, NR=not reactive, SOT=solid organ transplantation.

In the case of an anti-HCV reactive result, confirmation of the result may be preferable before a donor is rejected or the organs are discarded based on a result obtained through this screening algorithm. As this process is time-consuming, 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.

Figure 8.3. **Screening algorithms for HBV infection in organ donors**

For the risk pathway shown below, a threshold of > 10 IU/L anti-HBs has been used, since this is the lower threshold where most laboratories define the result as reactive. It should be considered that due to HBV-mutants the testing algorithm might fail in some countries.
Irrespective of anti-HBs titres in the donor, organs can be transplanted when the donor is tested HBsAg non-reactive and anti-HBc reactive, provided safety precautions are taken in the recipient (see section 8.4.2.6). If HBV-NAT is available, then measurement of liver tissues and blood may provide more specific information.



Hepatitis B: increased risk for infection

1. Proceed with the algorithm according to standard risk.
2. Accurately communicate elevated risk for infection, including all donor 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 based on a result obtained through this screening algorithm. As this process is time-consuming, 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.

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. Recovery from HAV infection (RL 3) or prophylactic vaccination status (RL 5) is indicated by anti-HAV-IgG reactivity. Since 2013, increased numbers of HAV infection have been reported by 11 EU member states. It is potentially linked to the ongoing HAV outbreak in EU with frozen berries as a potential common, continuous source of infection in the EU/EEA [30].

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), most of them without further complications [2].

In donors with HBV viraemia (indicated by an HBsAg reactive result), HBV will be transmitted by any organ or tissue (RL 2). Usually, anti-HBc will also be reactive (or will subsequently become reactive in rare cases of *de novo* infection). 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 hyper Immune-immunoglobulin (HBIG), or when the recipient is already immune [31-33]. Life-long monitoring for HBV is necessary. However, a breakout of HBV 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 [22, 31]. However, grafts from such donors should preferably be used in recipients with current or previous HBV infection or successful vaccination. Lifelong monitoring is recommended (RL 3) [33]. 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 (RL 2-3) [34].

In anti-HBc reactive donors (with non-reactive HBsAg and irrespective of anti-HBs titres), the hepatocytes remain latently infected with the virus, and reactivation of lytic infection can occur in the setting of immune-suppression, particularly in liver transplant recipients. In such cases, in liver recipients without initial protection against HBV, life-long treatment with HBV-specific anti-viral therapies (and HBIG) will be required [35]. 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 [35]. Any recipients of HBsAg reactive or anti-HBc reactive donor livers should be monitored throughout life [35] 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 mutants [36]. The epidemiology of HBV mutants is not well studied for all European countries, but the different HBV-mutants cause difficulties in screening as well as in the case of an anti-HBc reactive and anti-HBs reactive donor, HBIG prophylaxis of the recipient will be ineffective.

The clinical relevance of isolated anti-HBc reactivity, without reactivity of any other HBV serological marker, is uncertain [37]. This is suggestive of prior HBV-infection in the donor without maintenance of anti-HBs. HBV is present in the hepatocytes (viral covalently closed circular DNA [cccDNA] in the genome), but viraemia is unlikely or below the detection level of most available sensitive HBsAg tests. Livers have been transplanted successfully using HBIG and HBV anti-viral therapy [31], as outlined above (RL 2-3). Regrettably, there is still an unacceptable rate of false positive screening results in some licensed anti-HBc assays.

In the case of an anti-HBc reactive donor, only negative HBV-NAT from liver tissue can exclude HBV infection. This can be done as a complementary investigation after transplantation to decide whether prophylaxis against HBV reactivation or infection must be continued in the (liver) recipient.

HBV infection by HBV pre-core mutants is frequent (> 60 %) in some areas of Europe [38]. 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 anti-HBc, only reactive donor organ sero-conversion of recipients has been observed in recipients. Furthermore, HBV escape mutants also occur (despite anti-HBs prophylactic treatment), which lack the genetic information for production of HBsAg; these donors are usually HBsAg negative, anti-HBs and anti-HBc reactive and HBV-DNA reactive [39-41].

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 section 8.4.2.7). Then, even a liver graft from a HBsAg-reactive donor may be used with proper safety precautions [42].

In every donor, HBsAg and anti-HBc must be determined. In any case of a reactive result for HBsAg or anti-HBc, adhere to the algorithm presented in Figure 8.3 in order to provide all information needed for the summary below. A summary of the potential risks of organs used for transplantation from HBV infected donors according to their screening results is provided in Table 8.3.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information can be obtained.

Table 8.3. **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+	Chronic 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 life-long monitoring

+ = reactive; – = non-reactive.
* HBV prophylaxis = anti-viral treatment (and HBIG) as well as life-long 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 [34, 35].
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 not available).

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 [3]. In donors with anti-HCV reactive results and viraemia ruled out definitively by HCV-NAT this may not occur [27], 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, with extensive variation according to geographic prevalence and occurrence of risk behaviours, e.g. intravenous drug abuse, intra-nasal cocaine sniffing, medical procedures [20, 26].

Virus load fluctuates in HCV-infected people. In some cases of confirmed anti-HCV reactivity, the virus load may temporarily fall below the detection level of NAT (< 10 IU/mL). These individuals can still transmit the infection to the recipient. This fluctuation can also be caused by acute reinfection of people who were able to clear acute HCV-infection spontaneously [43]. Often, in chronically infected people, the viral load exceeds 1 000 IU/mL.

Spontaneous clearance of viraemia can occur in up to 25 % of the people with acute HCV infection. Then anti-HCV reactive and HCV-NAT non-reactive results are obtained due to the innate and adaptive host immune response [43]. Which factors enhance or restrict this chance of clearance is a matter of extensive research. In the near future due to improvements in HCV-treatment, more people will achieve a sustained virological response with no viraemia detectable by HCV-NAT. The rare issue of potential HCV-persistence in such patients with sustained virological response is unresolved.

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. 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 will probably not occur [27]. Then such grafts can be used in recipients willing to accept the risk after informed consent.

Determination of the virus load does not help in decision-making about the risk of further infection.

The issue of HCV genotypes and decision-making with regard to the use of organs for transplantation from HCV-infected donors has also been a matter of research. 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 presenting with a different genotype, particularly since the response to anti-viral therapy has been shown to be better for genotypes 2 and 3 compared to 1 and 4. Whatever the benefits of knowing the donor HCV genotype, logistics usually preclude its determination at the time of organ donation. In addition, mixed HCV infection has not been associated with increased mortality [44, 45]. 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 [46, 47]. Some transplant centres apply the policy of transplanting HCV-infected grafts only into recipients who are viraemic for genotype 1, while in all other cases only organs without viraemia are accepted in HCV-infected and viraemic recipients.

Table 8.4. **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[1]	HCV transmission may occur: vital cases or viraemic recipients (with HCV-PRO)[2]	
Anti-HCV+ HCV-NAT+	HCV viraemia		
Anti-HCV– HCV-NAT+			
Anti-HCV+ HCV-NAT–	HCV viraemia unlikely[1]	HCV transmission may not occur, transplantation after informed consent of recipient in a specially designed study protocol possible (D+/R–, D+/R+)	

+ = reactive, – = non-reactive, # = result irrelevant for further conclusions.

1 HCV viraemia may be temporarily 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).

2 HCV-PRO = anti-viral treatment (if possible), as well as life-long monitoring by serology and NAT required.

Note: prospective HCV-NAT is only recommended for donors with an elevated risk of HCV-infection.

With the new available treatment options, policies regarding the use of organs from HCV donors should be reconsidered [48].

NAT-testing in recipients should be used for post-transplant donor-derived HCV surveillance, since recipients may remain sero-negative.

Recent advances in testing methods may provide fully automated HCV-antigen tests as an alternative to HCV-NAT for quantification of viral load [49], which needs further validation before consideration for donor screening can be discussed.

In every donor, anti-HCV must be determined. In any case of a reactive result, adhere to the algorithm presented in Figure 8.2.
In the event of an anti-HCV reactive result, HCV-NAT should be performed to assess whether clearance of viraemia exists or not (spontaneous or due to sustained virological response after therapy).
A summary of the potential risks of organs used for transplantation from HCV infected donors according to their screening results is provided in Table 8.4.

For the appropriate selection of transplant recipients, it is helpful to obtain the following information:

a. Has there been previous HCV infection?
b. Was any HCV treatment done 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?

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information can be obtained.

8.4.2.8. *Hepatitis D virus*

Hepatitis D virus (HDV: RNA-virus, the only agent of the genus *Deltaviridae*) infection, in addition to HBV infection, is mostly an issue for countries with a high prevalence of HDV (RL 1, 4).

Defective HDV requires the HBsAg for replication. Donor-transmitted HDV infections must be avoided by adequate screening of HBsAg reactive donors in endemic areas because therapeutic options do not currently exist.

Organs from donors with HDV infection are usually not accepted.

8.4.2.9. *Hepatitis E virus*

Currently, the relevance of Hepatitis E virus (HEV: RNA-virus, *Hepeviridae* family) infection cannot be assessed because of the variable endemic occurrence in European organ or blood donor populations. Sources of infection are insanitary water and contaminated food; maternal-foetal (vertical spread) and parenteral routes are less common modes of infection. The route of HEV transmission appears to be consumption of infected pork, game meats and shellfish.

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 up to 120 days, from the intestine. Chronic HEV infection is usually observed in patients with profound immune-suppression.

HEV infections have been observed in liver, lung, kidney, hematopoietic stem cell, heart and simultaneous kidney–pancreas recipients. Reactivation of HEV infection has been reported without association to the donor [50]. Currently one single case of HEV transmission through liver transplant has been reported from a donor with occult HEV infection [51]. Unfortunately, according to one study, 66 % of HEV-infected organ transplant recipients develop chronic hepatitis [52]. Therefore the issue is under discussion. Currently, information about persistence of HEV in the donor's liver and potential (re-)activation after transplantation are inconclusive.

In cases of acute infection in the donor with viraemia, organs should not be transplanted. After recovery from HEV infection, organs can be transplanted.

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 viraemia).

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] (RL 3). 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 latent 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 [53-56], while it is recommended not to overlook active infection.

Some cross-effectiveness exists between some anti-viral prophylaxis for CMV, HSV and VZV.

Organs can be accepted from donors with latent 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 herpes virus (KSHV) or human herpes virus-8 (HHV8)

KSHV is a herpes virus that is homologous with but different from the gamma herpes viridae, EBV and herpes virus saimiri. As is the case with all herpes viruses, the KSHV life-cycle includes both latent and lytic phase.

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 [57-67]. In immuno-compromised persons, fever, splenomegaly, lymphoid hyperplasia, pancytopenia and occasionally rapid onset Kaposi sarcoma, have been described in association with apparent primary KSHV infection [62, 64-67]. However, in immunocompromised transplant recipients, KSHV is more often associated with neoplastic diseases.

Various tests based on immunofluorescence have been developed: Western blot, and enzyme-linked immunosorbent assays (ELISAs) to detect antibodies against latent and lytic genes. So far, a number of good tools are available for sero-epidemiologic studies, although their usefulness in clinical daily practice is debated. Adding to the uncertainty of using serological assays for diagnosis are the non-standardised methodologies, since various assays are directed against different antigens. 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. It has been suggested that a combination of whole virion ELISA and lytic immunofluorescence assay may be the most sensitive method for diagnosing KSHV.

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, 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, the detection of KSHV antibodies could be done in the days following transplantation and the results transmitted retrospectively to physicians.

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 anti-latent antibodies is recommended in areas with high prevalence. In case of D+/R– match, a close monitoring of KSHV-DNA in blood is recommended on the recipient in order to identify early infection.

8.4.2.11. *Human immunodeficiency virus*

Organs from donors with human immunodeficiency virus (HIV: RNA-virus, *Retroviridae* family) infections have so far only been utilised intentionally in a limited number of cases as part of an experimental protocol for HIV-infected recipients in South Africa. The protocol requires strict adherence of the recipient to highly-active anti-retroviral treatment [68, 69]. HIV-infected donors have been inadvertently used after false negative testing, resulting in unintended transmission into previously uninfected recipients [70, 71].

Donors who present with evidence of HIV-viraemia or 'HIV-related diseases' should never be used (RL 1). 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 [69]. In the US, the HIV Organ Policy Equity act allows transplantation of organs from HIV-infected donors to HIV-infected recipients, under an experimental protocol [72]. In other countries this can also be done under a specifically designed protocol when approved and permitted by local regulation and national law. However, anti-HIV-1/2 reactive status in potential donors is still regarded as absolutely contraindicated for organ or tissue donation in most European countries.

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 sero-conversion. For increased risk individuals, NAT is recommended (see sections 8.2 and 8.4.1.1). 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 such areas.

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 [73, 74].

It should be noted that in some populations the target organs for HIV are the kidneys (e.g. HIV-nephropathy in South Africa).

Organs from anti-HIV reactive donors should not be used for HIV naïve recipients. They may be offered, under careful surveillance, to selected HIV recipients under a specifically designed protocol.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information can be obtained.

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 [16].

Human T-lymphotrophic virus-2 (HTLV-2) has not been definitively associated with human disease [16].

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 [75]. 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 time-consuming [16].

HTLV screening can only be recommended for endemic areas and in endemic populations [76] since a risk of infection may exist [77]. Because of the limited follow-up on recipients of HTLV-infected organs, no conclusive recommendations are possible [16]. 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 Iran) and Romania, as well as some higher-prevalence spots in some Chinese provinces, native population in north Australia and some US states [75] – the risk assessment for donor-derived HTLV-infection should balance: 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 (RL 2-4).

In 2010 the US ceased the mandatory testing of HTLV-1/2 [16]. Japanese experts suggest HTLV-infected organs can be transplanted into previously infected HTLV recipients [78]. In Europe, HTLV-1/2 screening is only mandatory in France – despite only a 0.0056 % sero-prevalence in new French blood donors [79] – 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) [75-76, 80]. 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 [80].

Any initial reactive test result must be confirmed as a true positive for HTLV-1 before further conclusions can be drawn [80].

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, though evidence-based policies do not exist.
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 (HPyVs) 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.

BK virus (BKPyV, DNA virus, *Polyomaviridae* family) associated nephropathy (BKPyVN) is a leading cause of renal allograft dysfunction and loss after kidney transplant [81-83]. 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 [84]. 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 leukenecephalopathy is addressed in section 8.9.

8.4.2.14. *West Nile virus*

West Nile virus (WNV: RNA-virus, *Flaviviridae* family) 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. However, infections may be asymptomatic.

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 temperate climates or late summer/early autumn in 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 [20]. WNV has been a recurrent seasonal problem in some areas of Italy [85-86]. 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 donors have been utilised [86-89]. Transmissible WNV may be present in potential donors in the absence of positive serology or NAT [90]. There is some evidence that WNV viral nucleic acids and infectious virus remain associated with blood cells after the clearance of virus from plasma [91]. Viraemia may persist after incubation for 2-4 weeks or exceptionally for a few months [92-94]. 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 [95]. WNV shedding in urine has been reported in humans, not only early post-infection [96], but even years later [97]. Because of longer shedding and higher viral load, urine samples may be more appropriate than blood for WNV testing in blood and organ donors [98]. Urine might become a specimen of choice to identify WNV in asymptomatic carriers. However, prospective studies are needed to verify the usefulness of WNV testing of urine of organ donors. Unfortunately an unpublished study of the CDC failed to confirm these results and thesis, and therefore no evidence exists to screen urine [99].

WNV-relatives exist (like the Usutu virus), which have infected birds via the consumption of infected mosquitoes in countries north of the Alps. WNV antibody-screening showed cross-reactivity, whereas NAT did not. This is a diagnostic pitfall in the case of febrile neuro-invasive illness.

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 prophylactic 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 with a transplant infectious disease expert.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information can be obtained.

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.

Growing evidence exists of an association between Zika virus infection during pregnancy and

adverse pregnancy outcomes, and post-infectious Guillain–Barré syndrome.

Outbreaks of primary infection are possible in regions with 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).

The risk of transmission by solid organ transplantation is currently unknown (February 2016), but 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 prophylactic 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 Zika virus should not be used without consulting with a transplant infectious disease expert.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information on emerging threats can be obtained.

8.4.2.16. *Other viruses*

Donor-derived infections caused by rabies [1, 2] and lymphocytic choriomeningitis virus (LCMV, RNA-virus) [1, 2] have been reported (RL 1 or RL 4). These rare infections cause life-threatening or fatal complications in recipients, without any possibility of treatment. Typical childhood infections may still occur in adulthood and can be transmitted through organ donation (RL 1-4). Parvovirus B-19 infection has been documented through bone marrow, blood and organ donation (RL 2-3).

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. Based on information about the donor's recent behavioural/disease patterns and the present endemic situation in various 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).

8.4.2.17. *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 – e.g. [13, 14]. The next influenza virus pandemic may require new or adapted pathways.

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 currently circulating RNA-respiratory viruses) in immunocompetent 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 health care systems in other continents. Again, proper surveillance and obtaining of appropriate information were the key issues for avoiding infection spread despite the safety precautions of hygiene as well as deferral intervals including the time of incubation in persons at risk of acquired infection [100-101]. 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.

Please refer to section 8.4.1 for the websites of the organisations where the most current epidemiological information on emerging threats can be obtained.

8.5. Bacterial infections

8.5.1. Acute infections

Intensive care units (ICU) should monitor all potential donors bacterial infection, with special attention to multidrug resistant (MDR) microorganisms (see section 8.5.5) [102-104]. 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 [7] 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 procurement organisation should have clear policies and procedures for following up on 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 broncho-alveolar lavage (BAL) during organ recovery, as well as from the organ preservation solution before transplantation [105]. Investigations should cover bacteria and fungi, as well as analysis of resistance patterns.

Most positive bacterial cultures or microbiologic assays lead to a diagnosis [2, 33]. 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 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 recovery from signs and symptoms of infection is demonstrated. Nevertheless, antibiotic treatment for a longer period may be necessary (e.g. endocarditis). Treatment of the recipient for an appropriate duration post-transplant is strongly recommended, with careful attention for evidence of embolic infection. Organs from bacteraemic donors should be accepted on a case-by-case basis, in direct consultation with the transplantation team for appropriate post-transplant care and monitoring (RL 2-4). The focus (organ) of such infections should not be transplanted. Sometimes, bacterial growth from blood cultures may be caused by contamination.

Localised infections without systemic spread do not contraindicate donation (RL 5) [8], 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 (RL 2-4) [8], but this should be confirmed by sterile cultures (RL 2-3). 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 (RL 2-4). 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.

When *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *paraphrophilus*), *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens* or *Kingella klingae* are detected in blood cultures, then endocarditis should be ruled out.

Translocation of intestinal bacteria may occur in patients without enteral nutrition. Feeding via a nasogastric/duodenal tube using uncontaminated fluids decreases this possibility (RL 5).

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 (RL 1-5).

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 [106]. This is particularly true in the case of MDR pathogens.

Organs with active bacterial infections limited to the organ should not be used (RL 1, 4) unless adequate antibiotic therapy of at least 24-48 h has been initiated in the donor, and subsequently, in the recipient (RL 2-3). 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 [2], the following issues should be considered:

a. Bacteraemia due to nosocomial pathogens (e.g. multi-resistant *Enterococci*, *Staphylococci* (MRSA), *S. pneumoniae*, *Pseudomonas*, *Escheria coli*, *Serratia*, *Acinetobacter spp.* and *Klebsiella spp.* or other *ESBL spp.*) is often related to the use of intravenous access and other medical support systems [1, 2]. Following transplantation, these pathogens can cause serious infections, particularly at anastomotic sites by colonising fluids and by forming abscesses or mycotic aneurysms [1, 2] (RL1). Despite negative blood cultures, infections may be transmitted in cases of unsuspected endocarditis or pneumonia (e.g. *S. pneumoniae*).

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 [107] (RL 2-3).

c. Donors with on-going sepsis (and positive blood cultures) should not be accepted, especially if effective therapy cannot be confirmed (RL 1). However, grafts from donors without sepsis, but incidentally-detected bacteraemia, have rarely resulted in disease transmission under correct antibiotic prophylaxis in the recipient (RL 2-3).

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 are available.

There is significant evidence that donors with proven bacterial meningitis caused by *N. meningitides*, *S. pneumonia* or *Haemophilis* 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, 8] (RL 2-3), 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 (RL 1-3). Treatment by targeted antibiotics is possible, but management of immuno-suppressed patients with *Listeria* infection 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.

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 % [8]. Following at least 48 h of effective antibiotic treatment and unimpaired pulmonary function, lungs (or at least unaffected lobes) may be considered for donation [8] (RL 2-4). 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. Given 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 [108].

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 used safely 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

Currently, 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 [109-111]. No specific donor risk factor may predict the infection or colonisation by MDR organisms. Prolonged (> 7 days) ICU stay, along with vasopressor use and need for cardiopulmonary resuscitation, have been reported as independent risk factors for predicting potentially infected donors [112]. 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 [113].

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, as outcomes in such circumstances are still unknown and because the accumulated literature deals with different types of organisms. Therefore, avoidance of such donors appears advisable until further data are available.

8.5.6. Tuberculosis

Late infections by *Mycobacteria tuberculosis* are troublesome for recipients [1, 2, 8]. Organs from donors with disseminated tuberculosis (TB) should not be utilised (RL 1). Organs from donors with a history of TB and with successful treatment for at least 6 months have been transplanted with success (RL 3). Prophylaxis and/or empiric treatment of the recipient should be considered in such cases, according to the guidelines [114].

Whereas in living donation evaluation of the donor can be performed according to the recommended guidelines, in deceased donation this is challenging [115-118]. 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 [115-118]. For lung donors, histopathological and microbiological

studies should be performed for ruling out active infection (e.g. BAL for acid-free staining smear, culture and PCR) [115-118]. 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 (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 [115]. In summary, the following considerations are important in deceased donors:

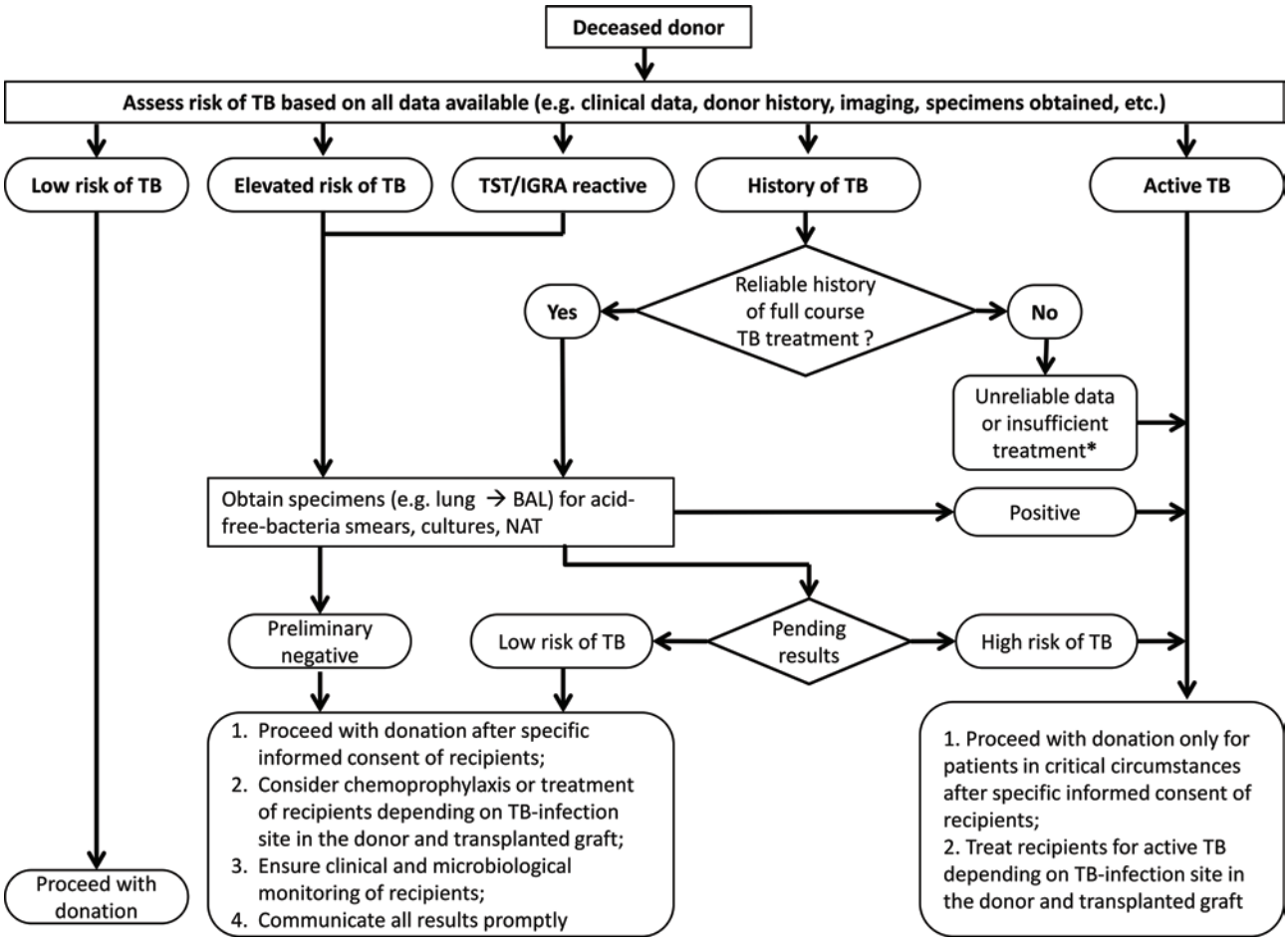
a. Stratify into low, moderate or increased risk of LTBI or active TB according to:
   i. country of prior residence and/or exposure (epidemiological history);
   ii. social risk factors (homelessness, incarceration, alcohol, known TB-contact, refugee-camp);
   iii. medical factors (history of untreated 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/m^2 in adults; diabetes mellitus; cigarette smoking; immuno-compromised, reactive IGRA or other TB-screening test) and
   iv. organ (consider extra-pulmonal manifestation in immunocompromised 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 genitourinary TB), consider IGRA (though the test might provide a clear result for further conclusions). There are often pending results when procurement is performed. Therefore ensure that all data will be forwarded as soon as 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 8.4. It is helpful to distinguish between grafts which are remote

Figure 8.4. **Algorithm for management of deceased donors**



* Obtain proper specimen to confirm diagnosis and communicate results promptly.

Source: adapted from Morris MI, Daly JS, Blumberg E et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report [115].

from the active TB-site and those affected by the active TB-site.

e. Targeted imaging studies are recommended in case of suspected or documented past TB.

All recipients documented to have LTBI should receive treatment to prevent reactivation 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 is detectable by standard serology [8]. Donors with positive RPR (rapid plasma reagin test) 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 [118]. 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] (RL 3). 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 within 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 section 8.7) apply (RL 4).

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 (RL 4).

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.

8.6. Fungal infections

Disseminated fungal infections (or fungaemia), confirmed by blood cultures, must be eradicated completely before donation [2, 5] (RL1). For localised infections, a case-by-case consideration is necessary; for example the trachea is often colonised by *Candida*.

Undetected fungal infections are a concern for lung transplant, so BAL during bronchoscopy prior to donation is recommended. Fluconazole-resistant *Candida sp.* or *Aspergillus sp.* are particularly problematic, especially among lung organ recipients. Dissemination of *Aspergillus sp.* infections must be ruled out.

In certain geographic areas, *Histoplasma*, *Coccidoides*, *Blastomycosis* and *Scedoporium spp.* are endemic and screening may be necessary to rule out active infection in at-risk donors [1, 2, 5, 119-121] (RL 1-4).

Cryptococcus infection may be associated with HIV infections, other immune-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 immune-suppressive therapies, there is increased risk of colonisation or infection by opportunistic pathogens, e.g. *Aspergillus* or *Pneumocystis jiroveci* (*carinii*) [119-122]. 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 [123]. In some donation procedures, contamination of preservation solution before implantation by various *Candida spp.* has been detected [123].

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 (RL 1). Exceptions may be possible if unacceptable risks for the recipients have been ruled out by transplant infectious disease specialists (RL 4).

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 includes muscle transplants) [2, 124] (RL 3). Serologies for toxoplasma are included in the standard screening of heart donors in order to avoid *de novo* infection through dissemination in a seronegative recipient [124]. 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 [125], a summary of which is included in Table 8.6. 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 (section 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 [126-127]. 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 8.6). 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, websites and Table 8.6) 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 (RL 1-2). Grafts can be used after successful treatment and recovery (RL 2-4), 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 reactivation of malaria in recipients of grafts from donors at risk of acquired malaria. Proper treatment of the recipient must be initiated immediately [128]. 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.

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).

Currently (2015) Chagas disease is endemic in the following countries: Argentina, Belize, Bolivia, Brazil, Chile, Costa Rica, Ecuador, Falkland Islands, French Guinea, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, South Georgia and the South Sandwich Islands, Surinam, Uruguay, Venezuela.

Asymptomatic parasitaemia is more common than symptomatic disease in potential donors [124, 129-130]. Antibodies against *Trypanosoma cruzi* indicate a former infection, but current assays have a high rate of false positivity, as well as significant variability in sensitivity and specificity. Acute parasitaemia may be detected by PCR and Strout-Test (microscopy of blood after blood concentration), but these are

generally not sufficiently sensitive for screening of organ donors because of intermittent parasitemia.

Prophylactic treatment (benznidazole) in D+/R– combinations is considered controversial but it has had some success [131]. All recipients of organs from Chagas disease-positive donors should be closely monitored for disease transmission by PCR or microscopy of blood [132-133]. 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 [116]. Cardiac or intestinal grafts should not be used from donors with a history of *Trypanosoma cruzi* infection (RL 1), whereas other organs can be considered (RL 2-3) [116-130, 132-133].

8.7.3. Echinococcosis

Echinococcosis (critical in liver or lung donations) requires an individual-based decision [8]. If there is evidence of disseminated echinococcosis in the donor, then organs should not be considered for transplant (RL 1). 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 (RL 3). 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 [8].

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. *Ankylostoma*, *Ascaris*, *Strongyloides* or *Schistosoma* with an increasing number of cases donor-transmitted [134]. In addition, some nematodes can be transmitted by *Culex* or *Anopheles* mosquitoes (e.g. lymphatic filariasis through *Wuchereria bancrofti* and *Brugia sp.*, *Mansonella*), black fly (e.g. *Onchocerca*) or tabanids (e.g. *Loa loa*) and may persist in the body for months (e.g. filariae) [135]. 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-immunosuppressed 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 [136]. 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) [137]. 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 [138]. 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 endemics in specific geographical regions (see section 8.10.6).

Recently in the UK, a rare case of donor-derived helminths transmission (*Halicephalobus gingivalis*) to kidney recipients was the subject of a lay press release [139].

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 [8]. 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 to 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 the UK 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 for 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 (i.e. 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 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 section 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.

Table 8.5. **Key questions to be asked of any potential donor to mitigate the risk of missing an unsuspected CNS 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 to 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
Immunosuppressed 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 [141].

Progressive multifocal leukoencephalopathy (PML), caused by JC virus and its mutants is typically observed in immunocompromised 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.

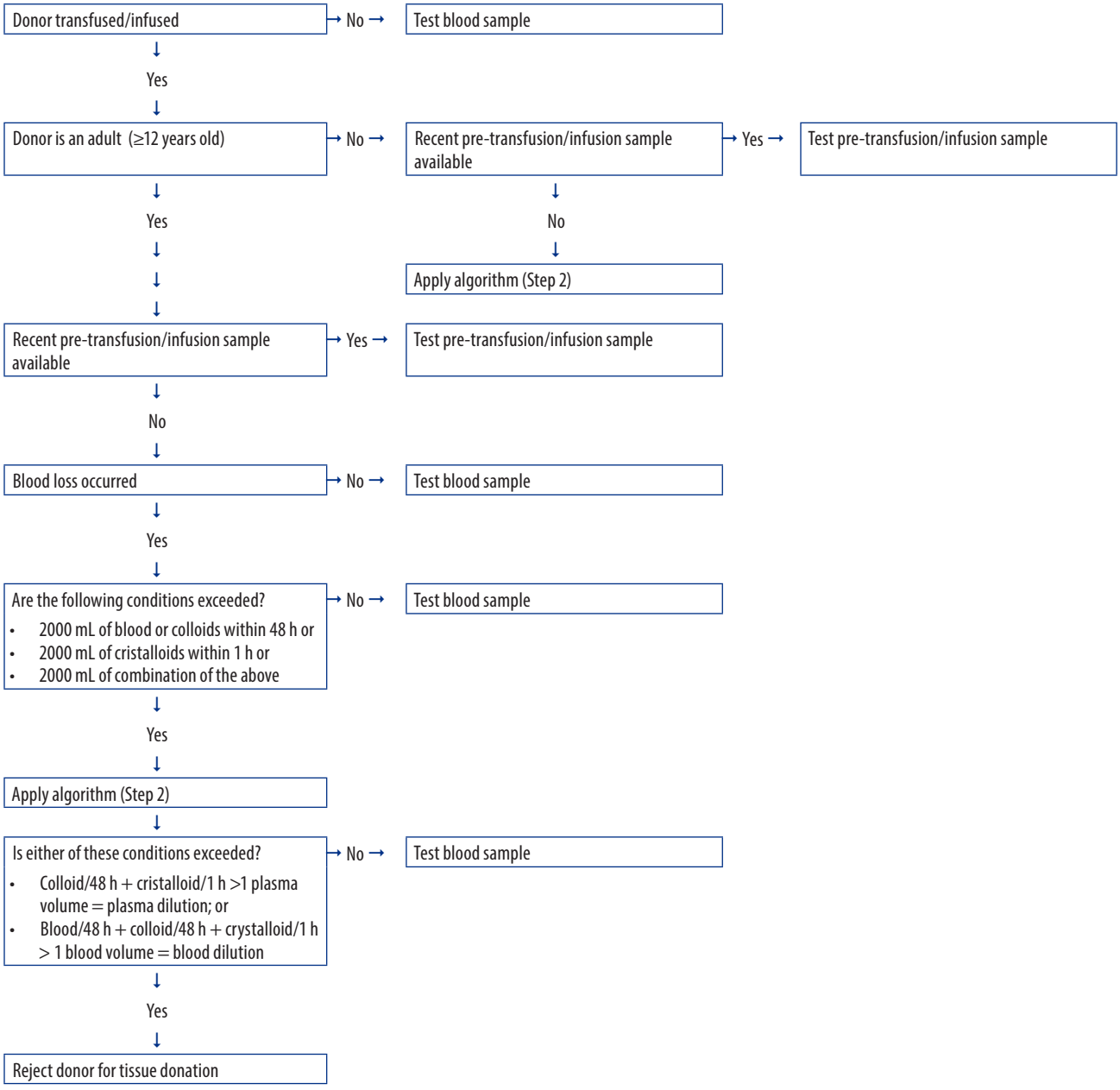
Acute disseminated encephalomyelitis is always diagnosed by exclusion of other causes. But unfortunately it has been associated with donor transmissions, including rare pathogens, e.g. *Balamuthia mandrillaris* [140].

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 organ procurement organisations 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 meningoencephalitis 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 [141].

Figure 8.5. **Recommended steps for the calculation of haemodilution**

Step 1. Donor evaluation pathway



Step 2. Algorithm for calculation of haemodilution in a donor if necessary		
Plasma volume	Donor weight in kg _____/0.025	_____mL
Blood volume	Donor weight in kg _____/0.015	_____mL
A) Total volume of blood transfusion/48 h	_____mL of RBC transfused/48 h _____mL whole blood transfused/48 h _____mL reconstituted blood/48 h	Sum A: _____mL
B) Total volume of colloid infused/48 h	_____mL plasma/48h _____mL platelets/48 h _____mL albumin/48 h _____mL HES or other colloids /48 h	Sum B: _____mL
C) Total volume of crystalloid infused/1 h	_____mL	Sum C: _____mL
Calculation plasma dilution	Sum B + Sum C > plasma volume	If either yes: haemodilution
Calculation blood dilution	Sum A + Sum B + Sum C > blood volume	

RBC=red blood cells; HES=hydroxyethyl starch.

Based on the algorithm developed by the Food and Drug Administration, USA [145].

The key questions summarised in Table 8.5 should be asked about any potential donor [141] 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.

A brain abscess is not *per se* a contraindication. Nevertheless, the potential causes of the brain abscess should be evaluated before accepting the organs.

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 confirmative 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 (e.g. anti-HBc reactive) 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 (e.g. reactive anti-HBc testing), 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).

8.10.2. Haemodilution and quality of specimen investigated

When 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 48h 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 48h preceding death (circulatory arrest), or if crystalloids were infused in the hour preceding death (circulatory arrest).

Refer to Figure 8.5 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 [142-146]. 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 a very small adult donors, or for paediatric donors.

Table 8.6. **Geographically restricted, rare or critical infectious diseases**

Disease (Pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmissible by SOT*
Aspergillosis (*Aspergillus spp.*).	Worldwide, risk for long-term and immuno-suppressed patients in ICUs.	Risk factors: prolonged stays in hospital, immuno-compromised, building renovations, damp conditions. Donors with invasive and disseminated Aspergillosis should not be used (RL 1).	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 (RL 1). a)-d) Pulmonary and other infections (RL 1-5). 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 (RL 4).	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 (RL 4). Prophylactic use of azole anti-fungals may reduce the incidence of donor-derived disease if infected donors are used.	No
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 (RL 4).	?
Candidiasis (*Candida spp.*).	Worldwide.	Donors with disseminated or invasive disease should not be used (RL 1).	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 (RL4); viraemia for ~ 2 weeks after first symptoms. Donors with viraemia should not be used.	?
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 (RL 3).	Yes
Coccidioidomycosis (*Coccidioides immitis*).	Southern USA, Mexico, Guatemala, Honduras, Nicaragua, Venezuela, Columbia, 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 (RL 4). 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 and serology at specified laboratories.	?

* Transmissible by solid organ transplantation: Yes = reported, No = not reported, ? = high probability of transmission without documented cases or data lacking for robust conclusions.

Disease (Pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmissible by SOT*
Cryptococcosis (*Cryptococcus neoformans*).	Worldwide.	Donors having died with meningoencephalitis caused by *Cryptococcus* should not be used (RL 1). *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 results in fatal complications (RL 1 or 4). 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 (RL 3). 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 (RL 4). 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 (RL 4). 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.*).	Some rural areas in Europe: rodent faeces contain virus (aerosol transmission).	Consider specific diagnostic test in case of acute renal damage associated with fever and pain.	?
HAV infection (Hepatitis A virus).	Worldwide, poor sanitary conditions.	After recovery from acute infection no transmission reported. Reports of transplants from donors with acute infection are lacking.	?
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 [3]:. • 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 (RL 1-3). 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-hyper-immune-globulin 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 (RL 3), in all other cases avoid de novo infections (RL 1-2). Check for latest therapy recommendations. Genotype is only important for response to therapy, but not for risk of infection. Use donors according to case-based decisions.	Yes

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Disease (Pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmissible by SOT*
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 (RL 1, 4).	?
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 not evaluated/unknown (RL 4).	Yes
Herpes virus infections (HSV-1 and 2, VZV, HHV 6).	Worldwide.	Avoid *de novo* infection of naïve recipients, frequent reactivation in recipients. (RL 2-4) Antiviral prophylaxis is recommended if D+/R–.	Yes
Kapsi Sarkoma herpes virus/human herpes virus 8 (KSHV/HHV8).	Serology (anti-latent and anti-lytic antibody; serological assays are not standardised and a variety of assays directed against different antigens have been reported).	Serology generally unavailable prior to transplant. Consider NAT monitoring if donor seropositive, recipient seronegative. Oncogenic potential (Kaposi sarcoma, PEL 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 (RL 3) or lung transplants. Reactivation or dissemination under immuno-suppression in previously infected recipients may occur and may require treatment.	Yes
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 sero-positive) are not used (RL1). Testing should detect HIV-1, HIV-2 and all subtypes.	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 (RL 1 or 4).	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 (RL 1).	Yes
Legionellosis (*Legionella spp.*).	Worldwide.	Water, air-conditioning, etc. (RL 4).	?
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 (RL4). 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, RL 1).	?
Leptospirosis (*Leptospira spp.*).	Standing water in (sub-)tropical areas.	Acute infection affects all organs (RL 1, 4).	?

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Disease (Pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmissible by SOT*
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 (RL 1, 2). Successfully treated and recovered donors may be used, with some exceptions, e.g. liver. Consider prophylactic treatment of recipients (RL 2-4).	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 (RL 4).	?
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 (RL 2-4).	Yes
Non-tuberculous mycobacteria infection (non-tuberculous mycobacteria).	Worldwide.	(RL 4).	?
Parvovirus B19 infection (human parvovirus B19).	Worldwide.	(RL 4).	Yes
South American Blasto-mycosis (*Paracoccidioides brasiliensis*).	Soil in (sub-)tropical Central and South America.	No precise exclusion criteria for organ donation are described (RL 4). Trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia is 'cross-effective'.	No
Pneumocystis pneumonia (*Pneumocystis jirovecicarinii*).	Worldwide: infection risk in long-term patients in ICU, immuno-suppressed or -deficient patients.	Partly avoidable problem with specific prophylaxis in recipients (RL 3). Disseminated infection in donors contra-indicated (RL 1).	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 (RL 1).	?
Algemia (*Prototheca spp.*).	Worldwide.	(RL 4).	Yes
Rabies (Rabies virus).	Animal bites or salivary contact (dogs, bats, other mammals). Worldwide, though some island territories are low-risk (Japan, Taiwan, UK, Iceland, Australia [where other Lyssavirus exist], New Zealand, Norway, Sweden, Finland).	Transmission lethal (RL 1) unless previously vaccinated. Only NAT of brain tissue after autopsy is confirmative, but not exclusive. History of animal contact (bites) and any kind of neurologic disorder in the past 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.	(RL 4).	?
Scedosporium apiospermum infection (*Scedosporium apiospermum*).	Worldwide in immuno-compromised people.	(RL 4).	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 [148]
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 and tracheal secretions for larvae, or blood (in case of eosinophilia) for eggs in donors from (or having travelled to) endemic areas. 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. In immuno-suppressed patients, a hyper-infective status exists, which requires pre-emptive treatment by, e.g. ivermectin. Otherwise lethal (RL 4).	Yes

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Disease (Pathogen)	Geographic distribution, endemic zones and risks	Remarks	Transmissible by SOT*
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 (RL 4). 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
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 (RL 1-4).	?
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 (RL 3).	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 (RL 4).	Yes
Syphilis (*Treponema pallidum*).	Worldwide.	Treatment by antibiotics successful (RL 3).	Yes
Sleeping sickness (*Trypanosoma brucei spp.*).	Sub-Saharan Africa, different sub-species.	African Sleeping Sickness: different sub-species cause variants with progressive symptoms. Lethal (RL 1).	?
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 (RL 1). 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. (RL 2-3). 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 [149]
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 (RL 1-3). 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 sero-positive 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 (RL 1). 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.	?

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Table 8.7. **General considerations for infections and vaccines**

In general	Geographic distribution, considerable risks	Remarks	Transmissible by SOT*
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 (RL 1-3).	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 (RL 1-2). 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 testing (RL 3 or 5).	No

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The rationale behind the calculation of the algorithm is that false negative results may occur in investigations for infectious diseases since low antibody titres, and potentially nucleic acid, may be present in the diluted specimen. Because 50-60 % of human IgG is distributed throughout the tissues outside blood vessels and is recycled back into the bloodstream within 48 h, it becomes possible to perform serologic tests without major concerns about significant haemodilution [3].

Ultimately, it is important to consider that calculating the degree of dilution only by one of the currently used formulas [143-144] 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 (see Chapter 5) according to the standards of intensive care medicine accepting haemodilution. Therefore, the recipient team should perform a proper risk–benefit assessment to evaluate the risk of a false negative result due to haemodilution against the potential benefit to the recipient [145].

Finally, the quality of the specimen sent for testing is important (no haemolysis, proper storage, no dilution when sample is drawn from donor) [146].

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 (RL 1 or 4) 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 (RL 3-5) 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. 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 certified 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. Complementary serologic screening of the mother 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.

8.10.6. Geographic restrictions

Table 8.6 is a non-exhaustive overview of geographically restricted, rare or critical infectious diseases that can be transmitted by solid-organ transplantation (modified from [3, 125, 147]). 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 8.7).

Finally, surveillance of disease transmission vectors contributes to detecting new transmission risks.

8.11. Vigilance methods and tracking

Extensive communication, in both directions between the organ procurement organisation and the transplant centres, before, during and after transplantation, is crucial [1, 2]. If a recipient develops any unexpected signs and/or symptoms, including unexplained fever, leukocytosis, altered mental status or other signs of hidden infection [4], 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.

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 14). Free and rapid exchange of data between the vigilance systems of each member state must occur in order to facilitate safe international organ exchange.

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. 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 [150].

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 [151].

c. Prophylactic vaccination may not be effective for some end-stage organ diseases [150].

d. Treatments with antibiotic-, antiviral- 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 militate against expected transmissible 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 [152]. Such strategies should be evaluated for improved effectiveness.

e. An antibody response to an infection acquired through the transplanted organ may not develop [71]. It is recommended to rely on NAT or other direct pathogen detecting assays (e.g. HBsAg) to screen organ recipients for transmitted infections [1]. As late manifestation of latent infections, e.g. CMV, may occur in recipients, long-term follow-up should include targeted screening for such risks.

8.13. References

1. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. *Am. J. Transplant* 2011; (11): 1123-30.
2. Fishman JA, Greenwald MA, Grossi PA. Transmission of infection with human allografts: essential

considerations in donor screening. *Clin Infect Dis* 2012; (55): 720-7.

3. Fischer-Fröhlich CL, Lauchart W, Patrzalek D. Evaluation of infectious disease transmission during organ donation and transplantation: viewpoint of a procurement co-ordinator. *Organs, Tissues and Cells* 2009; (12): 35-54.
4. Ison MG, Grossi P and the AST Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 22-30.
5. Fischer SA, Lu K and the AST Infectious Diseases Community of Practice. Screening of donor and recipients in solid organ transplantation. *Am J Transplant* 2013; 13(Suppl 4): 9-21.
6. Ison MG, Hager J, Blumberg E *et al.* Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. *Am J Transplant* 2009; (9): 1929-35.
7. Agence de la biomédicine. *Prévention de la transmission de bactéries et d'agents fongiques aux receveurs d'organes.* Version longue. 2008 (in French) [available from: www.infectiologie.com/UserFiles/File/medias/_documents/consensus/recommandations_biomedecinefongique_long.pdf, accessed 24 February 2016; alternatively the short version of the document at: www.agence-biomedecine.fr/IMG/pdf/prevention-de-la-transmission-de-bacteries-et-d-agents-fongiques-aux-receveurs-d-organes-texte-court.pdf].
8. Pumarola T, Moreno A, Blanes J. Criteria for the selection of organ donors with respect to the transmission of infections. *Organs and Tissues* 2000; (2): 79-85.
9. Sarmento A, Freitas F, Tavares AP. Viral screening in the donation/transplant process in Portugal: state-of-the-art in 2002. *Organs and Tissues* 2003; 6 (1): 23-30.
10. Depoortere E, Coulombier D, ECDC Chikungunya Risk Assessment Group. Chikungunya risk assessment for Europe: recommendations for action. *Eurosurveillance* 2006; 11 (19): pii=2956 [available from: www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2956, accessed: 30 January 2016].
11. Nanni Costa A, Grossi P, Porta E *et al.* Measures taken to reduce the risk of West Nile virus transmission by transplantation in Italy. *Eurosurveillance* 2008; 13 (42): pii=19009 [available from: www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19009, accessed 30 July 2016].
12. López-Medrano F, Cordero E, Gavaldá J *et al.* Management of influenza infection in solid-organ transplant recipients: consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). *Enferm Infecc Microbiol Clin* 2013; (31): 526.e1-20.
13. Kumar D, Morris MI, Kotton CN *et al.* Guidance on novel influenza A/H1N1 in solid organ transplant recipients. *Am J Transplant* 2010; (10): 18-25.
14. Danziger-Isakov LA, Husain S, Mooney ML *et al;* ISHLT Infectious Diseases Council. The novel 2009 H1N1 influenza virus pandemic: unique considerations for programs in cardiothoracic transplantation. *J Heart Lung Transplant* 2009; 28 (12): 1341-447 [available from: www.ncbi.nlm.nih.gov/pubmed/19854073, accessed 30 January 2016].
15. Pondrom S. Can transplantation be zero risk? *Am J Transplant* 2012; (12): 509-10.
16. Kaul DR, Taranto S, Alexander C *et al.* Donor screening for human T-cell lymphotrophic virus 1/2: Changing paradigms for changing testing. *Am J Transplant* 2010; (10): 207-13.
17. Centers for Disease Control and Prevention. HIV transmitted from a living organ donor – New York City, 2009. *MMWR* 2011; (60): 297-301.
18. Blumberg EA, Ison MG, Pruett TL *et al.* on behalf of the Optimal Testing of the Live Organ Donor Consensus Conference participants. Optimal testing of the live organ donor for blood-borne viral pathogens: the report of a consensus conference. *Am J Transplant* 2013; (13): 1405-15.
19. Seem DL, Lee I, Umscheid CA *et al.* PHS guideline for reducing transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) through solid organ transplantation. *Public Health Reports* 2013; (128): 247-304.
20. European Centre for Disease Prevention and Control: annual epidemiological report 2013: Reporting on 2011 surveillance data and 2012 epidemic intelligent data. Stockholm, Sweden: European Centre for Disease Prevention and Control, 2013 [available from: http://ecdc.europa.eu/en/publications/Publications/annual-epidemiological-report-2013.pdf, accessed: 24 February 2016].
21. Kucirka LM, Sarathy H, Govindan P *et al.* Risk of window period hepatitis C infection in highly infectious risk donors: systematic review and meta-analysis. *Am J Transplant* 2011; (11): 1188-1200.
22. Council of Europe, European Directorate for the Quality of Medicine & HealthCare (EDQM). *Technical Memorandum TS057, Risk behaviours having an impact on blood donor management.* Strasbourg: EDQM, 2011.
23. Len O, Garzoni C, Lumbreras C *et al.* on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH). Recommendations for screening of donor and recipient prior to solid organ

transplantation and to minimize transmission of donor-derived infections. *Clin Microbiol Infect* 2014; 20(Suppl 7): 10-18.

24. Challine D, Pellegrin B, Bouvier-Alias M *et al.* HIV and hepatitis C virus RNA in seronegative organ and tissue donors. *Lancet* 2004; (364): 1611-12.
25. Humar A, Morris M, Blumberg E *et al.* Nucleic acid testing (NAT) of organ donors: is the 'best' test the right test? A consensus conference report. *Am J Transplant* 2010; (10): 889-99.
26. Ellingson K, Seem D, Nowicki M *et al.* for the Organ Procurement Organization Nucleic Acid Testing Yield Project Team. Risk of human immunodeficiency virus and hepatitis C virus infection among potential organ donors from 17 organ procurement organizations in the United States. *Am J Transplant* 2011; (11): 1201-8.
27. Cruzado JM, Gil-Vernet S, Castellote J *et al.* Successful treatment of chronic HCV infection should not preclude kidney donation to an HCV negative recipient. *Am J Transplant* 2013; (13): 2773-4.
28. Simmons C, Farrar J, van Vinh N *et al.* Dengue. *NEJM* 2012; (366): 1423-32.
29. Tan F, Loh D, Prabhakaran K. Dengue haemorrhagic fever after living donor renal transplantation. *Nephrol Dial Trans* 2005; (20): 477-8.
30. European Centre for Disease Prevention and Control (ECDC). *Outbreak of hepatitis A in EU/EEA countries – second update*, 11 April 2014. Stockholm: ECDC, 2014 [available from: http://ecdc.europa.eu/en/publications/Publications/ROA-Hepatitis%20A%20virus-Italy%20Ireland%20Netherlands%20Norway%20France%20Germany%20Sweden%20United%20Kingdom%20-%20final.pdf, accessed: 24 February 2016].
31. Brock GN, Mostajabi F, Ferguson N *et al.* Prophylaxis against *de novo* hepatitis B for liver transplantation utilizing hep. B core (+) donors: does hepatitis B immunoglobulin provide a survival advantage? *Transpl Int* 2011; (24): 570-81.
32. Ouseph R, Eng M, Ravindra K *et al.* Review of the use of hepatitis B core antibody-positive kidney donors. *Transplant Rev* 2010; (24): 167-71.
33. Fishman, J. Infection in solid-organ transplant recipients, *N Engl J Med* 2007; (357): 2601-14.
34. Huprikar S, Danziger-Isakov L, Ahn J *et al.* Solid organ transplantation from hepatitis B virus positive donors: consensus guidelines for recipient management. *Am J Transplant* 2015; (15): 1162-72.
35. Levitsky J, Doucette K, AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant* 2013; (13): 147-68.
36. Veyer D, Bardou-Jacquet E, Legros L *et al.* Natural history and virological lessons from *de novo* HBV infection in a vaccinated recipient of a liver graft from an anti-HBc positive donor. *J Liver Dis Transplant* 2013; 2: 1. DOI: 10.4172/2325-9612.1000106 [available from www.scitechnol.com/2325-9612/2325-9612-2-106.php, accessed: 24 February 2016].
37. Hollinger F, Sood G. Occult Hepatitis B virus infection: a covert operation. *J Viral Hepatitis* 2010; (17): 1-15.
38. Roggendorf M, Roß S. Definition und Diagnsotik der akuten und chronischen Hepatitis B. *Z. Gastroenterol* 2004; (42): 679-81.
39. De Feo TM, Grossi P, Poli F *et al.* Kidney transplantation from anti-HBc+ donors: results from a retrospective Italian study. *Transplantation* 2006; (81): 76-80.
40. Dhillon GS, Levitt J, Mallidi H *et al.* Impact of hepatitis B core antibody positive donors in lung and heart-lung transplantation: an analysis of the United Network for Organ Sharing. *Transplantation* 2009; (88): 842-6.
41. Roche B, Roque-Afonso AM, Sebagh M *et al.* Escape hepatitis B virus mutations in recipients of antibody to hepatitis B core antigen-positive liver grafts receiving hepatitis B immunoglobulins. *Liver Transplantation* 2010; (16): 885-94.
42. Loggi E, Micco L, Ercolani G *et al.* Liver transplantation from hepatitis B surface antigen positive donors: a safe way to expand the donor pool. *J Hepatol* 2012; (56): 579-85.
43. Grebely J, Prins M, Hellard M *et al.* Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 2012; (12): 408-14.
44. Natov SN, Lau JY, Ruthazer R *et al.* The New England Organ Bank Hepatitis C Study Group. Hepatitis C virus genotype does not affect patient survival among renal transplant candidates. *Kidney Int* 1999; (56): 700-6.
45. Morales JM, Campistol JM, Domínguez-Gil B *et al.* Long-term experience with kidney transplantation from hepatitis C positive donors into hepatitis C positive recipients. *Am J Transplant* 2010; (10): 2453-62.
46. Vargas HE, Laskus T, Wang LF *et al.* Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. *Gastroenterology* 1999; (117): 149-53.
47. Gallegos-Orozco JF, Vargas HE, Rahela J. Virologically compromised donor grafts in liver transplantation. *J Hepatol* 2004; (41): 512-21.
48. Jazwinski A, Muir A. The horizon: new targets and new agents. *Clinical Liver Disease* 2012; (1): 24-7.
49. Park Y, Lee JH, Kim BS *et al.* New automated hepatitis C virus (HCV) core antigen assay as an alternative to real-time PCR for HCV-RNA quantification. *J Clin Microbiol* 2010; (48): 2253-6.

50. Legrand-Abravanel F, Kamar N, Sandres-Saune K *et al.* Hepatitis E virus infection without reactivation in solid-organ transplant recipients, France. *Emerg Infect Dis* 2011; (17): 30-7.
51. Schlosser B, Stein A, Neuhaus R *et al.* Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. *J Hepatol* 2012; (56): 500-2.
52. Kamar N, Dalton HR, Abravanel F *et al.* Hepatitis E virus infection. Clin Microbiol Rev 2014; (27): 116-38.
53. Anuras S, Summers R. Fulminant herpes simplex hepatitis in an adult: report of a case in renal transplant recipient. *Gastroenterology* 1976; (70): 425-8.
54. Taylor RJ, Saul SH, Dowling JN *et al.* Primary disseminated herpes simplex infection with fulminant hepatitis following renal transplantation. *Arch Intern Med* 1981; (141): 1519-21.
55. Dummer JS, Armstrong J, Somers J *et al.* Transmission of infection with herpes simplex virus by renal transplantation. *J Infect Dis* 1987; (155): 202-6.
56. Koneru B, Tzakis AG, DePuydt LE *et al.* Transmission of fatal herpes simplex infection through renal transplantation. *Transplantation* 1988; (45): 653-6.
57. Regamey N, Tamm M, Wernli M *et al.* Transmission of human herpes virus 8 infection from renal-transplant donors to recipients. *N Engl J Med* 1998; (339): 1358-63.
58. Luppi M, Barozzi P, Santagostino G *et al.* Molecular evidence of organ-related transmission of Kaposi sarcoma-associated herpesvirus or human herpesvirus-8 in transplant patients. *Blood* 2000; (96): 3279-81.
59. Barozzi P, Luppi M, Facchetti F *et al.* Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. *Nature Med* 2003; (9): 554-61.
60. Parravicini C, Olsen SJ, Capra M *et al.* Risk of Kaposi's sarcoma-associated herpesvirus transmission from donor allografts among Italian post transplant Kaposi's sarcoma patients. *Blood* 1997; (90): 2826-9.
61. Andreoni M, Goletti D, Pezzotti P *et al.* Prevalence, incidence and correlates of HHV-8/KSHV infection and Kaposi's sarcoma in renal and liver transplant recipients. *J Infect* 2001; (43): 195-9.
62. Marcelin AG, Roque-Afonso AM, Hurtova M *et al.* Fatal disseminated Kaposi's sarcoma following human herpesvirus 8 primary infections in liver-transplant recipients. *Liver Transpl* 2004; (10): 295-300.
63. Francès C, Marcelin AG, Legendre Ch *et al;* Skin and Organ Transplantation Group of the French Society of Dermatology. The impact of pre-existing or acquired Kaposi sarcoma herpesvirus infection in kidney transplant recipients on morbidity and survival. *Am J Transplant* 2009; 9 (11): 2580-6.
64. Luppi M, Barozzi P, Schulz TF *et al.* Bone marrow failure associated with human herpes virus 8 infection after transplantation. *N Engl J Med* 2000; (343): 1378-85.
65. Pietrosi G, Vizzini G, Pipitone L *et al.* Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. *Am J Transplant* 2011; (11): 2715-23.
66. Lebbe C, Porcher R, Marcelin AG *et al;* Skin and Organ Transplantation Group of the French Society of Dermatology. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. *Am J Transplant* 2013; (13): 207-13.
67. Riva G, Barozzi P, Quadrelli C *et al.* Human herpes virus 8 (HHV8) infection and related diseases in Italian transplant cohorts. *Am J Transplant* 2013; (13): 1619-20.
68. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. *N Engl J Med* 2010; (362): 2336-7.
69. Muller E, Barday Z, Mendelson M *et al.* HIV-positive to HIV-positive kidney transplantation – results at 3 to 5 years. *N Engl J Med* 2015; (327): 613-20.
70. Villa E, Petrini C, Venettoni S *et al.* Crisis management, ethical issues and the impact of HIV+ organ transplantation on donation in Italy. *Organs, Tissues and Cells* 2007; (10): 167-70.
71. Ison MG, Llata E, Conover CS *et al.* Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. *Am J Transplant* 2011; (11): 1218-25.
72. The Library of Congress: Bill Summary & Status, 113th Congress (2013-2014), S.330, Public Law 113-51 – Nov. 21, 2013 HIV Organ Policy Equity Act. Washington DC, USA, 2013 [available from: www.gpo.gov/fdsys/pkg/PLAW-113publ51/pdf/PLAW-113publ51.pdf, accessed: 30 January 2016].
73. Stock PG, Barin B, Murphy B *et al.* Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 2010; (363): 2004-14.
74. Terrault NA, Roland ME, Schiano T *et al.* HIV-TR Investigators. Outcomes of liver transplantation in HCV-HIV co-infected recipients. *Liver Transplant* 2012; (18): 716-26.
75. European Centre for Disease Prevention and Control. Geographical distribution of areas with a high prevalence of HTLV-1 infection. Stockholm: ECDC, 2015 [available from http://ecdc.europa.eu/en/publications/Publications/geographical-distribution-areas-high-prevalence-HTLV1.pdf, accessed: 24 February 2016].
76. Toro C, Benito R, Aguilera A *et al.* Infection with human T lymphotropic virus type I in organ

transplant donors and recipients in Spain. *J Med Virol* 2005; (76): 268-70.

77. Ramanan P, Deziel PJ, Norby SM *et al.* Donor-transmitted HTLV-1-associated myelopathy in a kidney transplant recipient – case report and literature review. *Am J Transplant* 2014; (14): 2417-21.
78. Nakamura N, Tamaru S, Ohshima K *et al.* Prognosis of HTLV-I-positive renal transplant recipients. *Transplant Proc* 2003; (37): 1779-82.
79. Pillond J, Le Marec N, Girault A. Epidemiological surveillance of blood donors and residual risk of blood borne infections in France, 2001-2003. *Transfusion clinique et biologique* 2005; (12): 239-46.
80. European Centre for Disease Control (ECDC). Risk assessment of HTLV-1/2 transmission by tissue/cell transplantation. Part 1: Epidemiological review. Stockholm: ECDC, 2012 [available from: http://ecdc.europa.eu/en/publications/Publications/120403-RA-Human-T-lymphotropic-Virus-transmission.pdf, accessed: 24 February 2016]. Part 2: Risks by tissue type, impact of processing and effectiveness of prevention measures. Stockholm: ECDC, 2012 [available from: http://ecdc.europa.eu/en/publications/Publications/20120620_RA_HTLV_Part2.pdf, accessed: 24 February 2016].
81. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 179-88.
82. Hirsch HH, Babel N, Comoli P *et al.* European perspective on human polyomavirus infection, replication and disease in solid organ transplantation. *Clin Microbiol Infect* 2014; 20 (Suppl 7): 74-88.
83. Fishman JA, Grossi PA. Donor-derived infection – the challenge for transplant safety. *Nat Rev Nephrol* 2014; (10): 663-72.
84. Schmitt C, Raggub L, Linnenweber-Held S *et al.* Donor origin of BKV replication after kidney transplantation. *J Clin Virol* 2014; (59): 120-5.
85. Morelli MC, Sambri V, Grazi GL *et al.* Absence of neuroinvasive disease in a liver transplant recipient who acquired West Nile virus (WNV) infection from the organ donor and who received WNV antibodies prophylactically. *Clin Infect Dis* 2010; (51): e34-7.
86. Costa AN, Capobianchi MR, Ippolito G *et al.* West Nile virus: the Italian national transplant network reaction to an alert in the north-eastern region, Italy 2011. *Euro Surveillance* 2011; (16): 41-89.
87. Centers for Disease Control and Prevention. West Nile virus infections in organ transplant recipients – New York and Pennsylvania, August-September, 2005. *Morb Mortal Wkly Rep* 2005; (54): 1-3.
88. Centers for Disease Control and Prevention. West Nile virus transmission via organ transplantation and blood transfusion – Louisiana, 2008. Morb Mortal Wkly Rep 2009; (58): 1263-7.
89. Iwamoto M, Jernigan DB, Guasch A *et al.* Transmission of West Nile virus from an organ donor to four transplant recipients. *N Engl J Med* 2003; (348): 2196-203.
90. Centers for Disease Control and Prevention. West Nile virus infections in organ transplant recipients – New York and Pennsylvania, August-September, 2005. *Morb Mortal Wkly Rep* 2005; (54): 1-3.
91. Lanteri MC, Lee TH, Wen L *et al.* West Nile virus nucleic acid persistence in whole blood months after clearance in plasma: implication for transfusion and transplantation safety. *Transfusion* 2014; (54): 3232-41.
92. Singh N, Levi ME, AST Infectious Diseases Community of Practice. Arenavirus and West Nile virus in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 361-71.
93. Winston DJ, Vikram HR, Rabe IB *et al;* West Nile Virus Transplant-Associated Transmission Investigation Team. Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. *Transplantation* 2014; (97): 881-9.
94. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. *JAMA* 2013; (310): 308-15.
95. Komar N, Langevin S, Hinten S *et al.* Experimental infection of North American birds with the New York 1999 strain of West Nile virus. *Emerg Infect Dis* 2003; (9): 311-22.
96. Tonry JH, Brown CB, Cropp CB *et al.* West Nile virus detection in urine. *Emerg Infect Dis* 2005; (11): 1294-6.
97. Murray K, Walker C, Herrington E *et al.* Persistent infection with West Nile virus years after initial infection. *J Infect Dis* 2010; (201): 2-4.
98. Barzon L, Pacenti M, Franchin E *et al.* Excretion of West Nile virus in urine during acute infection. *J Infect Dis* 2013; (208): 1086-92.
99. Levi ME, Kumar D, Green M *et al;* AST ID Community of Practice. Considerations for screening live kidney donors for endemic infections: a viewpoint on the UNOS policy. *Am J Transplant* 2014; (14): 1003-11.
100. European Centre for Disease Prevention and Control (ECDC). Risk of transmission of Ebola virus via donated blood and other substances of human origin in the EU. Stockholm: ECDC, 6 October 2014 [available from: http://ecdc.europa.eu/en/publications/Publications/ebola-risk-transmission-via-donated-blood-substances-human-origin-october-2014.pdf, accessed 30 January 2016].
101. Kaul DR, Mehta AK, Wolfe CR *et al.* Ebola virus disease: implications for solid organ transplantation. *Am J Transplant* 2015; (15): 5-6.

102. Cooper B, Medley G, Bradley S *et al.* An augmented data method for the analysis of nosocomial infection data. *Am J Epidemiol* 2008; (168): 548-57.

103. Witte W, Strommenger B, Klare I *et al.* Bakterielle Erreger von Krankenhausinfektionen mit besonderen Resistenzen und Multiresistenzen: Teil 1, Diagnostik und Typisierung. *Bundesgesundheitsblatt – Gesundheitsforsch – Gesundheitsschutz* 2004; (47): 352-62 (in German).

104. Witte W, Strommenger B, Klare I *et al.* Bakterielle Erreger von Krankenhausinfektionen mit besonderen Resistenzen und Multiresistenzen: Teil 2, Erfassung und Bewertung gem. §23 Abs.1IfSG in einem regionalen Netzwerk. *Bundesgesundheitsblatt – Gesundheitsforsch – Gesundheitsschutz* 2004; (47): 363-8 (in German).

105. Agence de la biomédecine. Prévention de la transmission de bactéries et d'agents fongiques aux receveurs d'organes. *Med Mal Inf* 2009; (39): 682-97.

106. Len O, Gavaldà J, Blanes M *et al.* Donor infection and transmission to the recipient of a solid allograft. *Am J Transplant* 2008; (8): 2420-5.

107. Caballero F, López-Navidad A, Perea M *et al.* Successful liver and kidney transplantation from cadaveric donors with left sided bacterial endocarditis. *Am J Transplant* 2005; (5): 781-7.

108. Ruiz I, Gavalá J, Monforte V. Donor to host transmission of bacterial and fungal infection in lung transplantation. *Am J Transplant* 2006; (6): 178-82.

109. European Centre for Disease Prevention and Control (ECDC). Carbapenemase-producing bacteria in Europe: interim results from the European Survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. Stockholm: ECDC, 2013 [available from: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-carbapenemase-producing-bacteria-europe.pdf, accessed: 30 January 2016].

110. Mathers AJ, Cox HL, Bonatti H *et al.*Fatal cross infection by carbapenem-resistant Klebsiella in two liver transplant recipients. *Transpl Infect Dis* 2009; (11): 257-65.

111. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D *et al.* Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation. *Transpl Infect Dis* 2012; (14): 198-205.

112. Wu TJ, Lee CF, Chou HS *et al.* Suspect the donor with potential infection in the adult deceased donor liver transplantation. *Transplant Proc* 2008; (40): 2486-8.

113. Martins N, Martins IS, de Freitas WV *et al.* Severe infection in a lung transplant recipient caused by donor-transmitted carbapenem-resistant Acinetobacter baumannii. *Transpl Infect Dis* 2012; (14): 316-20.

114. Bumbacea D, Arend SM, Eyuboglu F *et al.* The risk of tuberculosis in transplant candidates and recipients. *Eur Respir J* 2012; (40); 990-1013.

115. Morris MI, Daly JS, Blumberg E *et al.* Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. *Am J Transplant* 2012; (12); 2288-300.

116. Pinazo MJ, Miranda B, Rodríguez-Villar C *et al.* Recommendations for management of Chagas diseases in organ and hematopoietic tissue transplantation programs in non-endemic areas. *Transplant Rev* 2011; (25): 91-101.

117. Aguado JM, Torre-Cisneros J, Fortún J *et al.* Tuberculosis in solid-organ transplant recipient: consensus statement of the Group for study of infection in transpant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Mircrobiology. *Clin Infect Dis* 2009; (48): 1276-84.

118. Theodoropoulos N, Jaramillo A, Penugonda S *et al.* Improving syphilis screening in deceased organ donors. *Transplantation* 2015; (99): 438-43.

119. Gabardi S, Kubiak D, Chandraker A *et al.* Invasive fungal infections and antifungal therapies in solid organ transplant recipients. *Transplant Int* 2007; (20): 963-1015.

120. Huprikar S, Shoham S, the AST Infectious Disease Community of Practice. Emerging fungal infections in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 262-71.

121. Miller R, Assi M, the AST Infectious Disease Community of Practice. Endemic fungal infections in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 250-61.

122. Martin SI, Fishman JA, the AST Infectious Disease Community of Practice. Pneumocystis pneumonia in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 272-79.

123. Singh N, Huprikar S, Burdette SD *et al.* American Society of Transplantation, Infectious Diseases Community of Practice, Donor-Derived Fungal Infection Working Group. *Am J Transplant* 2012; (12): 2414-28.

124. Schwartz BS, Mawhorter SD, the AST Infectious Disease Community of Practice. Parasitic infections in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 280-303.

125. Martín-Dávila P, Fortún J, López-Vélez R *et al.* The transmission of tropical and geographically restricted infections during solid organ transplantation. *Clin Microbiol Rev* 2008; (21): 60-96.

126. Hamilton KW, Abt PL, Rosenbach MA *et al.* Donor-derived *Strongyloides stercoralis* infections in renal transplant recipients. *Transplantation* 2011; (91): 1019-24.

127. Kotton CN, Elias N, Delmonico FL *et al.* Case 15-2009: A 25-year-old man with coma after cardiac arrest. *N Eng J Med* 2009; (360): 2118-25.
128. Rodriguez M, Tome S, Vizcaino L *et al.* Malaria infection through multi-organ donation: an update from Spain. *Liver Transpl* 2007; (7): 1302-4.
129. Lescure FX, Le Loup G, Freilij H. Chagas disease: changes in knowledge and management. *Lancet Infect Dis* 2010; (10): 556-70.
130. Chin-Hong PV, Schwartz BS, Bern C *et al.* Screening and treatment of Chagas disease in organ transplant recipients in the United States: recommendations from the Chagas in transplant working group. *Am J Transplant* 2011; (11): 672-80.
131. Salvador F, Len O, Molina I *et al.* Safety of liver transplantation with Chagas disease-seropositive donors for seronegative recipients. *Liver Transpl* 2011; (17): 1304-8.
132. The Chagas Disease Argentine Collaborative Transplant Consortium, Casadei D. Chagas' disease and solid organ transplantation. *Transplant Proc* 2010; (42): 3354-9.
133. Cura CI, Lattes R, Nagel C *et al.* Early molecular diagnosis of acute Chagas disease after transplantation with organs from *Trypanosoma cruzi*–infected donors. *Am J Transplant* 2013; (13): 3253-61.
134. Le M, Ravin K, Hasan A *et al.* Single donor-derived strongyloidiasis in three solid organ transplant recipients: case series and review of the literature. *Am J Transplant* 2014; (14): 1199-1206.
135. Arbeitskreis Blut at the Robert Koch Institut. Arbonematoden – durch Arthopoden übertragbare Nematoden-Infektionen. *Bundesgesundheitsbl.* 2012; (55): 1044-56 (in German) [available from: www.rki.de/DE/Content/Kommissionen/AK_Blut/Stellungnahmen/download/stArbonematoden.pdf, accessed: 30 January 2016].
136. Román-Sánchez P, Pastor-Guzmán A, Moreno-Guillén S *et al.* High prevalence of *Strongyloides stercoralis* among farm workers on the Mediterranean coast of Spain: analysis of the predictive factors of infection in developed countries. *Am J Trop Med Hyg* 2003; (69): 336-40.
137. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: local transmission of *Schistosoma haematobium* in Corsica, France – 16 May 2014. Stockholm: ECDC, 2014 [available from: http://ecdc.europa.eu/en/publications/Publications/schistosoma-haematobium-risk-assessment-France-Germany.pdf, accessed: 24 February 2016].
138. Hoare M, Gelson WT, Davies SE *et al.* Hepatic and intestinal schistosomiasis after orthotopic liver transplant. *Liver Transpl* 2005; (11): 1603-7.
139. Cardiff and Vale University health board, Quality, Safety and Experience Committee: Renal transplant serious incident update, 2015 [available from: www.cardiffandvaleuhb.wales.nhs.uk/opendoc/258062, accessed: 30 January 2016].
140. Gupte AA, Hocevar SN, Lea AS *et al.* Transmission of *Balamuthia mandrillaris* through solid organ transplantation: utility of organ recipient serology to guide clinical management. *Am J Transplant* 2014; (14): 1417-24.
141. Kaul DR, Covington S, Taranto S *et al.* Solid organ transplant donors with central nervous system infection. *Transplantation* 2014; (98): 666-70.
142. Fehily D, Warwick R, Loty B. Tissue donation and banking. In: Manyalich M., Cabrer C., Paredes D *et al.*, editors, *Transplant co-ordination manual*. Barcelona: TPM Les Heures, Universitat de Barcelona, 2001: 251-68.
143. US Department of Health and Human Services: Food and Drug Administration. Guidance for Industry. Screening and testing of donors of human tissue intended for transplantation. US Department of Health and Human Services: Food and Drug Administration, Washington DC, USA, 1997 [available from: www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM188251.pdf, accessed: 30 January 2016].
144. Department of Health: Guidance on the microbiological safety of human tissues and organs used in transplantation. Department of Health, London, 2000 [available from: www.gov.uk/government/uploads/system/uploads/attachment_data/file/215959/dh_130515.pdf, accessed: 30 January 2016].
145. Eastlund T. Hemodilution due to blood loss and transfusion and reliability of cadaver tissue donor infectious disease testing. *Cell Tissue Bank* 2000; (1): 121-7.
146. Kitchen A, Gilian H. The serological screening of deceased tissue donors within the English Blood Service for infectious agents – a review of current outcomes and a more effective strategy for the future. *Vox Sanguinis* 2010; (98): e193-200.
147. Martín-Dávila P, Fortún J, López-Vélez R *et al.* The transmission of tropical and geographically restricted infections during solid organ transplantation. *Clin Microbiol Rev* 2008; (21): 60-96.
148. Pannegeon V, Masini JP, Paye F *et al.* Schistosoma mansoni infection and liver graft. *Transplantation* 2005; (80): 287.
149. Huprikar S, Bosserman E, Patel G *et al.* Donor-derived *Trypanosoma cruzi* infection in solid organ recipients in the United States, 2001-2011. *Am J Transplant* 2013; (13): 2418-25.

150. Danzinger Isakov L, Kumar D, the AST Infectious Disease Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 311-17.

151. Kotton C, Hibberd P, the AST Infectious Disease Community of Practice. Travel medicine and Transplant Tourism in solid organ transplantation. *Am J Transplant* 2013; 13 (Suppl 4): 337-47.

152. Höcker B, Böhm S, Fickenscher H *et al.* (Val)ganciclovir prophylaxis reduces Ebstein–Barr-virus primary infection in pediatric renal transplantation. *Transpl Int* 2012; (25): 723-31.

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, the magnitude of that risk is small, given careful donor selection, with approximately 0.05 % of organ recipients developing a donor-transmitted cancer [6-9]. This risk needs to be considered against the perspective of the important, life-enhancing and life-saving benefits afforded by organ transplant. Nevertheless, due to the potentially serious consequences for the individuals affected and for the entire donation and transplantation system, it is mandatory to select all potential donors carefully with the intention of minimising the risk of transmission of neoplastic disease.

The increasing number of patients on waiting lists, along with the shortage of organs available for transplant, 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 also a legal requirement for EU member states [13], and should include information on any previous history or on the incidental finding of any malignancy in the donor.

Difficult decisions confront transplant clinicians regarding the use of organs from donors who are known to have, or have had, cancer. Moreover, increased acceptance of older donors, in whom malignancy is more common, further increases the risk of transmission of occult cancers.

In this context, 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 of appropriate agencies to report the incident and inform 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 base upon which an evidence-based surveillance system can be built and applied.

Preventative 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 9.4-9.7. 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, section 6.2). 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 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 chorio-carcinoma.

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, grading);
   iii. treatment received (surgery, chemotherapy and/or radiotherapy) including dates;
   iv. follow-up conducted, last follow-up (dates, results, complete remission and/or tumour recurrence at any time).

d. Intra-cranial tumours or metastases should always be excluded in donors diagnosed with intra-cranial 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 below).

A careful physical examination of the donor should be conducted, paying particular attention to the skin, looking for potential neoplasms or scars of previous surgical procedures.

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 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's history, 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.

Levels of human chorionic gonadotropin beta (βHCG) may be determined in women of child-bearing age with a history of menstrual irregularities or miscarriages to detect a chorio-carcinoma.

9.2.3. Radiological tests

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, section 6.2).

Further radiological tests (e.g. CT-scans) may be required for thorough donor evaluation in justified cases, especially in patients with suspected malignancy or in donors in whom it is thought that appropriate intraoperative examination of the thoraco-abdominal cavities cannot be adequately carried out for any reason.

In patients with any history of neoplastic disease, CT-scans of thorax and abdomen should be carried out where possible to evaluate the current disease status and to ensure the highest possible safety for organ recipients.

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 lymphade-

nopathy. Any suspicious lesion must be investigated immediately by frozen section by an experienced pathologist (see Figure 9.1 and Table 9.1).

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 and 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; • seek informed consent from the recipient prior to transplantation; • carry out careful follow-up,bearing in mind the possibility of transmission.
During donor assessment/ procurement and before transplantation	Neoplasia incidentally found during clinical donor assessment or surgical inspection.	• immediately take frozen section for definite diagnosis; • immediately inform recipient centres; • transplant centres may take decision to accept the organs; • oncologist advice can be sought; • seek informed consent from the recipient prior to transplantation; • carry out careful follow-up bearing in mind the possibility of transmission.
After transplantation of any recipient	a) Frozen section misinterpreted (e.g. renal oncocytoma), final diagnosis malignant (e.g. 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 after procurement, results after 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 inform organ procurement organisation and all transplant centres concerned (for other transplanted organs and tissues); • immediately inform recipients; • in situation b), especially in case 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; • report serious adverse events (SAE) in situations a), b) or c), serious adverse reaction (SAR) in situation d); • carry out strict follow-up.

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 perirenal fat is required to ensure detailed inspection of the kidneys before the kidneys leave the donor hospital.

Obviously, none of these examinations rule out small metastases or micro-metastases.

9.2.5. Histopathological examination

When a mass in any organ or a lymphadenopathy with a malignant appearance 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.

In donors with an intracranial space-occupying lesion, a histological diagnosis of the lesion should be performed before any organ is transplanted. Furthermore, for tumours in which different histological grades can co-exist, a complete histopathological examination of the tumour should be carried out. Without the histological diagnosis of an intracranial space-occupying lesion, organs should only be used in recipients whose probable waiting list mortality justifies the extra risk, and after consultation with the recipient and their family. In some cases, the extraction of the Central Nervous System (CNS), *in situ* macroscopic study and determination of the histological type and grade of the tumour by frozen section can be performed within 2-3 h. However, this is not always the case and it might be necessary to embed the tumour biopsy material in paraffin for at least 24 h, so that its histological diagnosis can be determined more accurately.

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 notified immediately. In cases where organs have already been transplanted and histology reveals a possibly metastatic malignancy (e.g. incidental cancer in lung lobe, discarded due to size reduction), a full donor autopsy should be requested to obtain detailed information about tumour origin and dissemination.

If no precise histological diagnosis of a suspicious mass can be obtained, the donor should be excluded, although the final decision should be made on the basis of an individual risk–benefit analysis. Transplantation should only be performed on a fully informed recipient, requiring a critical emergency intervention.

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 explantation or re-transplantation may be appropriate.

Whenever only preliminary donor autopsy or biopsy results are available and final results are awaited, all professionals involved should be advised on the importance of timely notification of the final results. Since autopsy results often come in very long after the transplantation event, urgent requests for results may be helpful in these cases. Prompt communication is essential for the benefit of the recipient (see Figure 9.1 and Table 9.1).

9.3. General considerations to minimise the transmission of neoplasias

9.3.1. Transmission risk and registry data

Although neither the exact frequency of donors with malignancies, nor the risk of malignancy transmission through organ transplant is accurately known, there is some information based on the data available in the following registries (see 9.3.1.1-9.3.1.8 below). Additional data, from the many published case reports regarding all kinds of malignancy transmissions, can only serve as supporting information but will not contribute to a proper risk estimation.

9.3.1.1. *The United Network for Organ Sharing Registry (USA)*

A first United Network for Organ Sharing (UNOS) report (1994-96) [14] documented a frequency of 1.7 % 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.

An updated report (2000-05) [15] analysed 1 069 donors with a history of cancer and showed transmissions of 2 donor tumours: one glioblastoma multiforme (active at the time of donation) was transmitted to 3 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 CNS neoplasms (1992-99) [16], 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) [17] described 11 donor-transmitted non-CNS malignancies into 15 (0.017 %) of 108 062 recipients transplanted during this period. The tumours transmitted were: 1 melanoma (4 recipients), 1 small-cell neuro-endocrine tumour (2 recipients), 1 adenocarcinoma, 1 pancreas cancer, 1 undifferentiated squamous cell carcinoma, 2 lung cancers, 1 oncocytoma, 1 papillary tumour of unknown origin, 1 breast cancer and 1 prostate cancer [from a donor with metastatic (positive lymph nodes) prostate adenocarcinoma found in post-procurement autopsy]. They were diagnosed in the recipients from 3 to 40 months after transplantation (mean 14.2 months).

9.3.1.2. *Organ Procurement and Transplantation Network/Disease Transmission Advisory Committee (USA)*

Ison *et al.* [5] reported 28 confirmed donor-transmitted malignancies (7 renal cell carcinomas [RCC], 4 lung carcinomas, 2 melanomas, 1 liver cancer, 3 pancreas cancers, 2 ovarian cancers, 2 neuroendocrine malignancies, 6 lymphomas, 1 glioblastoma multiforme) from 2005 to 2009. Nine recipients died of the transmitted tumours.

Green *et al.* [18] reported Disease Transmission Advisory Committee (DTAC) data for the year 2013 and showed 5 additional donor malignancies transmitted into 8 recipients (3 melanoma, 2 adenocarcinoma, 3 other malignancies) with 2 tumour-related deaths.

In 2011 Nalesnik *et al.* [11] suggested a new classification for assessing the clinical risk of donor malignancies (see section 9.3.3).

9.3.1.3. *The Israel Penn International Transplant Tumor Registry (USA)*

The Israel Penn International Transplant Tumor Registry (IPITTR) [19] (historical data from 1965 to 2003) reported higher frequencies of malignancy transmission than other registries mentioned in this section. The discrepancy might be 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. It does not cover the outcome of all recipients transplanted from donors with malignancies in the analysed time range. Donor malignancies would have escaped any documentation if none of the respective recipients suffered from transmission. 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 recip-

ients 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 9 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 [20, 21] or transplantation of kidneys with small renal cancers [22] 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 (6 RCC, 4 lung cancer, 1 lymphoma, 1 neuroendocrine carcinoma, 1 colon carcinoma) with 3 subsequent recipient deaths.

Another study [23] 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, 6 medulloblastomas, 10 breast cancers, 5 lymphomas, 4 sarcomas, 3 melanomas, 8 other malignancies). No transmission was reported in 133 recipients of organs from these 61 donors.

Watson *et al.* [24] 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, 9 medulloblastomas).

In 2014 the Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) set up 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, 5 (0.29 per thousand donors) transmitted their malignancy into 10 recipients (0.06 % of all recipients in this period): 1 soft tissue sarcoma (3 recipients), 1 germinal cell cancer (3 recipients), 1 undifferentiated carcinoma (2 recipients) and 2 RCC. These latter 2 cases corresponded to 2 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 Nazionali di Trapianti Registry (Italy)*

Since 2001, the Centro Nazionali di Trapianti (CNT) has had a new strategy for evaluating the safety and acceptability of donors [25]. This strategy analyses donors with infections and tumours and has established some donor risk levels. Analysis of the years 2001-02 showed a frequency of 2.9 % of donors with tumours. Approximately half of these were rejected as donors before procurement, in a quarter the tumour was detected between recovery and transplantation and, in the remainder, a neoplasm was detected following transplant. 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 [26].

Taioli *et al.* [27] 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 malignancies from 2002 to 2005 (mostly prostate and RCC) by Zucchini *et al.* [28] and for 28 donors from 2003 to 2010 in southern Italy [29].

9.3.1.7. *MALORY – MALignancy in Organ Donors and Recipient SafetY (Germany)*

A 6-year analysis of data from 2006-11 of 248 organ donors with 254 malignancies (702 organs transplanted into 648 recipients) was performed [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 recom-

mendations. The most frequent CNS malignancies were glioblastoma multiforme 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: 7 donors without any suspected malignant disease transmitted their occult carcinoma (3 RCCs, 2 neuroendocrine carcinomas, 1 breast cancer, 1 colorectal cancer) into 13 recipients. As of October 2015, 7 of these recipients had died as a result of the transmitted tumour (4 liver, 2 kidney, 1 lung recipient).Three kidney recipients (neuroendocrine and breast cancer) were disease-free after metastatic disease treated by transplant nephrectomy, withdrawal of immune-suppression and chemotherapy. The three kidney recipients from donors with undetected RCC have never shown any clinical symptoms of the malignancy (all three kidney recipients underwent transplant nephrectomy after transplant due to thrombosis or rejection; pathological examination revealed incidental RCC).

However, the follow-up period is still 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 [30] linked all organ donors in a single transplant centre of a 27-year period to the Danish tumour registry. They identified 13 malignancies among 626 donors (2 %), of which 8 were detected after the organs had been transplanted (1.3 %). Of those 8 donors, only one transmitted the malignancy to the recipient, a melanoma (stage unknown at recovery) (0.2 %).

The risk of tumour transmission through organ transplant does exist and the number of organs accepted from donors with a previous or current history of malignancy is increasing, but the frequency of documented tumour transmission is low. Under-reporting of transmission cases due to lack of mandatory reporting cannot be ruled out. With the new European legal framework [13] and mandatory reporting to national health authorities of serious adverse reactions (including suspected/confirmed cases of malignancy transmission) , the frequency of malignancy transmission through organ transplant will be assessed more precisely.

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 histotype, stage and grade of the tumour is absolutely necessary prior to acceptance and must be performed according to international criteria (AJCC Cancer Staging Manual, 7th edition, 2010, Springer) [31, 32].

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.

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 > 5-10 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).

e. 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.

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 %.

f. Regarding potential organ recipients, detailed informed consent should be 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 9.2. **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?
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: Nalesnik MA, Ison MG. Organ transplantation from deceased donors with cancer: is it safe? [33].

Table 9.3 shows the current transmission risk categorisations published by DTAC/USA [11], SaBTO/UK [12] and CNT/Italy [34]. Two of them specify estimated transmission risks in percentages according to their national data. The Council of Europe classification proposes a risk classification that consciously omits any numerical estimation due to the limited evidence currently available. Details regarding the risk classification of specific tumours will be found in the subsections that follow.

The physician performing the transplantation of a graft has overall responsibility for its use in a particular recipient, regardless of the estimated risks according to the above mentioned classifications.

9.3.3. Circulating tumour cells

Circulating tumour cells (CTCs) have been detected in the blood of many cancer patients – e.g. breast [35], colorectal [36], prostate [37] – including in 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 % [38] and 42 % [39] of patients with glioblastoma multiforme. 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 nonspecific responses (decreased in transplant patients) and the abilities to induce a blood supply and initiate growth. The weakness of glioblastoma multiforme in this respect might be (since there is no evidence yet) that these cells have a limited capacity to do that outside the brain. Brain tumours only rarely show extra-cranial metastases.

Recent clinical evidence suggests that the risk of transmission of glioblastoma multiforme through organ transplantation may be even lower than historically believed, but the literature does contain a number of examples of glioblastoma transmission, and additional evidence would be desirable. An analogous situation might be in the prostate, where it is suspected that organs are transplanted from many older donors who have prostate cancer (statistically), and yet there are no data suggesting a higher incidence of transmitted prostate cancers when older donors are used. Studies of localised prostate cancers also show CTCs in some patients [37].

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. In only 10 to 7.5 mL of blood investigated in the setting of organ donation it is more or less likely to obtain a false negative result due to investigating an unrepresentative specimen [40, 41].

9.4. Solid organ tumours

Acceptance of donors with particular malignancies varies among European countries as well as worldwide. Recently published recommendations [11, 12, 34, 42] 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 presumed to be 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 variant tumours depending on their histotype, stage and grade and 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 recommendations

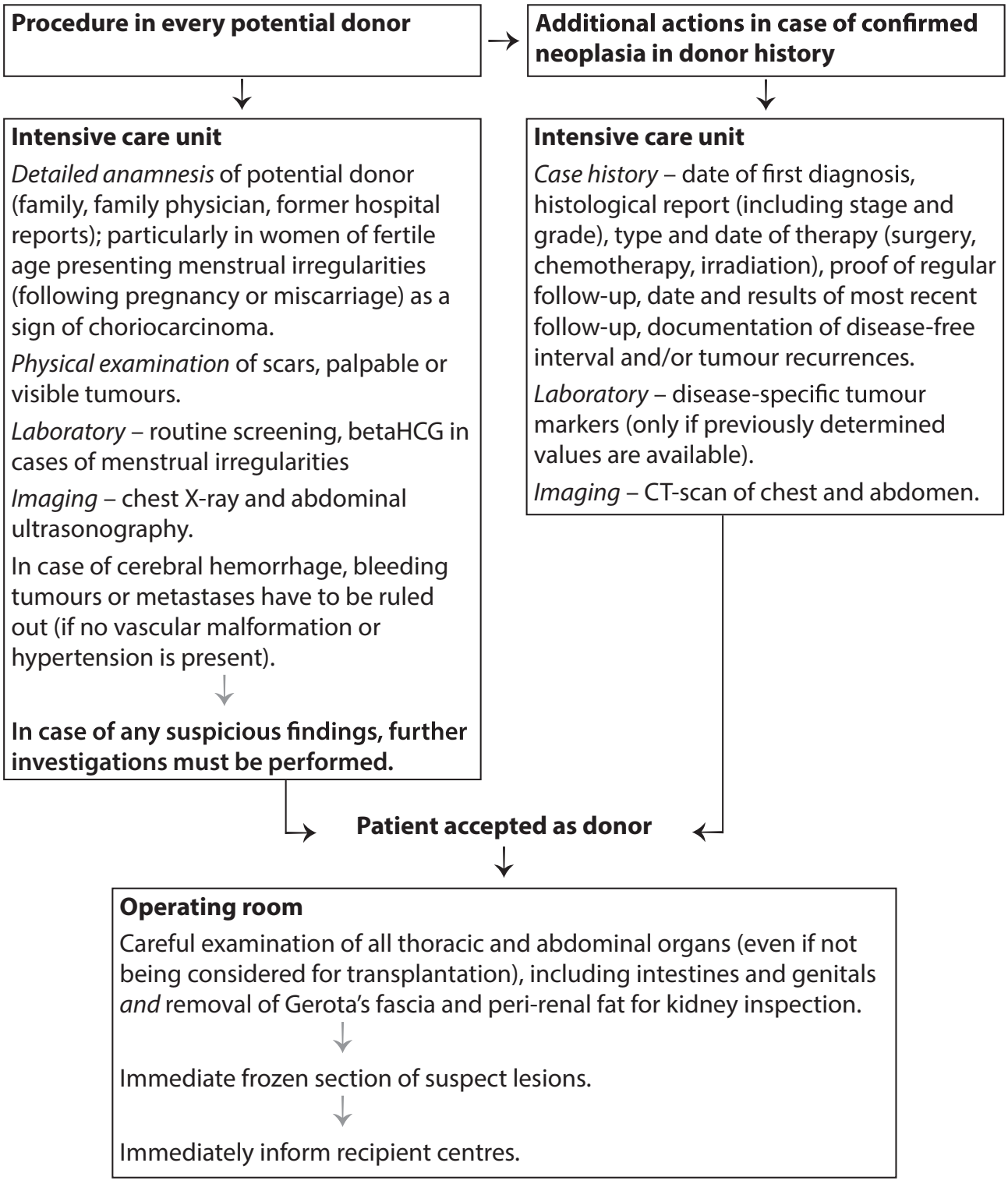
may vary from > 5 to > 10 years to never for the same tumour type and stage.

An individual risk–benefit assessment must be performed for every potential recipient. Additionally, it should be taken into account that transmitted tumours may find ideal surroundings for growth in the immunosuppressed recipient.

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 according to 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 [43] as well as other frequently reported donor malignancies. Ad-

Figure 9.1. **Workflow: actions for the detection/assessment of malignancies in potential organ donors**



ditionally, for neoplasms that are not mentioned in any literature concerning 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 9.4.12.

9.4.2. Biliary cancer

See 9.4.14.

9.4.3. Breast cancer

Since breast cancer has high potential for late and aggressive recurrences and metastases, even after many years of complete remission, patients with this cancer should be accepted as organ donors only for very selected recipients and with the highest caution.

Friedman *et al.* reported 2 cases of breast cancer transmission in kidney recipients at 4 and 12 months after transplantation [44]. 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 [45], but the number of cases was not reported. Another case of transmission of an occult ductal breast adenocarcinoma was reported by Kauffman *et al.* [17]. 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 metastatic donor breast cancer into 4 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.

For recommendations regarding *in situ* breast cancer go to section 9.4.4.

Breast cancer diagnosed during donor procurement
Newly-diagnosed breast cancer is an unacceptable risk for organ donation.

Breast cancer in the donor history
Organs from donors with breast cancer might be accepted in selected cases after full treatment, complete remission, stringent follow-up for > 5-10 years depending on the initial stage and hormone receptor expression, always bearing in mind the risk of transmission due to possible late metastases.
Breast cancer stage 1 (AJCC, 7th edition 2010 [31, 32]) with curative surgery and cancer-free period > 5 years seems to be associated with a low to intermediate risk for transmission.
All other 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 2003/2012	DTAC/USA 2011	SaBTO/UK 2014	Council of Europe Guide 2016
—	No significant risk	—	—
Standard risk	Minimal risk (< 0.1 %)	Minimal risk (< 0.1 %)	*Minimal risk* Donor acceptable for all organs and all recipients
Increased but 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	
Increased but acceptable risk only for urgencies	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 recipient
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 intraepithelial 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.

Tumour transmission risk seems to be negligible for *in situ* cancer of the uterine cervix and many others, with no transmissions being reported.

Historical recommendations turned down patients with very aggressive malignancies, like melanoma and lung cancer, as organ donors in any stage of the disease, even in case of *in situ* tumours [46, 47]. Also, high grade *in situ* breast cancer is supposed to be more aggressive than breast cancer *in situ* without high risk features [45] and it entails the possibility of undetected micro-invasive carcinoma. Since carcinoma *in situ* is a very early, non-invasive tumour stage, patients with these diagnoses might be acceptable as organ donors with increased caution. Nevertheless, late recurrences have been reported in non-transplanted patients who had melanomas < 1 mm in thickness, so this should be evaluated very carefully in the potential donor.

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 intraepithelial neoplasia (PanIN), grades 1-3, represent a non-invasive precursor lesion to pancreatic adenocarcinoma with cellular atypia but without risk for metastases. PanIN do not necessarily form a mass, and are frequently associated with chronic pancreatitis. In the context of organ donation, PanIN will be found in two circumstances. First, they may be known about 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. 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 may be considered minimal risk. Transplantation of the pancreas itself in the case of PanIN is not recommended.
Non-muscle-invasive carcinoma *in situ* of the urinary bladder (pTis, high grade flat tumour) and non-invasive papillary carcinoma of the urinary bladder (pTa, low grade) – see AJCC, 7th Edition 2010 [31, 32] – are considered minimal risk for non-renal transplants. Renal transplants from these donors should 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.

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 carcinoma *in situ* of the urinary bladder (pTis, high grade flat tumour) and non-invasive papillary carcinoma of the urinary bladder (pTa, low grade) – see AJCC, 7th Edition 2010 [31, 32] – are considered minimal risk for non-renal transplants. 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 [45]. Occasional cases of unrecognised donor choriocarcinoma resulting in multiple transmissions continue to be reported [48]. 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 time.

9.4.6. Colorectal cancer

There are two case reports describing metastatic transmission of occult colorectal carcinoma of the donor into liver recipients [49, 50]. 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.

Buell *et al.* [45] 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, 15, 27, 29, 30] (section 9.3.1) without subsequent disease transmission.

Colorectal cancer diagnosed during donor procurement
Acceptance of pT1-tumours – see AJCC, 7th Edition 2010 [31, 32] – has been discussed but seems to have a certain risk of lymph node and distant metastases in the donor. Therefore this should, if at all, only be accepted for organ donation with the highest 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
pT1/pT2 colorectal carcinoma (infiltration of submucosa/muscularis propria) of the donor without lymph node or distant metastases is assumed to have a Low transmission risk after adequate treatment and disease-free survival of 5-10 years. Risk increases with stage, and probability of presumed cure has to be taken into account.
Even donors with an initially diagnosed pN1 stage have been accepted under special circumstances (full treatment and recurrence-free follow-up of 5-10 years, depending on the stage, with presumed cure), which might be associated with a higher transmission risk.
An individual risk–benefit analysis should always be made. Lungs and liver should only be transplanted with the highest caution, since these are the organs most likely to present colorectal metastases.

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, active tumour. Recent clinical findings show significant influence of submucosal infiltration depth (sm1-3), lymphovascular invasion (L0-1), tumour budding and microsatellite instability on the risk of lymph node and distant metastases in pT1 tumours [51-53]. 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 9.4.14.

9.4.8. Gastrointestinal stromal tumour

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours and count 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 4 main prognostic factors [54]: tumour localisation, mitotic count (tumour cell proliferation), tumour size and tumour rupture before or during surgery.

Small 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.

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 GIST < 2 cm 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 higher mitotic count are associated with an increased risk of metastases and a high risk of transmission.

GIST in the donor history
Small GIST < 2 cm 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 higher 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 9.4.14.

9.4.10. Lung cancer

Several registries [5, 7, 17, 45] and case reports [55, 64] 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.

A recent systematic review [65] of tumour transmission in the case of renal transplant showed 9 cases of lung cancer with a median onset time of 13 months post-transplant and with metastatic disease at presentation in 7 of 9 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. Carcinoma *in situ* and pancreatic intraepithelial neoplasia.

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 [45]. Transmission events continue to be reported in case reports and in recent registry data [5, 15, 18, 30].

Most cases of reported donor-transmitted melanoma were cases where tumour diagnosis was missed in the donor [45, 66]. It has to be kept in mind that malignant melanoma often recurs, even after many years of disease-free survival.

The data of Buell *et al.* [45], compiled from transmissions voluntarily reported to the IPITTR registry, conflict with those reported by Kauffman *et al.* [15] in the 2007 UNOS review: in 140 registered transplants with grafts from donors diagnosed with melanoma, only 1 transmission was reported (via a single lung). The donor had a melanoma resection 32 years before lung procurement and no transmission was reported from all 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 etc. of the donor melanomas, may help to clarify the issue. In the future, *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.

Currently, in most published reports of donors with a known history of melanoma these precise data about staging, therapy and follow up are missing [15, 30, 45]. Some yet unpublished cases, in which organs have been transplanted from donors with melanoma stage pT1a No Mo, resected (Ro), with recurrence-free survival > 5 years are currently under evaluation.

Because of the above-mentioned obstacles, caution is recommended when considering donors with a history of melanoma [67], unless the tumour can definitely be confirmed as *lentigo maligna* or *in situ* tumour and curative therapy has been adequate. In all other cases of melanoma the recommendation is to obtain all data about staging, 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 go 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/UK 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.

9.4.12. Non-melanoma skin cancer

Basal cell carcinoma and squamous cell carcinoma of the skin usually do not metastasise and should therefore be 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 are not acceptable as organ donors.

For recommendations regarding non-melanoma skin *in situ* cancers go 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. Neuroendocrine neoplasms

This section refers to high-grade neuroendocrine carcinoma (NEC), low-grade neuroendocrine 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 [61, 62, 64, 68-70]. All these tumours were high-grade (small cell) neuroendocrine 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 re-transplantation 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 occur up to 20 years after initial tumour resection [71].

In the absence of lymph node or distant metastasis (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 (383 g for malignant v. 73 g for benign), confluent tumour necrosis, vascular invasion and extensive local invasion [72]. Thompson [73] 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 especially the mitotic index 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 % [74].

One single case report describes a kidney transplant from a donor with intraoperatively found PCC. 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 [75]. The contralateral kidney recipient died of tumour-unrelated causes shortly after transplantation.

A case of transmission of PGL has been reported [76].

Careful risk–benefit consideration is necessary in individual cases of PCC and PGL.

Neuroendocrine tumours diagnosed during donor procurement
Due to their potential for undetected metastasis, high-grade neuroendocrine carcinomas (NEC) are an unacceptable risk for organ donation.
Insufficient information exists to guide practice for neuroendocrine tumours (NET), carcinoid tumours, phaeochromocytomas and paragangliomas.

Neuroendocrine tumours in the donor history
No data is available from the literature. Due to this and their potential for undetected metastasis, treated high grade neuroendocrine neoplasms in the donor history are classified as high risk for organ donation.
In case of a previous history (5-10 years) of NET 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 cancer, gastric cancer, pancreatic cancer, liver cancer and biliary cancer

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 [27], but no information about initial stage and recurrence-free survival of the donor is provided. No transmission of oesophageal cancer has been described so far. This might be a reporting bias and should not lead physicians to freely accept organs from donors with such aggressive tumours.

Regarding gastric cancer there is one case report [77], 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 1 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 [78]. 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 [17] 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 liver cancer [5].

Yamacake *et al.* [79] 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. There is no literature available regarding biliary cancer and organ donation.

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, biliary cancer in the donor history
Treated tumours are classified as high risk due to their aggressive behaviour. Risk may decrease for early stages after curative therapy, with recurrence-free time and with increasing probability of cure, especially in cases of long-term survivors.

9.4.15. Oropharyngeal cancer

No transmission reports 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 [15]. However, the aggressiveness of these tumours should be kept in mind.

Oropharyngeal cancer diagnosed during donor procurement
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, the risk category might decrease individually.

9.4.16. Ovarian cancer

There is a published case report [80] about transmission of ovarian cancer into two kidney recipients, 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.* [81]. 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, the risk category might decrease individually.

9.4.17. Pancreatic cancer

See 9.4.14.

9.4.18. Pancreatic intraepithelial neoplasia

See 9.4.4.

9.4.19. Paraganglioma

See 9.4.13.

9.4.20. Phaeochromocytoma

See 9.4.13.

9.4.21. Prostate cancer

Given that the incidence of prostate cancer increases with age, and given the increasing age profile of donors, it is certain that – in many of the organ transplants now being performed – organs from donors with undiagnosed prostate cancer are being used.

Sanchez-Chapado *et al.* [82] evaluated prostate cancer in a consecutive series of prostate glands collected at the *post mortem* examination of 162 male patients born and living in Spain, dying from trauma. They reported prostate cancer in 23.8 % of males aged 50-59 years, 31.7 % aged 60-69 years and 33.3 % aged 70-79 years.

Yin *et al.* have shown incidental prostate adenocarcinoma in 12 % (41/340) of presumed healthy organ donors in a 13-year period [83]. Incidence of prostate cancer by age group was similar to the above findings (23.4 %/50-59 years, 34.7 %/60-69 years, 45.5 % 70-81 years).

The guidelines for detection of early stages of prostate carcinoma have changed in recent years. Specifically, the validity of repetitive PSA testing in combination with digital rectal examination has been questioned. There is broad consensus that single testing is not of high prognostic value [84]. Moreover, there is no agreement as to what PSA levels should be considered suspicious or even normal.

For confirmed prostate cancer, the Gleason score is the current grading system and 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 of them with significant differences in outcome (higher scores result in poorer outcomes): low (≤ 6), intermediate (= 7) and high Gleason score (≥ 8).

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 [85], meaning that they will not undergo surgery but are surveyed at short intervals for further disease progression. This strategy has 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.

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 [86]. Donors were classified regarding the transmission risk as: standard risk (no prostate cancer or intra-prostatic tumour with a Gleason score ≤ 6), non-standard risk (intra-prostatic tumour with a Gleason score 7) or unacceptable risk (pT3a/b extra-prostatic cancer or lymph nodes and/or distant metastases). Overall, 94 % of the donors were classified as standard risk, which had been 63 % before implementation of this protocol. A significant increase in the number of transplanted organs has been achieved by expanding the criteria for standard risk donors. No tumour transmission has been reported after 60 months of follow-up (personal communication, A. D'Errico).

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 [87]. This case is referred to in various registry reports [3, 17, 20].

OPTN/DTAC reported 5 autopsy-proven cases of donor prostate adenocarcinoma without evidence of transmission [5]. A recent review by Doerfler *et al.* [88] documented 120 organ transplants from donors with confirmed prostate cancer with no evidence of disease transmission.

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 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 anamnestic prostate cancer are strongly correlated to 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 unsuspicious follow-up.
Prostate cancer Gleason > 6 after curative treatment and cancer-free period > 5 years is considered minimal risk.
Higher stages and higher Gleason grades require an individual risk assessment.
A history of extra-prostatic tumour extension poses a high risk for transmission.

9.4.22. Renal cell carcinoma

Cumulated experience with the treatment of renal cell carcinoma (RCC) and several reports in the literature suggest that organs from donors with RCC Fuhrman grade I-II/IV that measure < 4cm show only rare neoplastic transmission [4, 7, 9, 11, 42].

The ONT Registry did not detect any tumour transmission among 59 recipients transplanted with grafts from 47 donors registered with RCC (15 kidneys, 29 livers, 7 hearts and 5 lungs). Prophylactic removal of the graft was performed in 9 of these kidneys, 2 livers and 1 heart. After 3 years of follow-up, tumour transmission had not appeared in any of the cases. As mentioned previously, 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.

Serralta *et al.* [89] reported 4 donors with RCC, all detected in the kidneys after the respective liver had been transplanted and without tumour transmission after a mean follow-up of 58.5 months.

Furthermore, in relation to the use of other organs from donors with cancerous kidneys, Carver [90] refers to a liver and a contra-lateral kidney transplant without evidence of a tumour transmission after 4 years of follow-up.

The MALORY initiative [9] described a 6-year experience with the transplantation of organs from 35 donors with RCC (3 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.

However, further cases of transmission do exist, all of them resulting from donor RCC which were undetected before transplantation; therefore it was impossible to assess a transmission risk. In 1995, Penn [4] described 17 recipients with transmission of undetected malignant kidney tumours at time of procurement. Of these, 10 recipients were recurrence-free at an average of 59 months after transplant nephrectomy but 7 recipients developed metastatic disease after an average of 12 months and died subsequently. In 1997, Sack [91] 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 [92] referred to a contra-lateral 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, the perinephric fat having not been 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, and the perinephric fat had not been removed to facilitate organ examination at the time of transplantation. Llamas *et al.* [93] reported the transmission of sarcomatoid carcinoma in two kidney recipients after transplant without any evidence of tumour in the organs at the time of transplantation. Buell *et al.* [20] reported 2 metastatic donor RCCs (detected after transplantation of organs) that were transmitted in lung and heart/lung recipients who both died of metastatic disease. Organs from 3 further donors with RCCs detected during procurement and confined to the kidney were transplanted without transmission in follow-up at 30, 36 and 70 months. OPTN/DTAC [5] showed 7 recipients with confirmed transmissions from 64 donors with RCCs. Desai *et al.* [7] described 6 transmitted RCCs incidentally detected in biopsies performed as protocol biopsies or to assess graft dysfunction. The recipients of other organs of those donors were tumour-free.

The tumour type is an extremely important consideration since some kidney tumours exhibit benign behaviour (e.g. oncocytoma). Chromophobe carcinoma can present morphological features very similar to oncocytoma on frozen sections, but it is a malignant neoplasm. RCCs can be multifocal and

have a bilateral incidence in 5 % of cases [94]. Careful examination and the use of ultrasound analysis are necessary for the identification of this tumour in both kidneys after removal, especially in cases of papillary RCC.

Nephron-sparing surgery is an established curative approach for the oncological treatment of RCC ≤ 5 cm [95] with cancer-specific survival rates comparable to radical nephrectomy [96].

In 2014, Yu *et al.* [97] reviewed 20 case reports or case series describing the outcome of a total of 97 donor kidneys transplanted after resection of small RCCs, all < 4 cm with tumour-free margins. Of these, 27 RCCs were detected incidentally during organ procurement – no transmission was reported after mean follow-up periods of 15-200 months – and 70 RCCs had been diagnosed prior to donation (no chemo-/radiotherapy performed). Of these, one possible tumour recurrence was reported [98], but it occurred 9 years after transplantation and the lesion was remote from the initial resection site which implies that it was a *de novo* rather than a transmitted tumour. Besides, the recipient refused diagnostics and treatment and the final nature of the lesion could never be determined. All other kidney recipients showed no tumour transmission after mean follow-up periods of 14-135 months. The authors additionally reviewed reports of 21 contralateral, healthy kidneys from donors with RCC. Except for the above described transmission case of Barrou *et al.* [92], there was no reported transmission from these kidneys.

Additionally, Musquera *et al.* [99] reported the transplantation of 8 kidneys after R0-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 shown by Penn [4] who reported two donor RCCs that were consciously not excised or inadvertently incompletely excised at procurement and transmitted into the recipients.

In 2012, the International Society of Urological Pathology (ISUP) launched a new grading system for RCC [100], based on the assessment of the nucleolar grade (grades 1-4). This has shown to provide outcome predictions superior to Fuhrman grading for both clear cell and papillary RCC [101, 102]. Nucleolar grade can be considered similar to Fuhrman grade.

RCC diagnosed during donor procurement
To provide a valid histological staging, complete tumour resection (R0) is required for the 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.
RCC < 1 cm and nucleolar grade I/II (Fuhrman grade I/II) can be considered minimal risk for transmission.
RCC 1-4 cm and nucleolar grade I/II (Fuhrman grade I/II) are considered low risk.
RCC > 4-7 cm and nucleolar grade I/II (Fuhrman grade I/II) are considered intermediate risk.
RCC > 7 cm and nucleolar grade I/II (Fuhrman grade I/II) are considered high risk.
All RCC with nucleolar grade III/IV (Fuhrman grade III/IV) are considered high risk for transmission.

RCC in the donor history
The transmission risk of treated RCC depends on the 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, the guidance in most cases (with a few exceptions, e.g. GIST, see section 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 transplant ectomy [20, 103, 104], but the usual outcome after transmission is fatal [6, 105, 106]. For this reason, sarcoma or a history of sarcoma is at present considered a contraindication to organ or tissue donation.

Sarcoma diagnosed during donor 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 the donor history
Due to the very aggressive behaviour of sarcoma, they are mostly considered 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 underway at present, with specific mutations linked to prognosis in some cases [107]. However, this information is still fragmentary and is typically unavailable in the setting of transplantation. Recommendations have therefore been based to date on the aggregate behaviours based on 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.* [108] documented ureteric obstruction as the first symptom in their recipient and a separate patient reported by Ferreira *et al.* [109] developed gross haematuria 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 tumour that arose in the allograft separately reported by Backes *et al.* [110]. Penn [4] reported metastatic transmission of two undetected donor transitional cell carcinomas into 2 kidney recipients who died of the tumour.

Mannami *et al.* [111] reported the transplantation of 8 'restored' donor kidneys with confirmed transitional cell carcinoma of stages pTa (3), pT1 (1), pT2 (2), pT3 (1). 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. Mitsuhata *et al.* [112] described the transplantation of 3 'restored' kidneys with urothelial carcinoma, pT1/G1 (1), pT2/G2+3 (2), without tumour recurrence in the recipients after 62-109 months.

In general, the highly aggressive behaviour 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
Newly diagnosed invasive urothelial cancer is considered an unacceptable risk for organ donation.

Urothelial cancer in the donor history
Strict follow-up must have been provided after primary diagnosis due to the fact that these tumours may be multicentric and tend to recur with a need for repeated TUR-B and for restaging. Kidney transplantation will be associated with an increased risk but this has not been classified in the literature yet.
After a disease-free interval > 5 or > 10 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 [30], 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 and uterine cervix cancer diagnosed during donor procurement
Presence of invasive cancers is considered an unacceptable risk for organ donation.

Uterus and uterine cervix cancer in the donor history
After a disease-free interval > 5 or > 10 years, transmission risk of invasive uterus and cervix cancer will be dependent on the probability of cure, and has to be assessed individually before accepting the potential organ 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 [113-116]. In a recent systematic review of donor transmitted cancer in renal transplant recipients, Xiao *et al.* [65] 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 [117] and, conversely, donor leukaemia has presented as a solid tumour (promyelocytic sarcoma) in an organ recipient [118]. Haematopoetic 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 regarding 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.* [119] reported a donor-related peritoneal plasmacytoma 3 years after transplantation in the liver recipient, showing chimeric donor and recipient origin. No further literature exists regarding plasmacytoma in organ donors.

Leukaemia, lymphoma and plasmacytoma diagnosed during donor procurement
These 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.

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 mono-clonal protein is a significant predictor of malignant progression. In this context, electrophoretic analysis is helpful in suspected cases [34], which should be discussed with a haematologist and possibly be investigated further with a bone marrow biopsy.

9.5.2. Myeloproliferative neoplasms

Myeloproliferative neoplasms (MPNs) [120, 121] are a group of chronic malignant diseases caused by dysregulated multipotent hematopoietic stem cells, mostly diagnosed beyond the age of 50 but around 20 % of cases are in patients below the age of forty.

In three MPN diseases, the clonogenic stem cells produce increased numbers of blood cells in the peripheral blood which can cause e.g. thromboembolic 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 following MPN 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, 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 thrombembolic complications [122]. The only curative therapy is allogenic stem cell transplantation (mainly for PMF but rarely also for selected patients with PV and ET).

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). Besides, it cannot be ruled out that they 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 will behave in an immunosuppressed recipient.

MPN diagnosed during donor procurement
Due to the current lack of literature on MPNs 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.

MPN 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 transplant (and in the immuno-suppressed recipient), their transmission risk can currently not 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 central nervous system (CNS) represent 3-4 % of the causes of death in organ donors.

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 [123, 124].

Extra-neural 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 extra-neural dissemination of CNS neoplasms [125]:

a. specific histological types and high degree 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 [126]. It is estimated that 10 % of these tumour metastases occur without prior surgical intervention and even within 3-6 months of their diagnoses [126].

With respect to the histological type, the neuro-ectodermic tumours that metastasise with greatest frequency outside the cranial cavity are glioblastoma multiforme and medulloblastoma. However, this phenomenon has also been described for several forms of gliomas (i.e. different grades of astrocytomas, malignant ependymomas and anaplastic oligodendrogliomas) as well as malignant meningiomas and germinal cell tumours. In a series of 116 cases of extra-cranial metastases of CNS neoplasms, the most common primary tumour was glioblastoma (41.4 %), followed by medulloblastoma (26.7 %), ependymoma (16.4 %), astrocytoma (10.3 %) and oligodendroglioma (5.3 %) [124].

The World Health Organization (WHO) provides a comprehensive classification of CNS neoplasia (see Table 9.4), based on the specific cell type involved [127]. This WHO classification provides a parallel grading system (I to IV) for each type of tumour, depending on its behaviour and, hence, dictates the choice of therapy and predicts prognosis. WHO grade I applies to lesions with low proliferative potential and the possibility of being cured following surgical resection alone. Neoplasms designated WHO grade II are generally infiltrative in nature and, despite low-level proliferative activity, often recur. Some WHO grade II tumours tend to progress to higher grades of malignancy, i.e. low-grade diffuse astrocytomas that transform to anaplastic astrocytoma and glioblastoma. Similar transformation occurs in oligodendroglioma and oligoastrocytomas. 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 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.

Several clinical cases of transmission of CNS neoplasms through organ transplantation have been reported in the literature [5, 20, 128-139]. Most of the reported cases are related to high grade CNS tumours, usually in association with other risk factors for extra-cranial 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 [140].

Follow-up registries containing information on recipients transplanted from donors with a CNS malignancy have shown a greatly reduced risk of disease transmission, placing the aforementioned cases in perspective. In 1999 the Australian and New

Zealand Organ Donation Registry published a series of 46 donors with a primary CNS tumour, of which 28 were classified as malignant including 4 gliomas, 4 glioblastomas, 10 astrocytomas, 5 medulloblastomas, 1 malignant meningioma and 4 histologically unspecified tumours. Seven donors had undergone a craniotomy, of whom 3 had ventriculoperitoneal shunts; three others had ventriculoperitoneal shunts without craniotomy. None of the 96 recipients of organs from these donors developed a transmitted tumour [141].

The Czech Republic has reported no cases of transmission among 89 recipients (79 kidneys, 5 livers, 4 hearts and 1 lung) transplanted with organs from 41 donors with CNS malignancies (13 meningiomas, 9 glioblastoma multiforme, 3 astrocytomas, 2 medulloblastomas, 1 craniopharingioma, 1 acoustic neuroma, 2 pituitary adenomas, 1 lymphoma and 8 histologically unspecified tumours) [142].

Similarly, in 2002, the UNOS registry published 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-pancreata, 16 pancreata, 6 heart-lungs and 3 intestinal transplants [16]. 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 a glioblastoma multiforme. These 19 donors with known high grade tumours supplied a total of 56 transplanted organs: 26 kidneys, 2 kidney-pancreata, 15 livers, 10 hearts and 3 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 been transplanted with organs from donors with a previous history of CNS malignancy including 175 transplants from donors with a history of glioblastoma multiforme [15]. 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 multiforme [15, 135].

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 [24]. The types of CNS tumours were (with variable grades according to the WHO classification): astrocytoma (astrocytoma unspecified, pilocytic, gemistocytic, fibrillary), gliomatosis cerebri, glioblastoma, giant cell glioblastoma, oligodendroglioma, ependymoma, malignant glioma, mixed malignant glioma meningioma, medulloblastoma, Ewing's sarcoma, primitive neuroectodermal 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, 1 double kidney, 72 livers, 1 combined liver-kidney, 12 heart-lungs, 13 double lungs, 51 hearts, 10 single lungs, 8 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, the Advisory Committee for the Safety of Blood, Tissues and Organs (SaBTO) in the UK estimated the risk of extra-neural 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 estimated as 2.2 %, with a 6.4 % upper 95 % confidence limit [12, 143]. The risk of extra-neural 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 [21]. 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, 3 medulloblastomas and 2 cerebellar tumours). Of the 36 donors 24 received some form of cancer therapy before organ donation, including ventriculo-peritoneal or ventriculo-atrial shunts (n = 12), craniotomy (n = 6), radiation therapy (n = 4) and chemotherapy (n = 2) and 62 organs were transplanted from the 36 donors, including 35 kidneys, 12 hearts, 10 livers, 2 pancreata and 3 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 [144].

In 2011, based on information available at the time of their report, the Disease Transmission Advisory Committee (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) with 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.

Drawing on the available information and the variable estimates of disease transmission derived from the previously described registries, a qualitative classification of CNS malignancies is proposed, based on the risk of tumour transmission, as shown here:

Based on the available information and the estimated risks of tumour transmission, a qualitative classification of CNS malignancies is proposed:

- 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 unacceptable risk. Recent analyses indicate that this may overestimate the risk, since several transplantations 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 extra-cranial spread of a primary cerebral tumour. This includes 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 and any shunt that may be present to exclude extra-cranial growth.

9.7. Review of specific tumours of the central nervous system

9.7.1. Neuroectodermic tumours

9.7.1.1. *Medulloblastoma*

Medulloblastoma (WHO grade IV) is the most common primitive neuroectodermal tumour and represents 6 % of all intra-cranial gliomas and 44 % of gliomas in children. Normally, they originate in the fourth ventricular layer and invade the cerebellar vermis. Medulloblastomas that occur during childhood are the ones that most frequently metastasise outside the core of the CNS. Extra-neural 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, 8 (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) [145]. All patients with metastatic disease had undergone complete or subtotal resection and cranial irradiation.

Table 9.4. **WHO classification and grading of CNS neoplasias**

	I	II	III	IV
Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours				
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocyoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neyrocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid/rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic/malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurophypophysis	•			
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 [127].

In a more recent series 1 % of 1 011 patients with CNS tumours developed extra-neural metastases, of which 6 were children with medulloblastomas [146]. In a third series 3.6 % of children with medulloblastoma developed extra-neural metastases [147]. All three series report bone, bone marrow, and cervical lymphatic glands as common sites for metastatic medulloblastoma, with intra-abdominal and intrathoracic metastases less common.

Neoplastic transmission from organ donors with medulloblastomas to recipients has been described. Lefrançois *et al.* [129] 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 ventriculoperitoneal shunt [21]. 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 probability of tumour transmission.

9.7.1.2. *Gliomas*

Gliomas comprise astrocytomas, oligodendrogliomas, and ependymomas. The incidence of extra-cranial glioma dissemination is calculated to be 0.4-2.3 %, mostly from glioblastoma and predominantly to the lung, pleura, lymph nodes, bone and liver [123]. 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 glioblastoma (n = 34, 13 %) being misdiagnosed [148].

9.7.1.2.1. Astrocytomas

Astrocytomas are divided into:

a. malignant astrocytomas [anaplastic astrocytoma (WHO grade III), and glioblastoma multiforme (WHO grade IV)]; and

b. low-grade disease astrocytomas [pilocytic astrocytoma (WHO grade I), and diffuse astrocytoma (WHO grade II)], representing 55 % and 20 % of all intra-cranial gliomas respectively.

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 fluid and, although this is a frequent attribute, may not necessarily locally invade the leptomeninges. Metastases occur with greater frequency if tumour growth reaches the ventricular ependyma or if it is followed by anaplastic changes, thereby acting as a malignant glioma. Pollack *et al.* [149] 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 [150].

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.
Extra-neural 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 more aggressive malignancy are ruled out. Since astrocytomas have a tendency to relapse with a histologically higher grade of malignancy, new histological examinations should be performed where relapse occurs to regrade the tumour.
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 (see section 9.7.1.2.1.2.).

Anaplastic astrocytomas (WHO grade III) and glioblastoma multiforme (WHO grade IV)

At least 80 % of malignant gliomas are glioblastoma multiforme, representing the most undifferentiated type of adult CNS tumour. 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 30s and 40s, while glioblastoma multiforme more often presents in adults aged in their 50s and 60s. 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 decompression, transgression of the *dura mater* can occur with greater ease when ventriculo-peritoneal shunts or radiotherapy have been performed.

Dissemination of a glioblastoma multiforme through the cerebrospinal fluid is not uncommon, and generally occurs because of invasion or rupture within the ventricular cavity. Extra-cranial metastases of anaplastic astrocytomas and glioblastoma multiforme have been observed in the absence of prior surgery [124, 132], although they occur with greater frequency following surgery or ventriculo-peritoneal drainage [151]. When extraneural metastases do

occur from anaplastic astrocytomas and glioblastoma multiforme, they are most commonly found in bone (especially vertebrae), liver, lungs and cervical lymph nodes.

Transmission of neoplastic diseases from donors with glioblastoma multiforme has been documented in individual reports [5, 15, 130-132, 134-136]. 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 [20, 152].

Fecteau *et al.* [153] 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.

Similarly, the IPITTR has described a series of 25 organ transplants from 16 donors with astrocytomas during the period 1970-2002, where 14 of those organs had risk factors for tumour transmission: 4 WHO grade III/IV astrocytomas, 5 prior craniotomies, 4 prior radiotherapy and 4 prior chemotherapy [21]. 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, 8 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 9 had high WHO grade III/IV gliomas), and 8 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 extra-neural metastases and suggests the possible utility of mTOR inhibitors as immuno-suppressant drugs for organ recipients in such donor cases [136].

Spontaneous extra-neural metastases of anaplastic astrocytomas and glioblastoma multiforme are rare, but have been observed, and 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 multiforme (WHO grade IV) are considered intermediate to high risk for transmission depending on the 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 malignant primary brain tumours [154]. There are two main types: low grade oligodendrogliomas (WHO grade II) and anaplastic oligodendrogliomas (WHO grade III). Recent advances in molecular genetics have allowed subtyping of gliomas, including oligodendrogliomas in which deletions in chromosomes 1p and 19q affect prognosis and sensitivity to different chemotherapeutics [155].

Low grade oligodendrogliomas (WHO grade II) are the most frequent form and are difficult to distinguish from astrocytomas. They typically appear in adults aged in their 20s and 30s. They grow slowly and infiltrate the cortex and even the leptomeninges. They are extensively vascularised tumours and often calcified. Low grade oligodendrogliomas present, in many cases, as spontaneous cerebral haemorrhages. Some low grade oligodendrogliomas can progress to become anaplastic oligodendrogliomas (WHO grade III).

Anaplastic oligodendrogliomas are very aggressive tumours that behave like glioblastoma multiforme. Extra-cranial metastases of anaplastic oligodendrogliomas have been observed after multiple craniotomies and massive infiltration of the extra-cranial tissues [156]. 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].

The transmission risk of mixed gliomas is equivalent to other gliomas and classified according to the respective WHO grade of the tumour (see above).

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 intra-cranial gliomas and are the third most common brain tumour in children. In fact, 50-70 % of ependymomas are infratentorial, are located in the IV 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 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, extra-neural metastases of the intra-cranial and spinal ependymoma have been observed, although the majority were recurrent neoplasms in which the extra-neural dissemination followed tumour invasion of the adjacent soft tissues or resulted from seeding from surgery [157-159].

In a series of 81 ependymomas, Newton *et al.* [160] reported five cases (6.2 %) with extra-cranial 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. Extra-neural 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 [161], but most reports have followed multiple surgical resections, radiotherapy and chemotherapy [162-166].

To date, no case of transmission of ependymomas to an organ recipient has been reported.

Extra-neural 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. Thus, a low grade (WHO I or II) ependymoma represents a minimal risk of transmission whereas an anaplastic ependymoma (WHO III) will be associated with a 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 [154]. They are more often found in the supratentorial levels in children but in adults they are more frequent in the IV 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 [167].

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 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 [168-171].

No cases of transmission of pineocytomas/pineoblastomas through organ transplantation have been reported in the literature to date.

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 intra-cranial primitive tumours**

9.7.2.1. *Benign meningiomas, atypical meningiomas, anaplastic or malignant meningiomas*

Meningiomas represent 20 % of all the intra-cranial 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 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 extra-cranial metastases. Younis *et al.* [172] presented a series of 18 patients with aggressive meningeal tumours of which 12 were malignant (anaplastic) meningiomas (WHO III) and 6 atypical meningiomas (WHO II). Three (16 %) developed extra-cranial metastases (2 malignant meningiomas and 1 atypical meningioma). In these three cases, pulmonary and bone metastases were the most frequent. All 3 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 [173-178]. One study suggested that meningiomas expressing high levels of CD90 were atypical and more likely to metastasise [176].

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.* [133]. The tumour regressed following transplant nephrectomy and interferon alpha treatment.

Extra-neural metastases by histologically benign meningiomas are very rare.
Organs from potential donors with these types of tumours have a minimal risk of transmission.
Anaplastic or malignant meningiomas (WHO grade III) are more aggressive meningeal tumours that occasionally can be associated with extra-neural 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 intra-cranial sarcomas, meningeal sarcomas and haemangiopericytomas*

Intra-cranial sarcomas represent 1% of all tumours of the CNS. The most anaplastic forms of sarcomas metastasise through the cerebrospinal fluid. However, extra-neural metastases are rare, probably due to the fact that the rapid development of these tumours does not provide sufficient time for the extra-neural 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.* [179] described the existence of extra-cranial metastases in gliosarcomas.

Meningeal sarcomas and anaplastic haemangiopericytomas are locally aggressive meningeal tumours that are frequently associated with extra-neural metastases and multiple recurrences. Younis *et al.* [172] described four cases of haemangiopericytoma and three meningeal sarcomas in a review of aggressive meningeal tumours. Three of these seven cases developed extra-cranial 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.* [180] reviewed 20 cases of haemangiopericytoma with extra-neural metastases, commonly to bone, liver, lung and lymph nodes.

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 hemagiopericytoma 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.* [181] observed two spontaneous cases of extra-neural metastases.

In 20 % of cases, haemangioblastomas appear to be associated with other tumours as part of Von Hippel-Lindau's syndrome, which is also associated with a high incidence of renal cell carcinoma.

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's syndrome are ruled out.
Recommendation for a particular tumour must be considered in the context of any coincidental neoplasms.
In case of Von Hippel-Lindau's syndrome particular attention has to 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. Intra-cranial germinomas most frequently occur in the pineal gland. They are histologically malignant, infiltrating tumours that usually disseminate through the third ventricle. Nongerminomatous germ cell tumours may be associated with increased levels of human choriogonadotrophin (HCG), alpha fetoprotein (AFP) and placental alkaline phosphatase (PLAP) in serum and cerebrospinal fluid. Extra-gland metastases have been observed following craniotomies, cranial-spinal radiotherapy or ventriculo-peritoneal diversion [181].

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. Extra-cranial metastases have been reported in the lungs [182].

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 extra-cranial 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 intra-cranial lymphomas appear with greater frequency in immuno-suppressed patients, such as those diagnosed with AIDS. Their prognosis is bad and they progress to extra-cranial dissemination.

There is a reported transmission of a primary intracranial Non-Hodgkin's Lymphoma into both kidney recipients. 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 (PTLD), in immuno-suppressed patients – or from donor cells. PTLD, even if of donor origin, is not considered to represent a donor-transmitted disease as it is a post-transplant process. It is important to distinguish between donor-transmitted tumours, which are already present in the donor (detected or undetected) and transmitted with the transplanted organ to the recipient, 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). It must be admitted, however, that in some cases this distinction might be arbitrary (e.g. RCC arising 2-4 years after transplant).

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, or suspected malignancy transmission in another recipient(s) from the same donor.

Some scenarios [183] that would raise reasonable suspicion of a possible donor-transmitted tumour include:

a. Cancer (other than 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. renal cell carcinoma 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 reveals that isolated tumour cells might be transmitted through the organ (e.g. leukaemia and Kaposi's sarcoma).

Clearly, recipients who received organs from donors with a confirmed malignancy are to be strictly followed up to detect a possible transmission as early as possible. However, 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 [184]. 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 comprehensive 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 transmissions

Transmission of a malignant tumour is considered a serious adverse reaction (SAR) in the recipient. Reporting of suspected transmission events to the assigned national health authority, consecutive investigation and review of the cases is required, and mandatory according to Directive 2010/53/EU [13] (see Chapter 14).

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 14, section 14.3.2.).
b. The respective recipient centres of the same donor as well as tissue organisations and the organ procurement organisation will be alerted by the Health Authority in charge of coordinating vigilance and the examination and 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 donor/recipient DNA should be achieved to prove or exclude transmission of a donor malignancy.

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 known in the donor before the transplant or immediately after transplantation, 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. Therefore, for example, if a kidney with a small papillary carcinoma (< 4 cm) is transplanted and a few months after transplantation the graft shows a papillary neoplasm, histology can recognise the histotype and immunohistochemistry can pinpoint a relevant phenotypic subtype, whereas molecular-based studies can help to identify the donor origin of the neoplasm. 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/immuno-histochemical 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 recipient DNA [68]. In cases of a positive test match between donor and tumour material, a second method is performed to definitively confirm the donor origin of the tumour. 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 necessarily eliminate the transmitted tumour in every case. 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 material 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 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. After lowering or completely withdrawing immunosuppression, it takes time until the immune system recovers and can potentially reject allogenic tumour cells in occasional cases. 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]. A final report of each case has to be prepared after a defined period of 3 months [13] (see Chapter 14, section 14.3.2.4).

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. 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

1. Murray JG, Batholomay R, Batholomay A. Fourth report of the Human Kidney Transplant Registry: 16 September 1964 to 15 March 1965. *Transplant Proc* 1965; 3 (5): 684-99.
2. McPhaul JJ, McIntosh DA. Tissue transplantation still vexes. *N Engl J Med* 1965; (272): 105.
3. Penn I, Transmission of cancer from organ donors. *Ann Transplant* 1997; 2 (4): 7-12.
4. Penn I, Primary kidney tumors before and after renal transplantation. *Transplantation* 1995; 59 (4): 480-5.
5. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. *Am J Transplant* 2011; 11 (6): 1123-30.
6. Garrido G, Matesanz R. The Spanish National Transplant Organization (ONT) tumor registry. *Transplantation*, 2008; 85 (Suppl 8): S61-3.
7. Desai R, Collett D, Watson CJ *et al.* Cancer transmission from organ donors – unavoidable but low risk. *Transplantation* 2012; 94(12): 1200-7.
8. Nalesnik MA. Donor-transmitted tumors in relation to cancer and allograft types: a report of the OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC). Presented at the American Transplant Congress 2012.
9. Moench K, Schnitzbauer A, Breidenbach T *et al.* 6-year-survey of organ donors with malignancies in Germany. Presented at the 24th International Congress of The Transplantation Society. Berlin, Germany, 2012.
10. Lopez-Navidad A, Caballero F. Extended criteria for organ acceptance: strategies for achieving organ safety and for increasing organ pool. *Clin Transplant* 2003; 17 (4): 308-24.
11. Nalesnik MA, Woodle ES, Dimaio JM *et al.* Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. *Am J Transplant* 2011; 11 (6): 1140-7.
12. SaBTO (Advisory Committee on the Safety of Blood, Tissue and Organs). Transplantation of organs from deceased donors with cancer or a history of cancer. April 2014 [available from: www.odt.nhs.uk/pdf/transplantation_of_organs_from_deceased_donors_with_cancer_or_a_history_of_cancer.pdf, accessed: 9 March 2016].
13. European Parliament and the Council of the European Union. Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation, 7 July 2010 [available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX-:32010L0053:EN:NOT, accessed 17 Dec 2015].
14. Kauffman HM, McBride MA, Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: donors with a history of cancer. *Transplantation* 2000; 70 (12): 1747-51.
15. Kauffman HM, Cherikh WS, McBride MA *et al.* Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. *Transplantation* 2007; 84 (2): 272-4.
16. Kauffman HM, McBride MA, Cherikh WS *et al.* Transplant tumor registry: donors with central nervous system tumors. *Transplantation* 2002; 73 (4): 579-82.
17. Kauffman HM, McBride MA, Cherikh WS *et al.* Transplant tumor registry: donor related malignancies. *Transplantation* 2002; 74 (3): 358-62.
18. Green M, Covington S, Taranto S *et al.* Donor-derived transmission events in 2013: a report of the Organ Procurement Transplant Network *Ad Hoc* Disease Transmission Advisory Committee. *Transplantation* 2015; 99 (2): 282-7.
19. Feng S, Buell JF, Cherikh WS *et al.* Organ donors with positive viral serology or malignancy: risk of disease

transmission by transplantation. *Transplantation* 2002; 74(12): 1657-63.

20. Buell JF, Trofe J, Hanaway MJ *et al.* Transmission of donor cancer into cardiothoracic transplant recipients. *Surgery* 2001; 130 (4): 660-6; discussion 666-8.
21. Buell JF, Beebe TM, Trofe J *et al.* Donors with central nervous system malignancies: are they truly safe? *Transplantation* 2003; 76 (2): 340-3.
22. Buell JF, Hanaway MJ, Thomas M *et al.* Donor kidneys with small renal cell cancers: can they be transplanted? *Transplant Proc* 2005; 37(2): 581-2.
23. Desai R, Collett D, Watson CJ *et al.* Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg* 2014; 101 (7): 768-74.
24. Watson CJ, Roberts R, Wright KA *et al.* How safe is it to transplant organs from deceased donors with primary intracranial malignancy? An analysis of UK Registry data. *Am J Transplant* 2010; 10 (6): 1437-44.
25. Venettoni S, Curtoni ES, Scalamogna M *et al.* Strategies for evaluation of suitable donors: Italian experience. *Ann Transplant* 2004; 9 (2): 15-16.
26. Nanni Costa A, Grossi P, Quality and safety in the Italian donor evaluation process. *Transplantation* 2008; 85 (Suppl 8): S52-6.
27. Taioli E, Mattucci DA, Palmieri S *et al.* A population-based study of cancer incidence in solid organ transplants from donors at various risk of neoplasia. *Transplantation* 2007; 83 (1): 13-16.
28. Zucchini, N, Fiorentino M, D'Errico GA *et al.* The Italian multiorgan donor cancer screening protocol: 2002-2005 experience. *Transplantation* 2008; 85 (Suppl 8): S57-60.
29. Fiaschetti P, Pretagostini R, Stabile D *et al.* The use of neoplastic donors to increase the donor pool. *Transplant Proc* 2012; 44 (7): 1848-50.
30. Birkeland SA, Storm HH. Risk for tumor and other disease transmission by transplantation: a population-based study of unrecognized malignancies and other diseases in organ donors. *Transplantation* 2002; 74 (10): 1409-13.
31. https://cancerstaging.org/, accessed 31 July 2016.
32. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; 17 (6): 1471-4.
33. Nalesnik MA, Ison MG. Organ transplantation from deceased donors with cancer: is it safe? *Open Access Surgery* 2011; (4): 11-20.
34. CNT. General criteria for evaluation of donor suitability adopted in Italy; www.trapianti.net/en/regulation, accessed 17 Dec 2015.
35. Franken B, de Groot MR, Mastboom WJ *et al.* Circulating tumor cells, disease recurrence and survival in newly diagnosed breast cancer. *Breast Cancer Res* 2012; 14 (5): R133.
36. van Dalum G, Stam GJ, Scholten LF *et al.* Importance of circulating tumor cells in newly diagnosed colorectal cancer. *Int J Oncol* 2015; 46 (3): 1361-8.
37. Loh J, Jovanovic, Lehman M *et al.* Circulating tumor cell detection in high-risk non-metastatic prostate cancer. *J Cancer Res Clin Oncol* 2014; 140 (12): 2157-62.
38. Muller C, Holtschmidt, Auer M *et al.* Hematogenous dissemination of glioblastoma multiforme. *Sci Transl Med* 2014; 6 (247): 247ra101.
39. Nahed B, Circulating tumor cells in patients with glioblastoma. *Neurosurgery* 2014; 61 (Suppl 1): 226.
40. Coumans FA, Ligthart ST, Uhr JW *et al.* Challenges in the enumeration and phenotyping of CTC. *Clin Cancer Res* 2012; 18 (20): 5711-18.
41. Fischer JC, Niederacher D, Topp SA *et al.* Diagnostic leukapheresis enables reliable detection of circulating tumor cells of nonmetastatic cancer patients. *Proc Natl Acad Sci USA* 2013; 110 (41): 16580-5.
42. Organización Nacional de Trasplantes, Comisión de Trasplantes del Consejo Interterritorial. Documento Consenso: Criterios para prevenir la transmisión de enfermedades neoplásicas en la donación de órganos. Madrid: Organización Nacional de Trasplantes, Comisión de Trasplantes del Consejo Interterritorial, 2006 [available from: www.ont.es/infesp/DocumentosDeConsenso/tumores.pdf, accessed: 24 February 2016].
43. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J *et al.* Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49 (6): 1374-403.
44. Friedman AL *et al.*, Collective experience with renal transplantation from donors with a history of breast cancer. *Am J Transplant* 2003; (Suppl 3): 288.
45. Buell JF, Beebe TM, Trofe J *et al.* Donor transmitted malignancies. *Ann Transplant* 2004; 9 (1): 53-6.
46. Feng S, Buell JF, Chari RS *et al.* Tumors and transplantation: the 2003 Third Annual ASTS State-of-the-Art Winter Symposium. *Am J Transplant* 2003; 3 (12): 1481-7.
47. Nalesnik, M. Tumors and solid organ transplantation: intersections at multiple levels. *Medscape* 2003 [available from http://cme.medscape.com/viewarticle/449388, accessed 30 Jan 2015, open access after free registration for healthcare professionals].
48. Braun-Parvez L, Charlin E, Caillard S *et al.* Gestational choriocarcinoma transmission following multiorgan donation. *Am J Transplant* 2010; 10 (11): 2541-6.

49. Zelinkova Z, Geurts-Giele I, Verheij J *et al.* Donor-transmitted metastasis of colorectal carcinoma in a transplanted liver. *Transpl Int* 2012; 25 (1): e10-15.
50. Snape K, Izatt L, Ross P *et al.* Donor-transmitted malignancy confirmed by quantitative fluorescence polymerase chain reaction genotype analysis: a rare indication for liver retransplantation. *Liver Transpl* 2008; 14 (2): 155-8.
51. Beaton C *et al.* Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. *Colorectal Dis* 2013; 15 (7): 788-97.
52. Mou S, Soetikno R, Shimoda T *et al.* Pathologic predictive factors for lymph node metastasis in submucosal invasive (T1) colorectal cancer: a systematic review and meta-analysis. *Surg Endosc* 2013; 27 (8): 2692-703.
53. Kang J, Lee HW, Kim IK *et al.* Clinical implications of microsatellite instability in T1 colorectal cancer. *Yonsei Med J* 2015; 56 (1): 175-81.
54. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25 (Suppl 3): iii21-6.
55. Forbes GB, Goggin MJ, Dische FE *et al.* Accidental transplantation of bronchial carcinoma from a cadaver donor to two recipients of renal allografts. *J Clin Pathol* 1981; 34 (2): 109-15.
56. Conlon PJ, Smith SR. Transmission of cancer with cadaveric donor organs. *J Am Soc Nephrol* 1995; 6 (1): 54-60.
57. Winter TC, Keller PR, Lee PT Jr *et al.* Donor-derived malignancy: transmission of small-cell lung cancer via renal transplantation. *J Ultrasound Med* 2001; 20 (5): 559-62.
58. Lipshutz GS, Baxter-Lowe LA, Nguyen T *et al.* Death from donor-transmitted malignancy despite emergency liver retransplantation. *Liver Transpl* 2003; 9 (10): 1102-7.
59. de Perrot M, Wigle DA, Pierre AF *et al.* Bronchogenic carcinoma after solid organ transplantation. *Ann Thorac Surg* 2003; 75 (2): 367-71.
60. Nair BT, Bhat SH, Narayan UV *et al.* Donate organs not malignancies: postoperative small cell lung carcinoma in a marginal living kidney donor. *Transplant Proc* 2007; 39 (10): 3477-80.
61. Schroettner P, Gruellich C, Hasskari J *et al.* Achievement of a continuous complete remission in a kidney transplant patient with advanced donor-derived small cell carcinoma. *Transplantation* 2010; 90 (1): 94-5.
62. Bodvarsson S, Burlingham W, Kusaka S *et al.* Donor-derived small cell lung carcinoma in a kidney transplant recipient. *Cancer* 2001; 92 (9): 2429-34.
63. Morath C, Rohmeiss P, Schwenger V *et al.* Transmission of donor-derived small-cell carcinoma cells by a non-tumor-bearing allograft. *Transplantation* 2005; 80 (4): 540-2.
64. Göbel H, Gloy J, Neumann J *et al.* Donor-derived small cell lung carcinoma in a transplanted kidney. *Transplantation* 2007; 84 (6): 800-2.
65. Xiao D, Craig JC, Chapman JR *et al.* Donor cancer transmission in kidney transplantation: a systematic review. *Am J Transplant* 2013; 13(10): 2645-52.
66. Morris-Stiff G, Steel A, Savage P *et al.* Transmission of donor melanoma to multiple organ transplant recipients. *Am J Transplant* 2004; 4 (3): 444-6.
67. Strauss DC, Thomas JM. Transmission of donor melanoma by organ transplantation. *Lancet Oncol* 2010; 11 (8): 790-6.
68. Baehner R, Magrane G, Balassanian R *et al.* Donor origin of neuroendocrine carcinoma in 2 transplant patients determined by molecular cytogenetics. *Hum Pathol* 2000; 31 (11): 1425-9.
69. Foltys D, Linkermann A, Heumann A *et al.* Organ recipients suffering from undifferentiated neuroendocrine small-cell carcinoma of donor origin: a case report. *Transplant Proc* 2009; 41 (6): 2639-42.
70. Begum R, Hamois D, Satyanarayana R *et al.* Retransplantation for donor-derived neuroendocrine tumor. *Liver Transpl* 2011; 17 (1): 83-7.
71. Szalat A, Fraenkel M, Doviner V *et al.* Malignant pheochromocytoma: predictive factors of malignancy and clinical course in 16 patients at a single tertiary medical center. *Endocrine* 2011; 39 (2): 160-6.
72. Linnoila RI, Keiser HR, Steinberg SM *et al.* Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol* 1990; 21 (11): 1168-80.
73. Thompson LD. Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. *Am J Surg Pathol* 2002; 26 (5): 551-66.
74. Pham TH, Moir C, Thompson GB *et al.* Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. *Pediatrics* 2006; 118 (3): 1109-17.
75. Abdalla AH, Rassoul Z, Mousa DH *et al.* A pheochromocytoma in a cadaver kidney donor: to transplant or not to transplant? *Nephrol Dial Transplant* 1996; 11 (10): 2080-2.
76. Sharma S, Wray C, Nourmand H. Anesthetic management for resection of hepatic paraganglioma metastatic from the donor organ in an orthotopic liver transplant recipient: a case report. *Transplant Proc* 2013; 45 (2): 817-19.

77. Fujiwara T, Hosoya Y, Sakuma Y *et al.* Liver transplantation from a living donor with early gastric cancer. *Am J Transplant* 2005; 5 (3): 627-9.
78. Gerstenkorn C, Thomusch O. Transmission of a pancreatic adenocarcinoma to a renal transplant recipient. *Clin Transplant* 2003; 17 (5): 473-6.
79. Yamacake KG, Antonopoulos IM, Piovesan AC *et al.* Donor transmission intestinal carcinoma after kidney transplantation: case report. *Transplant Proc* 2015; 47 (3): 827-30.
80. Lipshutz GS, Mihara N, Wong R *et al.* Death from metastatic donor-derived ovarian cancer in a male kidney transplant recipient. *Am J Transplant* 2009; 9 (2): 428-32.
81. Nickkholgh A, Frey E, Krenzel C *et al.* The need for vigilance in extended criteria donors with a past history of malignancy: a case report and review of literature. *Ann Transplant* 2011; 16 (1): 75-9.
82. Sanchez-Chapado M, Olmedilla G, Cabeza M *et al.* Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study. *Prostate* 2003; 54 (3): 238-47.
83. Yin M, Bastacky S, Chandran U *et al.* Prevalence of incidental prostate cancer in the general population: a study of healthy organ donors. *J Urol* 2008; 179 (3): 892-5; discussion 895.
84. Frutos MA, Daga D, Ruiz P *et al.* Prostate-specific antigen in the assessment of organ donors. *Transplant Proc* 2003; 35 (5): 1644-6.
85. EAU guidelines on prostate cancer 2014 [available from: http://uroweb.org/guideline/prostate-cancer/, accessed: 9 March 2016].
86. D'Errico-Grigioni A, Fiorentino M, Vasuri F *et al.* Expanding the criteria of organ procurement from donors with prostate cancer: the application of the new Italian guidelines. *Am J Transplant* 2010; 10 (8): 1907-11.
87. Loh E, Couch FJ, Hendricksen C *et al.* Development of donor-derived prostate cancer in a recipient following orthotopic heart transplantation. *JAMA* 1997; 277 (2): 133-7.
88. Doerfler A, Tillou X, Le Gal S *et al.* Prostate cancer in deceased organ donors: a review. *Transplant Rev* (Orlando) 2014; 28 (1): 1-5.
89. Serralta AS, Orbis FC, Sanjuan FR *et al.* If the donor had an early-stage genitourinary carcinoma and the liver has already been implanted, should we perform the transplantectomy? *Liver Transpl* 2003; 9 (12): 1281-5.
90. Carver BS, Zibari GB, Venable DD *et al.* Renal cell carcinoma detected in a cadaveric donor after orthotopic liver and contralateral renal transplantation in two recipients: four-year follow-up. *Transplantation* 2001; 71 (9): 1348-9.
91. Sack FU, Lange R, Mehmanesh H *et al.* Transferral of extrathoracic donor neoplasm by the cardiac allograft. *J Heart Lung Transplant* 1997; 16 (3): 298-301.
92. Barrou B, Bitker MO, Delcourt A *et al.* Fate of a renal tubulopapillary adenoma transmitted by an organ donor. *Transplantation* 2001; 72 (3): 540-1.
93. Llamas F, Gallego E, Salinas A *et al.* Sarcomatoid renal cell carcinoma in a renal transplant recipient. *Transplant Proc* 2009; 41 (10): 4422-4.
94. Grimaldi G, Reuter V, Russo P. Bilateral non-familial renal cell carcinoma. *Ann Surg Oncol* 1998; 5 (6): 548-52.
95. EAU guidelines on renal cell carcinoma 2014 [available from: http://uroweb.org/guideline/renal-cell-carcinoma/, accessed: 9 March 2016].
96. Van Poppel H, Da Pozzo L, Albrecht W *et al.* A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2011; 59 (4): 543-52.
97. Yu N, Fu S, Fu Z *et al.* Allotransplanting donor kidneys after resection of a small renal cancer or contralateral healthy kidneys from cadaveric donors with unilateral renal cancer: a systematic review. *Clin Transplant* 2014; 28 (1): 8-15.
98. Nicol DL, Fujita S. Kidneys from patients with small renal tumours: a novel source of kidneys for transplantation. *BJU Int* 2008; 102 (2): 188-92; discussion 192-3.
99. Musquera M, Pérez M, Peri L *et al.* Kidneys from donors with incidental renal tumors: should they be considered acceptable option for transplantation? *Transplantation* 2013; 95 (9): 1129-33.
100. Delahunt B, Cheville JC, Martignoni G *et al.* The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* 2013; 37 (10): 1490-504.
101. Delahunt B, Sika-Paotonu D, Bethwaite PB *et al.* Grading of clear cell renal cell carcinoma should be based on nucleolar prominence. *Am J Surg Pathol* 2011; 35 (8): 1134-9.
102. Sika-Paotonu D, Bethwaite PB, McCredie MR *et al.* Nucleolar grade but not Fuhrman grade is applicable to papillary renal cell carcinoma. *Am J Surg Pathol* 2006; 30 (9): 1091-6.
103. Ortiz JA, Manzarbeitia C, Noto KA *et al.* Extended survival by urgent liver retransplantation after using a first graft with metastasis from initially unrecognized donor sarcoma. *Am J Transplant* 2005; 5 (6): 1559-61.
104. Kreisel D, Engels FH, Krupnick AS *et al.* Emergent lung retransplantation after discovery of two primary

malignancies in the donor. *Transplantation* 2001; 71 (12): 1859-62.

105. Detry O, De Roover A, de Leval L *et al.* Transmission of an undiagnosed sarcoma to recipients of kidney and liver grafts procured in a non-heart-beating donor. *Liver Transpl* 2005; 11 (6): 696-9.
106. Thoning J, Liu Y, Bistrup C *et al.* Transmission of angiosarcomas from a common multiorgan donor to four transplant recipients. *Am J Transplant* 2013; 13 (1): 167-73.
107. Kim JG. Molecular pathogenesis and targeted therapies in well-differentiated thyroid carcinoma. *Endocrinol Metab* (Seoul) 2014; 29 (3): 211-16.
108. Huurman VA, Baranski AG, Groeneveld JH *et al.* Transfer of ureteral carcinoma in a transplanted kidney presenting by early stenosis of the proximal ureter. *Clin Transplant* 2008; 22 (6): 847-50.
109. Ferreira GF, de Oliveira RA, Jorge LB *et al.* Urothelial carcinoma transmission via kidney transplantation. *Nephrol Dial Transplant* 2010; 25 (2): 641-3.
110. Backes AN, Tannuri ACA, de Mello ES *et al.* Transmission of clear cell tumor in a graft liver from cadaveric donor: case report. *Pediatr Transplant* 2012; 16 (8): E352-5.
111. Mannami M, Mannami R, Mitsuhata N *et al.* Last resort for renal transplant recipients, 'restored kidneys' from living donors/patients. *Am J Transplant* 2008; 8 (4): 811-18.
112. Mitsuhata N, Ito S, Mannami M *et al.* Donor kidneys with small renal cell cancer or low-grade lower ureteral cancer can be transplanted. *Transplantation* 2007; 83 (11): 1522-3.
113. Gassel AM, Westphal E, Hansmann ML *et al.* Malignant lymphoma of donor origin after renal transplantation: a case report. *Hum Pathol* 1991; 22 (12): 1291-3.
114. Herzig KA, Falk MC, Jonsson JR *et al.* Novel surveillance and cure of a donor-transmitted lymphoma in a renal allograft recipient. *Transplantation* 2000; 70 (1): 149-52.
115. Harbell JW, Dunn TB, Fauda M *et al.* Transmission of anaplastic large cell lymphoma via organ donation after cardiac death. *Am J Transplant* 2008; 8 (1): 238-44.
116. Dziewanowski K, Drozd R, Parczewski M *et al.* Multiorgan transplantation from a deceased donor with intravascular diffuse large B-cell lymphoma: transmission of the disease and results of treatment. *Clin Transplant* 2014; 28 (10): 1080-3.
117. Kowal M, Hus M, Dmoszynska A *et al.* Acute T cell lymphoblastic leukemia in the recipient of a renal transplant from a donor with malignant lymphoma. *Acta Haematol* 2008; 119 (3): 187-9.
118. Williams T, Aljitawi OS, Moussa R *et al.* First case of donor transmitted non-leukemic promyelocytic sarcoma. *Leuk Lymphoma* 2012; 53 (12): 2530-4.
119. Sosin M, Nassif SR, Girlanda R *et al.* Isolated peritoneal donor-related plasmacytoma 3 years after liver transplantation: a case report. *Am J Transplant* 2014; 14 (2): 472-6.
120. *WHO Classification of tumours of the hemopoietic and lymphoid tissues*. Geneva: WHO Press, 2008.
121. National Cancer Institute. *Chronic myeloproliferative neoplasms treatment – for health professionals*. Bethesda MD, USA: National Cancer Institute, 2015 [available from: www.cancer.gov/types/myeloproliferative/hp/chronic-treatment-pdq, accessed 24 February 2016].
122. Barbui T, Barosi G, Birgegard G *et al.* Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European Leukemia Net. *J Clin Oncol* 2011; 29 (6): 761-70.
123. Pasquier B, Pasquier D, N'Golet A *et al.* Extraneural metastases of astrocytomas and glioblastomas: clinicopathological study of two cases and review of literature. *Cancer* 1980; 45 (1): 112-25.
124. Liwnicz BH, Rubinstein LJ. The pathways of extraneural spread in metastasizing gliomas: a report of three cases and critical review of the literature. *Hum Pathol* 1979; 10 (4): 453-67.
125. Cavaliere R, Schiff D. Donor transmission of primary brain tumors: A neurooncologic perspective. *Transplantation Reviews* 2004; 18 (4): 204-13.
126. Hoffman HJ, Duffner PK. Extraneural metastases of central nervous system tumors. *Cancer* 1985; 56 (Suppl 7): 1778-82.
127. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *Classification of tumours of the central nervous system*, World Health Organization, editor. Lyon: IARC, 2007.
128. Detry O, Honoré P, Hans MF *et al.* Organ donors with primary central nervous system tumor. *Transplantation* 2000; 70 (1): 244-8; discussion 251-2.
129. Lefrançois N, Touraine JL, Cantarovich D *et al.* Transmission of medulloblastoma from cadaver donor to three organ transplant recipients. *Transplant Proc* 1987; 19 (1 Pt 3): 2242.
130. Ruiz JC, Cotorruelo JG, Tudela V *et al.* Transmission of glioblastoma multiforme to two kidney transplant recipients from the same donor in the absence of ventricular shunt. *Transplantation* 1993; 55 (3): 682-3.
131. Colquhoun SD, Robert ME, Shaked A *et al.* Transmission of CNS malignancy by organ transplantation. *Transplantation* 1994; 57 (6): 970-4.
132. Jonas S, Bechstein WO, Lemmens HP *et al.* Liver graft-transmitted glioblastoma multiforme. A case report and experience with 13 multiorgan donors

suffering from primary cerebral neoplasia. *Transpl Int* 1996; 9 (4): 426-9.

133. Bosmans JL, Ysebaert D, De Cock AM *et al.* Interferon-alpha and the cure of metastasis of a malignant meningioma in a kidney allograft recipient: a case report. *Transplant Proc* 1997; 29 (1-2): 838.
134. Frank S, Müller J, Bonk C *et al.* Transmission of glioblastoma multiforme through liver transplantation. *Lancet* 1998; 352 (9121): 31.
135. Armanios MY, Grossman SA, Yang SC *et al.* Transmission of glioblastoma multiforme following bilateral lung transplantation from an affected donor: case study and review of the literature. *Neuro Oncol* 2004; 6 (3): 259-63.
136. Collignon FP, Holland EC, Feng S. Organ donors with malignant gliomas: an update. *Am J Transplant* 2004; 4 (1): 15-21.
137. Kashyap R, Ryan C, Sharma R *et al.* Liver grafts from donors with central nervous system tumors: a single-center perspective. *Liver Transpl* 2009; 15 (10): 1204-8.
138. Zhao P, Strohl A, Gonzalez C *et al.* Donor transmission of pineoblastoma in a two-yr-old male recipient of a multivisceral transplant: a case report. *Pediatr Transplant* 2012; 16 (4): E110-14.
139. Nauen DW, Li QK. Cytological diagnosis of metastatic glioblastoma in the pleural effusion of a lung transplant patient. *Diagn Cytopathol* 2014 Jul; 42 (7): 619-23.
140. Morse JH, Turcotte JG, Merion RM *et al.* Development of a malignant tumor in a liver transplant graft procured from a donor with a cerebral neoplasm. *Transplantation* 1990; 50 (5): 875-7.
141. Chui AK, Herbertt K, Wang LS *et al.* Risk of tumor transmission in transplantation from donors with primary brain tumors: an Australian and New Zealand registry report. *Transplant Proc* 1999; 31 (1-2): 1266-7.
142. Pokorna E, Vitko S. The fate of recipients of organs from donors with diagnosis of primary brain tumor. *Transpl Int* 2001; 14 (5): 346-7.
143. Warrens AN, Birch R, Collett D *et al.* Advising potential recipients on the use of organs from donors with primary central nervous system tumors. *Transplantation* 2012. 93 (4): 348-53.
144. Detry O. Extended criteria donors: the case for liver procurement in donors with a central nervous system malignancy. *Liver Transpl* 2009; 15 (6): 670-1.
145. Berger MS, Baumeister B, Geyer JR *et al.* The risks of metastases from shunting in children with primary central nervous system tumors. *J Neurosurg* 1991; 74 (6): 872-7.
146. Varan A, Sari N, Akalan N *et al.* Extraneural metastasis in intracranial tumors in children: the experience of a single center. *J Neurooncol* 2006; 79 (2): 187-90.
147. Nikitović M, Bokun J, Paripović L *et al.* Bone metastases in medulloblastoma – single institution experience. *Pediatr Hematol Oncol* 2013; 30 (2): 80-91.
148. Metellus P, Barrie M, Figarella-Branger D *et al.* Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients. *Brain* 2007; 130 (Pt 5): 1338-49.
149. Pollack IF, Hurtt M, Pang D *et al.* Dissemination of low grade intracranial astrocytomas in children. *Cancer* 1994; 73 (11): 2869-78.
150. Arulrajah S, Huisman TA. Pilomyxoid astrocytoma of the spinal cord with cerebrospinal fluid and peritoneal metastasis. *Neuropediatrics* 2008. 39 (4): 243-5.
151. Newton HB, Rosenblum MK, Walker RW. Extraneural metastases of infratentorial glioblastoma multiforme to the peritoneal cavity. *Cancer* 1992; 69 (8): 2149-53.
152. Hornik L, Tenderich G, Wlost S *et al.* Organs from donors with primary brain malignancy: the fate of cardiac allograft recipients. *Transplant Proc* 2004; 36 (10): 3133-7.
153. Fecteau AH, Penn I, Hanto DW. Peritoneal metastasis of intracranial glioblastoma via a ventriculoperitoneal shunt preventing organ retrieval: case report and review of the literature. *Clin Transplant* 1998; 12 (4): 348-50.
154. Ostrom QT, Gittleman H, Farah P *et al.* CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol* 2013; 15 (Suppl 2): ii1-56.
155. Robertson T, Koszyca B, Gonzales M. Overview and recent advances in neuropathology. Part 1: Central nervous system tumours. *Pathology* 2011; 43 (2): 88-92.
156. Mazza E, Belli C, Terreni M *et al.* Breast metastases from oligodendroglioma: an unusual extraneural spread in two young women and a review of the literature. *Crit Rev Oncol Hematol* 2013; 88 (3): 564-72.
157. Davis MJ, Hasan F, Weinreb I *et al.* Extraventricular anaplastic ependymoma with metastasis to scalp and neck. *J Neurooncol* 2011; 104 (2): 599-604.
158. Chao MM, Packer RJ, Myseros JS *et al.* Isolated extracranial recurrence of anaplastic ependymoma. *Pediatr Blood Cancer* 2011; 56 (2): 317-18.
159. Kinoshita M, Izumoto S, Kagawa N *et al.* Long-term control of recurrent anaplastic ependymoma with extracranial metastasis: importance of multiple surgery and stereotactic radiosurgery procedures – case report. *Neurol Med Chir* (Tokyo) 2004; 44 (12): 669-73.
160. Newton HB, Henson J, Walker RW. Extraneural metastases in ependymoma. *J Neurooncol* 1992; 14 (2): 135-42.
161. Perez-Bovet J, Rimbau-Munoz J, Martin-Ferrer S. Anaplastic ependymoma with holocordal and

intracranial meningeal carcinomatosis and holospinal bone metastases. *Neurosurgery* 2013; 72 (3): E497-503; discussion E503-4.

162. Schreiber D, Schneider J, Heller T *et al.* [Intracranial ependymoma with extraneural metastases]. *Zentralbl Allg Pathol* 1989; 135 (1): 57-64.
163. Wakabayashi T, Yoshida J, Kuchiwaki H *et al.* [Extraneural metastases of malignant ependymoma inducing atelectasis and superior vena cava syndrome – a case report and review of the literature]. *No Shinkei Geka* 1986; 14 (1): 59-65.
164. Alzahrani A, Alassiri A, Kashgari A *et al.* Extraneural metastasis of an ependymoma: a rare occurrence. *Neuroradiol J* 2014; 27 (2): 175-8.
165. Hussain M, Mallucci C, Abernethy L *et al.* Anaplastic ependymoma with sclerotic bone metastases. *Pediatr Blood Cancer* 2010; 55 (6): 1204-6.
166. Graf M, Blaeker H, Otto HF. Extraneural metastasizing ependymoma of the spinal cord. *Pathol Oncol Res* 1999; 5 (1): 56-60.
167. Valladares JB, Perry RH, Kalbag RM. Malignant choroid plexus papilloma with extraneural metastasis. Case report. *J Neurosurg* 1980; 52 (2): 251-5.
168. Lesoin F, Cama A, Dhellemmes P *et al.* Extraneural metastasis of a pineal tumor. Report of 3 cases and review of the literature. *Eur Neurol* 1987; 27 (1): 55-61.
169. Constantine C, Miller DC, Gardner S *et al.* Osseous metastasis of pineoblastoma: a case report and review of the literature. *J Neurooncol* 2005; 74 (1): 53-7.
170. Charafe-Jauffret E, Lehmann G, Fauchon F *et al.* Vertebral metastases from pineoblastoma. *Arch Pathol Lab Med* 2001; 125 (7): 939-43.
171. Jacobs JJ, Rosenberg AE. Extracranial skeletal metastasis from a pinealoblastoma. A case report and review of the literature. *Clin Orthop Relat Res* 1989; (247): 256-60.
172. Younis GA, Sawaya R, DeMonte F *et al.* Aggressive meningeal tumors: review of a series. *J Neurosurg* 1995; 82 (1): 17-27.
173. Sato M, Matsushima Y, Taguchi J *et al.* [A case of intracranial malignant meningioma with extraneural metastases]. *No Shinkei Geka* 1995; 23 (7): 633-7.
174. Lanfranchi M, Nikpoor N. Detection of meningioma metastasis to liver and lung using somatostatin receptor scintigraphy. *Clin Nucl Med* 2013; 38 (8): 668-70.
175. Alexandru D, Glantz MJ, Kim L *et al.* Pulmonary metastases in patients with recurrent, treatment-resistant meningioma: prognosis and identification by (1)(1)(1) Indium-octreotide imaging. *Cancer* 2011; 117 (19): 4506-11.
176. Scognamiglio G, D'Antonio A, Rossi G *et al.* CD90 expression in atypical meningiomas and meningioma metastasis. *Am J Clin Pathol* 2014; 141 (6): 841-9.
177. Abboud M, Haddad G, Kattar M *et al.* Extraneural metastases from cranial meningioma: a case report. *Radiat Oncol* 2009; (4): 20.
178. Adlakha A, Rao K, Adlakha H *et al.* Meningioma metastatic to the lung. *Mayo Clin Proc* 1999; 74 (11): 1129-33.
179. Cerame MA, Guthikonda M, Kohli CM. Extraneural metastases in gliosarcoma: a case report and review of the literature. *Neurosurgery* 1985; 17 (3): 413-18.
180. Kaneko T, Harada A, Isshiki A *et al.* Hemangiopericytomatous meningioma metastasized to the liver: report of a case and review of the literature. *Surg Today* 1993; 23 (7): 644-8.
181. Hoffman HJ, Yoshida M, Becker LE *et al.* Pineal region tumors in childhood. Experience at the Hospital for Sick Children, 1983. *Pediatr Neurosurg* 1994; 21 (1): 91-103; discussion 104.
182. Yamagami T, Handa H, Takeuchi J *et al.* Choriocarcinoma arising from the pituitary fossa with extracranial metastasis: a review of the literature. *Surg Neurol* 1983; 19 (5): 469-80.
183. Nalesnik MA. DTAC news, 2nd edition, December 2010.
184. Kim B, Woreta T, Chen PH *et al.* Donor-transmitted malignancy in a liver transplant recipient: a case report and review of literature. *Dig Dis Sci* 2013; 58 (5): 1185-90.

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 and donors diagnosed with different inherited diseases and other disorders. Reviewing the endless list of rare diseases in a single chapter is an impossible task. Detailed information on many of these diseases is available at the Orphanet Portal (www.orpha.net), including a brief section about organ donation in the emergency guidelines adapted to take account of many of these rare diseases.

10.2. Poisoning

There are more than 3 000 deaths by poisoning or intoxication per year reported in the United Kingdom. Published data are not sufficient to determine whether these deaths occur under circumstances that would allow diagnosis of brain death and the subsequent recovery of organs. However, most poisoning cases arrive in the hospital still alive and they represent a group of patients in whom organ donation should be considered [1].

Brain death can be the ultimate manifestation of fatal poisoning. The number of cases varies among registries where poisoning is the direct cause of brain death, but the rate is far below 1 %. 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). 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.

Carbon monoxide (CO) is one of the leading causes of fatal poisoning, followed by analgesics, anti-depressants and opioids. There is a great variety of reports on successful transplantation using different 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 summarises case reports, expert opinions and other knowledge in this field [2]. 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 [3]. 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 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). 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 electro-physiological tests (e.g. barbiturates can affect electro-encephalogram results). Other ancillary tests (e.g. evoked potentials) are less influenced by drugs. Primary hypothermia due to secondary complications after poisoning must be corrected before undertaking brain death testing.

Usually in patients admitted to intensive care unit most (or all) of the toxin can be eliminated before brain death diagnosis has been initiated. But when complete detoxification cannot be confirmed or the toxin is still able to influence central nervous system cell function, then interference with electro-physiological measurements should not be ignored.

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. Often the precise toxins involved in poisoning are not known, or there might be poisoning by different toxic substances which interfere with each other to inhibit metabolism while causing secondary cell damage.

g. 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 coexisting behavioural risk factors concerning the acquisition of a potentially transmissible infection (e.g. chronic intravenous drug abuse is associated to a higher probability for recent hepatitis C infection; see Chapter 8, section 8.2).

10.2.1. Basic considerations

Generally, organ donation is considered possible if there is no evidence of functional or structural damage of the organs in question. The organs from 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 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 re-distribution 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 pre-conditions 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 or, alternatively, 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 case of chronic substance abuse, consideration should be given to the risks discussed in Chapter 8 and Chapter 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 or hypoxia arising from the poisoning [2-9].

The kind of toxic agent and the damage caused by it to organs and tissues, directly or indirectly, must be determined in donors with acute poisoning or chronic substance abuse. Elimination of the poison by therapy may limit or avoid further damage. Transmission of the toxic agent to the recipient by a graft or tissue, and consequent side-effects, is more or less a theoretical concern.

Toxin uptake may occur by accident, through suicide or wilfully by a third party.

10.2.2. Poisoning agents

Table 10.1. **Reported cases of toxins and poisons leading to successful organ transplantation following brain stem death**

Organ	Poison
Heart	Barbiturates, benzodiazepines, brodifacoum (rodenticide), carbon monoxide, cyanide, ecstasy, insulin, methanol, paracetamol, venlafaxine
Kidney	Barbiturates, benzodiazepines, brodifacoum, carbon monoxide, cocaine, cyanide, ecstasy, insulin, malathion, methanol, paracetamol, tricyclic antidepressants
Liver	*Amanita phalloides* mushroom, barbiturates, benzodiazepines, brodifacoum, carbon monoxide, cocaine, cyanide, ecstasy, lead, malathion, methaqualone, methanol, tricyclic antidepressants
Lung	Brodifacoum, carbon monoxide, ecstasy, methanol
Pancreas	Brodifacoum, carbon monoxide, cyanide, ecstasy, insulin methanol, paracetamol

Source: Wood DM, Dargan PI, Jones AL. Poisoned patients as potential organ donors: postal survey of transplant centres and intensive care units [1].

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*. 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 (> 2000 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. Burning
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 case of certified brain death.

d. 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 [8-9].
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.

e. Chemical solvents
This requires 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.

f. Cocaine
This narcotic causes early atherosclerotic lesions and also dilated cardiomyopathy in case 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. 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. 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). A careful study of the donor case history is advised. 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. Some authors suggest that, in organ donors with a history of cocaine use, a coronary angiography should always be performed to document coronary anatomy before heart transplantation.

g. Cyanide

Cyanide is rapidly absorbed through the skin and can lead to irreversible inhibition of mitochondrial cytochrome oxidase. The toxicity of cyanide may be reversed rapidly by specific therapy (hydroxocobalamin). 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.

h. Ethylene glycol (see also methanol)

Ethylene glycol (EG) 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 EG) 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. EG poisoning may occur in combination with methanol.

i. 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.

j. Ethanol

All organs may be used, except for those confirmed with organ damage related to chronic abuse.

k. 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.

l. Lead

This will probably never occur, with prolonged discussion on what could be a non-toxic lead level in donor or recipient. Heavy metal poisoning is not generally compatible with donation.

m. Methanol (see also 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.

n. 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, 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.

o. Organophosphate pesticides

This requires 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) [5].

p. 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.

q. Rodenticides (dicoumarin) and other anticoagulants

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.

r. Selective serotonin re-uptake inhibitors

Fatalities following selective serotonin re-uptake inhibitors (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).

s. Smoke inhalation

This 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).

t. 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].

10.3. Inherited or congenital diseases

Many lethal incidents occur independently of genetic disorders or inherited disease, where organ donation must be considered. But some genetic disorders 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 metabolism except for the one linked to the liver tissue and therefore they may be a major cause for contraindicating liver transplantation. 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 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 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 it remains a growing summary of guidelines for an endless list of rare diseases. International case references can also be found at www.rarediseases.org/rare-disease-information/rare-diseases or http://ghr.nlm.nih.gov/BrowseConditions.

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 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 [10], and may require re-transplantation. In some heterozygous defects, the disease may only manifest in the recipient, for example Protein S deficiency [11]. Genetic disorders should be considered when assessing donors with known thrombocytopenia, 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 hyperammonemia in a brain dead person suggests a disorder of the urea cycle such as ornithine transcarbamylase deficiency. Although this deficiency is a contraindication for liver donation, this does not extend to other organs such as kidneys, as these organs are not affected by the disease [12].

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 [13].

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:

- 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.
- 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.
- 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 inter-disciplinary approach. As a rule of thumb, donors that have survived for many decades with a genetic defect will not have multi-organ damage, while such damage must be considered in very young donors.

Helpful links: www.orpha.net, www.rarediseases.org and http://ghr.nlm.nih.gov/BrowseConditions/.

Table 10.2. **Examples of successful/unsuccessful donation in cases of inherited, congenital or otherwise acquired disease**

Disease	Organs	Comment
Rendu–Osler–Weber syndrome	Kidney [21]	Successful transplantation is reported.
HELLP syndrome	Kidney [22]	Successful transplantation is reported.
Domino transplantation (re-use of recipient's organ as graft)	Heart [23]	Without structural or functional impairment grafts from heart-lung recipients can be used.
	Liver [23] [30]	Acceptable outcome in mid-term in case of familial amyloid polyneuopathy, fibrinogen An *a*-chain amyloidosis, maple syrup disease, familial hypercholesterolaemia with proper care. Serious adverse outcome in case of hyperoxaluria, acute intermittend porphyria, apolipoprotein A1 amyloidosis, lysozyme amyloidosis, acute intermittent porphyria.
IgA-Nephropathy	Kidney [24]	Depending on the degree of kidney damage the graft may be used, since immune-suppressive therapy may be therapy of original disease.
	Other organs	Can be used for transplantation.
Moyamoya disease	Heart, kidney, liver, lung [25]	After exclusion of defects in other organs due to vascular defects transplantation is possible.
Reye syndrome	Kidney, lung [26]	Successful transplantation is reported.
Gilbert syndrome	Liver [27] [30]	Gene defect causes unconjugated hyperbilirubinemia. Impaired long term outcome not observed.
Horseshoe kidney	Kidney [28]	Different vascular in- and outflow observed with a range known from one graft procured with aortic and/or caval patch due to multiple vessels, to splitting into two grafts after proper identification of a safe dissection area in the parenchmal bridge. Usually this condition is associated with vascular anomality to liver and pancreas, which is challenging at procurement.
	Other organs	
Situs inversus totalis	Liver [29]	Except for challenges associated with procurement and implantion, no adverse events should be expected.
	Other organs	
Bleeding disorders	Liver [30]	In cases with isolated factor XII, VII, XI deficency in short term, no adverse events are observed (haemophilia A should be excluded).
	Other organs	Can be used for transplantation.

Disease	Organs	Comment
Thrombotic disorders	Liver [30]	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.
	Other organs	Can be used for transplantation.
Hereditary haemochromatosis	Liver [30]	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 Deficiency	Liver [12] [30] [anti-coagulation]	Fatal outcome in deceased donation.
	Other organs	Can be used for transplantation.
Alpha-1-antitrypsin deficiency	Liver [30]	Very likely to develop cirrhosis or fibrosis with intermediate retransplantation necessary; no long-term follow-up.

10.3.2. Examples of inherited disorders in cases of organ donation

a. Familiar amyloid polyneuropathy

A remarkable example of genetic disorders affecting the question of graft use is familiar amyloid polyneuropathy (FAP). 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 on-going 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 among two recipients) waiting for liver transplant in a so-called domino liver transplantation procedure [14-17]. However, FAP is, without exception, ultimately transmitted to these domino transplant recipients and clinically manifests after a variable time period [6]. Since liver transplantation is nowadays associated with graft survival of more than 25 years, careful consideration of recipient selection criteria is recommended in cases of FAP-related domino transplants in specialised centres. In cases of high probability of re-transplantation (within 10 to 20 years), transmission of FAP will be an unavoidable but acceptable risk because FAP will not manifest before the graft has to be exchanged.

b. Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is not a contraindication to organ donation; even polycystic liver and kidneys can be considered for transplant. 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 [18]. 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 [19]. 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, such as Factor V Leiden mutation

Affected patients with recurrent thrombosis need anti-coagulation therapy, thereby exposing them to the risk of intra-cerebral 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.

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. 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 [20].

g. Defects in specific cell structures (e.g. mitochondria)

Damage to specific cell structures will typically impair all organs. Transferring such defects to an eligible recipient is high risk and requires an individualised decision in consultation with experts. In particular, it is challenging when paediatric intensive care units present a potential infant donor having such cell defects. Consultation with experts having knowledge of long-term survivorship is essential.

h. Neurofibromatosis

The term neurofibromatosis refers to multiple 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 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

i. 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 [21-30].

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 thrombocytopenia) [31]. 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 [32]. Due to immune-suppressive treatment in the recipient, an imbalance between donor-type B-cell and T-lymphocyte activation and inhibition occurs, which may permit transient stimulation of donor-type B-lymphocytes producing antibodies transmitted with an organ. Such effects can either be mitigated or aggravated by immuno-suppression according to the different individual host-versus-graft and graft-versus-host responses in the recipient in addition to the various genetic susceptibility factors between different autoimmune conditions in the host and/or graft. 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 that passenger lymphocytes from the donor may cause in the recipient due to minor ABO blood group donor–recipient mismatch or previous immunisation of the donor against other erythrocyte antigens [33].

Although such (transient) complications of post-transplant autoimmunity are rare, awareness about this issue, early identification and appropriate treatment are important in patients at risk.

Organs from donors with autoimmune diseases can be transplanted when relevant organ damage can be excluded. This must be considered individually for each organ. 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 emer-

gency guidelines provided by www.orpha.net or by application of the algorithm provided in Table 7.1 (see Chapter 7, section 7.2).

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 lymphocytes 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 [34-40]. 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. 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 (long-term persisting).

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 from a donor with known allergies (e.g. food allergy with anaphylactic reactions), recipients should be instructed to avoid exposure to such allergens unless harm can be excluded after controlled exposure tests, since skin prick tests are not sensitive enough to properly exclude the risk.

Due to post-transplant immuno-suppression, recipients may acquire *de novo* allergies which are related to the graft and to the kind of immuno-suppression received, such as tacrolimus or cyclosporine [41], but not to the issue of passive transfer from donor to recipient via donor lymphocytes or mast cells contained in the graft.

In the case of known anaphylactic reactions in the donor history, this information must be included in the donor characterisation (section autoimmune issues).
Lung, liver and probably intestinal transplant recipients should be taught to avoid such allergen exposure (especially in cases of 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.

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 leukoencephalopathy, 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,

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.

10.8. References

1. Wood DM, Dargan PI, Jones AL. Poisoned patients as potential organ donors: postal survey of transplant centres and intensive care units. *Crit Care* 2003; (7): 147-54. (© Wood *et al.*, licensee BioMed Central Ltd. This is an Open Access article: verbatim copying and redistribution of this article are permitted in all media for any purpose, provided this notice is preserved along with the article's original URL.) Available at: http://ccforum.biomedcentral.com/articles/10.1186/cc1880, accessed 10 August 2016.
2. Hantson P. Organ procurement from poisoned donors. PhD thesis, Université Catholique de Louvain, Bruxelles, 1999.
3. Costanzo MR, Dipachand A, Starling R *et al.* The International Society for Heart and Lung Transplantation guidelines for the care of heart transplant recipients. Task force 1: Peri-operative care of the heart transplant recipient. *J Heart Lung Transpl* 2010; (29): 914-56.
4. Caballero F, López-Navidad A, Coturruelo J *et al.* Ecstasy-induced brain death and acute hepatocellular failure: multiorgan donor and liver transplantation. *Transplantation* 2002; (74): 532-7.
5. Mariage JL, Galliant A, Hantson P. Organ donation following fatal organophosphate poisoning. *Transpl Int* 2012; (25): e71-2.
6. Leikin JB, Heyn-Lamb R, Aks S *et al.* The toxic patient as a potential organ donor. *Am J Emerg Med* 1994; (12): 151-4.
7. Tenderich G, Koerner MM, Posival H *et al.* Hemodynamic follow-up of cardiac allografts from poisoned donors. *Transplantation* 1998; (66): 1163-7.
8. Luckraz H, Tsui SS, Parameshwar J *et al.* Improved outcome with organs from carbon monoxide poisoned donors for intrathoracic transplantation. *Ann Thorac Surg* 2001; (72): 709-13.
9. Komokata T, Nishida S, Ganz S *et al.* The impact of donor chemical overdose on the outcome of liver transplantation. *Transplantation* 2003; (76): 705-8.
10. Plöchl W, Spiss CK, Plöchl E. Death after transplantation of a liver from a donor with unrecognized ornithine transcarbamylase deficiency. *N Engl J Med* 1999; (341): 921-2.
11. Schuetze S, Linenberge M. Acquired protein S deficiency with multiple thrombotic complications after orthotopic liver transplant. *Transplantation* 1999; (67): 1366-9.
12. Caballero F, Ris J, Puig M *et al.* Successful kidney transplantation from a brain-dead donor with ornithine transcarbamylase deficiency. *Transplantation* 2013; (96): e63-4.
13. Morioka D, Takada Y, Kasahara M *et al.* Living donor liver transplantation for noncirrhotic inheritable metabolic liver diseases: impact of the use of heterozygous donors. *Transplantation* 2005; (80): 623-8.
14. Furtado AJ. Domino liver transplantation using FAP grafts. HUC experience – hopes and realities. *Amyloid* 2003; 10 (Suppl 1): 84-7.
15. Herlenius G, Wilczek H, Larrson M *et al.* Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation* 2004; (77): 64-71.
16. Adams D, Samuel D, Slama M. Liver transplantation for familiar amyloid polyneuropathy. *Presse Med* 2010; (39): 17-25.
17. Adams D, Samuel D, Slama M. Treatment of familial amyloid polyneuropathy. *Presse Med* 2012: (41): 793-806.
18. Olsburgh JD, Godbole HC, O'Donnell PJ *et al.* Transplantation of kidneys from deceased adult polycytic donors. *Am J Transplant* 2006; (6): 2809-11.
19. Caballero F, Domingo P, López-Navidad A. Successful liver transplantation using a polycystic donor liver. *J Hepatol* 1997; (26): 1428.
20. Hisatake GM, Chen TW, Renz JF *et al.* Acquired hemophilia A after liver transplantation. *Liver Transpl* 2003; (9): 523-6.
21. Caballero F, Leal J, Puig M *et al.* Organ donation and Rendu-Osler-Weber syndrome. *Transplantation* 2013; (95): e47-8.
22. Flynn MF, Power RE, Murphy DM *et al.* Successful transplantation of kidneys from a donor with HELLP syndrome. *Transpl Int* 2001; (14): 108-10.
23. Lowell JA, Smith CR, Brennan DC *et al.* The domino transplant: transplant recipients as organ donors. *Transplantation* 2000; (69): 372-6.
24. Koselj M, Rott T, Vizjak A *et al.* IgA nephropathy as a donor transmitted disease in renal transplant recipients. *Transplant Proc* 1991; (23): 2643-6.
25. Diaz-Guzman E, Neltner JM, Hoopes CW. Organ donation and Moyamoya disease. *Am J Transplant* 2012; (12): 1353-5.
26. Firlit CF, Jonasson O, Kahan BD *et al.* Reye syndrome cadaveric kidneys: their use in human transplantation. *Arch Surg* 1974; (109): 797.
27. Kaneko J, Sugawara Y, Maruo Y *et al.* Liver transplantation using donors with Gilbert syndrome. *Transplantation* 2006; (82): 282-5.

28. Pontinen T, Khanmoradi K, Kumar A *et al.* Horseshoe kidneys: an underutilized resource in kidney transplant. *Exp Clin Transplant* 2010; (8): 74-8.
29. Sun XY, Qin K, Dong JH *et al.* Liver transplantation using a graft from a donor with situs inversus totalis: a case report and review of the literature. *Case Rep Transplant* 2013; 2013: 532865.
30. Schielke A, Filomena C, Goumard C *et al.* Liver transplantation using grafts with rare metabolic disorders. *Dig Liver Dis* 2015; (47): 261-70.
31. Friend PJ, McCarthy LJ, Filo RS *et al.* Transmission of idiopathic (autoimmune) thrombocytopenic purpura by liver transplantation. *N Engl J Med* 1990; (323): 807-11.
32. Bradely V, Kemp EH, Dickinson C *et al.* Vitiligo following a combined liver-kidney transplant. *Nephrol Dial Transplant* 2009; (24): 686-8.
33. Nadarajah L, Ashmann N, Thuraisinghma R *et al.* Literature review of passenger lymphocyte following renal transplantation and two case reports. *Am J Transplant* 2013; (13): 1594-1600.
34. Chehad M, Nowak-Wegrzyn A, Kaufmann SS *et al.* *De novo* food allergy after intestinal transplantation; a report of three cases. *J Pediatr Gastroneterol Nutr* 2004; (38): 545-7.
35. Legendre C, Caillat-Zucman S, Samuel D *et al.* Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med* 1997; (337): 822-4.
36. Phan TG, Strasser SI, Koorey D *et al.* Passive transfer of nut allergy after liver transplantation. *Arch Intern Med* 2003; (163): 237-9.
37. Khalid I, Zoratti E, Stagner L *et al.* Transfer of peanut allergy from the donor to a lung transplant recipient. *J Heart Lung Transplant* 2008; (27): 1162-4.
38. Boyle RJ, Hardikar W, Tang ML. The development of food allergy after liver transplantation. *Liver Transpl* 2005; (11): 326-30.
39. Schuller A, Barnig C, Matau C *et al.* Transfer of peanut allergy following lung transplantation. A case report. *Transplant Proc* 2011; (43): 4032-5.
40. Dewachter P, Vézinet C, Nicaise-Roland P *et al.* Passive transient transfer of peanuts allergy by liver transplantation. *Am J Transplant* 2011; (11): 1531-4.
41. Öner Özdemir. New developments in transplant-acquired allergies. *World J Transplant* 2013; (24): 30-5.

Chapter 11. Organ procurement, preservation and transportation

11.1. Introduction

There are a number of key components in a high quality organ procurement, preservation and transport programme to enable recovery teams to procure donated organs and to preserve and transport them safely for transplantation [1].

But we know that opportunities for transplantation are lost during all stages of the pathway from offering to implantation. In most cases, there are clearly valid clinical reasons for this loss of opportunity such as a brain death testing that cannot be done because the potential donor remains unstable, or the organ may be unsuitable, such as a fatty liver that would not function if transplanted. In other cases, the reasons are less clear.

The procurement team is responsible for recovering those organs suitable for transplantation for which consent has been given and for which a suitable recipient has been identified. This requires clear written procurement protocols, covering where appropriate Donation after Brain Death (DBD) and Donation after Circulatory Death (DCD).

The European Commission is funding the Cope Consortium – the official organ preservation task force of the European Society for Organ Transplantation (ESOT). The Consortium is working on improving preservation and reconditioning strategies for kidney and liver organs procured for transplant. It aims to advance and develop organ preservation technologies by testing a number of novel clinical approaches to repairing and preserving high-risk donor organs, investigating novel scientific approaches to organ repair and regeneration and developing new methods to measure and predict the viability and outcome of donated organs and ultimately develop and implement new medical therapies and devices in organ transplantation.

This chapter provides guidance on procurement, preservation and transportation of donor organs. Further information is available in a number of guidance documents, some of which have been referenced throughout this Guide.

11.2. Facilities, personnel and equipment for organ procurements

Deceased donation is a complex process. There is a range of actions that must be taken which 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 hospital level has been identified as the most important

step towards supporting organ donation [2]. The main tasks of the donor co-ordinator are: the identification of a potential donor, alerting the procurement team and supporting the procurement and allocation of organs to enable more people to benefit from a transplant. Chapter 2 gives more information about the identification of potential deceased donors. In summary, some patients will die following an unexpected cardiac arrest, and may be suitable as 'uncontrolled' DCD donors (Maastricht categories I and II) [3]. Some patients may be diagnosed dead by neurological criteria before referral for organ recovery, or patients may be admitted to intensive care where brain death will be confirmed (potential DBD donors). 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) [3]. For various reasons, countries may procure organs from Maastricht category II donors rather than III, or vice versa. However, it is vital that particular attention is given to the donor management, organ procurement and preservation of extended criteria donors. This has been summarised in the *Critical Pathway for Organ Donation* at the Third WHO Global Consultation on organ donation and transplantation, held in Madrid in March 2010 [4].

Chapters 1, 4, 5, 6, and 7 give further information about the role of the donor co-ordinator. In some countries the job is undertaken by one individual, in other countries, by a team with specific roles within the process. These could include co-ordinating action to optimise all opportunities for deceased 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, with the surgical teams for recovery and with the potential recipient surgical team for transplantation. The donor co-ordinator may also arrange theatre availability for procurement, provide follow-up for donor families and data and 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 effective recovery, allocation and transport arrangements are put in place. This requires good co-ordination to manage the timing of the abdominal and cardio-thoracic 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 [5]. Some countries may only authorise or license specific hospitals for organ procurement (e.g. in European Union Member States, as specified in Directive 2010/53/EU).

11.2.3. Procurement teams

It is recommended where possible that fully staffed on-call procurement teams be available 24/7 for organ recovery. Teams will include an experienced surgeon(s) who is able to procure specific organs, an assisting surgeon, a co-ordinator who monitors the donation process and a technician to support organ perfusion and preservation. The composition of the team will vary in terms of personnel coming from the 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 retrieval team and their roles within the recovery process. It is essential to perform the entire recovery procedure in a competent 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 recovery task, including the use of novel technologies for perfusion and preservation where necessary. In some member states, adequate training and certification for organ recovery surgery has become normal practice.

11.3. Multi-organ procurement procedures

Each procurement team/transplant centre must have clear written protocols for both DCD and DBD recovery. 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 which might impact on other donated organs, e.g. the use of hypothermic or normothermic regional perfusion as the *in situ* preservation strategy in a DCD procedure (see Chapter 12).

The procedure usually begins with a laparotomy and, if the chest is opened, a thorough inspection of the thoracic organs should be undertaken to exclude malignancy and any other pathology which might mean the organs cannot be used for transplant. 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 and also in DBD donors who are haemodynamically unstable. A less hasty, more considered approach to multi-organ recovery, with examination and preservation of vascular structures, is typically performed in stable DBD donors. In donors with excellent liver function, *in situ* splitting of the liver could 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.

For the recovery of thoracic organs, inspection and dissection of the thoracic organs 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.

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 if 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; 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 and should be recovered first. 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.

The procurement team is responsible for the 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 sensitive disposal of the body.

Any damage (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 recovery 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 for another potential recipient in another transplant centre if necessary.

In the case of unexpected anatomical findings, additional examinations, for example through biopsies, should be performed and the recipient team informed about any findings.

11.4. Organ preservation

Recovered organs should be flushed with suitable and sufficient preservation fluid while keeping the organ cool in order to slow down its metabolism. There are a number of preservation solutions available [6]. Some have been used for cardiothoracic organ preservation and others are restricted for use in abdominal organs. 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 within the national settings 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 recovery. The solutions should be specified in the standard operating procedures (SOPs) 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 SOPs. 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 technologies for organ perfusion and preservation

For many years, and in most transplant centres in Europe, cold perfusion of donor organs has been the usual organ preservation method. However, studies are in progress on optimal temperature, preservation solutions and preservation techniques [7-8]. In the light of the worldwide shortage of deceased-donor organs and consequently the increasing use of DCD donors and extended criteria donors, several novel technologies are being evaluated to see whether their use will result in more organs being transplanted. These evaluations include assessment of the potential novel technologies set out below, for each individual organ, considering their costs and benefits, including the effect on hospital stay, on readmission rates, delayed graft function and rejection rates.

a. Normothermic regional perfusion
In situ perfusion of the abdominal organs, in the DCD donor before and at the time of organ recovery (see Chapter 12).

b. *Ex vivo* perfusion
On the bench, once the organ has been transported to the transplant centre. This includes *ex vivo* normothermic perfusion and *ex vivo* hypothermic perfusion.

c. Machine preservation
Including transport:
   i. Hypothermic machine preservation.
   ii. Hypothermic machine preservation with the delivery of oxygen.
   iii. Normothermic oxygenated machine preservation.

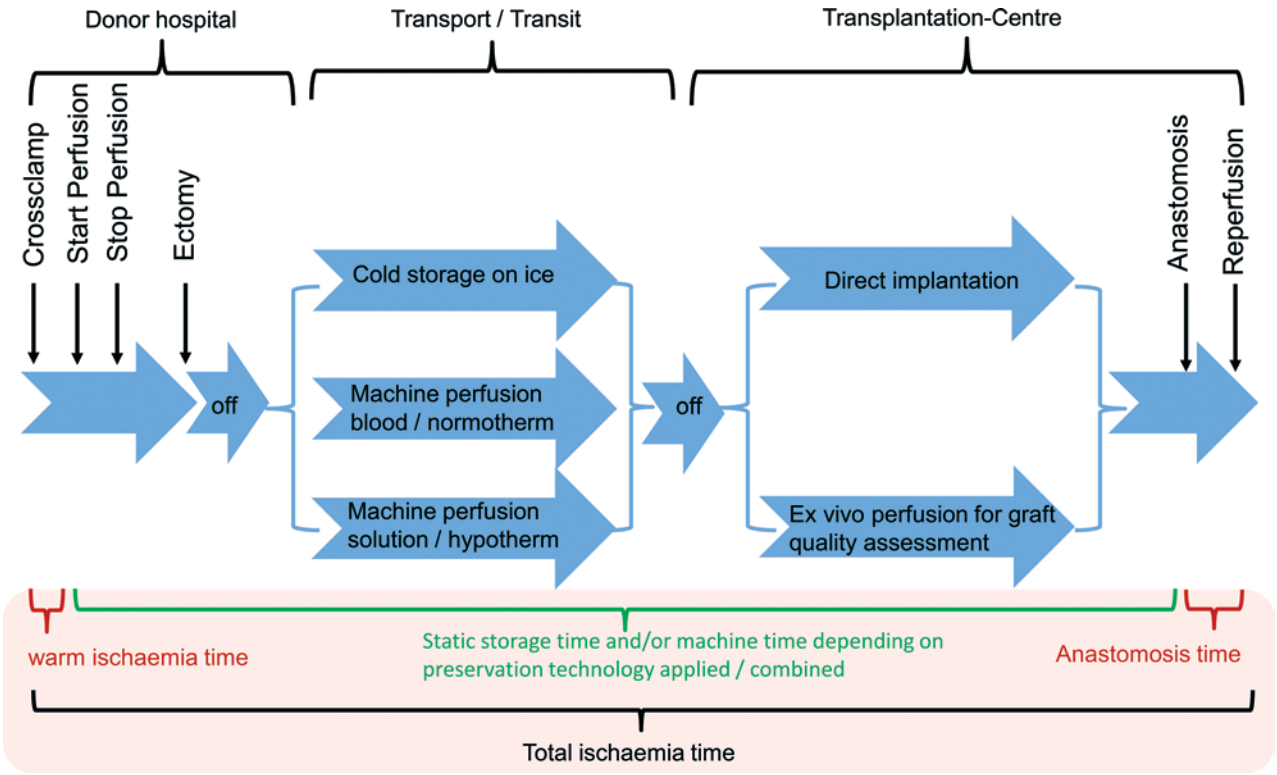
In the UK, NHS Blood and Transplant has undertaken an evaluation of the current status of novel technologies in organ transplantation [10]. Within the next few years it will become clearer whether organ preservation and utilisation can be optimised by using normothermic and/or hypothermic modalities to optimise patient and graft survival.

11.4.2. Ischaemic times

This chapter does not recommend optimal cold ischaemia times. Much will depend for example on the specific organ, age and co-morbidities of the donor [11] 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 transplant.

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 the transit from the donor hospital to the transplantation centre, the organ is stored either in static cold solution or it is put on a preservation machine and flushed by different kinds of solutions and technologies with different aims, e.g. expanding the transport time without harm or eval-

Figure 11.1. **Events during ischaemia**



uation of 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.

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.

11.5. Packaging and transportation of organs

11.5.1. Organ packaging

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 down 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 plane). 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, whilst preserving the anonymity of the donor.

Labelling should include, as a minimum, the following: anonymised donor identification;

a. Contents of the package, including the type of organ/tissue and, where appropriate, whether it is the right or left organ.
b. Address of destination, including details of the person to be notified upon arrival.
c. Address of the shipping institution and details of the person to be notified in the event of unexpected complications.
d. Recommended transport conditions, including instructions for keeping the container at an appropriate temperature and position, as well as a 'HANDLE WITH CARE' mark.

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'). There are vessels and potentially other donor material that are essential for the graft to be transplantable. They should be clearly identified within the package label. The outer organ transport box should be properly sealed [5].

The surgeons and co-ordinators responsible for the organ recovery and transplantation should be notified of the progress and results of all procedures pertinent to the organ recovery operation. In cases of delay or unexpected findings, the recipient centres should be informed. Detailed organ documentation should include:

a. blood group of donor;
b. place of donation;
c. time and date of donation;
d. time of perfusion or organ preservation;
e. anonymous medical details of the donor and recovery process;
f. detailed descriptions of the graft anatomy and a full report of any damage;
g. type and volume of preservation fluid and start of ischaemia time;
h. members of the recovery team.

11.5.2. Organ transport

For transport between hospitals, shipping containers should conform to local, national and international regulations [12]. Transit times should be minimised and cold storage (where appropriate) must be maintained throughout transit. The means and route of transportation should be properly 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

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 [5]. Organ procurement and allocation organisations must also 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 problems that may arise during recovery 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 (see Chapter 14), feedback (see section 11.5.4) and quality assurance (see Chapter 15) to ensure that any serious adverse reactions/events can be reported, monitored and acted on as appropriate. Careful follow-up and documentation of transplant outcomes is a pre-requisite 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 recovery, 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 received and inspected, to the recovery team. Any injuries or missed abnormalities should be included to enhance quality and competency. In several member states, such quality circles are now available for other member states to adopt.

Table 11.1. **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.*)**

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)

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 11.1 [13]. Appendix 10 includes another example for evaluating organ recovery.

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 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.

11.7. References

1. Organ Procurement Committee of Eurotransplant Foundation. *Eurotransplant Manual*, Chapter 9: The donor. Leiden, The Netherlands: Eurotransplant Foundation (version 3.0. 2013-03-05) [available from: www.eurotransplant.org/cms/mediaobject.php?file=Chapter9_thedonor7.pdf, accessed: 30 January 2016].
2. Commission of the European Communities. Communication from the Commission: Action Plan on Organ Donation and Transplantation (2009-2015): strengthened cooperation between member states. Brussels: Commission of the European Communities, 2008 [available from: http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_action_en.pdf, accessed: 30 January 2016].
3. Koostra G, Deamen JH, Oomen AP. Categories of non-heart-beating donors. *Transpl Proc* 1995; (27): 2893-4.
4. Domínguez-Gil B, Delmonico F, Faissal AM *et al.* The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. *Transplant Int* 2011; (24): 373-8.
5. Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. *Official Journal of the European Union*. 2010; (53): 14-29.
6. Council of Europe, editors. Solutions for organ preservation, Monograph 1264, Ph. Eur. 7th edition. Strasbourg, France: Council of Europe; 2011 (vol. 2).
7. Moers C, Smits J, Maathuis MH *et al.* Machine perfusion or cold-storage in deceased donor kidney transplantation. *N Engl J Med* 2009; (360): 7-19.
8. Watson C, Wells A, Roberts R *et al.* Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multi-center randomized control trial. *Am J Transplant* 2010; (10): 1991-9.
9. Moers C, Pirenne J, Paul A *et al.* Machine perfusion or cold storage in deceased donor kidney transplantation. *N Engl J Med* 2012; (366): 770-1.
10. *NHS Blood and Transplant evaluation of the current status of the novel technologies in organ transplantation*. NHS Blood and Transplant, Bristol, UK, 2014 [available from: www.nhsbt.nhs.uk/news-and-media/news-articles/news_2014_11_14_2.asp, accessed 24 April 2015].
11. Frühauf NR, Fischer-Fröhlich CL, Kutschmann M *et al.* Joint impact of donor and recipient parameters on the outcome of liver transplantation in Germany. *Transplantation* 2011; (92): 1378-84.
12. Conrad R, Polster F, Wesslau C *et al.* Validation of transport systems for abdominal organs intended for transplantation. *Organs, Tissues and Cells*. 2010; (11): 171-8.
13. National Standards for Organ Retrieval from Deceased Donors. NHS Blood and Transplant, Bristol, UK, 2013 [available from: www.bts.org.uk/Documents/9.1.13%20Retrieval%20Standards%20

Document%20v2%206%20effective%20010113.pdf, accessed: 30 January 2016].

Related document: Appendix 10. Proposal for auditing retrievals (NHS Blood and Transplant, United Kingdom, English-language version).

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 neurologic activities, i.e. donation after brain death (DBD). However, the shortage of organs to cope with the transplant needs of patients has led to a renewed interest in donation from persons whose death has been determined by circulatory criteria, i.e. Donation after Circulatory Death (DCD).

The first attempt to classify DCD donors dates from 1995, when the first International Workshop on what was then called 'non-heart-beating donation' took place in Maastricht (Netherlands) [1]. As Table 12.1 shows, DCD donors were classified in one of four categories depending on the circumstances of death, each category determining the specificities of the DCD-related process to follow.

The Maastricht classification has since been updated at a dedicated conference held in Paris (France) in February 2013 (see Table 12.1) and can be described thus:

a. Category I: Donation from persons who have suffered a cardiac arrest and in whom cardiopulmonary resuscitation (CPR) is not attempted for obvious 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 attempts at CPR have been exhausted and deemed unsuccessful by the attending team. This type of donation includes two subcategories:

i. Category IIa: cardiac arrest occurred out of hospital. The moment of loss of consciousness is documented and the duration of cardiac arrest can be estimated. Emergency services try to revive the patient, but according to international standards (American Heart Association, European Resuscitation Council and International Liaison Committee on Resuscitation), cardiac arrest is considered irreversible.

ii. Category IIb: cardiac arrest has occurred in a hospitalised patient (e.g. emergency room, hospital ward), with otherwise similar settings to category IIa. Donation is often unlikely due to advanced age and/or other co-morbidities.

c. Category III: Donation from patients in whom a 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 who suffer 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). Category IV donation may also be considered after planned aborted donor management to ac-

commodate the possibility of donation, when the DBD process cannot be developed (e.g. in countries where the determination of death based on neurologic criteria is not accepted yet and on occasions when the family wish to be with the donor at the time of cessation of the heartbeat).

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 an 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 [2]. This is due to legal and ethical obstacles in countries where legislation does not enable this type of donation. In other settings, DCD has not evolved due to the lack of technical expertise or organisational capability. There are also considerable differences in the practice of DCD between countries [3]. In Australia, Belgium, the Netherlands, the United Kingdom and the United States, DCD donors are predominantly controlled, whereas in Spain and France DCD donors are most commonly uncontrolled (although both countries have also recently embarked on cDCD programmes). The fact that countries have focused on one specific type of DCD may be related to different legislations, ethical concerns, practices at the end-of-life (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 [4]. Countries engaging in these activites need to discuss various legal and logistic 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 of practice. 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 of the steps of the different processes, provided that this activity is possible within a given jurisdiction.

12.2. Uncontrolled donation after circulatory death

Uncontrolled donation after circulatory death (uDCD) refers to donation from persons whose death has occurred following an unexpected cardiac arrest and who have not been successfully resuscitated.

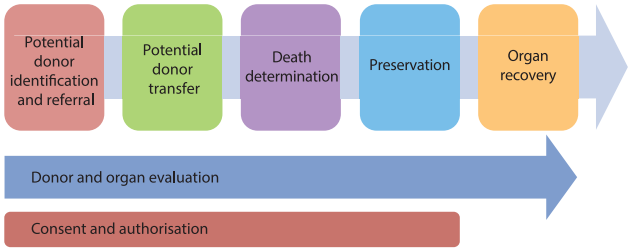
uDCD should be developed under clear national regulations and protocols at every emergency service and hospital engaged in this activity. Smooth co-operation between specially trained and equipped out-of-hospital emergency services (OHES) and a hospital with adequate infrastructure is essential.

Although this type of donation can substantially increase the potential donor pool, it is still restricted to a few countries. France and Spain have the largest experience with uDCD, although it has also been developed in other countries such as Belgium, Italy and the Netherlands or more recently in Portugal, Russia and Scotland.

Excellent long-term kidney graft survival has been reported from uDCD procedures, despite an increased incidence of delayed graft function (DGF) [5-17]. The results of liver transplant are mixed and do not consistently provide similar outcomes compared with livers from DBD donors, mainly due to a higher incidence of primary graft dysfunction, graft

non-function and biliary complications [18-23]. There is only limited experience in uDCD lung transplantation, however encouraging the preliminary results are [24-26].

Figure 12.1. **The process of uncontrolled donation after circulatory death**



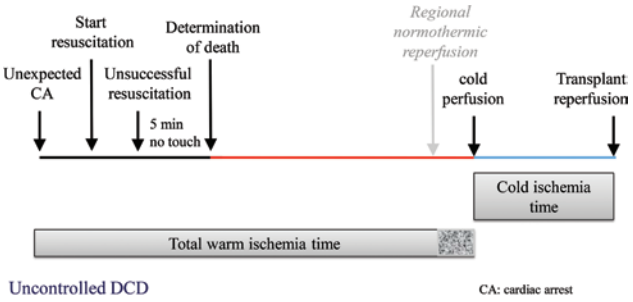
This section describes key aspects for successful realisation of every step of the process of uDCD, particularly category IIa (see Figure 12.1), noting that the IIb process would be identical, except for the absence of an out-of-hospital stage and the step of donor transfer. Category IIa uDCD donors can be considered excellent for a variety of reasons. First, the application of very strict selection criteria usually translates into good quality organs. Second, donors are usually healthy individuals with a normal lifestyle until sudden death. Third, they have not been previously admitted to an intensive care unit (ICU) with the consequent risk of nosocomial infections and neither have they undergone a period of brain death during which many neuro-endocrine and haemodynamic alterations take place with possible detrimental effects on the organs to be transplanted (see Chapter 5). Counterbalancing these considerations, uDCD donors are considered to have expanded criteria because of the deleterious effect of warm ischaemia. There is also the risk of being unable to obtain all medical data precisely 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 organ.

The process of uDCD is summarised according to its key steps in Figure 12.1. The complementary Figure 12.2 marks the limits of warm ischaemia time (WIT) and cold ischaemia time (CIT). For definitions of WIT see section 12.3.6.1.

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 according to international standards and deemed unsuccessful by the attending team – this will also include novel CPR techniques if these are components of specific local CPR protocols [27, 28]. Potential donors should be medically suitable based on similar criteria to those applied in the DBD process. In addition, some specific selection criteria need to be met and there are limits to the interval between cardiac arrest and initiation of *in situ* preservation strategies, traditionally referred to as duration of WIT (see Figure 12.2).

Figure 12.2. **Procedure for uncontrolled donation after circulatory death, specifying limits of warm and cold ischaemia times**



When Regional Normothermic Reperfusion is used before cold perfusion, warm ischemia time ends with the start of regional perfusion and the cold ischemia time starts with the start of cold perfusion.

The specific selection criteria for uDCD donors common to the majority of existing programmes, particularly type IIa, are detailed in Table 12.2.

Table 12.2. **Standard selection criteria for uDCD donors**

Advanced CPR started within a maximum of 15 min of the witnessed cardiac arrest (some programmes accept a maximum of 30 min for kidney).
Age between 18 and 60 years (some programmes accept donation from donors aged ≥ 60 years).
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 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.

When an individual dies suddenly or unexpectedly 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 legislation, the irreversibility of the cardiac arrest can be declared under general circumstances, 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 with an unsuccessfully resuscitated out-of-hospital cardiac arrest can be transferred to hospital with the purpose of incorporating the option of organ donation into their end-of-life care. In this setting, the potential donor is kept under mechanical ventilation and external cardiac compression, but with no fluid or drug perfusion, since advanced CPR for resuscitative purposes has been considered futile. The team identifying the potential donor contacts the receiving hospital informing them of the potential donor transfer and activating the uDCD procedure. The hospital is informed of the estimated time of arrival. Once the hospital has been informed, the hospital staff gets ready to receive the potential donor. Simultaneously, the medical team starts to prepare for the initiation of *in situ* preservation measures.

e. In other programmes (e.g. in the Netherlands), the possibility of uDCD in the setting of an irreversible cardiac arrest is considered only 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 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 the OHES team. Transfer of the potential uDCD donor is performed in an intensive care mobile unit (ambulance) maintaining the lines, but with no fluid perfusion or 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, 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. Mechanical ventilation can be provided through portable devices, or through circuits like the Boussignac ventilation system.

If needed, the OHES 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 to later assess the quality of the organs for transplant 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 (see section Figure 12.9), where the permanent cessation of circulation ('will not return') is used as a surrogate of the irreversible cessation of circulation ('cannot return') for the diagnosis of death [29-32]. The difference is that, in uDCD, CPR has been applied and is unsuccessful, whilst in cDCD there is a cessation of supportive therapy. These different approaches to the determination of death have been discussed internationally [33-36].

Death by circulatory criteria should be determined and certified by professional(s) independent from donation and transplantation teams. In practice, this is usually done by the team taking over the CPR manoeuvres for cases transferred from the out-of-hospital setting.

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 and definitive preservation manoeuvres are established. In other countries, reassumption of cardiac compression and mechanical ventilation are avoided. 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 and then *in situ* preservation strategies be initiated. Other anticoagulant strategies are currently being explored but there are no data to support their benefit.

12.2.5. Abdominal preservation procedure

There are two different kinds of procedure applied for the *in situ* preservation of abdominal organs in uDCD procedures: Hypothermic or Normothermic Regional Perfusion and *in situ* cooling. The two procedures are described below.

12.2.5.1. *Establishment of a femoro–femoral bypass for extracorporeal circulation with membrane oxygenation – hypothermic or normothermic regional perfusion*

This entails the following (see Figure 12.3):

a. Cannulating the femoral vein and artery of one leg for the connection to the 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 Hypothermic Regional Perfusion (HRP) or Normothermic Regional Perfusion (NRP), once the correct position of this catheter has been checked radiologically.

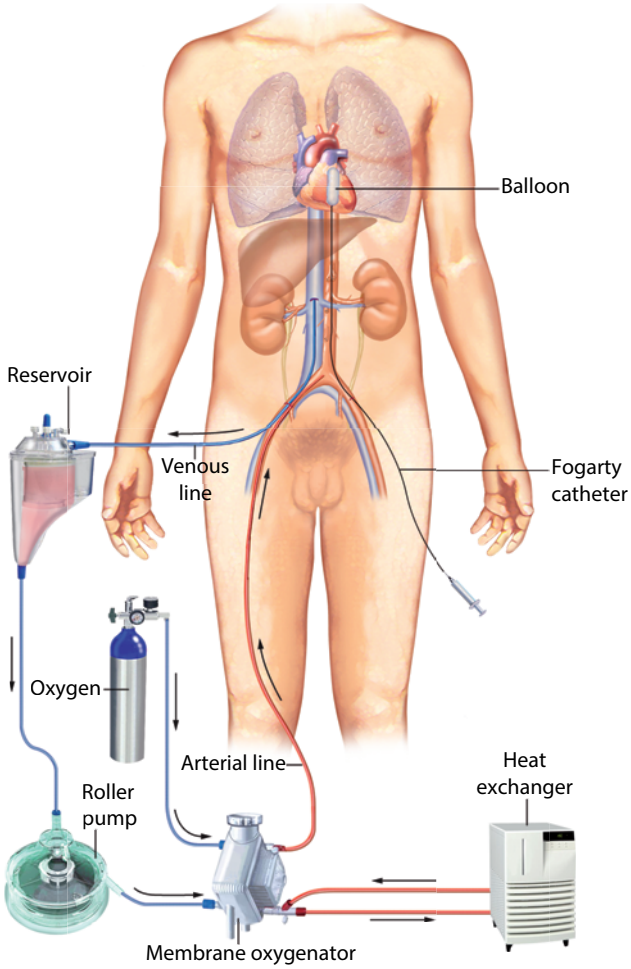
e. The maximum duration of HRP or NRP in uDCD procedures has been established empirically at 240 min in existing programmes. If liver donation is planned, NRP rather than HRP should be established. If lung donation is planned, HRP is preferred to avoid warming the thoracic cavity. Dual temperature (cold 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 [26]. 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 for donation 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**



12.2.5.2. In situ *cooling preservation with the double balloon catheter*

This method uses a double balloon catheter that is placed in the aorta, with one of the balloons inflated above up to the renal artery level, and the other one 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

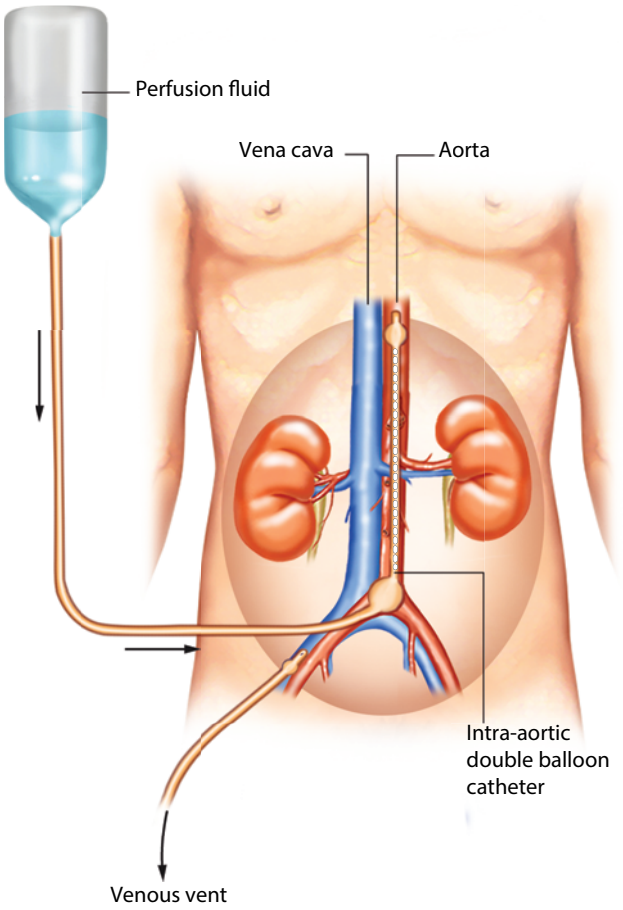
2 h. This method does not allow recovery of liver for transplantation with acceptable results, but it is compatible with lung donation.

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).

Kidney transplants from uDCD donors have yielded good results with the previously described *in situ* preservation strategies, with only one study directly comparing the three different techniques [5-17]. Valero *et al.* observed that the incidence of DGF and primary non-function was significantly lower when preservation was based on NRP (n = 8) v. HRP (n = 8) and *in situ* cooling preservation (n = 44) [5]. Also, duration of DGF was significantly shorter with the use of NRP compared with *in situ* cooling.

In the field of liver transplantation from uDCD donors, promising results (although inferior to those obtained with DBD livers) have been obtained with the use of NRP [18-23].

Figure 12.4. **In situ cooling preservation of kidneys with the double balloon catheter technique**



12.2.6. Lung preservation procedure

Lung recovery and transplantation has been successfully developed in some of the existing uDCD programmes. There is a specific method to preserve the lungs of uDCD donors based on topic cooling developed in Spain [37, 38]. Currently, dual preservation (cooling up above the diaphragm and normothermia below the diaphragm) is possible, although the experience is still preliminary [26]. 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 (second 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, midaxillary 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 and 15 °C, which is excellent to preserve lungs until recovery.

Once lungs are preserved and consent/authorisation has been obtained to proceed with recovery, 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 cm H_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 cm H_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.

12.2.7. Consent and authorisation process

The process for consent to organ recovery (and preservation where appropriate) in the process of 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).

In France and Spain, with an opt-out system, consent is focused on checking any expressed opposition towards donation during the 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 the context of uDCD, consent may be obtained at different times along the process: as soon as the irreversibility of the cardiac arrest is established by the OHES, or until *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 the uDCD process, the registry may be consulted as soon as the OHES announces that a potential donor is being transferred to the hospital. In case of registered opposition, the organ donation process is not pursued. If no opposition towards 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 recovery is not continued if the family opposes or if the family interview cannot be held within the first 2 h following the initiation of preservation measures.

12.2.7.1. *Family interview*

Communication with the family is especially challenging in the uDCD process. While death based on circulatory criteria is easier to understand than death based on neurologic criteria, the unexpected nature of the cardiac arrest makes the circumstances particularly 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 specific situation of the family during the said process.

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 he/she feels 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 and space for information exchange and 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 OHES 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.

12.2.7.2. *Judicial authorisation*

uDCD donors are frequently under a judge's investigation or under forensic medical investigation since death has occurred in the context of traffic or occupational accidents or the cause of the cardiac arrest is not clear. 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.

12.2.8. 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 for a DBD procedure, donor and organ evaluation are based on a review of the past and present medical history and risk behaviours of the potential uDCD donor, 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 OHES 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 OHES 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. On the other hand, some OHES are able to discard potential uDCD donors at the scene of the cardiac arrest by using rapid drug tests and strip-based HIV testing (if authorisation to do this exists). This practice avoids the unnecessary activation of the protocol and the related use of resources.

12.2.9. Organ-specific evaluation criteria

12.2.9.1. *Kidney evaluation criteria*

For kidneys, the history of the donor is the cornerstone for considering donation. Of course a history of renal disease is a formal contraindication for donation (for more information on organ-specific contraindications see Chapter 7). Biochemical determination on arrival – mainly values of serum creatinine, urea and LDH – help in the decision regarding kidney donation. Ex situ hypothermic non-oxygenated pulsatile preservation of kidneys is today used in many uDCD programmes. When using pulsatile machine preservation, 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 transplant. This measurement must be considered together with other kidney selection criteria, including biochemical, anatomical and histological assessments (see Chapter 11).

12.2.9.2. *Liver evaluation criteria*

The liver is very sensitive to ischaemia, and is the most difficult organ to obtain for transplant in uDCD procedures. During preservation time, while the donor is under NRP, ischaemic preconditioning must be performed and the evolution of liver enzymes must be closely monitored. The initial Spanish experience suggests that during NRP a pump flow greater than 1.7 L/min combined with ALT/AST levels below 3 times the upper normal values at the beginning of NRP, and less than 4 times the upper normal value at the end of NRP, are indicators that the liver can be recovered and utilised [19]. Maximum duration of NRP has been empirically established at 240 min.

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. Validation should be based on general and specific selection parameters, as well as on macroscopic evaluation of the organ and histology.

12.2.9.3. *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. 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.

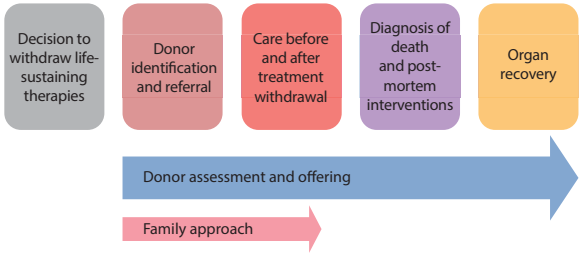
There is no experience with the transplantation of other organs in the uDCD setting. Special consideration must be given to the contribution of uDCD programmes to tissue donation.

12.3. Controlled donation after circulatory death

In the case of cDCD, cardiac arrest occurs following a planned WLST after it has been demonstrated that further intensive care medicine therapy is no longer in the best interests of a critically ill patient according to the patient's personal rights. Unlike other types of DCD, in cDCD the cardiac arrest is anticipated and expected, which allows the retrieval 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 DCD donors, but also to support and maintain the trust of grieving families and to decide how best to minimise the consequences of warm ischaemia in a fashion that is professionally, ethically and legally acceptable.

Figure 12.5. **The key steps in the controlled donation after circulatory death process**



In countries practising cDCD, these donors have become an increasingly important source of organs for transplantation. 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 3 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 [39]. It also found that the incidence of brain death was nearly 4 times more frequent in these southern European countries than in the northern European countries. cDCD has become an increasingly important source of organs for transplant in countries like Belgium, the Netherlands and the United Kingdom. For example, between 2007/8 and 2013/14 the number of DCD donors increased year on year in the United Kingdom, resulting in an increase of 170 %. DCD donors currently represent around 40 % of United Kingdom deceased donors and provide 25 % of all organs transplanted.

A key issue is whether grafts procured from cDCD donors are equivalent in quality to grafts procured from DBD donors, due to exposure to ischaemia. DGF is more common in transplanted kidneys recovered from cDCD donors, but the long-term outcome is similar to that of kidneys recovered from DBD donors [40]. This finding was confirmed in a large United Kingdom registry study [41]. The same study also showed that the results of re-transplantation with cDCD kidneys were slightly inferior to those recovered from DBD donors.

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 [42]. The consequences of warm ischaemia and the CIT 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 DCD lung recipients than for DBD recipients, with 2-year survival rates of 87 % and 69 % respectively [43]. However, it is recognised that variations in donor and recipient selection criteria and surgical technique may make comparison of outcomes difficult.

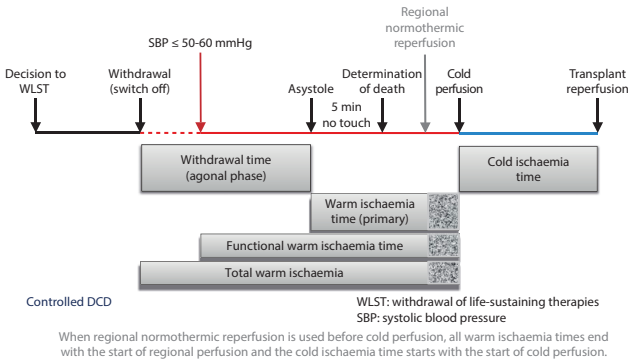
The outcomes of liver transplantation from cDCD donors are also considered acceptable, with a 3-year survival rate of 63 % for recipients of livers from DCD donors compared to 72 % for recipients of livers from DBD donors. However, between 10 and 15 % of the grafts are lost within the first year post-transplant (patient death or relisting for transplantation, United Kingdom NHSBT data). Furthermore, the incidence of primary graft failure is increased from 6 % to 12 % in recipients of a liver from a cDCD donor and there is also a higher incidence of bile duct complications, particularly with longer WIT [44-47], many of these patients requiring re-transplantation. Strict criteria for the selection and acceptance of livers from DCD donors are therefore required to reduce these complications. The use of *in situ* NRP or *ex situ* normothermic perfusion of the liver may be helpful in reducing the effects of warm ischaemia [48].

Results from a short-term comparative study on pancreas transplantation from DCD and DBD donors in the United Kingdom reported similar one-year pancreas and recipient survival rates for transplants from DCD and DBD donors, with pancreas graft survival significantly better in the DCD cohort if performed as a simultaneous pancreas–kidney transplant [49]. Similar promising results have been published with data derived from the OPTN/UNOS Registry [50].

More recently, hearts recovered from cDCD donors have been successfully transplanted in Australia [51] and the United Kingdom [52]. The long-term results of this encouraging initiative are eagerly anticipated.

The process of cDCD is summarised in the key steps in Figure 12.5; the steps from decision on WLST to transplant reperfusion are shown in Figure 12.6. For definition of terms, see section 12.3.6.1.

Figure 12.6. **The controlled donation after circulatory death procedure after decision to withdraw life-sustaining treatment**



When regional normothermic reperfusion is used before cold perfusion, all warm ischaemia times end with the start of regional perfusion and the cold ischaemia time starts with the start of cold perfusion.

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 interest 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 withdrawal of life-sustaining therapies (WLST) is being made, but particularly when cDCD is a possibility [53]. National end-of-life care guidance that recognises organ donation [54] 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 (see Chapter 2). 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 DCD should 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 [53]. Procurement teams must not advise on how treatment should be withdrawn.

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, WIT is reduced by avoiding transferring the donor from ICU to theatre after death. However, it is important that this practice does not compromise the delivery of end-of-life care, and units that choose to locate 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 [55].

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 a minimum of 3 h in the United Kingdom. While more than 90 % of cDCD donors will have died within 2 h of WLST, successful kidney recovery has occurred more than 4 h after WLST in circumstances where the functional warm ischaemic time (FWIT) has been acceptable (time extending between significant hypoperfusion and cardio-respiratory arrest) [56]. 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 communicated to 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.

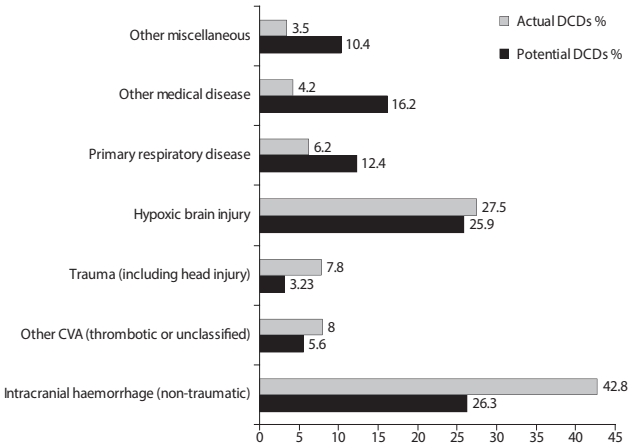
12.3.2. Identification of potential donors

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. When identifying such patients as potential cDCD donors, it is important to consider whether death by neurologic criteria can be certified while cardio-respiratory stability is maintained and the WLST is delayed. 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 such as end-stage respiratory failure or neuromuscular disease. Figure 12.7 shows diagnostic categories for 7 504 potential DCD donors and 877 actual cDCD donors between October 2009 and March 2012 in the United Kingdom [57].

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* [58].

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 (currently 40 % in the United Kingdom), 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 [59, 60] 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 [61]. Consequently, centres may choose to initiate a donation process in every potential donor.

Figure 12.7. **Diagnostic categories for potential and actual cDCD donors in a UK study**

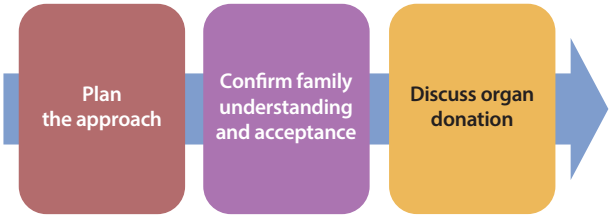


Data from Potential Donor Audit (courtesy of NHSBT) [57].

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. The approach for cDCD should take place in three stages (see Figure 12.8) [62].

Figure 12.8. **The three discrete stages in approaching the family of a potential cDCD donor**



Source: NHS Blood and Transplant 2013. Approaching the families of potential organ donors. Best practice guidance [62].

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 ap-

proach 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, and provide support 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. 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 DCD 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 his/her relatives and/or can be reasonably controlled [53, 63]. 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 [64]. Using this balance (see Figure 12.9), interventions like delaying WLST, altering the location of WLST, collecting blood samples for tissue typing and virology before death and/or simple measures to maintain cardio-respiratory stability, will be considered ethically and legally justifiable. Other interventions, such as *ante mortem* cannulation of the femoral vessels and the administration of heparin, are more controversial [65].

Each country needs clear legal and/or professional guidance as to which *ante mortem* interventions are considered acceptable, which interventions should be accepted with the specific consent of family after appropriate information has been given and which interventions are never acceptable. 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.

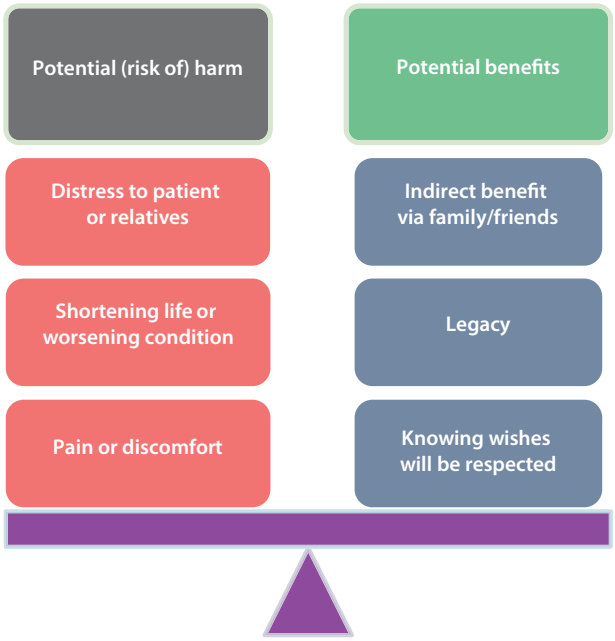
After the death of the patient further interventions are quickly undertaken before or during the recovery operation, to reduce the ischaemic time or to optimise organs before transplantation. cDCD protocols should acknowledge the potential risks associated with *post mortem* interventions that may restore 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 can reduce the warm ischaemic damage to vulnerable transplantable organs by re-circulating 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 should be excluded by the use of vessel clamps or intravascular balloons [66]. 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. Protocols describing the recovery of lungs from cDCD donors should consider each necessary intervention – its potential to inadvertently restore the cerebral circulation – and how this should be prevented [66].

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 res-

piration 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.

Figure 12.9. **Balance of risks and benefits when assessing the acceptability of an *ante mortem* intervention in cDCD**



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 [67]. 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 trans-oesophageal echocardiography. If only an ECG is used, then asystole must be observed for 5 min [66]. 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 retrieval or transplant process.

The time of 5 min is based on the concept of 'permanent' loss of circulation, i.e. there is no possibility of spontaneous resumption of circulation, rather than the concept of 'irreversibility' which is more variable and dependent on the available technologies [66]. It follows that diagnosing death at 5 min is conditional on there being no intention to resume cardiopulmonary resuscitation or to introduce interventions that may potentially restore cerebral circulation after the declaration of death (see Figure 12.10). This does not preclude the use of organ reperfusion techniques since they can be 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 donation) and agree a 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 times have been defined:

a. Withdrawal time (agonal phase): the time from WLST to cardiac arrest.
b. Warm ischaemia time, primary (asystolic time): the time from cardiac arrest to (*in situ*) perfusion.
c. Functional warm ischaemia time (FWIT): the time between first episode of systolic blood pressure ≤ 50 or 60 mmHg and *in situ* perfusion [29].
d. Total warm ischaemia: withdrawal time + warm ischaemia time.

The definition of FWIT is yet to be universally agreed, but in general a sustained fall in systolic blood pressure ≤ 50 or 60 mmHg is accepted both in Europe and the United States [31, 68]. In addition, the United States guidelines define the total donor WIT as the time from WLST to *in situ* perfusion.

The acceptable FWIT varies for different organs and ranges from 30 min for the liver and pancreas to 60 min for kidneys and lungs [69]. There is a lack of evidence supporting these times and several reports suggest that longer times yield transplantable organs [56, 70].

Following WLST, the donor co-ordinator must communicate the vital signs (blood pressure, mean arterial pressure and pulse) every 5 min to the procurement team.

12.3.6.2. *Organ recovery procedure – 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 personel involved should make an effort to personalise care within the given time constraints.

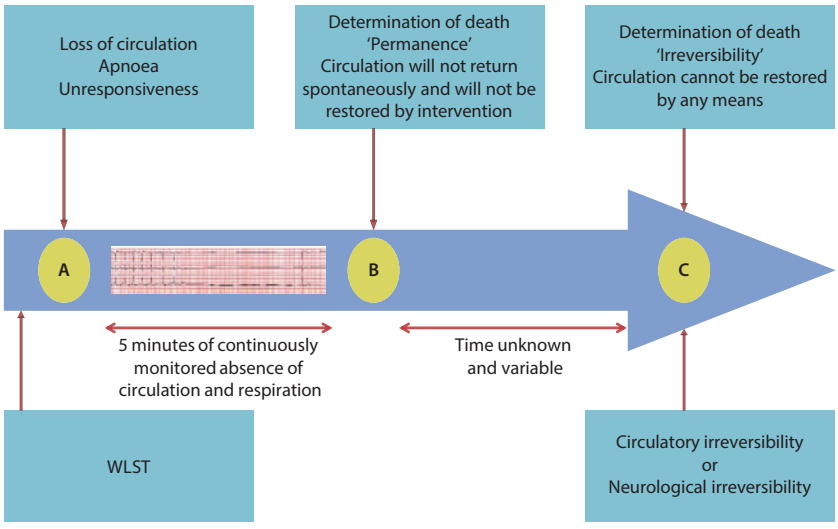
Once death has been confirmed after the mandatory no-touch period, and after final confirmation of identity, a rapid midline laparotomy from the sternal notch to pubis is undertaken. The recovery procedure follows the super-rapid technique described by Casavilla [71]. After laparotomy, the caecum, terminal 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. The inferior vena cava can be vented in the abdomen or in the chest, and this should be undertaken immediately prior to the start of cold perfusion to avoid congestion of the abdominal organs. Cold perfusion begins simultaneously using a low-viscosity solution or any preservation solution with 20 000 units of heparin under pressure (150-200 mmHg). Topical cooling is instituted and a median sternotomy is then carried out. The pericardium is incised and the supra-hepatic inferior vena cava (IVC) 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. Following the initial heparinised low-viscosity perfusion, further perfusion should be undertaken using approved solutions for this indication. If the liver is to be recovered, it is advisable to cannulate and perfuse the portal vein. This is isolated in the hepato-duodenal ligament following division of the common bile duct. The portal vein is completely divided to enable pancreas drainage without congestion, and is perfused using heparinised preservation solution. The gallbladder is then opened and the bile duct is flushed with normal saline. The subsequent steps are similar to rapid recovery technique in unstable DBD donors.

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 (SMA) during bench dissection. The duodenum is fully kocherised to expose the IVC. 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 SMA is divided at the aortic origin and the supraceliac aorta is transected. The bloc is removed and separated on the bench.

Figure 12.10. **Diagnosis of death in cDCD**

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.



Kidneys can be removed individually or *en bloc*. If they are removed separately, the left renal vein is divided flush with the IVC, 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. If removed *en bloc*, the ureters are divided as they cross the iliac arteries and then dissection is carried in the plane behind the IVC, 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: thoracic organs*

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 the aorta clamped. These early manoeuvres lessen the WIT and allow time for the removal of the liver, which is highly sensitive to the 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.

The use of DCD hearts is still limited but rapid removal, followed by *ex situ* normothermic machine perfusion has been proposed by the Sydney group [51].

12.3.6.4. *Organ recovery procedure using normothermic regional perfusion*

Following Spanish experience in uDCD, several countries have explored the feasibility of normothermic regional perfusion (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 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 is a haemorrhagic lesion) and specific informed consent is obtained [72]. A similar protocol has been developed in the United States [73]. Although both interventions are thought by clinicians to yield organs of higher quality in greater numbers for transplantation, there is still no clear evidence of the superiority of using these *ante mortem* interventions.

In cases where *ante mortem* cannulation of femoral vessels is performed (see section 12.2.5.1), the correct position of the aortic balloon must be radiologically confirmed prior to WLST. The balloon will be inflated after death has been determined, initiating the NRP.

In cases where *ante mortem* cannulation of femoral vessels is not performed, once death has been confirmed, 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 IVC is then dissected and encircled using a vascular snugger. The distal end is clamped or ligated. The venous cannula is inserted into the IVC. The tip should sit just below the diaphragm to allow clamping of the suprahepatic IVC 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 the NRP before undertaking the sternotomy. This approach would allow the cardiothoracic team to undertake the sternotomy, and mobilise the lung and clamp the descending aorta (if simultaneous lung recovery). Once the 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 2 h, although the optimal duration remains to be determined. The pump parameters are yet to be fully established but 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) [74].

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.

If thoracic (lung) recovery is planned in a donor where NRP is undertaken [75], the supra-hepatic IVC is clamped at the cavo-atrial junction. The ascending aorta is clamped, the main pulmonary artery (PA) 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 Perfadex 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 IVC 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 PA 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 endo-tracheal 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.

An alternative approach is currently under investigation extending the NRP to involve the thoracic organs but excluding the cerebral circulation. This approach allows the recovery of lungs as well as hearts (Papworth unpublished study protocol). The bithermic/dual technique approach used in uDCD can also be used in the cDCD setting, but the experience is limited (see section 12.2.6) [26].

12.3.6.5. *Organ preservation:* in situ *cold preservation*

A variety of preservation solutions can be used. There are 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. Often used solutions are University of Wisconsin (UW) solution, HTK solution, EuroCollins solution and Celsior. Different studies have been undertaken to investigate the differences in performance (organ cooling, DGF) of these solutions in regard to different organs [76, 77]. A total volume of 4-5 L is used during multi-organ abdominal recovery, but it is mandatory to adjust this according to the instructions of the manufacturer and the clinical situation [78, 79].

It is important that the initial bags of perfusion solution contain heparin (20 000 U/L perfusion); if dual perfusion is used (as is the case for the liver: aorta and portal vein), both must contain heparin.

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 normothermic regional perfusion (NRP) has not been fully established. An example combination includes [74]:

- 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 UW solution.

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 [80] but no survival benefit at one year [81], whilst a subsequent three-year extension [82] as well as a United Kingdom based study [83] 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 [84] and normothermic machine preservation for the liver [85], kidney [86], lungs and heart. 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 pressors 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 [31].

The absolute contraindications to DCD 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 of circulation, DCD assessment is much more difficult and is subjective to surgeon's experience.

The decision to utilise the cDCD organs should also take into account the recovery factors such as duration of WIT.

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 with serial biochemical and blood gas analyses which are undertaken (every 30 min) to evaluate function. Given the limited experience, further clarification of the factors that are important is required.

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 donor's age, the timings of recovery (such as the length of WIT, the agonal phase duration or the length of predicted cold ischaemic time) and specific pre-existent co-morbidity (such as cardio-vascular disease, hypertension, diabetes or liver disease).

12.3.8.1. *Kidney evaluation criteria*

The absolute contraindications for cDCD kidney transplantation include end-stage kidney disease (chronic kidney disease stage 5, eGFR < 15 mL/min), chronic kidney disease stage 4 (eGFR 15-30 mL/min) and acute cortical necrosis on pre-implantation kidney biopsy [31].

Acute kidney injury, even when requiring dialysis, is not a relative or absolute contraindication to donation but is associated with a higher incidence of DGF.

In addition to donor and recovery issues, factors such as hypertension and cardio-vascular 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 [86, 87], allowing dual transplantation to be considered [87].

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 [88], 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 [89]. 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 mandate organ discard.

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. 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 ischaemic type biliary lesions (ITBL) [90, 91].

b. Body mass index (BMI) – Increased BMI appears to be associated with higher recipient mortality and a higher risk of graft loss [92, 93].

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 [94, 95].

d. Agonal time – A shorter time (< 10 min) is beneficial for graft function [96].

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 [95, 97].

Based on these considerations, the United Kingdom guidelines describe the ideal cDCD and the extended criteria cDCD, and make recommendations for their use (see Table 12.3) [31].

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 factors *a* to *e* above, macrovesicular steatosis (> 40 %) 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 ALT/AST is probably an indication not to use the liver. Nevertheless, clarification of the liver function test range that would preclude transplantation is needed. For example, in uDCD in Spain [18, 19], the initial ALT/AST should be < 3 times the upper limit of normal. During NRP the ALT/AST should not rise to more than 4 times the upper limit of normal at the end of the procedure. However this experience in uDCD cannot be directly transferred to cDCD, but would requires further studies and evidence.

12.3.8.3. *Pancreas evaluation criteria*

Similar to cDCD liver grafts, utilisation of the pancreata is more restrictive, with a lower donor age and BMI (< 28 kg/m^2) and a short (< 30 min) FWIT. Currently there are no standard criteria for pancreas evaluation and graft assessment relies on the quality of perfusion, the degree of fatty infiltration and the texture of the graft.

Based on the donor criteria, United Kingdom cDCD guidelines [31] suggest classification and graft utilisation shown in Table 12.4.

Table 12.4. **Categorisation of the cDCD pancreas donor**

	Standard cDCD donor	Expanded cDCD donor
Age (year)	< 45	45-60
BMI (kg/m^2)	< 28	28-30
WIT (min)	≤ 30	> 30
CIT (hr)	≤ 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 the CIT is < 8 h. The islet isolation purity and functionality remains to be further defined but early DCD islet transplantation is encouraging [98, 99].

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. A systemic arterial PO_2 < 30 kPa on 100 % FIO_2 and 5 cmH_2O PEEP, a bronchoscopy showing inflammation/soiling of the airway and a sustained peak airway pressure > 30 cmH_2O suggest that the lungs should be further evaluated using *ex situ* normothermic perfusion (EVNP). Additional indications for using EVNP include FWIT > 30 min and < 60 min for cDCD donors, difficult-to-recruit atelectasis, 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 [31]. EVNP assesses the ability of the lung to provide perfusate oxygenation, together with the lung compliance, airway resistance and tidal volume.

12.3.8.5. *Heart evaluation criteria*

The use of cDCD hearts is at an early stage and the evaluation criteria are evolving [51].

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 very particular challenges. 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. Criteria for donor selection are expanding as the results of DCD transplants are becoming more favourable. 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 transplants. 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.

It is important for countries which are considering DCD programmes to develop a regulatory framework which 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

1. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; (27): 2893-4.
2. International figures on donation and transplantation – 2014. *Newsletter Transplant* 2015 [available from: www.edqm.eu/en/organ-transplantation-reports-73.html, accessed: 30 January 2016].
3. Domínguez-Gil B, Haase-Kromwijk B, Van LH *et al.* Current situation of donation after circulatory death in European countries. *Transpl Int* 2011; (24): 676-86.
4. Ysebaert D, Van Beeumen G, De Greef K *et al.* Organ procurement after euthanasia: Belgian experience. *Transplant Proc* 2009; (41): 585-6.
5. Valero R, Cabrer C, Oppenheimer F *et al.* Normothermic recirculation reduces primary graft dysfunction of kidneys obtained from non-heart-beating donors. *Transpl Int* 2000; (13): 303-10.
6. Mizutani K, Ono Y, Kinukawa T *et al.* Use of marginal organs from non-heart-beating cadaveric kidney donors. *Transplantation* 2001; (72): 1376-80.
7. Hattori R, Ono Y, Yoshimura N *et al.* Long-term outcome of kidney transplant using non-heart-beating donor: multicenter analysis of factors affecting graft survival. *Clin Transplant* 2003; (17): 518-21.
8. Gagandeep S, Matsuoka L, Mateo R *et al.* Expanding the donor kidney pool: utility of renal allografts procured in a setting of uncontrolled cardiac death. *Am J Transplant* 2006; (6): 1682-8.
9. Sánchez-Fructuoso AI, Marques M, Prats D *et al.* Victims of cardiac arrest occurring outside the hospital:

a source of transplantable kidneys. *Ann Intern Med* 2006; (145): 157-64.

10. Fieux F, Losser MR, Bourgeois E *et al.* Kidney retrieval after sudden out of hospital refractory cardiac arrest: a cohort of uncontrolled non heart beating donors. *Crit Care* 2009; (13): R141.
11. Barlow AD, Metcalfe MS, Johari Y *et al.* Case-matched comparison of long-term results of non-heart-beating and heart-beating donor renal transplants. *Br J Surg* 2009; (96): 685-91.
12. Hoogland ER, Snoeijs MG, Winkens B *et al.* Kidney transplantation from donors after cardiac death: uncontrolled versus controlled donation. *Am J Transplant* 2011; (11): 1427-34.
13. Abboud I, Viglietti D, Antoine C *et al.* Preliminary results of transplantation with kidneys donated after cardiocirculatory determination of death: a French single-centre experience. *Nephrol Dial Transplant* 2012; (27): 2583-7.
14. de Gracia MC, Osorio JM, Perez-Villares JM *et al.* A new program of kidney transplantation from donors after cardiac death in Spain. *Transplant Proc* 2012; (44): 2518-20.
15. Hanf W, Codas R, Meas-Yedid V *et al.* Kidney graft outcome and quality (after transplantation) from uncontrolled deceased donors after cardiac arrest. *Am J Transplant* 2012; (12): 1541-50.
16. Pieter Hoogland ER, van Smaalen TC, Christiaans MH *et al.* Kidneys from uncontrolled donors after cardiac death: which kidneys do worse? *Transpl Int* 2013; (26): 477-84.
17. Miranda-Utrera N, Medina-Polo J, Pamplona M *et al.* Donation after cardiac death: results of the SUMMA. *Clin Transplant* 2013; (27): 283-8.
18. Fondevila C, Hessheimer AJ, Ruiz A *et al.* Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. *Am J Transplant* 2007; (7): 1849-55.
19. Fondevila C, Hessheimer AJ, Flores E *et al.* Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. *Am J Transplant* 2012; (12): 162-70.
20. Suarez F, Otero A, Solla M *et al.* Biliary complications after liver transplantation from Maastricht category-2 non-heart-beating donors. *Transplantation* 2008; (85): 9-14.
21. Otero A, Gómez-Gutiérrez M, Suarez F *et al.* Liver transplantation from Maastricht category 2 non-heart-beating donors. *Transplantation* 2003; (76): 1068-73.
22. Quintela J, Gala B, Baamonde I *et al.* Long-term results for liver transplantation from non-heart-beating donors maintained with chest and abdominal compression-decompression. *Transplant Proc* 2005; (37): 3857-8.
23. Jiménez-Galanes S, Meneu-Diaz MJ, Elola-Olaso AM *et al.* Liver transplantation using uncontrolled non-heart-beating donors under normothermic extracorporeal membrane oxygenation. *Liver Transpl* 2009; (15): 1110-18.
24. de Antonio DG, Marcos R, Laporta R *et al.* Results of clinical lung transplant from uncontrolled non-heart-beating donors. *J Heart Lung Transplant* 2007; (26): 529-34.
25. Gómez-de-Antonio D, Campo-Cañaveral JL, Crowley S *et al.* Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. *J Heart Lung Transplant* 2012; (31): 349-53.
26. Gámez P, Díaz-Hellin V, Marrón C *et al.* Development of a non-heart-beating lung donor program with 'Bithermia Preservation', and results after one year of clinical experience. *Arch Bronconeumol* 2012; (48): 338-41.
27. Nolan JP, Soar J, Cariou A *et al.* European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: Section 5 of the European Resuscitation Council guidelines for resuscitation, 2015. *Resuscitation* 2015; (95): 202-22.
28. Neumar RW, Shuster M, Callaway CW *et al.* Part 1: Executive summary: 2015 American Heart Association guidelines – update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; 132 (18 Suppl 2): S315-67.
29. Bernat JL, Capron AM, Bleck TP *et al.* The circulatory-respiratory determination of death in organ donation. *Crit Care Med* 2010; (38): 963-70.
30. Shemie SD, Baker AJ, Knoll G *et al.* National recommendations for donation after cardiocirculatory death in Canada: donation after cardiocirculatory death in Canada. *CMAJ* 2006; 175 (8): S1.
31. British Transplantation Society. *United Kingdom guidelines: transplantation from donors after deceased circulatory death*. [available from: www.bts.org.uk/Documents/2013-02-04%20DCD%20guidelines.pdf:2013, accessed: 30 January 2016].
32. Graham S, Tooley A, Huckson S *et al.* National Health and Medical Research Council, Australian Organ and Tissue Donation and Transplantation Authority, Australian Government, Organ and Tissue Authority. *National protocol for donation after cardiac death*, 2010 [available from: www.donatelife.gov.au/sites/default/files/files/DCD%20protocol%20020311-0e4e2c3d-2ef5-4dff-b7ef-af63d0bf6a8a-1.PDF, accessed: 31 July 2016].
33. Munjal KG, Wall SP, Goldfrank LR *et al.* A rationale in support of uncontrolled donation after circulatory

determination of death. *Hastings Cent Rep* 2013; (43): 19-26.

34. Bernat JL. Determining death in uncontrolled DCDD organ donors. *Hastings Cent Rep* 2013; (43): 30-3.
35. Bernat JL, Bleck TP, Blosser SA *et al.* Circulatory death determination in uncontrolled organ donors: a panel viewpoint. *Ann Emerg Med* 2014; (63): 384-90.
36. Matesanz R, Coll E, Domínguez-Gil B. Response to circulatory death determination in uncontrolled organ donors: a panel viewpoint. *Ann Emerg Med* 2014; (63): 87-9.
37. de Antonio DG, Marcos R, Laporta R *et al.* Results of clinical lung transplant from uncontrolled non-heart-beating donors. *J Heart Lung* Transplant 2007; (26): 529-34.
38. Gomez-de-Antonio D, Campo-Cañaveral JL, Crowley S *et al.* Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. *J Heart Lung Transplant* 2012; (31): 349-53.
39. Sprung CL, Cohen SL, Sjokvist P *et al.* End-of-life practices in European intensive care units: the Ethicus Study. *JAMA* 2003; (290): 790-7.
40. Weber M, Dindo D, Demartines N *et al.* Kidney transplantation from donors without a heartbeat. *N Engl J Med* 2002; (347): 248-55.
41. Summers DM, Johnson RJ, Allen J *et al.* Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet* 2010; (376): 1303-11.
42. Van Raemdonck DE, Jannis NC, Rega FR *et al.* Extended preservation of ischemic pulmonary graft by postmortem alveolar expansion. *Ann Thorac Surg* 1997; (64): 801-8.
43. Mason DP, Thuita L, Alster JM *et al.* Should lung transplantation be performed using donation after cardiac death? The United States experience. *J Thorac Cardiovasc Surg* 2008; (136): 1061-6.
44. Grewal HP, Willingham DL, Nguyen J *et al.* Liver transplantation using controlled donation after cardiac death donors: an analysis of a large single-center experience. *Liver Transpl* 2009; (15): 1028-35.
45. Fujita S, Mizuno S, Fujikawa T *et al.* Liver transplantation from donation after cardiac death: a single center experience. *Transplantation* 2007; (84): 46-9.
46. Abt PL, Desai NM, Crawford MD *et al.* Survival following liver transplantation from non-heart-beating donors. *Ann Surg* 2004; 239(1): 87-92.
47. Abt P, Crawford M, Desai N *et al.* Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. *Transplantation* 2003; (75): 1659-63.
48. St Peter SD, Imber CJ, López I *et al.* Extended preservation of non-heart-beating donor livers with normothermic machine perfusion. *Br J Surg* 2002; (89): 609-16.
49. Muthusamy AS, Mumford L, Hudson A *et al.* Pancreas transplantation from donors after circulatory death from the United Kingdom. *Am J Transplant* 2012; (12): 2150-6.
50. Salvalaggio PR, Davies DB, Fernandez LA *et al.* Outcomes of pancreas transplantation in the United States using cardiac-death donors. *Am J Transplant* 2006; (6): 1059-65.
51. Dhital KK, Iyer A, Connellan M *et al.* Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet* 2015; (385): 2585-91.
52. BBC News Health. Europe's first non-beating heart transplant [available from: www.bbc.co.uk/news/health-32056350, accessed: 30 January 2016].
53. Academy of Medical Royal Colleges Donation Ethics Committee. An ethical framework for controlled donation after circulatory death, 2011 [available from: www.aomrc.org.uk/doc_view/9425-an-ethical-framework-for-controlled-donation-after-circulatory-death, accessed: 9 March 2016].
54. General Medical Council. *Treatment and care towards the end of life: good practice in decision*, 2010 [available from: www.gmc-uk.org/static/documents/content/Treatment_and_care_towards_the_end_of_life_-_English_0914.pdf, accessed: 9 March 2016].
55. Thomas I, Caborn S, Manara AR. Experiences in the development of non-heart beating organ donation scheme in a regional neurosciences intensive care unit. *Br J Anaesth* 2008; (100): 820-6.
56. Reid AW, Harper S, Jackson CH *et al.* Expansion of the kidney donor pool by using cardiac death donors with prolonged time to cardiorespiratory arrest. *Am J Transplant* 2011; (11): 995-1005.
57. Murphy P, Allen J, Manara A *et al. Who should be considered for Maastricht 3 DCD.* Presented at ETCO 2012, Dubrovnik [available from: www.odt.nhs.uk/pdf/who_should_be_considered_for_maastricht_3_dc_(etco-edc_2012).pdf, accessed: 30 January 2016].
58. NHS Blood and Transplant 2012. *Timely identification and referral of potential organ donors* [available from: www.odt.nhs.uk/pdf/timely-identification-and-referral-potential-donors.pdf, accessed: 30 January 2016].
59. Lewis J, Peltier J, Nelson H *et al.* Development of the University of Wisconsin donation After Cardiac Death Evaluation Tool. *Prog Transplant* 2003; (13): 265-73.
60. DeVita MA, Brooks MM, Zawistowski C *et al.* Donors after cardiac death: validation of identification criteria (DVIC) study for predictors of rapid death. *Am J Transplant* 2008; (8): 432-41.

61. Wind J, Snoeijs MG, Brugman CA *et al.* Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med* 2012; (40): 766-9.
62. NHS Blood and Transplant 2013. *Approaching the families of potential organ donors. Best practice guidance* [available from: www.odt.nhs.uk/pdf/family_approach_best_practice_guide.pdf, accessed: 30 January 2016].
63. Coggon J, Brazier M, Murphy P *et al.* Best interests and potential organ donors. *BMJ* 2008; (336): 1346-7.
64. Academy of Medical Royal Colleges Donation Ethics Committee. *Interventions before death to optimise donor organ quality and improve transplant outcomes: guidance from the UK Donation Ethics Committee* [available from: www.aomrc.org.uk/dmdocuments/Generic-interventions-guidance-Sept-2014.pdf, accessed: 30 January 2016].
65. Department of Health. *Legal issues relevant to non-heart-beating organ donation*, 2009 [available from: www.bts.org.uk/Documents/Publications/Legal%20issues%20relevant%20to%20non-heartbeating%20organ%20donation.pdf, accessed: 30 January 2016].
66. Department of Health. *Organ donation after circulatory death. Report of a consensus meeting.* Intensive Care Society, NHS Blood and Transplant, and British Transplantation Society, 2010 [available from: www.bts.org.uk/Documents/Guidelines/Active/DCD%20for%20BTS%20and%20ICS%20FINAL.pdf.Accessed: 9 March 2016].
67. Gardiner D, Shemie S, Manara A *et al.* International perspective on the diagnosis of death. *Br J Anaesth* 2012; 108(Suppl 1): i14-28.
68. Reich DJ, Mulligan DC, Abt PL *et al.* ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant* 2009; (9): 2004-11.
69. Bernat JL, D'Alessandro AM, Port FK *et al.* Report of a national conference on donation after cardiac death. *Am J Transplant* 2006; (6): 281-91.
70. Suntharalingam C, Sharples L, Dudley C *et al.* Time to cardiac death after withdrawal of life-sustaining treatment in potential organ donors. *Am J Transplant* 2009; (9): 2157-65.
71. Casavilla A, Ramirez C, Shapiro R *et al.* Experience with liver and kidney allografts from non-heart-beating donors. *Transplantation* 1995; (59): 197-203.
72. *Donation after circulatory death in Spain: current situation and recommendations. National consensus document* 2012 (in Spanish) [available from: www.ont.es/infesp/DocumentosDeConsenso/DONACIÓN%20EN%20ASISTOLIA%20EN%20ESPAÑA.%20SITUACIÓN%20ACTUAL%20Y%20RECOMENDACIONES.pdf, accessed: 9 March 2016].
73. Rojas-Pena A, Sall LE, Gravel MT *et al.* Donation after circulatory determination of death: the University of Michigan experience with extracorporeal support. *Transplantation* 2014; (98): 328-34.
74. Oniscu GC, Randle LV, Muiesan P *et al.* In situ normothermic regional perfusion for controlled donation after circulatory death – the United Kingdom experience. *Am J Transplant* 2014; (14): 2846-54.
75. Oniscu GC, Siddique A, Dark J. Dual temperature multi-organ recovery from a Maastricht category III donor after circulatory death. *Am J Transplant* 2014; (14): 2181-6.
76. Southard JH. The right solution for organ preservation. Business briefing: *North American Pharmacotherapy* 2004; (2): 10.
77. Stewart ZA, Cameron AM, Singer AL *et al.* Histidine-Tryptophan-Ketoglutarate (HTK) is associated with reduced graft survival in deceased donor livers, especially those donated after cardiac death. *Am J Transplant* 2009; (9): 286-93.
78. Timsit MO, Tullius SG. Hypothermic kidney preservation: a remembrance of the past in the future? *Curr Opin Organ Transplant* 2011; (16): 162-8.
79. O'Callaghan JM, Knight SR, Morgan RD *et al.* Preservation solutions for static cold storage of kidney allografts: a systematic review and meta-analysis. *Am J Transplant* 2012; (12): 896-906.
80. Moers C, Smits JM, Maathuis MH *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; (360): 7-19.
81. Jochmans I, Moers C, Smits JM *et al.* Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. *Ann Surg* 2010; (252): 756-64.
82. Moers C, Pirenne J, Paul A *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2012; (366): 770-1.
83. Watson CJ, Wells AC, Roberts RJ *et al.* Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. *Am J Transplant* 2010; (10): 1991-9.
84. Dutkowski P, Schlegel A, de Oliveira M. HOPE for human liver grafts obtained from donors after cardiac death. *J Hepatol* 2014; (60): 765-772.
85. Brockmann J, Reddy S, Coussios C *et al.* Normothermic perfusion: a new paradigm for organ preservation. *Ann Surg* 2009; (250): 1-6.
86. Hosgood SA, Nicholson ML. First in man renal transplantation after *ex vivo* normothermic perfusion. *Transplantation* 2011; (92): 735-8.
87. Remuzzi G, Grinyo J, Ruggenenti P *et al.* Early experience with dual kidney transplantation in adults using

expanded donor criteria. Double Kidney Transplant Group (DKG). *J Am Soc Nephrol* 1999; (10): 2591-8.

88. Hosgood SA, Nicholson ML. Ex vivo normothermic perfusion of declined human kidneys after inadequate *in situ* perfusion. *Am J Transplant* 2014; (14): 490-1.
89. Talbot D, D'Alessandro A. *Organ donation and transplantation after cardiac death* (2009) ISBN 978-0-19-921733-5. Oxford: Oxford University Press, 2009.
90. Mateo R, Cho Y, Singh G *et al.* Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant* 2006; (6): 791-6.
91. Jay C, Ladner D, Wang E *et al.* A comprehensive risk assessment of mortality following donation after cardiac death liver transplant – an analysis of the national registry. *J Hepatol* 2011; (55): 808-13.
92. Chan EY, Olson LC, Kisthard JA *et al.* Ischemic cholangiopathy following liver transplantation from donation after cardiac death donors. *Liver Transpl* 2008; (14): 604-10.
93. Mathur AK, Heimbach J, Steffick DE *et al.* Donation after cardiac death liver transplantation: predictors of outcome. *Am J Transplant* 2010; (10): 2512-19.
94. Lee KW, Simpkins CE, Montgomery RA *et al.* Factors affecting graft survival after liver transplantation from donation after cardiac death donors. *Transplantation* 2006; (82): 1683-8.
95. Hong JC, Yersiz H, Kositamongkol P *et al.* Liver transplantation using organ donation after cardiac death: a clinical predictive index for graft failure-free survival. *Arch Surg* 2011; (146): 1017-23.
96. Taner CB, Bulatao IG, Willingham DL *et al.* Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transpl* 2012; (18): 100-11.
97. de Vera ME, Lopez-Solis R, Dvorchik I *et al.* Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant* 2009; (9): 773-81.
98. Saito T, Gotoh M, Satomi S *et al.* Islet transplantation using donors after cardiac death: report of the Japan Islet Transplantation Registry. *Transplantation* 2010; (90): 740-7.
99. Zhao M, Muiesan P, Amiel SA *et al.* Human islets derived from donors after cardiac death are fully biofunctional. *Am J Transplant* 2007; (7): 2318-25.

Related documents: Appendix 11. Donation after circulatory death – reporting form (Belgium, 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 particular dilemmas:

a. The living donor (LD) is not a patient – not suffering from an illness – but on the contrary is a person in perfect health, even healthier than the general population. This fact makes it 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 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 the overall 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). Countries like the Netherlands, Norway, Turkey and the United Kingdom have quite a long history of living donation with good results [4, 5]. In contrast, in other countries – like 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 (DGF) is decreased.

c. Living donation makes pre-emptive kidney transplant (transplantation prior to dialysis) more feasible, especially for young recipients.

Another option is pre-emptive re-transplantation in patients whose graft has failed, before having restarted dialysis – which potentially decreases the immunisation/sensitisation risks.

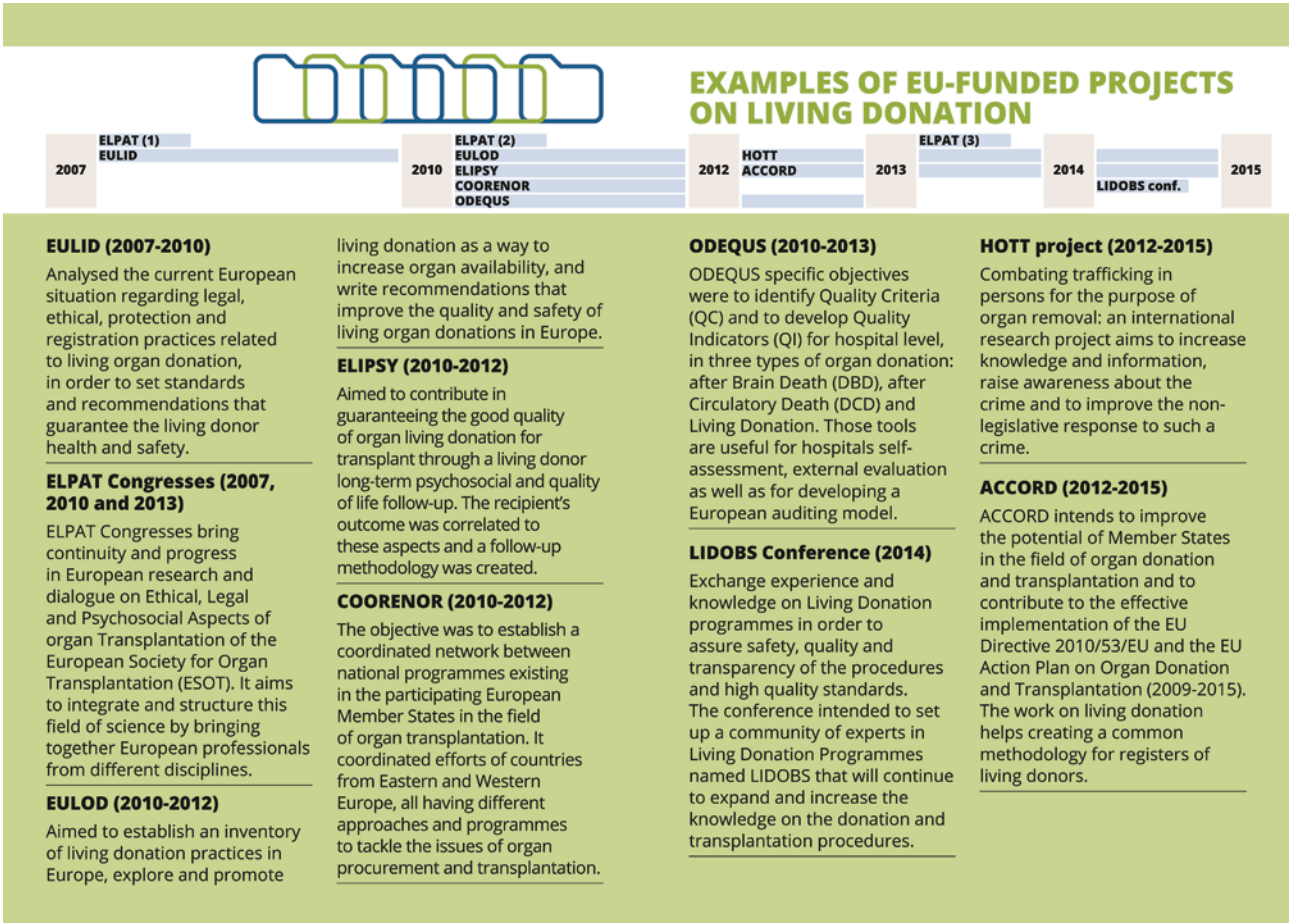
In addition, the implementation of an effective LD programme may shorten the DD waiting time for those patients with no LD available or who do not wish to receive an LD organ.

Regarding liver transplant, the advantage of using LD livers is most obvious in urgent cases, adult to adult and 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 and chronic' liver failure. This may specifically be the case of patients with expanded Milan criteria for hepatocarcinoma, patients with high mortality and morbidity while on the waiting list, and some elective patients [9]. In countries with extensive LD liver transplant experience, like 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.

The safety and protection of the LD becomes the essential component of any LD programme and must be grounded on an appropriate regulatory framework. Living donation must be performed according to best practices 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] and the Vancouver Forum on the Care of the Live Organ Donor: Lung, Liver, Pancreas, and Intestine [11].

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* [12] and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism [13]. The recently adopted Council of Europe Convention against Trafficking in Human Organs [14] and the Council of Europe Convention on Action against Trafficking in Human Beings [15]

Figure 13.1. **Summary of European Union funded projects in living donation**



Source: LIDOBS Conference recommendations [19] Final leaflet.

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 [16] and its Additional Protocol on Transplantation [17], 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 [18].

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 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).

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.

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 [20, 21].

Donor consent and autonomy are definitely 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 non-competent persons from being LDs [22]. 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 [23].

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:
- Prohibition of donation by minors and persons unable to provide valid consent.
- Prohibition and criminalisation of trafficking in persons for the purpose of the removal of organs and organ trafficking.
- Authorisation of centres for recovering organs from LDs under the control of health authorities.
- Provisions to protect the non-resident LD. This 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.
- 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).
- 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 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 should 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 the risk of surgery by the physician 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.

d. The potential LD must also be informed about possible adverse outcomes in the organ recipient: risk of organ rejection, medical and surgical 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 [24] (see Tables 13.2 and 13.3), to assure that the risk of the surgery does not exceed the expected benefits and will not compromise the health of the donor.

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 providing appropriate medical evidence. This should include appropriate documentation, provided by the head of the medical team which will perform organ procurement and implantation, about the purpose and legitimacy of surgery as well as the expected outcome.

c. If contraindications exist or the donor's health could be compromised by living donation then organ donation must be abandoned, regardless of whether the potential donor would consent or not.

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 a fallback in the event of unexpected withdrawal of consent or medical disqualification of the LD.

e. Each LD must be provided with permanent long-term care in order to monitor the donor's

health, including the option for intervention in case of expected or unexpected complications. Information about the health status at the time of donation and in the long term after procurement should be documented in a dedicated registry of LDs.

f. The LD should not demand or receive any material benefits from the organ recipient or from a third party. However, living donation should be cost-neutral for the donor, who should receive reimbursement of all expenses related to donation. The LD should not be subject to any prejudice detrimental to employment, insurance coverage or obtaining of credit, loans or mortgages.

g. Organ procurement from LDs must only be performed at specifically authorised centres and by medical staff who have formal permission and appropriate qualifications.

13.3.3. Authorisation to living donation from non-residents

Authorisation of donation in case of the non-resident LDs should be performed according to the legal and medical rules valid for the country where donation takes place. This type of donation should not proceed unless full adherence to all recommendations specified in sections 13.2 and 13.3 can be assured. It should be noted that non-resident LDs may be especially vulnerable. In addition, donor–recipient relationship and donor motivations may be difficult to assess due to language barriers, cultural differences, etc.

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. 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-/long term.

Perioperative mortality, based on large compiled series of mostly open, conventional LD nephrectomies (LDNs), has typically been reported at 0.03-0.05 % [8, 25]. The immediate perioperative risks are: bleeding, deep vein thrombosis, pulmonary embolism, wound complications, urinary tract infection, atelectasis and pneumothorax.

Minimally invasive LDNs – either laparoscopic or retroperitoneoscopic – have, in recent years, been shown to be superior to the open procedure regarding postoperative pain, hospital stay, sick leave and cosmetics. Long-term benefits in quality of life and wound discomfort have also been suggested (and the observation time will soon be long enough to provide evidence). Complication rates have been shown to be equal to or even lower than those of the open procedure [27]. Furthermore, the hand-assisted alternative (laparoscopic or retroperitoneoscopic) may further improve safety [28]. During the first part of the laparoscopic era (1995-2005), a probably increased rate of fatal cases was reported. However, with increasing experience with minimally invasive LDNs 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 LDN era. Therefore, in transplant centres with sufficient laparoscopic competence, minimally invasive LDN should be the method of choice.

In the long term, the recipient and donor outcomes are generally excellent. Kidney donation is considered a safe procedure supported by more than five decades of experience. However, a slight increase in cardiovascular and all-cause mortality, and in end-stage renal disease, cannot be completely excluded [2, 3]. In spite of this, the incidence is still lower than in the general population. 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 (GFR), blood pressure and glucose tolerance tests. There is a long-term trend towards a slight increase in blood pressure and proteinuria. Female donors of childbearing potential should be aware that there is a slightly increased risk of pre-eclampsia after nephrectomy. Therefore it seems advisable to have completed a planned family before donation.

13.4.2. Medical evaluation and exclusion criteria for living kidney donation

All potential LDs should have a complete 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 a clinician or a surgeon 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 national guidelines. An example is provided in Table 13.2.

Exclusion medical criteria for living kidney donation are detailed below:

a. Significant chronic disease (cardiac, pulmonary, hepatic, neurological or autoimmune).
b. Obesity.
c. Uncontrolled hypertension, hypertension with end-organ damage or controlled hypertension with one drug but multiple cardiovascular risk factors.
d. Diabetes or intolerance to oral glucose test.
e. Disorders requiring anticoagulation.
f. Chronic viral infection (HIV, HBV, HCV, HTLV) as outlined in section 13.6.1.
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 GFR.
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 (i.e. multiple renal vessels) that do not allow a safe surgery.
l. Nephrocalcinosis, bilateral kidney stones or recurrent nephrolithiasis.

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 • 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* • *Trypanozoma 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 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 section 13.6.1 and section 8.3.1.2.

13.5. Medical and surgical aspects of living liver donation

13.5.1. Risks of living liver donation

The safety issue is even more pronounced than with LDN, because the perioperative risk is definitely higher. 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 % [29, 30, 31]. Right-sided resections have been considered to involve a higher risk.

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.

Taking into account the clearly substantial mortality risk (compared with LDN), the preopera-

tive 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 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, from 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. The incidence of complications is generally higher for right than for left hepatectomy or left lateral hepatectomy, and may be related to the larger resection of liver parenchyma.

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, 2 transplantations and 1 vegetative state) [11]. Worldwide, 19 cases of documented donor deaths have been reported, 14 of which were definitely related to the donor surgery. 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. In addition, there was evidence that globally, right lobe liver donors presented with a higher mortality rate (0.5 %) compared to left lobe liver donors (0.1 %).

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 postoperative 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 start and 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 a liver donor has two sides. It has to ensure that a graft of adequate size is procured, while it also has 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 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.

Table 13.3. **Basic routine screening of the potential living liver donor**

Assessment of kidney function	**Cardio-respiratory system**
• ASAT, ALAT, bilirubin, ALP, albumin, GGT • PT, INR	• 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 • 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* • *Trypanozoma 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) • Coagulation screening (PT and APTT) • ASAT, ALAT, bilirubin, ALP, albumin, GGT • Biochemical profile • Creatinine, urea, and electrolytes • Proteinogram • Blood lipids • Thyroid function tests • Alpha-fetoprotein • B-HCG • CSF • CEA • Pregnancy test (if indicated) • PSA (if indicated)

APTT: activated partial thromboplastin time; B-HCG: human chorionic gonadotropin; CEA: carcinoembryonic antigen; CSF: neuron-specific enolase; 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 section 13.6.1.

13.6. Medical evaluation of the LD with regard to the risk of disease transmission

Disease transmission from donor to recipient can occur in the context of living donation procedures. Contrary to the situation with DDs, sufficient time is usually available for appropriate donor investigations. Therefore more extensive diagnostic procedures should be attempted for safer risk assessments. In general, the investigations recommended in DDs should be performed (see Chapter 6 and the principles summarised in Chapter 7).

13.6.1. Risk of transmission of infectious diseases

Addressing the risk of transmission of infectious diseases through living donation should adhere to the same principles applied in deceased organ donation, as outlined in Chapter 8. In the case of living donation, an infection can be acquired by the LD between screening and organ recovery. Therefore, basic screening tests should be performed first at initial counselling for living organ donation, as well as 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 should 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 about how the LD can avoid infections like HIV, HCV and HBV should be undertaken, to further reduce these risks.

Some other special considerations might be of interest in reducing the risks of transmission of infectious diseases through living donation:

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 Chapter 8, section 8.4.1.4).

c. In the case of Epstein–Barr virus (EBV) D+/R–, protocols for close monitoring of such recipients contribute to reducing the fatal complications of post transplant lymphoproliferative disorders by earlier diagnosis. EBV-DNA mon-

itoring and early treatment should be adopted for all D+/R– recipients (see Chapter 8, section 8.4.2.4).

d. In the case of a donor with HBV-infection, the principles outlined in Chapter 8, sections 8.4.2.6 and 8.4.2.8 should be applied and in the case of HCV-infection, the principles of section 8.4.2.7. After treatment of the possible donor with new antiviral drugs, donation might be considered when full virological response has been achieved, but transmission risks may persist due to the unknown issue of occult hepatitis.

e. Transmission of Kaposi sarcoma herpes virus (HHV-8) from organ donor to recipient has been documented through seroconversion and by molecular epidemiologic studies. Although the optimal serologic assay technique has not been determined, the combination of whole virion ELISA (enzyme-linked immunosorbent assay) and lytic IFA 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 of developing HHV-8 associated disease for the recipient. 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 (Paolo Grossi, personal communication).

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 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 Chapter 8, section 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 multidrug resistant pathogens.

i. Donors with curative treatment of tuberculosis (TB) can be used in living donation with some care and follow-up of the recipient. The risk of latent TB with transmission risks, as outlined in Chapter 8, section 8.5.6, should be considered; in living donation IGRA-Tests of donor and recipient are helpful. LDs with a positive TST or IGRA should be offered treatment for latent TB 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 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 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 Chapter 8, section 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 Chapter 8, section 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 section 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 eosinophilia 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 Chapter 8, 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 Chapter 8, section 8.12.

13.6.2. 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 should 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 should be 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 (pT1N0M0, 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 a good and routine practice (see Chapter 9, section 9.4.14).

Regarding donor malignancy transmission risks, the recommendations of Chapter 9 apply.

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.

13.7. Psychosocial aspects of living donation

13.7.1. Psychological risks and evaluation of living donors

Despite kidney living donation being a safe practice in general, several long-term studies on its medical, psychological and social outcomes suggest that LDs may be at increased risk of end-stage renal disease, cardiovascular mortality and all-cause mortality [2-3, 32-33]. About 25 % of LDs report psycho-

logical distress, depression and anxiety disorders, and about 30 % find that their health has worsened since donation [34]. In the recent 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 [35]. Deterioration of 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) [36]. 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 [37].

It has been recently suggested that even undergoing a donor evaluation may carry its own potential risks such as, for example, the 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 [38]. 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, 39, 42]. The most recent consensus conference held in the US identified best practices in living kidney donation and concluded, for instance, that one of the main characteristics of living kidney donors' education should be the provision of accurate and comprehensive risk–benefit information about donation [43]. Such education must include individualised and sound information to each donor, which requires the assessment of case-specific risk factors. However, only 66 % of US transplant programmes include the potential impact of donation on the donor's lifestyle in their informed consent [38]. Psychological contraindications to living donation usually include financial gain or reward, active substance abuse or dependence and, classically, active mental health problems or instability. However, a mental health evaluation is required by only 74 % of living kidney donation programmes in the US [38]. We agree with Rodrigue *et al.* that, though current figures improve on the 46 % reported twenty years ago [44], they still seem insufficient.

Other psychological factors that are considered warnings to be taken into account before indicating a living donation procedure 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 living donation outcomes. There is little doubt that further prospective studies are needed to define the precise effect of these potential risk factors. Meanwhile, 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 [34]:

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.

Finally, the recent loosening of the requirements concerning the nature of the donor–recipient relationship has led to disinterested parties, such as colleagues, now being considered as potential LDs. The relationships involved here may be far 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 [42].

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 competency; knowledge and understanding of donation risks and benefits; psychological functioning, motivations and expectations; the donor–recipient relationship; and social support (see Table 13.4) [42, 45, 46, 47].

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.

However, we agree with Abecassis *et al*. that the psychological assessment may be even more useful if applied to improving the donation procedure rather than being merely a tool to identify contraindications [41]. For instance, the detection of expectancies 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, or are willing to 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 [48]. 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 [49]. Donors who have received a pre-donation intervention on ambivalence have shown better outcomes, both physical (fewer physical symptoms, fewer unexpected medical problems, lower fatigue and pain, and shorter recovery times) and psychological (lower anxiety and fewer unexpected family problems) after donation [37]. Potential improvements in this area include: prevention of depression; promotion of health behaviours (which tend to remain unchanged after donation) other than the rate of medical check-ups; and prevention of obesity (which proportionally increases with time since donation) [50]. All these preventive interventions require a thorough assessment of risk factors.

13.7.2. 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).

Table 13.4. **Risks and exclusion criteria for living donation detectable during psychosocial evaluation**

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.
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 significant other. Donors with a strong feeling of making an autonomous decision cope better with the postoperative course. Ambivalence worsens physical and mental outcomes [37], whereas comfort with decision to donate protects the mental health quality of life [35].
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 [51], donation as a moral obligation [48], desire for recognition, using donation for publicity).

Expectations	Detect and modify unrealistic or idealised expectations (e.g. improve relationship with recipient [52]; solve psychological problems and familial conflicts [53], shorter time of recovery than can be expected [35]). Expectations define transplantation success from the patients' point of view [54].
Donor-recipient relationship	In 20 % of all cases, unresolved problems appear (e.g. unilaterally dependent relationships), half of them resign from transplant [55]. 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 [35].
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 [56].
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 expectancies of benefit while lower optimism is associated with expectation of negative consequences from donation [57].

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 his 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.

13.8. 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 member states must ensure that harmonised national LD registries are developed and maintained according to Resolution CM/Res (2015) 11 [58]. The appendix to this resolution provides characteristics and general guidelines for the construction of national/international LD registries and the explanatory memorandum details the parameters (mandatory and optional) 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 countries to develop a 'register or record of living donors' [18].

International professional standards, such as the 2004 International Forum on the Care of the Live Kidney Donor [10], have also recommended regular life-long 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 [19] that would continue to expand and increase knowledge of donation and transplant procedures through a network (http://lidobs.eulivingdonor.eu/).

13.9. ABO bloodgroup incompatible transplantation

ABO-incompatible transplantation (ABOiTx) has been introduced during the past 30 years

worldwide as a strategy to expand the donor pool in living donor transplantation – mostly kidneys. The success of centres performing ABOiT 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 ABOiTx are pre-transplant antibody removal by plasmapheresis and/or immunoadsorption to prevent hyperacute rejection and patient-tailored maintenance immunosuppression combined with immunomonitoring for early detection of re-increasing antibody titres. Still there are cases, where protocols for antibody removal fail for unknown reasons.

13.10. 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 the outcome of LD procedures performed in each country.

13.11. References

1. The Madrid Resolution on Organ Donation and Transplantation. National responsibility in meeting the needs of patients, guided by the WHO principles. *Transplantation* 2011; 91 (Suppl 11): S29-S31.
2. Muzaale AD, Massie AB, Wang MC *et al.* Risk of end-stage renal disease following live kidney donation. *JAMA* 2014; (311): 579-86.
3. Mjøen G, Hallan S, Hartmann A *et al.* Long-term risks for kidney donors. *Kidney Int* 2014; (86): 162-7.
4. IRODAT. *International Registry in Organ Donation and Transplantation* [available from: www.irodat.org, accessed: 30 January 2016].
5. International figures on donation and transplantation – 2014. *Newsletter Transplant* 2015 [available from: www.edqm.eu/en/organ-transplantation-reports-73.html, accessed: 30 January 2016].
6. Sutherland DE, Radosevich D, Gruessner R *et al.* Pushing the envelope: living donor pancreas transplantation. *Curr Opin Organ Transplant* 2012; (17): 106-15.
7. Kim J, Zimmerman MA. Technical aspects for live-donor organ procurement for liver, kidney, pancreas, and intestine. *Curr Opin Organ Transplant* 2015; (20): 133-9.
8. Matas AJ, Delmonico FL. Living donation: the global perspective. *Adv Chronic Kidney Dis* 2012; (19): 269-75.
9. Lee SG. A complete treatment of adult living donor liver transplantation: a review of surgical technique and current challenges to expand indication of patients. *Am J Transplant* 2015; (15): 17-38.
10. Delmonico F. Council of The Transplantation Society. A report of the Amsterdam Forum on the care of the live kidney donor: data and medical guidelines. *Transplantation* 2005; 79 (Suppl 6): S53-66.
11. Barr ML, Belghiti J, Villamil FG *et al.* A report of the Vancouver Forum on the care of the live organ donor: lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation* 2006; 81 (10): 1373-85.
12. *WHO Guiding Principles on human cell, tissue and organ transplantation* [available from: www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf?ua=1, accessed: 9 March 2016].
13. The Declaration of Istanbul on Organ Trafficking and Transplant Tourism. *Clin J Am Soc Nephrol* 2008; (3): 1227-31.
14. Council of Europe Convention against Trafficking in Human Organs [available from: http://conventions.coe.int/Treaty/EN/Treaties/Html/216.htm, accessed: 30 January 2016].
15. Council of Europe Convention against Trafficking in Human Beings [available from: www.coe.int/es/web/conventions/full-list/-/conventions/treaty/197, accessed: 30 January 2016].
16. 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 [available from: http://conventions.coe.int/treaty/en/Treaties/Html/164.htm, accessed: 30 January 2016].
17. Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin [available from: http://conventions.coe.int/treaty/en/Treaties/Html/186.htm, accessed: 30 January 2016].
18. Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation [available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0053, accessed: 30 January 2016].
19. Lidobs [available from: http://wp2.eulivingdonor.eu/wp-content/uploads/2015/08/

FINAL-LIDOBS-Consensus-Leaflet.pdf, accessed: 30 January 2016].

20. Venkat KK, Eshelman AK. The evolving approach to ethical issues in living donor kidney transplantation: a review based on illustrative case vignettes. *Transplant Rev* (Orlando). 2014; (28): 134-9.
21. Panocchia N, Bossola M, Silvestri P *et al.* Ethical evaluation of risks related to living donor transplantation programs. *Transplant Proc* 2013; (45): 2601-3.
22. Manyalich M, Ricart A, Martínez I *et al.* Eulid project: European living donation and public health. *Transplant Proc* 2009; (41): 2021-4.
23. Hays RE, LaPointe Rudow D, Dew MA *et al.* The independent living donor advocate: a guidance document from the American Society of Transplantation's Living Donor Community of Practice (AST LDCOP). *Am J Transplant* 2015; (15): 518-25.
24. Monaco AP, Morris PJ. Care of the live kidney donor: consensus on the ultimate gift, The Amsterdam Forum. *Transplantation* 2005; (79): S53–66.
25. Tooher RL, Rao MM, Scott DF *et al.* A systematic review of laparoscopic live-donor nephrectomy. *Transplantation* 2004; (78): 404-14.
26. Segev DL, Muzaale AD, Caffo BS *et al.* Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010; (303): 959-66.
27. Mjøen G, Øyen O, Holdaas H *et al.* Morbidity and mortality in 1022 consecutive living donor nephrectomies: benefits of a living donor registry. *Transplantation* 2009; (88): 1273-9.
28. Mjøen G, Holdaas H, Pfeffer P *et al.* Minimally invasive living donor nephrectomy – introduction of hand-assistance. *Transpl Int* 2010; (23): 1008-14.
29. Abecassis MM, Fisher RA, Olthoff KM *et al.* Complications of living donor hepatic lobectomy – a comprehensive report. *Am J Transplant* 2012; (12): 1208-17.
30. Iida T, Ogura Y, Oike F *et al.* Surgery-related morbidity in living donors for liver transplantation. *Transplantation* 2010; (89): 1276-82.
31. Cheah YL, Simpson MA, Pomposelli JJ *et al.* Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. *Liver Transpl* 2013; (19): 499-506.
32. Garg AX, Boudville N. ACP Journal Club. Live kidney donation was associated with increased mortality and end-stage renal disease at 15 years. *Ann Intern Med* 2014; (160): JC12.
33. Steiner RW, Ix JH, Rifkin DE *et al.* Estimating risks of *de novo* kidney diseases after living kidney donation. *Am J Transplant* 2014; (14): 538-44.
34. Dew MA, Jacobs CL. Psychosocial and socioeconomic issues facing the living kidney donor. *Adv Chronic Kidney Dis* 2012; (19): 237-43.
35. Gross CR, Messersmith EE, Hong BA *et al.* Health-related quality of life in kidney donors from the last five decades: results from the RELIVE study. *Am J Transplant* 2013; (13): 2924-34.
36. Clemens KK, Thiessen-Philbrook H, Parikh CR *et al.* Psychosocial health of living kidney donors: a systematic review. *Am J Transplant* 2006; (6): 2965-77.
37. Dew MA, Dimartini AF, Vito Dabbs AJ *et al.* Preventive intervention for living donor psychosocial outcomes: feasibility and efficacy in a randomized controlled trial. *Am J Transplant* 2013; (13): 2672-84.
38. Rodrigue JR, Pavlakis M, Danovitch GM *et al.* Evaluating living kidney donors: relationship types, psychosocial criteria, and consent processes at US transplant programs. *Am J Transplant* 2007; (7): 2326-32.
39. Adams PL, Cohen DJ, Danovitch GM *et al.* The nondirected live-kidney donor: ethical considerations and practice guidelines: a national conference report. *Transplantation* 2002; (74): 582-9.
40. The Ethics Committee of the Transplantation Society. The consensus statement of the Amsterdam Forum on the care of the live kidney donor. *Transplantation* 2004; (78): 491-2.
41. Abecassis M, Adams M, Adams P *et al.* Consensus statement on the live organ donor. *JAMA* 2000; (284): 2919-26.
42. Dew MA, Jacobs CL, Jowsey SG *et al.* Guidelines for the psychosocial evaluation of living unrelated kidney donors in the United States. *Am J Transplant* 2007; (7): 1047-54.
43. LaPointe RD, Hays R, Baliga P *et al.* Consensus conference on best practices in live kidney donation: recommendations to optimize education, access, and care. *Am J Transplant* 2015; (15): 914-22.
44. Bia MJ, Ramos EL, Danovitch GM *et al.* Evaluation of living renal donors. The current practice of US transplant centers. *Transplantation* 1995; (60): 322-7.
45. Leo RJ, Smith BA, Mori DL. Guidelines for conducting a psychiatric evaluation of the unrelated kidney donor. *Psychosomatics* 2003; (44): 452-60.
46. Olbrisch ME, Benedict SM, Haller DL *et al.* Psychosocial assessment of living organ donors: clinical and ethical considerations. *Prog Transplant* 2001; (11): 40-9.
47. Rodrigue JR, Bonk V, Jackson S. Psychological considerations of living organ donation. In: Rodrigue JR, editor. *Biopsychosocial perspectives on transplantation*. New York: Kluwer Academic/Plenum Publishers, 2001: 59-70.
48. Jowsey SG, Jacobs C, Gross CR *et al.* Emotional well-being of living kidney donors: findings from the RELIVE Study. *Am J Transplant* 2014; (14): 2535-44.
49. Gordon EJ, Reddy E, Gil S *et al.* Culturally competent transplant program improves Hispanics' knowledge

and attitudes about live kidney donation and transplant. *Prog Transplant* 2014; (24): 56-68.

50. Myaskovsky L, Doebler DA, Posluszny DM *et al.* Rates and correlates of health maintenance behaviors after living kidney donation. *Prog Transplant* 2012; (22): 147-54.
51. Dew MA, Switzer GE, Dimartini AF *et al.* Psychosocial aspects of living organ donation. In: Tan HP, Marcos A, Shapiro R, editors. *Living donor organ transplantation*. New York: Taylor & Francis, 2007.
52. Papachristou C, Walter M, Schmid G *et al.* Living donor liver transplantation and its effect on the donor-recipient relationship – a qualitative interview study with donors. *Clin Transplant* 2009; (23): 382-91.
53. Heck G, Schweitzer J, Seidel-Wiesel M. Psychological effects of living related kidney transplantation – risks and chances. *Clin Transplant* 2004; (18): 716-21.
54. Rodrigue JR, Hanto DW, Curry MP. Patients' expectations and success criteria for liver transplantation. *Liver Transpl* 2011; (17): 1309-17.
55. Schweitzer J, Seidel-Wiesel M, Verres R. Donor–recipient interaction: the Heidelberg model of evaluation and consultation. *Nephrol Dial Transplant* 2004; 19 (Suppl 4): iv75-8.
56. Rodrigue JR, Fleishman A, Vishnevsky T *et al.* Development and validation of a questionnaire to assess fear of kidney failure following living donation. *Transpl Int* 2014; (27): 570-5.
57. Rodrigue JR, Guenther R, Kaplan B *et al.* Measuring the expectations of kidney donors: initial psychometric properties of the Living Donation Expectancies Questionnaire. *Transplantation* 2008 15; (85): 1230-4.
58. Resolution CM/Res (2015) 11 on establishing harmonised national living donor registries with a view to facilitating international data sharing [available from: www.edqm.eu/sites/default/files/resolution_on_establishing_harmonised_national_living_donor_registries_with_a_view_to_facilitating_international_data_sharing_2015_11.pdf, accessed: 30 January 2016].

Chapter 14. **Biovigilance**

14.1. Introduction

This chapter provides guidance on the implementation of good Vigilance and Surveillance (V&S) practice for all those professionals involved in the process extending from organ donation to transplantation and follow-up of transplant recipients and living donors (LDs), and to regulation of the field.

A programme of V&S is essential for ensuring the quality and safety of human organs intended to be used for transplant. While the quality system focuses on preventing errors and maintaining a consistent standard of agreed specification for organs recovered for transplantation, occasionally residual risks or procedural errors result in graft failures, disease transmissions or situations where donors or patients were exposed to risk, even if not harmed. Based on European Union (EU) terminology, these occurrences can be classified as adverse events (AEs), which are process failures that might lead to harm in a recipient or LD, or as adverse reactions (ARs), which are adverse responses that have indeed occurred in a recipient or LD, including transmission of a disease. Therefore, an AE may or may not cause an AR. Similarly, an AR may or may not be related to an AE. The reporting of these incidents is critical for all professionals involved in the incident in question, particularly to prevent harm in patients exposed to risk. In fact, this is the key element of a V&S system. But it also represents important learning opportunities that can help all procurement organisations and transplant centres to improve their processes and to achieve higher levels of safety and quality [1, 2]. Therefore, based on a non-blame culture, the results of investigations of Adverse Reactions and Events (AREs) should be shared with the donation and transplant community.

According to Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation, a serious adverse event (SAE) is 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].

Directive 2010/53/EU defines a serious adverse reaction (SAR) 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'.

In summary, an SAR is an incident where an LD or a recipient has been seriously harmed, while an SAE is an incident that results in a risk of serious harm to an LD or recipient, although no harm has yet occurred. 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]. Ideally, all AREs should be reported by health professionals to the health

authorities that co-ordinate V&S within a given jurisdiction, to ensure that there is an appropriate investigation and that corrective and preventive actions are adopted, as needed. Those that are classified as 'serious' must always be notified in line with national or regional (e.g. EU) requirements.

Although AEs may occur at all stages from procurement to transplantation of organs, many of them are not severe, and may be managed through the Quality Management System (QMS) of the procurement organisation or transplant centre concerned. On the other hand, Serious Adverse Events and Reactions (SAREs) are rare and, therefore, there are significant benefits associated with consolidating V&S data on a regional, national or international scale.

14.2. Management and quality

As for other V&S systems, activities in the organ field should be considered and recognised at all levels of procurement organisations and transplant centres, beginning with the strategic and senior management levels. The organisation of the organ V&S system, as well as the role of the various parties involved, should be defined and broadly communicated within the centre and the organisation.

Health authorities should draw up procedures for organ V&S systems (including procedures for the connection with other vigilance systems, e.g. tissues and cells), develop notification forms, surveillance methods, acceptable risk criteria and examples of SAREs that should be reported. Appropriate communication and co-ordination between procurement organisations and transplant centres are of the utmost importance for an efficient V&S system. Any organisations or bodies involved in organ procurement and transplant should have operating procedures in place that describe how to identify, report, investigate and communicate ARE. The identification of a local vigilance co-ordinator or 'go-to person', who has responsibility for V&S specified in their job description, is an effective measure. It is recommended that the QMS and the V&S system, both of which contribute to risk management policy, should be co-ordinated at the central level according to guidelines established by the health authority.

Relevant operating procedures and the management of ARE, data collection and investigation should be evaluated during audits of procurement organisations and transplant centres. The implementation of computerised, integrated systems for ARE data collection and management is encouraged (see section 14.6.3). Further integration of these registries with other existing registries on organ procurement and transplantation activities within a given jurisdiction (e.g. outcomes of transplant recipients) can expand the possibilities of reporting and the effectiveness of V&S systems.

14.2.1. Non-serious adverse events and reactions

While this chapter focuses on the detection, reporting and investigation of SAREs, all AREs and non-compliances, including those with minor consequences, should be documented and regularly reviewed within the QMS of all involved institutions collaboratively. This allows trends to be monitored and actions to be taken to continually improve quality and safety. One important role for the health authority is to define and inform centres and professionals of those AREs that should be notified to them through vigilance and those which should be managed locally through the QMS of the centre.

14.2.2. Complaints

Complaints from any party (professionals, donors, patients or third parties) should also be managed within the QMS. They should be acknowledged immediately and investigated. A formal acknowledgement should be sent and corrective actions detailed, where appropriate. Each complaint should be considered for classification as an SAE or SAR and should be managed as such if it meets the criteria described in this chapter.

14.3. Adverse reactions

An AR has occurred when a patient or a living donor has been harmed by the process of donation or the clinical use of human organs. ARs must be detected, reported, investigated and assessed in terms of severity, imputability and frequency or probability of recurrence. Efficient review procedures must be in place where donors or recipients are found to have been exposed to a risk. Important learning outcomes from each AR should be appropriately communicated to relevant stakeholders.

A number of clinical situations should lead to an AR report. Here is a non-exhaustive list of reportable situations consistent with an SAR, modified from the list agreed upon in the EU-funded Efretos project [5]:

a. Unexpected[1] and serious immunological reactions that are outside the inherent known risk of the transplant procedure.
Example: Death due to an unintended ABO-incompatible transplantation.

b. Interruption of a transplant procedure involving unnecessary exposure to risk.
Example: Inappropriately procured or preserved organ is delivered, which is discovered once the potential recipient has been at least subjected to anaesthesia (this would be an SAR because the patient is already under anaesthesia; otherwise this would be an AE when there was no harm to the recipient). In contrast, the loss of an organ due to inappropriate procurement or preservation, with no recipient under anaesthesia is not to be considered an SAR; these incidents must be worked up within the QMS and the results must be shared with the medical community.

c. Unexpected[2] infection or serological conversion in an organ transplant recipient that might be donor-transmitted or derived.

d. Malignant disease in an organ transplant recipient that might be donor-transmitted.

e. Other unexpected disease in an organ transplant recipient that might be donor-transmitted.
Example: Metabolic disease suspected to have been transmitted through liver transplant.

f. Death of a recipient that might be related to the donor or the donation process.

g. Graft loss that might be related to the donor or the donation process (including a prophylactic transplantectomy).

h. Death of an LD as a consequence of donation.

i. Serious, surgical and non-surgical, complication in an LD that is related to the donation procedure.

j. Loss of a graft recovered from an LD before transplantation is performed.

1 Some transplant procedures are knowingly performed through ABO (or other blood group) incompatibility or through positive cross-match.

2 Some infectious disease transmissions in transplant recipients are expected in the context of a calculated risk and may not need reporting to a V&S system (e.g. CMV serological conversion when transplantation is knowingly performed with an organ from an anti-CMV reactive donor into an anti-CMV nonreactive recipient). Each jurisdiction should decide whether expected infections or serological conversions are also reported to the V&S system.

14.3.1. Detection of adverse reactions

Effective V&S relies heavily on all health professionals involved, from procurement to transplantation, namely:

a. transplant professionals who should be alert to adverse outcomes and be aware when such outcomes might be associated with the organs transplanted;

b. staff and personnel involved in organ procurement;

c. surgical and medical staff involved in organ donation and procurement activities who might be aware of or informed of additional safety information on donors during their follow-up;

d. any other staff involved in any procurement and transplant activities;

e. other vigilance systems (e.g. tissue and cell vigilance, material/device vigilance, pharmacovigilance, etc.) when issues of concern are detected that might impact on the safety of organs for transplantation.

Moreover, since V&S aims at improving patient safety, consideration should be given to the possible role of patients and patient organisations in the notification process for ARs.

As adverse transplant outcomes might result from many diverse factors associated with the surgical procedure, the patient's underlying condition and the chronic use of immuno-suppression, clinicians might not consider the transplanted organs as a possible source of the outcome. Health authorities in charge of co-ordinating vigilance, as well as organ procurement and exchange organisations, should encourage procurement and transplant professionals to always consider whether adverse outcomes might have been associated with the donation process or the transplanted organs, so that similar occurrences might be prevented in the future.

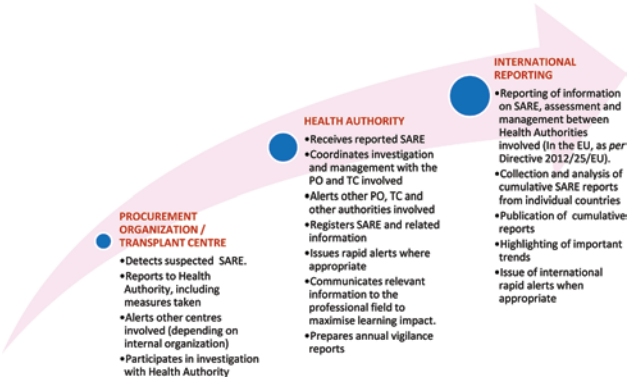
For most types of well-established organ transplants, detailed clinical outcome reporting by the transplant professionals to national and international follow-up registries is performed. This routine clinical follow-up is considered as part of vigilance if such follow up registries show up an unexpected drift in data. Also it is important that the outcomes of LDs are monitored by registries, which are required by Directive 2010/53/EU to compile information on complications related to living donation in the short, medium and long term. Therefore, collaboration between vigilance systems and registries on the outcomes of transplant recipients and LDs should be encouraged.

14.3.2. Managing and reporting adverse reactions

14.3.2.1. *Transplant centres to health authorities*

Health authorities co-ordinating vigilance within a given jurisdiction should provide transplant centres with clear instructions on how to report ARs, preferably using standardised documentation (Appendix 12 provides some examples of standardised forms for the reporting of AREs). Reporting should include a description of the AR and a root cause analysis, with the measures taken to resolve the problem and to prevent similar occurrences.

Figure 14.1. **Serious adverse reactions and events: reporting flow**



PO: Procurement organisation; SARE: Serious adverse reactions and events; TC: Transplant centre.

In general, suspected ARs should be reported promptly by professionals, before investigation or confirmation, to allow the health authority in charge of co-ordinating vigilance to take appropriate precautionary actions to prevent harm to other patients. This includes alerting all other health authorities and centres involved in a particular incident, as well as tissue establishments and clinical users of tissues if the corresponding organ donor was also a tissue donor. Professionals should be encouraged to report all kinds of suspected ARs to the health authority, serious and non-serious, allowing filtering of those that are considered serious. While ideally all ARs in transplant recipients should be reported as described, Directive 2010/53/EU sets down mandatory reporting only for SARs. The reporting flow would be identical, as represented in Figure 14.1.

14.3.2.2. *Procurement organisations to health authorities*

Similarly, health professionals at procurement organisations should report ARs in living donors to the health authority in charge of co-ordinating vigilance, even if the AR is only suspected to be donation-derived, so that the broader implications for other centres and donors can be considered without delay. Although ideally all ARs in LDs should be reported as described, Directive 2010/53/EU sets down mandatory reporting only for SARs. The reporting flow, as represented in Figure 14.1, would be identical in both cases.

A 'severity scale' can be used to decide whether a particular AR is an SAR. The EU-funded project Eustite [6] proposed a scale for tissue and cell vigilance, based on the one used for haemovigilance. This severity scale can be adapted to the field of organ vigilance as described in Table 14.1. In the EU, all ARs that meet the category of 'serious', 'life-threatening' or 'death' must be reported to the health authorities, since they meet criteria of SARs.

Table 14.1. **Severity scale for adverse reaction**

Severity	Comments
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 an LD 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 in the European Union.

Adapted from Eustite.

14.3.2.3. *Management of adverse reactions*

The health authority in charge of co-ordinating vigilance is responsible for providing procurement organisations, transplant centres and critical third parties with clear instructions, forms and guidance on how to notify ARs in accordance with national or local requirements (see section 14.6.3. and Appendix 12). AR reporting and management should be incorporated within the centre's QMS, with one or more operating procedures that describe the process 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 to protect the safety of recipients. This may involve a review of patients who have already 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.

Figure 14.2 illustrates a series of actions that need to be taken in the case of a report of suspected transmission of disease from a deceased organ and tissue donor, emphasising that communication with other organisations that might need to quarantine implicated tissues or cells, or conduct recalls or reviews (look-backs) should be quick and effective.

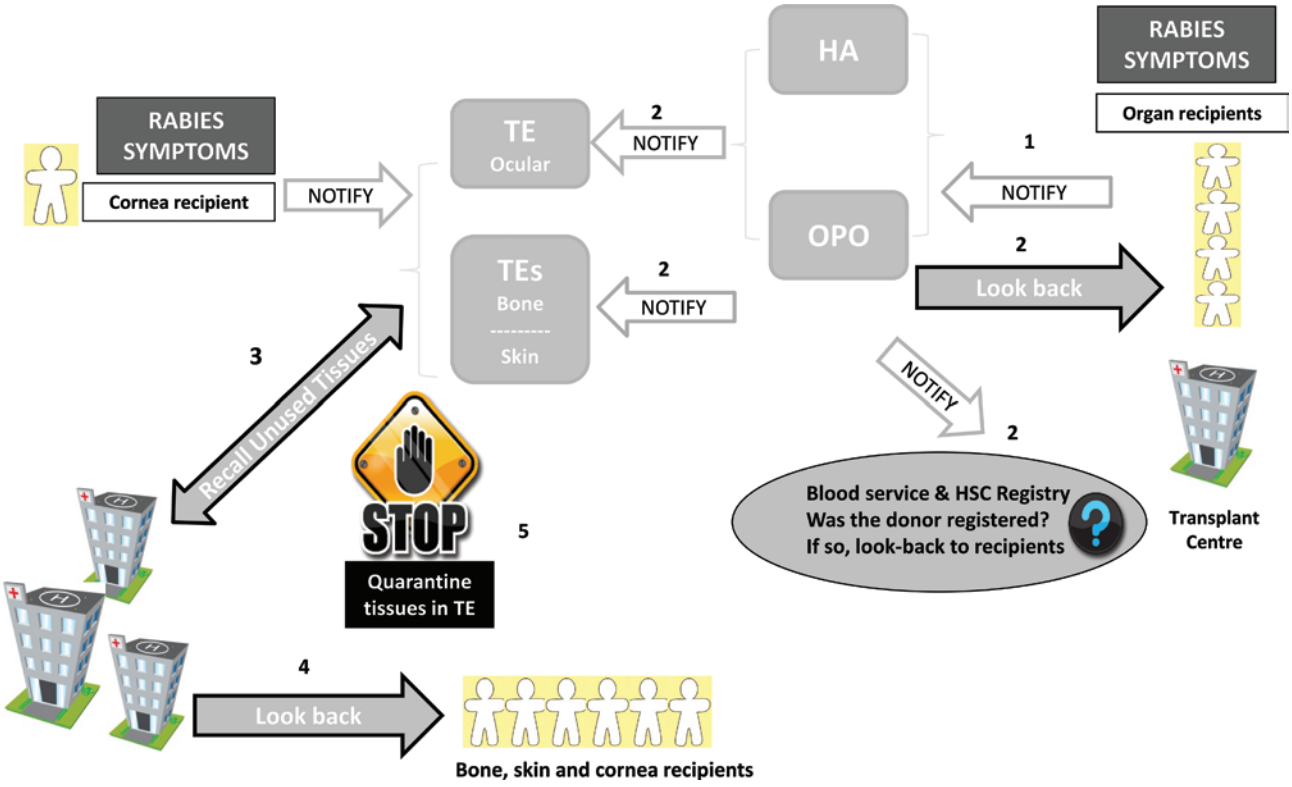
14.3.2.4. *International reporting*

Where SARs are detected in relation to organs that have entered international distribution channels, appropriate international collaboration should ensure that all stakeholders in all the countries concerned are informed and participate, as necessary, in the investigation and follow-up actions. In the EU, specific procedures have been set down by the European Commission in Implementing Directive 2012/25/EU laying down information procedures for the exchange, between Member States, of human organs intended for transplantation [7].

According to Directive 2012/25/EU, international co-operation is organised through the network of health authorities responsible for organ vigilance. Information on the corresponding SAR must be shared between them without undue delay, through a specific report containing pre-specified information (see section 14.6.3). Additional information should be shared as it becomes available during the investigation. The health authority of the country of origin of the organ has the obligation of preparing within 3 months a final report with the results of the investigation and management of the case.

In future, EU member states might share their annual reports of SAREs which have been reported within their countries with the European Commission, so that the Commission is able to compile a consolidated EU report. Such international reporting would allow for trend analyses on the basis of consolidated data. It is self-evident that, as well as international organ exchange, national health authorities co-ordinating vigilance should share their annual and cumulative reports on a European level with open access available to all member states. When a single case becomes of relevance for other national healthcare systems, then this should be shared in a rapid alert with other countries. The aim is to extract cumulative knowledge from SAREs occurring in each member state for developing preventive strategies. Thereby specific issues in a particular member state should be reviewed to establish whether they could become a pan-European issue or are restricted to the healthcare system in the particular member state. It is imperative that international organ exchange organisations contribute to sharing this information.

Figure 14.2. **Example of an adverse reaction involving quarantine, recall and review (look-back) in a complex case of organ and tissue donation**



HA: health authority; HSC: haematopoietic stem cells; OPO: organ procurement organisation; TE: tissue establishment.

14.3.3. Investigating and assessing adverse reactions

ARs in organ recipients should be investigated by a team that includes both the clinician in charge and the procurement organisation that provided the organ(s), under the co-ordination of the corresponding health authority in that country responsible for co-ordinating vigilance. Efficient co-ordination of the investigation is critical to rapid implementation of effective corrective actions. Where relevant, experts in particular fields such as viral transmission should also be invited to participate in the investigation of the AR. The investigation should focus on establishing the level of imputability, i.e. the extent to which the organs transplanted can be considered to have caused the AR. Where there is suspicion of infectious disease transmission, investigation will rely heavily on the availability of an archived sample of donor serum (see Chapter 8). It is therefore strongly recommended that frozen serum (and/or cells or DNA) samples be maintained for every donor for vigilance investigation purposes. Consideration should also be given to keeping pre-transplant serum archives for recipients to support imputability investigations [8]. Similarly, in the case of a *de novo* tumour suspected to be of donor origin in a graft recipient, appropriate investigations should be conducted to determine if the tumour developed from donor or recipient cells. If the malignancy is of donor origin, it should be further investigated if the malignancy is to be considered donor-transmitted or donor-derived (see Chapter 9).

Eustite developed a scale to describe the outcome of the imputability investigation in the field of tissue and cell vigilance, based on the one used in haemovigilance. A version of this scale adapted to the organ setting is presented in Table 14.2. It is proposed that all ARs be graded in terms of imputability.

Table 14.2 also recommends specific approaches to the establishment of imputability for suspected infectious or malignancy transmissions, as proposed by Garzoni and Ison [9]. Imputability grades might change in the course of an investigation and should generally be assigned at the point of initial notification and again at completion of the AR investigation. The evaluation of imputability should be based on scientific or clinical data. The European

Table 14.2. **Scale describing the possible outcomes of an imputability investigation**

	Adapted from Eustite-SoHO V&S [9]	**Criteria for infectious and malignant transmissions, adapted from the US Disease Transmission Advisory Committee [10]**
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 transplantation.
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 a 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, it should be noted that the same recipient was negative for the pathogen before transplant.

Centre for Disease Control (ECDC), the WHO and other sources of epidemiological or risk information may be able to support the process.

Certain ARs that have minor consequences for an individual donor or recipient might imply significant risk in a broader way. For example, an AR in a donor that then receives wide publicity might discourage donation in general, putting patients at risk through an impact on the supply of organs for transplant. These broader implications can be assessed using a tool that evaluates both the broad consequences and the probability of recurrence. An 'impact assessment tool' that was developed by the EUSTITE project can help procurement organisations, transplant centres and health authorities to decide on the level of response that might be appropriate, depending on the impact score that is allocated to a specific incident (see Appendix 13).

14.4. Adverse events

Adverse events (AEs) can occur at any moment from donor selection to clinical use of organs.

14.4.1. Detection of adverse events

For effective detection of AEs, all relevant stakeholders must be aware of their responsibilities for identifying errors or unexpected results. This includes all staff in procurement organisations and transplant centres and those working in organisations such as testing laboratories that provide third-party services to centres. In Directive 2010/53/EU, the definition of SAEs includes those incidents often referred to as 'near misses', i.e. 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.

14.4.2. Reporting of adverse events

Non-compliances with the operating procedures in place should be documented and investigated as part of the internal QMS. On occasion, however, a particular non-compliance may be of such importance that it should be considered an SAE and reported through the vigilance system. In the field of organ transplant, the evaluation of donor and organ suitability is subject to time constraints and to the inherent limitations of diagnostic tests available and used. It is therefore not infrequent that the risk related to the use of an organ is modified after the organ has been transplanted (e.g. a renal cell carcinoma is identified during the examination of the procured kidney, when a lung procured from that same donor has been already transplanted). These situations are not infrequent in the field and fall under the scope of what is defined as an SAE.

The list below enumerates situations reportable as SAEs and it aims at avoiding overburdening the organ donation and transplant system with unnecessary reports, while preserving the principles of V&S:

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: Inappropriate characterisation of donor or organ, inappropriate transmission of information related to donor HCV, HBV or HIV serology or to donor ABO group, inappropriate preservation of an organ (prolonged storage or inadequate temperature).

b. Inappropriate organs were used for transplant.

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 re-allocated it, had they been known in advance).[3]
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.
Example: Necropsy reveals a glioblastoma multiforme in a donor whose cause of death was spontaneous intracranial bleeding, after organs have been transplanted.

iii. Any other potentially transmissible disease discovered in an organ donor (deceased or living) when at least one organ has been transplanted.

3 The results of cultures, serologies, biopsies or histopathological examinations of a donor are often known only after transplantation. The information should be communicated from the procurement organisation to the transplant centre, directly or through the health authority (including any organ sharing office) as laid down in the relevant country. This is essential for good practice as this information might lead to preventive measures in the recipient. This does not imply that all positive cultures/serologies that are received after transplant (e.g. anti-CMV, anti-EBV, urine, blood or cultures) should be reported to the vigilance system, since overload could occur. As a cut-off point, only those conditions that would have prevented transplantation of the organ or could have modified its allocation should be reported to the system because they could definitely lead to an SAR.

Example: Metabolic disease in the donor undiagnosed at the moment of organ transplantation.

c. The event could have implications for other patients or donors because of shared practices, services, supplies or donors.

d. The event resulted in the loss of any organ.

14.4.3. Investigating and assessing adverse events

Despite the fact that SAEs, by definition, have not (or not yet) involved harm to recipients or donors, the impact of an SAE can be significant if considered in a broader way. The 'impact assessment tool' mentioned above (see Appendix 13) can also be applied to SAEs to help reach a decision on the response required.

14.5. Vigilance co-ordination

Co-ordination between various systems of vigilance (e.g. tissue and cell vigilance, medical device vigilance, pharmacovigilance) should be in place both at the local level (centres) and at the health authority level.

14.5.1. Rapid alerts

In some circumstances, a particular ARE requires rapid communication nationally or internationally to facilitate urgent action, such as a recall of products or critical materials (e.g. preservation liquids). Rapid alerts 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 within or between EU Member States:

a. 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).

14.6. Vigilance communication

14.6.1. 'No blame' culture

Effective communication of the results of vigilance systems is fundamental to ensuring that the benefits of these programmes are realised in practice. Regular feedback to health professionals is critical in supporting continued ARE notification. All stakeholders, health authorities, procurement organisations 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. The message that reporting and disseminating V&S information can result in positive improvements for donors and patients should be promoted.

14.6.2. Vigilance experience and feedback

Health authorities and professional societies should publish the results of their programmes 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 has gathered information on documented types of adverse occurrences in transplantation and assisted reproduction and reviewed the cases to identify general principles supporting detection and investigation. The database that has been constructed from the information gathered is accessible on a dedicated website [11]. 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 efficacy.

14.6.3. Practical considerations

Initially stakeholders identifying an incident as a potential SARE should report it to the health authority responsible for co-ordinating vigilance within a member state. International organ exchange organisations should provide the interfaces between the health authority of each member state and the health authority of the country of origin of the donor. This latter health authority should rapidly alert all parties concerned and further information should be collected at the centres involved in assessing the case as an SARE or an incident to be handled by the QMS. In the case of an SARE, an initial report has to be generated and after further work-up and investigation a final report issued. Thereby all stakeholders must supply the information as requested by the health authority of the country of origin of the donor.

The final report should include recommendations for management of the case, including recommendations on the need for dedicated long-term follow up of recipients at risk.

An SARE monitoring system should be introduced as a nationwide, centralised and web-based network integrated with other registries related to organ procurement and transplant (waiting list, co-ordination records of deceased donors, transplant registry, live donor registry). Such modern network technologies may connect all participants associated with organ donation and transplant (donor hospitals, tissue typing laboratories, qualifying centres, transplant centres, post-transplant care facilities, national transplant organisation). In each of these centres persons are designated as responsible for the notification of AREs [12].

National healthcare systems must provide appropriate human resources and technical resources for V&S.

14.7. Surveillance for new risks

Vigilance programmes should include an activity of scanning for new risks that have not previously been recognised. New risks may be related to 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 infectious diseases, for which targeted testing can be performed or which might imply the need to exclude certain donors, represent an example of one type of new risk. The ECDC monitors the epidemiology of diseases in Europe and publishes a weekly Eurosurveillance report that provides useful data to support the development of donor selection policy. 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 surveillance is the mosquito monitoring in Europe by the ECDC for detecting potential risks due to emerging vectors and implications for transmission risks (see Chapter 8).

14.8. Conclusions

V&S is a necessary element in optimising organ donation and transplant programmes, from donation to transplantation and follow-up care of patients. 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. The introduction of V&S systems facilitates the monitoring of adverse occurrences, leading to preventive and corrective measures, and to an overall improvement in safety.

14.9. References

1. Kohn LT, Corrigan JM, Donaldson MS, editors. *To err is human: building a safer health system*. Washington, DC: National Academy Press, 2000.
2. Leape LL. Reporting of adverse events. *N Eng J Med* 2002; (347): 1633-8.
3. Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation [available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:PDF, accessed: 30 January 2016].
4. Notify Library [available from: www.notifylibrary.org, accessed: 30 January 2016].
5. Report on the use of the European Registry of Registries. Efretos project [available from: www.efretos.org/images/EFRETOS_Deliverable%2011_FINAL.pdf, accessed: 30 January 2016].
6. Fehily D, Sullivan S, Noel L *et al.* Improving vigilance and surveillance for tissues and cells in the European Union: Eustite, SoHO V&S and Project Notify. *Organs, Tissues and Cells* 2012; (15): 85-95.
7. Commission Implementing Directive 2012/25/EU of 9 October 2012 laying down information procedures for the exchange, between Member States, of human organs intended for transplantation [available from: http://ec.europa.eu/health/blood_tissues_organs/docs/organs_impl_directive_2012_en.pdf, accessed: 30 January 2016].
8. Czerwiński J. Biobank concept in Poland. *Transplant Proc* 2012; (44): 2169-70.
9. Garzoni C, Ison M. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. *Transplantation* 2011; (92): 1297-1300.
10. *SoHO V&S Guidance for competent authorities: communication and investigation of serious adverse events and reactions associated with human tissues and cells* [available from: www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Communication%20and%20Investigation%20Guidance.pdf, accessed: 30 January 2016].
11. Fehily D, Strong DM, Minutoli D *et al.* Sharing vigilance experience and knowledge globally: a preliminary overview of the Notify Library. Organs, Tissues & Cells 2013; (16): 117-25.

12. Czerwiński J, Kaliciński P, Danielewicz R. Serious adverse events and reactions in organ donation and transplantation: a web-net tool-based nationwide system for referring and monitoring. *Ann Transplant* 2015; (20): 243-8.

Related documents: Appendix 12. Biovigilance standardised notification form for adverse events and reactions (France, English-language version); Appendix 13. Impact assessment tool for adverse events and reactions (Eustite and SoHO).

Chapter 15. Quality management in organ donation and transplantation

15.1. 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 donor 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.

15.2. 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.

There are three main models for quality management used in the healthcare sector, which are discussed below: ISO, JCAHO and EFQM. It must be very clear that these are different options.

15.2.1. The ISO model

ISO stands for International Organization for Standardization (a federation of national organisations) [1]. In ISO language, a 'standard' is a technical document that contains standardised specifications for a product, machinery, material, technique or service, for example. Compliance with the requirements set out in the standard allows certification of

the product, machinery, material, technique, service or whatever the standard refers to.

The ISO 9000 family, approved by CEN (European Committee for Standardization) as a European standard covering quality management systems, addresses various aspects of quality management and contains some of ISO's best known standards:

a. ISO 9001: 2008 – defines requirements of a quality management system
b. ISO 9000: 2005 – describes basic concepts and language
c. ISO 9004: 2009 – focuses on how to improve a quality management system
d. ISO 19011: 2011 – sets out guidance on internal and external audits of quality management systems.

ISO 9001: 2008 on quality management system requirements is particularly relevant to the provision of organs, and is the only standard in the family to which certification is possible. In essence, it is aimed at the formal and documentation-based aspects of the system and includes five basic requirements: a) quality management system; b) management responsibility; c) resource management; d) product and service realisation; and e) measurement, analysis and improvement. The standard can be applied in any organisation, regardless of its size or area of activity. Over one million organisations in over 170 countries have implemented this standard.

In 2012 a new European Standard was published: DIN EN 15224: 2012 on requirements for quality management systems in healthcare services. This standard is based on EN ISO 9001: 2008 but includes additional specifications for healthcare organisations (www.named.din.de).

This model is used both in the European Union (EU) and in the United States of America.

15.2.2. The JCAHO-JCI model

JCAHO stands for Joint Commission on Accreditation of Healthcare Organizations [2]. This standard-setting institute was created in 1951 on the basis of an agreement between healthcare-professional associations and the American Hospital Association. Its initial mission and general philosophy were similar to ISO: the creation of professional standards to provide voluntary self-regulation. Only instead of being in the industrial sector, it was specifically in the hospital setting; instead of 'rules', they talk about 'standards'; and instead of 'certify', they use the term 'accredit'. Like ISO, they have a programme with a predominantly external focus (audits), which provides a result (accreditation) that has to be renewed periodically.

The JCAHO evaluates and accredits over 20 000 healthcare organisations and programmes in the United States. Programmes include ambulatory and clinical laboratory, home care, hospital, long-term care, medical transport and primary care centre. There is also a special Disease-Specific Care certification for organisations that offer disease-specific and chronic healthcare, and an advanced level of certification for certain diseases, e.g. heart failure, chronic obstructive pulmonary disease, diabetes mellitus and chronic kidney disease.

The Joint Commission International (JCI) was established in 1994 by the JCAHO and brings their aims and goals onto an international level. JCI has a presence in over 90 countries all over the world.

Over time, changes have been made to the standards in an attempt to improve them from being purely structural to also include process and outcome indicators, while the aim is that the accreditation process should become an aid towards continuous improvement, and not just a process of external recognition.

15.2.3. EFQM model

EFQM stands for European Foundation for Quality Management [3]. The EFQM was set up in 1988 with EU support by 14 large European companies. It does not define a model for external certification, but has developed the EFQM Business Excellence Model as a reference framework for self-assessment of the excellence level in the business or in the service sector. To be eligible for general recognition (which is achieved through the attainment of a certain overall score), an external audit is required.

This model does not discuss rules or standards, but uses the term 'criteria' for the assessment. The criteria are in fact broad areas to be assessed (each 'criterion' actually includes several 'sub-criteria' and various levels of compliance), grouped into 'agent' criteria (similar to structure and process) and results' criteria.

It is used primarily in countries belonging to the EU.

15.2.4. Comparison of the three models

A comparison between the three models reveals that:

a. There are few philosophical differences among the three models. All have the 'customer' as the focus of the organisation and of the quality,

although in the EFQM model there is a more obvious focus on the concept of total quality.

b. In terms of practical application, all three models involve a monitoring scheme. The actual situation is compared with pre-established standards (ISO and JCAHO) or criteria (EFQM) 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 model is the only one 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.

d. For the moment, ISO and JCAHO are designed as external programmes which provide recognition (certification or accreditation), while the EFQM model provides for self-assessment, although an external audit is required if the organisation also wishes to receive recognition.

We can say that all three 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.

15.3. 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 maintain public and professional confidence in their safety and efficacy. 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.

Quality is the responsibility of the healthcare professionals involved in donation and transplant processes and 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 [4]. 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 [5] 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 possibly supported by EU funding, thus fully in line with a logic of continuous quality improvement.

Applying a systematic approach to quality management in this process involves separate reviews of:

a. Government and health authority responsibilities;

b. Quality management in organ donation;

c. Quality management in organ transplant.

15.4. Government and health authority responsibilities in organ donation and transplant: a framework for quality and safety

In order to reduce the risks and maximise the benefits of transplantation, 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 to ensure the highest possible quality, safety and transparency of the process.

The recovery and distribution of organs has to be properly regulated. The health authorities of the state must play a 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 [4], and other major recommendations [5-12] 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 through 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 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, traceability and accountability.

c. An organ-allocation system with strong guarantees, in terms both of 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 auditing 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 comprehensive framework for quality and safety for the whole chain, with the adoption and implementation of standard operating procedures (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. ensuring 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 needin liver, intestinal or heart transplant, life-threatening conditions, recipients highly sensitised against HLA-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 nonfunction, 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 'accessibility 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.

For further details about the recommendations and regulations in the donation and transplant field at international level see Table 15.4.

Nota bene: With the transposition of Directive 2010/53/EU into national laws, some of these principles are now mandatory requirements in EU member states and EEA countries, while some others fully remain under the competence of the member states. All remain nevertheless crucial recommendations.

15.5. 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.

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 which will allow us to improve outcomes, in terms of increasing both the number of donors and the number of organs transplanted.

Any of the quality management models presented earlier could help to achieve these objectives when applied to the process of organ donation in hospitals or donor procurement organisations. For the following description, the basic outline of the ISO model will be used, given its wider diffusion at international level.

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 [11, 12], best practices [13] and quality indicators (QI) [14, 15]. Quality criteria (QC), also called 'best or good practices', are conditions that have to be met by the healthcare practice in order to be considered a quality practice.

The EU-funded 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 [14]. The project identified 123 QC 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 [15].

The quality conditions that should be met in the different key activities of the donation process are reviewed below.

15.5.1. 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 competent health authorities to carry out these activities [4, 15].

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 [4].

There must be sufficient, suitably qualified personnel to carry out all tasks. Every Donation Team (DT) should consist of enough members to ensure that the donation activities can be carried out 24/7 [4, 13, 15]. 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 [4]. 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 [4, 10]. The ideal profile of the key donation person would include motivation, dedication, work capacity and good communication skills [13]. The key donation person should report directly to the head/director of their institution [15].

Every donor hospital should have an office for the exclusive use of the DT. It should be identified by a sign, secure and equipped with means of communication (telephone, fax, Internet) [15].

In addition, the organisation should include an independent head of quality management.

Table 15.1. **Quality indicators (QIs) 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	100 %
4 Long-term follow-up of living donors	LD	process	20 %
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.

Source: Project Odequs (Organ Donation European Quality System) [15].

15.5.2. 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 [10, 13, 15]. 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 DT should also define objectives for research projects, conference communications and scientific publications relating to donation [15].

15.5.3. Donation process – implementation of protocols

The following aspects of the donation process should be included in the protocols and monitored [4, 15]:

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 DT all possible donors whatever the medical situation is (age, past medical history, etc.). The DT 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 and selected by the DT in order to establish their suitability for organ donation 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 standard operating procedures 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 (see Article 8, 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 DT 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).

15.5.4. 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 [16].

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, 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.

Table 15.2. **Most important indicators applied in Dopki pilot experience**

Indicators applied in Dopki pilot experience (key indicators highlighted in bold)
a) Indicators relating to the potential for deceased organ donation
Of the number of deaths • **Brain deaths (possible and confirmed)/hospital deaths × 100** • **Brain deaths (possible and confirmed)/ICU deaths × 100** • Brain deaths (possible and confirmed)/Number of persons who died within the hospital containing among their primary and/or secondary diagnosis at least one of the ICD codes [11] representing diseases potentially progressing towards a situation of brain death × 100 • Brain deaths (possible and confirmed)/Number of persons who died within the ICU containing among their primary and/or secondary diagnosis at least one of the ICD codes [11] representing diseases potentially progressing towards a situation of brain death × 100
b) Indicators relating to areas for improvement in the deceased donation process
Of the number of brain deaths (BD) (possible and confirmed) • BD not referred/BD × 100 • BD lost because of medical contraindications to organ donation/BD × 100 • BD lost because of maintenance problems/BD × 100 • BD lost due to refusal for organ donation/BD × 100 • BD lost due to coroner refusal for organ donation/BD × 100 • BD lost due to organisational problems/BD × 100 • BD lost for other reasons/BD × 100
Of the total number of families approached and judicial requests to proceed with organ donation • Number of families who refused organ donation/Number of families approached to request organ donation × 100 • Number of coroner refusals of organ donation/Number of judicial requests for organ donation × 100
c) Indicators relating to the global effectiveness in the deceased donation process
Regarding the number of deaths • Actual donors/Hospital deaths × 100 • Actual donors/ICU deaths × 100 • **Actual donors/Brain deaths (possible and confirmed) × 100**
Other
• Multiple-organ donors/Actual donors × 100 • **Utilised donors/Actual donors × 100** • **Organs recovered/Actual donors × 100** • Organs utilised/Actual donors × 100 • **Organs utilised/Utilised donors × 100**

Actual donor: A donor from whom at least one organ has been recovered for the purpose of transplantation; Utilised donor: An actual donor from whom at least one organ has been transplanted.

Source: Coll E, Czerwinski J, De la Rosa G *et al.*, editors. Guide of recommendations for quality assurance programmes in the deceased donation process [12].

In relation to the organ donation process, 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) [12] and the others were developed in the Odequs project [14, 15]. Both projects were funded by the European Commission.

Table 15.3. **DD indicator 6b in the Odequs project: documentation of reason for non-donation**

Name	**6b. Documentation of cause of 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. Recommendation C.
Dimension	Appropriateness
Formula	$\frac{\text{Number of referred failed donors in which the cause of non-donation is properly documented}}{\text{Number of referred failed donors}} \times 100$
Explanation of terms	Donor referral: see glossary Possible donor: see glossary 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.
Reference	Coll E, Czerwinski J, De la Rosa G, Domínguez-Gil B (coord.): Guide of recommendations for quality assurance programmes in the deceased donation process. Dopki 2009. www.ont.es/publicaciones/Documents/DOPKI%20GUIA.pdf. Last accessed March 2016.

Source: Project Odequs (Organ Donation European Quality System) [15].

15.5.4.1. *Quality indicators developed by the Dopki project*

These recommendations 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 [17-21]. This includes group discussions on specific aspects and the pilot experience which took place during the project in a group of volunteer hospitals (30 hospitals in 10 European countries) with the aim of validating the pre-agreed methodology.

QIs developed by the Dopki Project were grouped as follows [12]:

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.

Indicators developed during the DOPKI pilot experience are shown in Table 15.2. Out of those, six key indicators were identified, in two groups:

a. Indicators related to the potential for deceased organ donation
   i. Number of brain deaths (possible and confirmed) compared with the number of hospital deaths.
   ii. Number of brain deaths (possible and confirmed) compared with the number of ICU deaths.

   Brain death should be considered as existing when the diagnostic procedure for brain death is initiated (possible brain death) and/or completed (confirmed brain death).

b. Indicators related to global effectiveness in the deceased donation process:
   i. Number of actual donors (persons from whom at least one organ was recovered for the purpose of transplant) out of the total number of brain deaths (possible and confirmed).
   ii. Number of utilised donors (persons from whom at least one organ was recovered and subsequently transplanted) out of the total number of actual donors.
   iii. Number of organs recovered per actual donor.
   iv. Number of transplanted organs per actual organ donor.

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 (i.e. consent rate) [12].

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 with regular external audits performed by experts from other hospitals, regions or countries, in order to further improve the process and provide greater transparency.

As a summary of the use of this group of indicators it is important to note that:

a. Periodic evaluation can inform us about the process of quality improvement in different aspects of organ donation.
b. DOPKI recommendations are exclusively focused on the process of DBD.
c. The groups of indicators forms 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.
d. Reference values (national, regional, etc.) 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 area we are analysing.
e. 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.

15.5.4.2. *Quality indicators developed by the ODEQUS project*

The ODEQUS consortium has developed a quality management system to assess the performance of organ procurement at hospital level. Their 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 [14].

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 re-

covery/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 QCs previously identified [15]. The list of QIs developed by Odequs is shown in Table 15.1, specifying 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 15.3 and 15.4 show 2 QIs of deceased donation: 'Documentation of reason for non-donation', valid for DBD/DCD (Table 15.3) and 'Controlled DCD donor identification' (Table 15.4). Each one of the QIs includes:

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; B: inconsistent or limited-quality patient-oriented evidence; and 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, i.e. 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 and comments (scientific soundness, face validity, reliability, references to literature regarding scientific evidence, etc.) [15].

Table 15.4. **DD indicator 10 in the Odequs project: cDCD donor identification**

Name	**10. Controlled DCD donor identification**
Justification	Seminars on organ donation. 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 nearly 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. Recommendation C.
Dimension	Effectiveness
Formula	$\frac{\textit{Number of patients who underwent WLST and who were apparently medically suitable for organ donation and were correctly identified and referred}}{\textit{Number of patients who underwent WLST and who were apparently medically suitable for organ donation}} \times 100$
Explanation of terms	WLST: withdrawal of life-sustaining therapies, in an ICU patient Identified and referred: the patient is reported to the Donation Team 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, sepsis with multiorgan failure or 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.
References	'Ethics Committee, American College of Critical Care Medicine; Society of Critical Care Medicine'. Recommendations for non heart beating organ donation. A position paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine." *Crit Care Med.* 2001 Sep; 29 (9): 1826-31. Reich DJ, Mulligan DC, Abt PL, *et al*. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant*. 2009 Sep; 9 (9): 2004-11. Steinbrook R. Organ Donation after Cardiac Death. *N Engl J Med*. 2007 Jul 19; 357 (3): 209-13. Bernat JL, D'Alessandro AM, Port FK, *et al*. Report of a National Conference on Donation after cardiac death. *Am J Transplant*. 2006 Feb; 6 (2): 281-91. Wind J, Snoeijs MG, Brugman CA, *et al*. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med*. 2012 Mar; 40 (3): 766-9.

DCD: donation after circulatory ceath; ICU: intensive care unit; WLST: withdrawal of life-sustaining therapy.

Source: Project Odequs (Organ Donation European Quality System) [15].

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 commitment to take action at the time the practice evaluated presents below-standard results, discuss these results, analyse the causes and 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 3 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.

Another EU-funded project should be mentioned here: the Joint Action ACCORD (2012-15) has a work package (Work Package 5) focused on deceased donation and more specifically on collaboration between ICUs and donor co-ordinations. 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 [22].

15.5.5. 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: DT personnel review each step in the process.
b. Internal audit: performed by the organisation's own quality personnel.
c. External audit: carried out by independent bodies, often designated as approved or competent authorities; it is often required for accreditation or licensing purposes.

Following international recommendations, as a complement to the self-assessments, each procurement organisation should perform an annual external audit of the organ donation process and should implement corrective measures when needed [11, 13, 15].

After each donation operation, a debriefing should take place with the DT 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 [15].

15.5.6. 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 and cover at least the following items:

a. A quality manual.
b. Standard operating procedures (SOPs) and protocols.
c. Records on performance of operations (e.g. donor selection, 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 [4]. 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. Facilities should have an alternative system that ensures continuous operation in the event that computerised data are not available.

15.5.7. 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 evaluation 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 [4].

15.5.8. 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 [4]. For further details about the biovigilance system, see Chapter 14.

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, 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 member states.

15.5.9. Risk assessment and mitigation

The procurement, manipulation and distribution of organs should be subject to a comprehensive risk assessment [4]. Where appropriate, a 'process flow' diagram listing all relevant steps, processes, reagents, 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.

15.5.10. Complaints and recalls

All complaints and concerns regarding donor material should be documented, carefully investigated and dealt with as quickly as possible. Effective written procedures must exist for recalling defective/suspect products [23]. 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.

15.5.11. 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.

Table 15.5. **Some quality indicators that could be used in organ transplantation, regardless of organ**

Indicators applied in organ transplantation
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 appointment request for transplant evaluation divided by number of patients referred for transplant evaluation multiplied by 100 for a given period. • Type: Process
Quality of clinical report by doctor responsible for referring a candidate to the TC • Definition: percentage of 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 divided by total reports sent to the committee multiplied by 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) divided by total number of patients on the waiting list multiplied by 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) divided by total number of patients placed on the waiting list multiplied by 100 for a given period. • 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 divided by total number of transplant patients for the same period multiplied by 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 divided by total number of transplant patients multiplied by 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). • Formula: number of organs in a given period preserved by cold ischaemia for more than 3, 5, 10, 15 and 20 h (as applicable) divided by total number of organs transplanted multiplied by 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 divided by number of transplanted organs (based on applicable national acceptance criteria for living donors) multiplied by 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 divided by number of transplant patients multiplied by 100, for the same period. • Type: Outcome
Early reoperation 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 reoperation in the first 15 days divided by number of transplant patients multiplied by 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 divided by number of transplant patients multiplied by 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. • Formula: number of re-transplants in a given period divided by total number of transplants in the series multiplied by 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) divided by 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) divided by 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 divided by number of transplant patients multiplied by 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: [25, 26, 27, 28, 29].

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 HLA 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.

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 case 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 their 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 reagents 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 [23]. 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.

15.6. 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 the cornerstone of this area of healthcare.

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' (TC) 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.

15.6.1. Organisational issues: legal framework, functional organisation and personnel

A TC 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 [24].

As multidisciplinary functional units, TCs 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. TCs 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 [25].

TCs 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 TC 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.

TCs must have adequate physical space to suit the needs of the different areas for inpatients and outpatient follow-up visits.

In addition, TC personnel should also include an independent head of quality management.

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 TCs, including the types and quantities of organs procured and transplanted [4].

15.6.2. 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 [4]. TCs 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 TC 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 and the training outcomes achieved, and effectiveness in meeting the envisaged objectives should also be evaluated.

15.6.3. 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 steps, which should be properly monitored and written into procedures and protocols [25]:

a. Assessment and consensus, which aims at assessing and agreeing whether a transplant is indicated for the patient and establishing a degree of urgency or priority and specific measures to optimise results. TCs 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 TC's waiting list and regional/national registries (as applicable).
  ii. Clinical monitoring of patients on the waiting list to enable the 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. 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. Correctly allocating organs to recipients.
   iii. Correctly preparing patients.
   iv. Optimising the time to start of surgery and immediate results in transplanting the organ.
   v. Transplanting the appropriate organ in line with the recipient's clinical characteristics.
   vi. 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, 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 his graft, but also more generally for the whole scientific community to learn from past transplants.

15.6.4. Quality indicators

Some medical societies and working groups have defined their systems of transplant quality management by selecting various quality indicators (QI) that, when monitored, enable relevant aspects of the process to be measured and evaluated periodically [25-29]. 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 TC 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 [16].

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 15.6.3.

The list of selected indicators is shown in Table 15.5, 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 25-29.

15.6.5. Audits and quality evaluation

As in the donation process (see section 15.5.5), the viability of a quality-indicator monitoring system should be evaluated by internal and external audits, thus enabling improvement measures to be subsequently taken as needed.

15.6.6. Documentation and registries, traceability, vigilance system, assessment and mitigation of risks, complaints and recalls, and resource management

The quality criteria relating to all of these support processes can be superimposed on those mentioned in the respective sections on quality man-

agement in organ donation, and so the reader is encouraged to review sections 15.5.6 to 15.5.11.

15.7. 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.

15.8. References

1. Organization for Standardization [available from: www.iso.org/iso/home/about.htm, accessed: 30 January 2016].
2. Joint Commission on Accreditation of Healthcare Organizations [available from: www.jointcommission.org/about_us/about_the_joint_commission_main.aspx, accessed: 30 January 2016].
3. European Foundation for Quality Management [available from: www.efqm.org, accessed: 30 January 2016].
4. Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. *Official Journal of the European Union* 2010; 53: 14-29 [available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32010L0053:EN:NOT, accessed: 30 January 2016].
5. Communication from the Commission. Action Plan on Organ Donation and Transplantation (2009-2015): strengthened cooperation between member states. COM(2008) 819/3. Commission of the European Communities [available from: http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_action_en.pdf, accessed: 30 January 2016].
6. Council of Europe Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities, 2004 [available from: https://wcd.coe.int/ViewDoc.jsp?id=802901, accessed: 30 January 2016].
7. Council of Europe Recommendation Rec (2001) 5 of the Committee of Ministers to member states on the management of organ transplant waiting lists and waiting times. 2001 [available from: https://wcd.coe.int/ViewDoc.jsp?id=190641, accessed: 9 March 2016].
8. Council of Europe Recommendation Rec (2006) 15 of the Committee of Ministers to member states on the background, functions and responsibilities of a National Transplant Organisation (NTO). 2006 [available from: https://wcd.coe.int/ViewDoc.jsp?id=1062653, accessed: 9 March 2016].
9. Directive 2012/25/EU of 9 October 2012 laying down information procedures for the exchange, between member states, of human organs intended for transplantation. *Official Journal of the European Union* 2012; (55): 27-30 [available from: http://ec.europa.eu/health/blood_tissues_organs/docs/organs_impl_directive_2012_en.pdf, accessed: 30 January 2016].
10. Council of Europe 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") [available from: https://wcd.coe.int/ViewDoc.jsp?id=870643, accessed: 30 January 2016].
11. Council of Europe Recommendation Rec (2006) 16 of the Committee of Ministers to member states on quality improvement programmes for organ donation [available from: https://wcd.coe.int/ViewDoc.jsp?id=1062721, accessed: 30 January 2016].
12. Coll E, Czerwinski J, De la Rosa G *et al.*, editors. *Guide of recommendations for quality assurance programmes in the deceased donation process*. DOPKI Project (European Commission) [available from: www.ont.es/publicaciones/Documents/DOPKI%20GUIA.pdf, accessed: 30 January 2016].
13. National Transplant Organisation (Spain). Good practice guidelines in the process of organ donation, 2011 [available from: www.ont.es/publicaciones/Documents/VERSI%C3%93N%20INGLESA%20MAQUETADA_2.pdf, accessed: 30 January 2016].
14. Manyalich M, Guasch X, Gomez MP *et al.* and ODEQUS Consortium. Organ Donation European Quality System: ODEQUS project methodology. *Transplant Proc* 2013; (45): 3462-5.
15. Project ODEQUS (Organ Donation European Quality System) [available from: www.odequs.eu/pdf/

ODEQUS_Quality_Criteria-Indicators.pdf, accessed: 30 January 2016].

16. Rubin HR, Pronovost P, Diette GB. From a process of care to a measure: the development and testing of a quality indicator. *International Journal for Quality in Health Care* 2001; (13): 489-96.
17. Wight C, Cohen B, Roels L *et al.* Donor action: a quality assurance program for intensive care units that increases organ donation. *Journal of Intensive Care Medicine* 2000; (15): 104-14.
18. Wesslau C, Grosse K, Krüger R *et al.* How large is the organ donor potential in Germany? Results of an analysis of data collected on deceased with primary and secondary brain damage in intensive care unit from 2002 to 2005. *Transpl Int* 2007; (20): 147-55.
19. Procaccio F, Rizzato L, Ricci A *et al.* Indicators of efficiency in potential organ donor identification: preliminary results from the national registry of deaths with acute cerebral lesions in Italian intensive care units. *Organs, Tissues and Cells* 2008; (2): 125-9.
20. 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.
21. Barber K, Falvey S, Hamilton C *et al.* Potential for organ donation in the United Kingdom: audit of intensive care records. *BMJ* 2006; (332): 1124-7.
22. EU Joint Action: achieving comprehensive coordination in organ donation throughout the European Union (Accord). Work Package 5: Increasing the collaboration between donor transplant co-ordinators and intensive care professionals [available from: www.accord-ja.eu/content/work-package-number-5-intensive-care-donor-transplant-coordination-collaboration, accessed: 9 March 2016].
23. European Centre for Disease Prevention and Control. Communicable disease threats report (CDTR), week 14, 1-7 April 2012: Contamination of a medical product – ViaSpan Multistate (worldwide) [available from: http://ecdc.europa.eu/en/publications/Publications/120410-SUR-CDTR.pdf, accessed: 30 January 2016].
24. Council of Europe. Recommendation Rec (2004) 19 of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities [available from: https://wcd.coe.int/ViewDoc.jsp?id=802901, accessed: 30 January 2016].
25. Taber DJ, McGillicuddy JW, Bratton CF *et al.* The concept of a composite perioperative quality index in kidney transplantation. *J Am Coll Surg* 2014; (218): 588-97.
26. Sultan H, Famure O, Phan NT *et al.* Performance measures for the evaluation of patients referred to the Toronto General Hospital's kidney transplant program. Healthcare Management Forum 2013; (26): 184-90.
27. Herrero JI and Sociedad Española de Trasplante Hepático. III Consensus Meeting of the Spanish Society of Liver Transplantation. Hepatitis C, living-donor liver transplantation, quality of liver grafts and of liver transplantation programs. *Gastroenterol Hepatol* 2011; (34): 641-59 (in Spanish).
28. Varona MA, Soriano A, Aguirre-Jaime A *et al.* Statistical quality control charts for liver transplant process indicators: evaluation of a single-center experience. *Transplant Proc* 2012; (44): 1517-22.
29. Alonso Gil M, editor, Arizón del Prado JM, Castro Fernández AJ *et al.* Trasplante cardíaco: proceso asistencial integrado. 1ª ed [Sevilla]: Consejería de Salud, 2004. Capitulo 6: Evaluación (in Spanish) [available from: www.juntadeandalucia.es/salud/sites/csalud/contenidos/Informacion_General/p_3_p_3_procesos_asistenciales_integrados/pai/trasplante_cardiaco_v3?perfil=org, accessed: 30 January 2016].

Appendix 1. **Abbreviations and acronyms**

ABO	blood group according to the ABO-system
ACLD	deaths with acute primary or secondary cerebral lesions
Accord	Achieving comprehensive co-ordination in organ donation throughout the European Union
ADH	anti-diuretic hormone
ADEM	acute disseminated encephalomyelitis
AE	adverse event
ADM	aggressive donor management
ADPKD	autosomal dominant polycystic kidney disease
AHA	American Heart Association
AJCC	American Joint Cancer Committee (USA)
ALAT	alanine amino transferase
ALL	acute lymphoblastic leukaemia
Alliance-O	European Group for Coordination of Research Programmes on Organ Donation and Transplantation (EU-funded research project)
ALT	aspartate aminotransferase
anti-CMV	antibodies against cytomegalovirus (total antibodies of IgG and IgM)
anti-EBV	antibodies against Epstein–Barr virus (anti-EBV-VCA-IgG is usually tested in donors)
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 human immunodeficiency virus (without definition of the subtype)
anti-HIV-1/2	antibodies against human immunodeficiency virus subtypes 1 or 2
anti-HIV-1	antibodies against human immunodeficiency virus subtypes 1 only
anti-HIV-2	antibodies against human immunodeficiency virus subtypes 2 only
HIV-1-p24-Ag	p24-antigen of human immunodeficiency virus, subtype 1
AOTDTA	Australian Organ and Tissue Donation and Transplantation Authority
APTT	activated partial thromboplastin test
AR	adverse reaction
ARE	adverse events and reactions
ASAT	aspartate amino transferase
AST	alanine aminotransferase
ATP	adenosinetriphosphate
Banff	Banff classification of renal allograft pathology
BAL	broncho-alveolar lavage
BCG	bacillus Calmette-Guérin
BD	brain death
BDD	brain death diagnosis
BKPyV	BK polyomavirus
BKV	BK virus
BM	bone marrow
BMI	body mass index in kg/m^2
CA	cardiac arrest
CAD	coronary artery disease
CAs	competent authorities
CB	cord blood

CBF	cerebral blood flow
CDC	Centers for Disease Control and Prevention (USA)
cDCD	controlled donation after circulatory death
CD-P-TO	European 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
CMV	cytomegalovirus
CNS	central nervous system
CNT	Centro Nazionali di Trapianti (Italy)
CO	carbon monoxide
Coorenor	Coordination of Crossborder Organ Exchange (project of European Union)
Cope	Consortium on Organ Preservation in Europe
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	computer tomography
CTA	computed tomographic angiography
CTC	circulating tumour cells
CVP	central venous pressure
DAA	direct acting anti-viral agents
DBD	donation after brain death
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
Dopki	improving the knowledge and practice of organ donation
DRI	donor risk index
DSO	Deutsche Stiftung Organtransplantation (Germany)
DT	donation team
DTAC	Disease Transmission Advisory Committee (USA)
D+/R–	donor has been infected by the pathogen, recipient is naïve (has not been infected)
D+/R+	both donor and recipient have been infected by the pathogen
D–/R+	donor is naïve (has not been infected), recipient has been infected by the pathogen
D–/R–	both donor and recipient are naïve (have not been infected) by the pathogen
EBV	Epstein–Barr virus
ECD	expanded criteria donor
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
ECMO	extracorporeal circulation with membrane oxygenation
ED	emergency department
EDD	European Donation Day
EDQM	European Directorate for the Quality of Medicines & HealthCare
EDTCO	European Donation and Transplant Coordination Organisation, a section of the European Society for Organ Transplantation
EEA	European Economic Area
EEG	electroencephalogram
EF	ejection fraction (echocardiography)
EFQM	European Foundation for Quality Management
Efretos	European Framework for the Evaluation of Organ Transplants
EG	ethylene glycol
eGFR	estimated glomerular filtration rate
Elipsy	European Living Donor Psychosocial Follow-Up (project of European Union)
ELISA	enzyme-linked immunosorbent assay

Elpat	Ethical, Legal and Psychosocial Aspects of Organ Transplantation Section of the European Society for Organ Transplantation
ELWI	extra-vascular lung water index
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
ESOT	European Society for Organ Transplantation
ESP	European Senior Program
ET [a]	Eurotransplant
ET [b]	essential thrombocythemia
$EtCO_2$	end-tidal carbon dioxide level
ETT	endotracheal tube
EU	European Union
Eulid	European Living Donation and Public Health (project of European Union)
Eulod	Living Organ Donation in Europe (project of European Union)
EuSCAPE	European Survey on Carbapenemase-Producing Enterobacteriaceae
Eustite	European Standards and Training in the Inspection of Tissue Establishments
FAP	familiar amyloid polyneuropathy
FFP	fresh frozen plasma
FIO_2	inspired oxygen fraction (respirator therapy)
FISH	fluorescence *in situ* hybridisation
Foedus	Facilitating Exchange of Organs Donated in EU Member States
FOUR	full outline of unresponsiveness (coma scale)
FP	framework programmes
FSME	endemic viral tick-borne encephalitis (abbreviation used in German-speaking countries)
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
GIST	gastro-intestinal stromal tumours
GLP	good laboratory practice
GMP	good manufacturing practice
GN	Gram negative
GSC	Glasgow coma scale
HAM	HTLV-associated myelopathy
HAV	hepatitis A virus
HBV	hepatitis B virus
HBsAg	surface antigen of hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis D virus
HEA	hydroxyethylamidons
HES	hydroxyethyl starch
HEV	hepatitis E virus
HELLP	syndrome of haemolysis, elevated liver enzymes, low platelets
HF (HR)	heart rate
HHV8	human herpes virus-8 – also known as Kaposi Sarcoma herpes virus
HIV	human immunodeficiency virus
HIV-1-p24-Ag	p24-antigen of HIV, subtype 1
HLA	human leukocyte antigen
HMPAO	hexamethylpropyleneaminoxime
HPA	hypothalamic-pituitary axis
HPC	haematopoietic progenitor cell
HPyVs	human polyomaviruses
HRP	hypothermic regional perfusion
HOTT	Combatting trafficking in persons for the purpose of organ removal (project of European Union)
HTK	Histidine-Tryptophan-Ketoglutarate
HTLV1/2	human T-cell-leukaemia virus subtype 1/2
HSV	herpes simplex virus
ICP	intracranial pressure
ICU	intensive care unit
ID-card	identification card
IGRA	interferon-gamma release assay
IHS	Intra-cerebral Haemorrhage Scale
ILCOR	International Committee responsible for co-ordination of all aspects of cardio-pulmonary and cerebral resuscitation worldwideIPITTR 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
ITBVI	intra-thoracic blood volume index
IVC	inferior vena cava
IVS	intraventricular septum
IVSd	thickness of intraventricular septum in diastole (echocardiography)
iVx	inactivated vaccine

JCAHO	Joint Commission on Accreditation of Healthcare Organization
JCI	Joint Commission International
JCPyV	JC polyomavirus
JPAC	Joint Professional Advisory Committee
KDIGO	kidney disease improving global outcome
KDP	key donation person
KSHV	Kaposi Sarcoma herpes virus – also known as human herpes virus-8 (HHV8)
LCMV	lymphocytic choriomeningitis virus
LD	living donor
LDH	lactate dehydrogenase [enzyme/test]
LDLT	living donor liver transplantation
LDN	living donor nephrectomy
LD-LR	living donor liver resection
LH	left hepatectomy
Lidobs	living donor observatory
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
MGUS	monoclonal gammopathies of undetermined significance
MI-LDN	minimally living donor nephrectomy
Mode	mutual organ donation and transplantation exchanges
MPHO	medical products of human origin
MPN	myeloproliferative neoplasm
MRI or MRT	magnetic resonance imaging or magnetic resonance tomography
MRSA	methillicine-resistant staphylococcus aureus
MSM	men who have sex with men
NAT	nucleic acid amplifying technique (the term 'nucleic acid testing' is used synonymously in the literature)
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 Global Vigilance and Surveillance Database for MPHO
NR	non-reactive
NRP	normothermic regional perfusion
NTO	national transplant organisation
Odequs	Organ Donation European Quality System
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
paCO2	partial pressure of carbon dioxide
PanIN	pancreatic intraepithelial lesions
paO2	partial pressure of oxygen
PAOP	pulmonary arterial occlusion pressure
PASS	Pheochromocytoma of the Adrenal gland Scaled Score
PBPC	peripheral blood progenitor cells collected from the peripheral blood
PCC	pheochromocytoma
PCR	polymerase chain reaction
PDSA (PDCA)	plan–do–study–act cycle (or plan–do–check–act cycle)
PEEP	positive end-expiratory pressure (respirator therapy)
PGL	paraganglioma
PHS	public health service (USA)
PLAP	placental alkaline phosphatase
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
PNF	primary non-function (or permanent non-function)
PPASS	pre-procurement pancreas allocation suitability score
PSA	prostate-specific antigen
pTis	tumour *in situ*
PTLD	post-transplant lympho-proliferative disorders
PV	polycythemia vera
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	vigilance and surveillance of Substances of Human Origin
SOP	standard operating procedure – written instructions that document all steps
SOT	solid-organ transplantation
SPECT	single-photon emission computed tomography
SSRI	selective serotonin re-uptake inhibitors
STD	sexually transmitted disease
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TAIEX	Technical Assistance and Information Exchange
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
UEMS	Union of Medical Specialists
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**

Actual organ donor	A consented eligible organ donor in whom an operative incision has been made with the intent 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 (AE)	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 (AR)	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'.
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 spontaneous breathing reflex regulated by the respiratory centres located in the brainstem.
Audit	Periodic, independent and 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. They 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 C. 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 based on 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 extra-cranial phenomena, such as hypoxia.
Cells	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 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 case 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 inconveniences related to the donation.
Competent Authority	See 'Health authority'.
Consent/authorisation to donation	Legally valid permission from a person to donate an organ. In cases of living donation, this person must beforehand be given appropriate information about the purpose and nature of the intervention as well as its consequences and risks.
Controlled donation after circulatory death	Donation from persons 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 for protecting 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.
Diabetes insipidus	Form of diabetes caused by a deficiency of the pituitary hormone vasopressin, which restricts in the kidney the rate of water excretion. Clinical triggers for identification of this complication in deceased organ donors, related to the failure of the hypothalamic-pituitary axis, are polyuria (in case of appropriate volume therapy) and hypernatriaemia.
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 based on the irreversible loss of neurological functions.
Donation after circulatory death	Donation from a person who has been declared dead based on circulatory criteria. Depending on the clinical scenario in which cardiac arrest occurs, it can be classified as controlled or uncontrolled and in the four different 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 global 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 the co-ordination and support of all the subsequent steps supporting organ donation, including organ procurement and distribution. They may also receive other names, such as 'transplant co-ordinator' or 'key donation person'.
Donor risk index	Scoring system describing organ quality in a population from whom this score has been derived by multivariable statistical methods.
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' concept.
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 no presence of a condition (the result is negative) when in reality it is present. An example of a false negative would be if a particular test designed to detect a given infection returns a negative result but the person actually does 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 it is not present. An example of a false positive would be if a particular test designed to detect a given infection returns a positive result but the person actually does 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 initiating post-donation or post-transplant interventions.
Graft	Part of the human body that is transplanted in the same 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 body to which has been 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 on a national or regional basis by their government. Other terms, such as Regulatory Authority, Regulatory Agency or, in the European Union, 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.
Ischaemia time	The period that an organ is deprived of its blood supply. See also 'cold ischaemia time' and 'warm ischaemia time'.
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 adecuate knowledge and understanding of relevant information, to donate or to undergo a diagnostic, therapeutic, or preventive procedure.
Ischaemia time	The period that an organ is deprived of its blood supply. See also 'cold ischaemia time' and 'warm 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 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 the following 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-laws, adopted, friend. *B/Unrelated = Non-related* Not genetically or emotionally related.
Lung-protective treatment	Strategy applied in potential organ donors with the goal of increasing the number of lungs eligible for transplant. It includes methods to prevent atelectasis and infection through continuous mucolysis, humidification of respiratory gases, aspiration of secretions, changes of body position and head-of-bed elevation (if no contra-indications).
Model for end-stage liver disease (MELD)	Scoring system for prediction of survival in end-stage liver disease based on form laboratory data (bilirubin, creatinine, 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. See also '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.
Operating procedure	See 'procedure'.
Opting-in donation system	A system where consent to donation has to be obtained explicitly by 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 when there is no objection registered to donation. In practice, operational variations do not exist 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 and minimise the risks for the recipient, and optimise organ allocation.
Organ procurement organisation	A healthcare establishment, a team or a unit of a hospital, a person, 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. See also '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.
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.
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 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 of a phenomenon or event and its intensity.
Quality management	Designates the co-ordinated activities to direct and monitor an organisation with regard to quality. This general term encompasses all aspects which ensure 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 estimation 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.
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.
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 in a donor until reperfusion by circulation in the recipient. During this time period multiple different 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	An alertness 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.
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.[1] By using these criteria, professionals performing potential donor audits can classify patients in one of five categories of 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 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 (see Table A):

- Aetiology + Conditions + 1 finding (at least) in clinical examination + 1 clinical sign (at least); or
- Aetiology + Conditions + 2 findings (at least) in clinical examination

Situation 3: Possible potential DBD donor

A patient is considered a possible potential DBD donor in the following circumstances (see Table A):

- Aetiology + Conditions + 1 finding (at least) in clinical examination; or
- Aetiology + Conditions + 1 clinical sign (at least)

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 additional information in the clinical chart or the clinical chart is not available.

1 De la Rosa G, Domínguez-Gil B, Matesanz R, Ramón S, Alonso-Alvarez J, Aráiz J, *et al.* Continuously Evaluating Performance in Deceased Donation: The Spanish Quality Assurance Program. *Am J Transplant* 2012; 12: 2507-2513.

- 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 to define 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, oculo-cephalic, 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. **Patient assessment rationale (United Kingdom)**

Rationale document for patient assessment form PA1 (v03)

Introduction

The purpose of patient assessment is firstly to determine if a potential donor is suitable to donate any organ or tissue and then to determine which organs and tissues can be donated. Whilst the donor may 'in general' be acceptable for donation, not all organs or tissues may be suitable due to 'system-specific' medical problems. 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 Patient Assessment Form (PA1).

The purpose of risk assessment is to determine risk factors for the transmission of disease from donor to recipient. It is the responsibility of the Specialist Nurse – Organ Donation (ODT), Nurse Practitioner/Assistant Nurse Practitioner (Tissue Services) and Tissue Transplant Co-ordinator (SNBTS) to collect comprehensive information on medical, behavioural and travel history and relay all of 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 of transplant for their individual patients. For tissues, it is the responsibility of the tissue establishment to make the final decision on donor suitability.

Risk is relative to the risks of not receiving a transplant.

The ODT, Nurse Practitioner/Assistant Nurse Practitioner (Tissue Services) and SNBTS must be familiar with the purpose of each question and must recognise when to expand the question in order to obtain more details and what additional information might be required. The conditions which will cause the deferral of a potential donation vary significantly between organs, ocular tissue and other tissues. For potential tissue donors further detailed information regarding the deferral criteria for each type of tissue can be found in the current version of the UKBTS Tissue Donor Selection Guidelines for Deceased Donors (TDSG-DD). Due to the avascular nature of corneal grafts, many of the deferral criteria for other tissues do not apply to cornea.

For all paediatric donors under the age of 18 months, and any infant donor over the age of 18 months but who has been breast-fed in the past 12 months, the mother is required to answer the questions in the patient assessment document with regard to both her own and her child's health.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding 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 viral infections from the mother to her child via breast milk. This may be determined by the mother's medical and behavioural history that is used as a surrogate for the infant's history. If yes, the medical history of the mother will need to be assessed and a maternal blood sample must be taken for virology testing.	Not an absolute contraindication; inform recipient centres and ensure the following sampling takes place: • All babies and children who have been breastfed within 12 months of donation should have maternal sampling. • Neonates (less than 2 months) – maternal only sampling. • Babies greater than 2 months not breastfed should have samples from the infant with maternal samples as a fall-back position if required. • Babies greater than 18 months not breastfed should only require infant sampling.	Provided the mother's blood sample is found to be negative for markers of viral infection, this is not a contraindication to donation. Ensure the following sampling takes place: • All babies and children who have been breastfed within 12 months of donation should have maternal sampling. • Neonates (less than 2 months) – maternal only sampling. • Babies greater than 2 months not breastfed should have samples from the infant with maternal samples as a fall-back position if required. • Babies greater than 18 months not breastfed should only require infant sampling.
For all female patients 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. This would have a direct effect upon whether donation is able to proceed or not.	If the foetus is not determined to be viable there is no contraindication to donation.	Donation acceptable.
General health information Did your relative/significant other:			
1. Visit his/her general practitioner in the last 2 years? Was he/she currently seeing or waiting to see their general practitioner or any other healthcare professional?	1.1. These are broad questions to quickly ascertain if the donor has on-going health problems. If the answer to either is yes, it is important to obtain as much information as possible.	Donation acceptable.	A positive answer is not itself a contraindication to donation: however each condition must be assessed for its acceptability as per the current version of TDSG-DD.
	1.2. Note: It is important to obtain accurate information on past medical history. Therefore it is a requirement that the GP be contacted to complete the NHSBT GP questionnaire (FRM1602).	For organ donation this should be done pre-donation. Attempts to should always be made to contact the GP before retrieval of organs. If these attempts do not enable contact with the GP this **must** be completed within 3 working days.	For tissue only donation this is usually done post-donation.
2. Have diabetes? If yes, were they on insulin?	Due to the effect diabetes can have on a number of organs particularly the kidneys additional tests/information relating to function may be necessary.	Not an absolute contraindication except for pancreas; inform recipient centres.	Donation acceptable except for pancreatic tissue.
3. Take regular medication?	3.1. Very few drugs are themselves contraindications to donation but knowledge of the donor's drug therapies may indicate an underlying disease that is itself a contraindication to donation for some tissues. It is useful to know why the medication was being taken although doses and frequency are not required.	Not an absolute contraindication; inform recipient centres.	Certain drugs may exclude the donation of specific tissues, e.g. long-term steroid therapy may affect the quality of bone and skin. See TDSG-DD and seek advice from tissue establishment.
	3.2. A small number of drugs may cause birth defects in babies exposed to them while in the womb (consider potentially pregnant organ recipients). It is important to allow time for the drugs to be cleared from the donor. It takes longer to clear some drugs than others.	Not an absolute contraindication; inform recipient centres.	For tissue donation other than cornea; isoretinoin (roaccutane), acitretinate (neotigason), etretinate (tigason) used to treat acne and dutasteride (avodart) and finasteride (proscar) used to treat prostatic hyperplasia all have specified deferral periods. See current version of TDSG-DD.
	3.3. Individuals being treated with immunosuppressive drug therapy, such as transplant recipients may not be eligible to donate; as the serology test may be misleading In addition any infection maybe masked.	Not an absolute contraindication; inform recipient centres.	Must not donate if immunosuppressed.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
4. Ever undergo any investigations for cancer or ever been diagnosed with cancer?	4.1. The presence, or previous history, of cancer poses a risk of transmission of cancer cells to a recipient. If yes, obtain further information regarding dates and treatments.	Not an absolute contraindication; inform recipient centres. It is important to assess the type and grade of cancer. Please refer to Council of Europe document (1997) for more information.	Depending on the type cancer can very often be acceptable for corneal tissue donation but usually not for other tissues. See current version of TDSG-DD.
5. Recently suffer from any significant weight loss?	5.1. Recent weight loss may be an indication of illness, which includes cancer. It is important therefore to obtain the reason for the weight loss.	Not an absolute contraindication; inform recipient centres.	Not an absolute contraindication – depends on underlying cause.
6. Have any signs of recent infection, e.g. colds, flu, fevers, night sweats, swollen glands, diarrhoea, vomiting and skin rash?	6.1. Bacterial, viral and protozoal infections can all be transmitted by transplantation. Successful antibiotic treatment may make donation acceptable.	Not an absolute contraindication; inform recipient centres. However it is important to ascertain specific information about the organism so that appropriate antibiotic/antifungal treatment may be administered to the recipient.	Active systemic infection is a contraindication to most tissue donation but cornea donation may be possible. Localised infection may be acceptable. Each condition must be assessed for its acceptability as per the current version of TDSG-DD.
	6.2 Many of these symptoms can also be signs of underlying malignancy.	Not an absolute contraindication; inform recipient centres.	Each condition must be assessed for its acceptability as per the current version of TDSG-DD.
7. Come into contact with any infectious diseases recently or have any immunisations within the last 8 weeks?	7.1. Potential donors who have been in recent contact with an infectious disease (for which they have no history of previous infection) may be in the asymptomatic stage of developing an infection at the time of donation.	Not an absolute contraindication; inform recipient centres.	See current version of TDSG-DD.
	7.2 Immunisations with live vaccine may cause severe illness in people who are immunosuppressed. By 8 weeks any infection caused by the immunisation should have been controlled and so should not be passed on through donated material. There are special rules for BCG and smallpox immunisations.	Not an absolute contraindication; inform recipient centres.	Unacceptable for tissue donation if less than 8 weeks since receiving a live immunisation.
8. Ever have hepatitis, jaundice or liver disease?	8.1. Viral hepatitis is readily transmitted by all types of transplantation. Any history of jaundice or hepatitis must therefore be investigated. Testing alone may not exclude all infectious donors and the donor history may suggest the need for additional testing. However, jaundice can be caused by many non-infectious conditions, e.g. gallstones, obstruction of the bile ducts, congenital biliary atresia or neonatal jaundice.	Not an absolute contraindication; inform recipient centres.	See current version of TDSG-DD.
9. Have a history of ocular disease or previous eye surgery or corrective laser treatment?	9.1 This question is specifically designed to assess the suitability of ocular tissue.	Not an absolute contraindication; inform recipient centres.	Corneal disease and infections, e.g. herpes, ocular inflammation, retinoblastoma and malignant tumours of the anterior segment are contraindications to eye donation. Laser refractive surgery (e.g. LASIK) to the cornea is also a contraindication. However, other existing eye disease or previous eye surgery does not necessarily exclude corneas from transplantation. See current version of TDSG- DD or where appropriate seek specific specialist advice.
10. Ever suffer from any bone, joint, skin or heart disease, e.g. rheumatic fever?	10.1. This question relates to the suitability of specific tissues. Whilst the donor may 'in general' be acceptable for donation not all tissues may be suitable due to 'system specific' medical problems. This question is aimed at identifying some of these medical diseases.	Inform recipient centres of details of specific diseases. Inform recipient centres of details of specific diseases.	The presence of disease in any of these systems may preclude donation of that specific tissue. See current version of TDSG-DD. See current version of TDSG-DD.
	10.2 Note however that some tissue specific symptoms may be part of a systemic disease, e.g. SLE, and therefore a general deferral for the donation of tissues.	Inform recipient centres of details of specific diseases.	See current version of TDSG-DD.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
11. Ever have any operations or illnesses, including an organ or tissue transplant?	11.1. The first part of this question is to quickly ascertain if the donor has had previous significant health problems. If the answer is yes, it is important to obtain as much information as possible. Surgery may be related to underlying malignancy.	Not an absolute contraindication; inform recipient centres.	Each condition must be assessed for its acceptability as per the current version of TDSG-DD.
	11.2. The question regarding transplantation is a SaBTO requirement. There is the risk of viral or prion transmission when someone has received a tissue transplant. There has been one definite and one probable case of CJD transmission by corneal transplants.	Individual assessment is required.	If dura mater or ocular tissue was transplanted no tissue donations can be accepted. A history of receipt of other tissue transplants since 1980 is a contraindication for most types of tissue donation, with the exception of skin or heart valve donation in some circumstances refer to TDSG-DD and seek advice from tissue establishment.
	11.3. There is the risk of viral or prion transmission when someone has received an organ transplant. Individuals being treated with immunosuppressive drug therapy, such as transplant recipients may not be eligible to donate, as the serology test may be misleading. In addition any infection may be masked.	Individual assessment is required.	A history of receipt of an organ is a contraindication for all types of tissue donation.
12. Ever have neurosurgical operations for a tumour or cyst of the spine/brain or implantation of dura mater, before August 1992?	12.1. This is to ascertain if the donor may have been given a dura mater graft as part of a neurosurgical procedure. This material is known to have transmitted CJD in around 200 cases. Brain surgery often required dura mater repair. Neurosurgeons may use different materials for this but before 1992; dura mater from cadaveric donors was used in brain and spinal surgery. Spinal fusion and burr holes did not usually involve using dura mater.	Not an absolute contraindication; inform recipient centres.	If yes, tissue donation can only be accepted if it can be shown that dura mater was not used.
13. Receive a blood transfusion/blood product/component transfusion (such as Fresh Frozen Plasma (FFP), Platelet, Cryoprecipitate or Immunoglobulins) in the last 12 months or at any other time (particularly since 1980)?	13.1. Blood or blood product/component transfusion (such as Fresh Frozen Plasma (FFP), Platelet, Cryoprecipitate or Immunoglobulins) transfusions have transmitted bacterial, viral, protozoan and prion infections. Testing of blood donors for markers of infection varies by country and also by date. A complex set of criteria exist for tissue donor acceptability depending on when and where the transfusion took place and also for the type of tissue to be donated. To date there have been 4 cases of vCJD and 2 cases of asymptomatic prion transmission by blood transfusion. The question regarding transfusion is a SaBTO requirement. See TDSG-DD for detailed guidance.	Not an absolute contraindication; inform recipient centres.	See current version of TDSG-DD.
	13.2. If there has been **significant blood loss and replacement of fluids** with blood components and/or colloids within the 48-h period prior to obtaining the donor's blood sample there may be significant haemodilution of the sample. This may result in 'false negative' results when testing the donor for viral markers of infection. If no pre-transfusion sample is available, a detailed assessment of all intravenous fluid intakes during the 48-h period before sampling is required to enable the haemodilution calculation to be performed.	Not an absolute contraindication; inform recipient centres.	If there is > 50% haemodilution no tissue donations can be accepted.
	13.3. The reason for the blood transfusion should be obtained as this may itself be a contraindication to donation.	Inform recipient centres of details of specific diseases.	See current version of TDSG-DD.
14. Ever told never to donate blood?	14.1. Must establish reason why person told never to give blood. There are a number of individuals who have been informed that they are classified as being at "increased risk" of CJD/vCJD for public health purposes because they have been exposed to possible risk through blood transfusion, surgery, or tissue transplantation. The individuals have all been informed that they should not donate blood, tissues or organs. Examples are: • Individuals who had surgery using instruments that had been used on someone who developed CJD. • Individuals who have given blood to someone who later developed vCJD. • Individuals who have received more than 80 units of blood or blood components.	Not a contraindication to donation; inform recipient centres.	Contraindication if person told never to give blood owing to CJD risk.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
	14.2. Individuals may have been told not to donate for other reasons, for example HCV infection or for a haematological disorder.	Not a contraindication to donation; inform recipient centres.	See current version of TDSG-DD.
15. Suffer from any autoimmune illnesses or disease of unknown aetiology, e.g. inflammatory bowel disease, multiple sclerosis and sarcoidosis?	15.1. Some diseases of unknown aetiology may have an infectious origin and may be transmissible.	Not an absolute contraindication; inform recipient centres.	Acceptance criteria are specific for each condition, see TDSG-DD. For example multiple sclerosis is an absolute contraindication for all tissues whilst for sarcoidosis ocular tissue can be donated provided there is no actual ocular involvement.
	15.2. Inflammatory bowel disease can also increase the risk of bacteria entering the blood stream.	Not an absolute contraindication; inform recipient centres.	Crohn's disease and ulcerative colitis are exclusions for tissue donation except for corneal donation.
	15.3 Autoimmune disease is caused by the body attacking itself and can be either limited to a single organ, e.g. thyroid disease or affect multiple systems, e.g. rheumatoid disease. Severe systemic disease may adversely affect the quality of a number of tissues. In addition treatment to suppress the condition may be with steroids, immunosuppressive drugs, anti-metabolites or antibodies directed against part of the immune system. This may well make the donor more susceptible to certain types of infection and also make some infections more difficult to diagnose.	Not an absolute contraindication; inform recipient centres.	Acceptance criteria are specific for each condition, see TDSG-DD. For example multiple sclerosis is an absolute contraindication for all tissues whilst for sarcoidosis ocular tissue can be donated provided there is no actual ocular involvement.
16. Suffer from any type of brain disease such as Parkinson's disease, Alzheimer's disease, motor neurone disease, recent memory loss, confusion or unsteady gait?	16.1. CNS disease may be: • of suspected infective origin, e.g. multiple sclerosis or CJD, or • a neurodegenerative condition of unknown aetiology, e.g. Parkinson's disease or Alzheimer's disease. There are concerns that Alzheimer's disease may mask symptoms of CJD. In the event of confusion or memory loss the risk of CJD has to be excluded.	Not an absolute contraindication; inform recipient centres.	Contraindication unless confusion and/or memory loss has an underlying clinical reason that is itself not a contraindication to transplantation.
17. Have a family history of CJD, vCJD, Gerstmann-Straussler-Schienker disease, or Fatal Familial Insomnia?	17.1. These are all varieties of prion-associated disease. 10-15% of classical CJD cases are associated with gene mutations (familial CJD). Individuals at familial risk of prion-associated disease are those who have 2 or more blood relatives with a prion-associated disease or where the family has been informed it is at risk following genetic testing and counselling.	Contraindication.	Contraindication.
18. Ever receive human pituitary extracts, e.g. growth hormones, fertility treatment or test injections for hormone imbalance?	18.1. Prior to 1985 treatment with growth hormone, infertility treatment and some thyroid diagnostic tests used material derived from the pituitary glands of untested cadavers, some of whom may have died from CJD. Around 200 recipients of this material subsequently developed CJD.	Not an absolute contraindication; inform recipient centres.	Contraindication.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
19. Ever have any other serious infection, e.g. tuberculosis, malaria, West Nile virus, SARS, typhoid fever, toxoplasmosis, rabies, encephalitis, Lyme disease or brucellosis?	19.1. This question picks up a range of infections which could be transmitted by transplantation. It is important to obtain as much information as possible to determine the degree of risk of transmission to a recipient. Please refer to the Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) (February, 2011) for further information. West Nile virus, which has been identified as a disease that is a potential risk to organ and tissue recipients, must be identified where possible. However, where some patients are asymptomatic, relevant travel risks must also been noted (Question 25). Note: West Nile virus is active during certain seasons, and migrates across the world; therefore healthcare professionals must remain vigilant as to areas of recent outbreaks.	Not an absolute contraindication; inform recipient centres. *Active Tuberculosis* Or treatment within 6 months is not an absolute contraindication to donation. If the donor has still to complete a course of chemotherapy the recipient patient will require appropriate drug treatment. A previous history of tuberculosis is not a contraindication to donation other than at the original site of infection, e.g. liver. *Malaria* Contraindication to donation if there is a known active infection and no curative chemotherapy has been given. *West Nile virus* Contraindication to donation if there is a known active infection. Incubation is up to 14 days; therefore relevant travel history is a requirement.	Each condition must be assessed for its acceptability as per the current version of TDSG-DD. In all cases active infection is a contraindication to donation. There are a variety of deferral periods relating to either the date of cessation of symptoms or the date of termination of treatment. Some infections are a permanent contraindication to donation, whilst for malaria it is also dependant on the results of antibody testing.
20. Have any acupuncture, tattooing, body piercing, Botox injections or cosmetic treatment that involves piercing the skin in the last 6 months?	20.1. This question aims to identify donors who may be at risk of having been exposed to reused needles. Acupuncture, tattooing, body piercing, Botox injections or cosmetic treatment that involves piercing the skin all carry a low risk to transmit viral disease. Most tattooist and piercers work to high standards, using disposable needles, but not all do. In the UK there have been occasional large outbreaks of both HBV and HCV as a result of poor hygienic standards. None of these activities are reasons to reject a donor if they were carried out more than 6 months prior to donation. It is helpful, if possible, to know where and when the treatment was carried out.	Not an absolute contraindication; inform recipient centres.	For tissue donors the deferral period has been reduced from 12 months to 6 months since all tissue donors are tested for anti-HBc.
21. In the last 12 months either been in close contact with a bat anywhere in the world or bitten by any mammal outside the UK?	21.1. Animal bites may result in many different infections. This question aims to identify donors who may be at risk of having been exposed to rabies. There have been 2 recent cases where organ donors transmitted rabies to all recipients of their organs and to the recipient of a blood vessel. Historically there have been a small number of cases of rabies transmitted by corneal transplantation. In the UK the only risk of rabies comes from contact with infected bats whilst outside the UK bites from infected mammals, especially dogs, are also major routes of infection.	Contraindication.	Contraindication – see TDSG-DD. In addition, bites from a non-human primate at any time are a **permanent** contraindication to tissue donation.
22. Ever have a sexually transmitted infection, e.g. syphilis, gonorrhoea, genital herpes, genital warts?	22.1. A history of sexually transmitted infection is often not immediately forthcoming from relatives when enquiring about someone's general health. This question is to specifically raise this topic in isolation to evoke either a positive or negative response. If the answer to it is yes, it is important to obtain as much information as possible. Untreated STDs can eventually cause damage to many organs and tissues.	Not an absolute contraindication; inform recipient centres.	Acceptance criteria are specific for each condition, see TDSG-DD.

Travel risk assessment

This group of questions is designed to establish the risk of donated organs and tissues transmitting a number of serious infections which are not found within the UK. Due to the forever changing pattern of infections worldwide, when a history of travel abroad has been obtained it is necessary to consult both the TDSG-DD and the Geographical Disease Risk Index (GDRI) for up-to-date information on the specific deferral criteria current at the time. These can be obtained by accessing the JPAC (Joint Professional Advisory Committee) website www.transfusionguidelines.org.uk which is updated as information becomes available. (If access to this website is not available to the SN-OD the NHSBT Duty Office will access this for you.)

Did your relative/significant other:

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
23. Ever travel outside the UK?	23.1. This opening question, if negative for travel, allows rapid progression to the next set of questions without the need to answer further travel questions. If the answer is yes, it is important to obtain as much information as possible based on the subsequent questions.	Not an absolute contraindication; inform recipient centres.	Refer to the TDSG-DD and GDRI.
24. Travel outside the UK in the last 12 months? If yes, please give details of date of visit/return and destination.	24.1. Twelve months is referred to as this is the longest temporary deferral period for tropical infections. Other infections (both tropical and non-tropical) have shorter deferral periods. Corneal tissue is treated differently from other tissues as it is avascular not considered to be a risk of transmitting protozoal infections such as malaria or Trypanosoma cruzi infection.	Not an absolute contraindication; inform recipient centres.	For corneal tissue malaria is not a deferral criterion. For non-corneal tissue, 'visitors' to a malarial area < 6 months ago are not acceptable, 6-12 months ago require a malaria antibody test, > 12 months ago are acceptable. Refer to the TDSG-DD and GDRI.
25. Ever have a fever or treatment for an illness whilst abroad or within 6 months of leaving an area where there is malaria or West Nile virus?	25.1. Malaria and other endemic infections such as West Nile virus can be transmitted by blood, viable organs, tissues and cells therefore it is important to determine the nature of the illness. Note: A malaria antibody test is of no use if taken prior to 6 month incubation period.	*Malaria* Not an absolute contraindication; inform recipient centres. **Ensure blood sample for malaria screen is sent to the appropriate reference laboratory for all high risk patients.** *West Nile virus* Contraindication.	For corneal tissue malaria is not a deferral criterion. For non-corneal tissue a malaria antibody test is required. Refer to the TDSG-DD and GDRI.
26a Ever live or work in rural Central or South America for a continuous period of 4 weeks or more?	26a.1. Individuals who have ever lived in Central or South America are at risk of Trypanosoma cruzi infection, which is caused by a parasite transmitted by an insect vector, which bites humans and animals at night time. Those at most risk are trekkers, backpackers and soldiers on manoeuvres in jungle areas as they may have been living in primitive areas and/or sleeping out in the jungle.	Not an absolute contraindication; inform recipient centres.	For corneal tissue T. cruzi is not a deferral criterion. For other tissues a T. cruzi antibody test is required. Refer to the TDSG-DD and GDRI.
26b. Was the deceased or their mother born in Central or South America?	26b.1. 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.	Not an absolute contraindication; inform recipient centres.	For corneal tissue T. cruzi is not a deferral criterion. For other tissues a T. cruzi antibody test is required. Refer to the TDSG-DD and GDRI.
26c. Given a blood transfusion in that country?	26c.1. As T. cruzi is endemic in this area and individuals remain asymptomatic for years after infection many blood donors are infected by this organism. T. cruzi is readily transmitted by blood transfusion from an infected donor. Screening and treatment of blood in this area is becoming more widespread but is still not universal. See also Question 13.	Not an absolute contraindication; inform recipient centres.	For corneal tissue T. cruzi is not a deferral criterion. For other tissues a T. cruzi antibody test is required. Refer to the TDSG-DD and GDRI.
27a. Ever stay for 6 months or longer in an area where there is malaria, at any time in his/her life?	27a.1. This question is designed to make it possible to establish whether a potential donor meets the required criteria of malaria area 'resident'. Individuals who have lived in a malaria affected area for more than 3 months before the age of 5 years develop a partial immunity to malaria through repeated exposure. Partial immunity means that people may be infected with the malaria parasite but show no symptoms, sometimes for years. These individuals were classified as 'residents' as opposed to 'visitors' and, as they pose a much higher risk of transmitting infection, were managed in a different way to people who had simply visited a malaria area. More recently the definition of 'resident' was extended to include all individuals who have resided in a malaria area for a continuous period of 6 months at any time in their lives. Note: A malaria antibody test is of no use if taken prior to 6 month incubation period.	Not an absolute contraindication; inform recipient centres. **Ensure a blood sample for malaria screen is sent to the appropriate reference laboratory for all high risk patients.**	For corneal tissue malaria is not a deferral criterion. For non-corneal tissue a malaria antibody test is required. Refer to the TDSG-DD and GDRI.
27b. If yes, ever travelled outside the UK since then?	27b.1. An individual who is classified as 'resident' is managed differently from a non-resident for each subsequent visit to a malaria area no matter how short the visit. A malaria antibody test is required for all non-corneal tissue even if it > 12 months since the last visit.	Not an absolute contraindication; inform recipient centres. Ensure a blood sample for malaria screen is sent to NHSBT Colindale for all high risk patients.	For corneal tissue malaria is not a deferral criterion. For non-corneal tissue a malaria antibody test is required. Refer to the TDSG-DD and GDRI.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
Behavioural risk assessment			
To the best of your knowledge did your relative:			
28a. Consume alcohol?	28a.1. The effect of alcohol can impact on the quality of liver tissue. If yes, it is important to obtain as much information as possible.	Not an absolute contraindication; inform recipient centres.	Not a contraindication.
28b. Smoke tobacco or other substances?	28b.1. The effect of smoking can impact on the quality of lung tissue. If yes, it is important to obtain as much information as possible.	Not an absolute contraindication; inform recipient centres.	Not a contraindication.
Behavioural risk assessment			
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 and HBV. Unfortunately it is not possible to exclude all cases of infection by relying on blood testing alone as infected donors may be missed 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 around 10-12 days to start to form antibodies and a number of weeks before the antibody levels are high enough to be detected by a test that is based on antibody detection. Tests that are based on antigen detection will pick up the infection earlier but it still takes 10-20 days (depending on the specific virus) for adequate numbers of viral particles to be present in the blood to be detected. During all this period the potential 'negative' donor is highly infectious and any organ or tissue transplant will transmit the infection. For this reason donors found to be in any of the known high risk groups must be excluded from tissue donation on the basis of history alone.			
To the best of your knowledge, is it possible any of the following applies to your relative:			
29a. Is or may be infected with HTLV, HIV or hepatitis B or C?	29a.1. HIV/hepatitis B or C can be transmitted via organ/tissue donation therefore it is vital to identify anyone who is known to be, or thinks that they may be infected with the viruses.	HIV disease is an absolute contraindication, however HIV infection is not. Hepatitis B or C are not absolute contraindications: inform recipient centres.	Contraindication.
29b Ever injected or been injected with non-prescribed drugs, including body-building drugs, even if it was a long time ago or only once?	29b.1. People with a history of intravenous drug use remain the largest group with HCV infection in the UK. They also have a higher rate of HIV and HBV infection. It is important to obtain as much information as possible to assess possible risk behaviour. Viral infection can be transmitted by sharing equipment used to inject drugs.	Not an absolute contraindication; inform recipient centres.	Contraindication.
29c. Ever received payment for sex with money or drugs?	29c.1 People who receive payment for sex have a higher risk of contracting HIV/hepatitis B or C and other sexually transmitted diseases due to the high number of sexual partners and the promiscuity of these partners. In addition this group of people often sell sex to fund a drug habit. This further increases the risk of infection within this group.	Not an absolute contraindication; inform recipient centres.	Contraindication.
29d. (for male patients only) Ever had sex with another man, with or without a condom?	29d.1. Men who have sex with men have a much higher prevalence of HIV infection and this activity remains the leading cause of HIV infection within the UK.	Not an absolute contraindication; inform recipient centres.	Contraindication.
29e. (for female patients only) Had sex in the last 12 months with a man who has ever had sex with another man, with or without a condom?	29e.1. As these infections can be transmitted sexually; there is also a higher risk of infection for the sexual partners of individuals who fall into any of these above categories. A temporary deferral for 12 months from the time of the last exposure is used to prevent the risk of any 'window period' infections from being transmitted.	Not an absolute contraindication; inform recipient centres.	Contraindication.
29f. Has been in prison or a juvenile detention centre for more than 3 consecutive days within the last 12 months? Note: This excludes those who have been in a police cell for < 96 h.	29f.1. It is known that there is a higher risk for individuals who are in prison of being exposed to transmissible viruses through sexual contact and intravenous drug abuse. For a living donor these questions would be asked directly but for a deceased donor this is not possible. It is felt that relatives, who sometimes do not even normally reside with the donor, are unlikely to be able to answer these questions especially relating to the period in prison. As it is essential to rely on virology testing only, the possibility of a 'window period' infection must be excluded by use of a deferral period. It is therefore important to identify individuals who have been exposed to this environment.	Not an absolute contraindication; inform recipient centres.	Contraindication.

Question	Reason for asking the question	Action to take regarding organ donation	Action to take regarding tissue donation
29g. Had sex in the last 12 months with: i. Anyone who is HIV or HTLV positive? ii. Anyone who has hepatitis B or C? iii. Anyone who had a sexually transmitted disease? iv. Anyone who has ever had payment for sex with money or drugs? v. Anyone who has ever injected drugs? vi. 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)?	29g.1. There is a higher risk of contracting HIV through heterosexual intercourse in some parts of the world where the virus is endemic. It is therefore important to identify individuals who fall within this category. As these infections can be transmitted sexually, there is also a higher risk of infection for the sexual partners of individuals who fall within the above categories. A temporary deferral for 12 months from the time of the last exposure is used to prevent the risk of any 'window period' infections from being transmitted.	Not an absolute contraindication; inform recipient centres.	Contraindication.
Having answered all the previous questions is there anyone else who you think may provide more information?		*This question provides the opportunity to suggest others who may have alternative knowledge of any aspects of the patient's history. For example parents for past medical history or close friends for behavioural history.*	

Appendix 5. **Donor patient history questionnaire (Germany, English language version)**

	Patients history questionnaire	
	identification	
	date and time	
	Interviewer	☐ attending physician ☐ coordinator
	kind of interview	☐ personally ☐ 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 at outpatient or inpatient treatment	☐ Yes ☐ No ☐ unknown
	If yes, where & 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
	hematologic 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 consumes (e.g. stimulants, amphetamine, LSD, marihuana, cocaine)*	☐ Yes ☐ No ☐ unknown
	Drug 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
	Head ache	☐ Yes ☐ No ☐ unknown
	Loss of weight	☐ Yes ☐ No ☐ unknown
	Diarrhea	☐ Yes ☐ No ☐ unknown
	Swelling of lymph nodes	☐ Yes ☐ No ☐ unknown
	Dysmenorrhea / 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 breastfeed 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, HVC, 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, blood-bank)	

7.	**Stay (during past 3 months) or immigration from outside Northern or Middle 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.	**Additional remarks**	☐ Yes ☐ No

Date & Name of physician / signature: _____

Date & Name of donor coordinator / signature: _____

This questionnaire aims to ensure that disease transmission risks are not missed. If in any section a 'yes' is marked, the donor co-ordinator should initiate appropriate investigations to support the acceptance/refusal of the potential donor.

Appendix 6. **Physical examination of an organ donor (American Association of Tissue Banks)**

The rationale for this form is to standardise the physical examination for potential organ and tissue donors. Therefore this form is equivalent to the one shown in the *Guide to the quality and safety of tissues and cells for human transplantation*, 2nd edition, Appendix 6.

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 check here □ if N/A (not present)

Personnel confirming donor identification: _____Date/time:_____

Evidence of Donation/Autopsy

Eye donor: □whole eyes □corneas only □N/A ; Organ donor: □Yes □No UNOS#: _____

Autopsy: tissue recovery is □pre or □post autopsy (□full □limited); □no autopsy planned;

or, □plan for autopsy 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

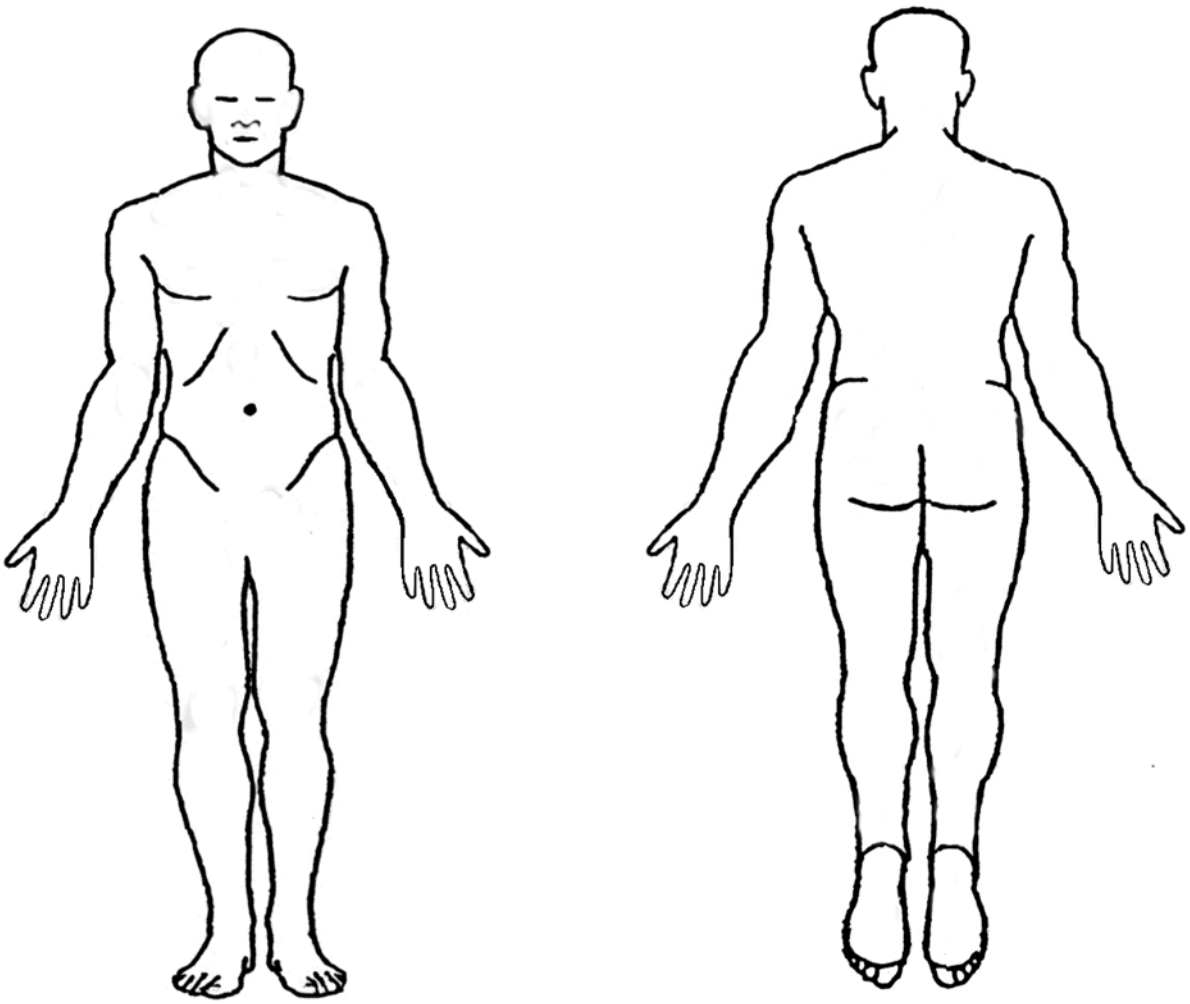
Cleanliness: □Good □Poor; Describe if "poor" _____

Personnel performing physical assessment: _____Date/time:_____

_____	_____	_____	_____
Name of Person Completing Form (Print)	Signature	Initials	Date

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 7. **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 characteristics described in this questionnaire are based on the considerations outlined in Chapters 6 and 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:**		

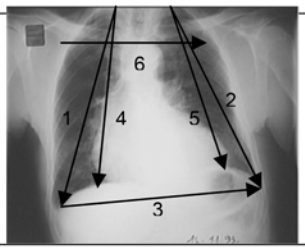
Other Diagnostics (* is mandatory)

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:

Appendix 8. **Donor examination by various means**

8.1. 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					

8.2. 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				

8.3. 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 measure-ment 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, malfor-mation (ASD / VSD))									
Examiner									

***LFV diastolic only when LVF systolic normal**

8.4. 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
QRS-changes remark				
ST-T-Segment changes	☐ none	☐ present (yes)		☐ not assessable
ST-T-Segment changes remark				
LV-hypertrophy	☐ none	☐ present (yes)	☐ not assessable	
QTc-time	☐ normal	☐ prolonged (yes) (QTc time in ms: ☐		☐ not assessable
Remark				
Examiner				

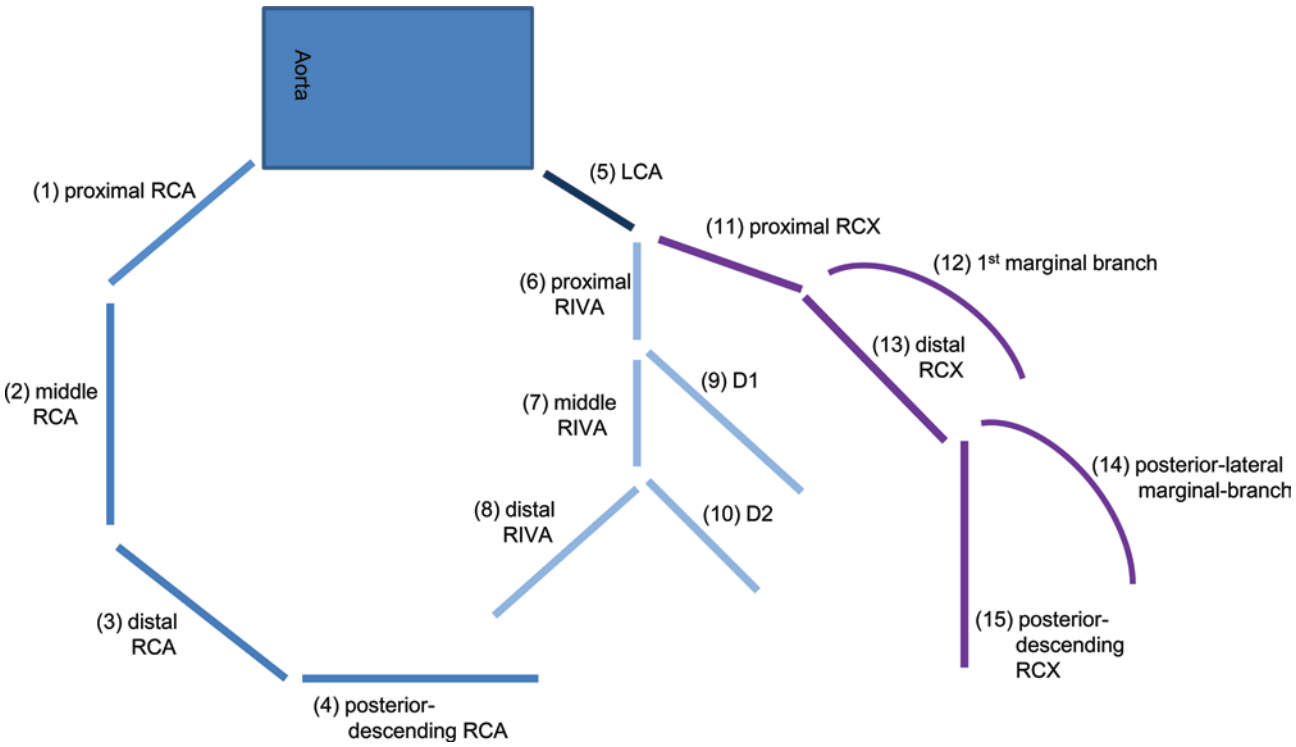
8.5. Donor examination by coronary angiography or alternative imaging (Eurotransplant, English-language version)

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 6.2.5.5. The pathway of standardised examination corresponds to Figure 6.5 and Table 6.7. 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.

8.6. 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.
	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		☐ normal	☐ splenomegaly	☐ haematoma ☐ liquid fringe ☐ multiple	☐ n.a.
	Size		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.

8.7. 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 9. Grading for biopsies at histo-pathological examinations (English-language version)

This table summarises a proposal of terms which can be used when investigating biopsies of a liver, or other samples, during donor characterisation or at procurement. The preferred concept is to use a standardised list of values instead of free text in order to allow correlation of clinical data with findings of histo-pathological examination.

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 (localization sampling point) • liver • pancreas • spleen • stomach • intestine (localization see sampling point) • kidney left • kidney right • urinary bladder • prostate, • ovar • 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
pathologic examination	• frozen section • intermediate report • final report	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
kind of specimen/biopsy	• sub-capsular wedge biopsy (liver) • wedge-biopsy • biopsy histology • core biopsy (via skin puncture) • other	liver	other

Field label	List of values	Item needed	
size of specimen	free text	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	
stetatohepatitis*	• 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
consult investigating pathologist	• yes • no	liver	other
→ at phone number	free text	liver	other

* facultative fields which should be considered according to the indication for investigation.

Appendix 10. Proposal for auditing retrievals (NHS Blood and Transplant, United Kingdom, English-language version)

A. Times to be recorded

- Time that each retrieval centre (abdominal & cardiothoracic) is first notified of the donor
- Time of telephone call from a donor coordinator asking retrieval centre to mobilise a retrieval team
- Time agreed with the donor coordinator that the retrieval team should leave base hospital
- Time that the main retrieval team leaves base hospital
- Time that the main retrieval team arrives at donor hospital
- Time that donor arrives in theatre
- Time that cardiothoracic assessment in theatre starts and ends (if applicable)
- Abdominal surgical start time ('knife to skin')
- Cardiothoracic surgical start time

The following times are collected by the surgical lead

- Time of aortic cross clamp, cessation of ventilation and start of in situ perfusion
- Time that each organ is removed from the body and placed in cold preservation solution
- Time that each organ is placed on hypothermic/normothermic machine perfusion device (if applicable)
- Time that each organ is placed on ice in the transport box
- Time that each organ leaves theatres (in its box or on the device)
- Time donor operation ends (completion of skin closure)

In addition for Donation after Circulatory Death (DCD) Donors

- Time withdrawal of life support in the donor
- Time systolic BP< 50 mmHg
- Time of circulatory arrest
- Time start no-touch period
- Time end no-touch period
- Time re-intubation for DCD lung donation
- Time of stand-down in DCD donors that do not progress to circulatory arrest

The following times are reported by the transplant centre on the transplant return form

- Time each organ is removed from cold solution (or device if applicable) for implantation into a recipient
- Time each organ is reperfused with blood

B. Constituent Personnel of NORS Team

Identity, Role and Status including e-mail address
e.g.

- Mr Smith, Lead abdominal surgeon, Consultant
- Ms White, Assistant surgeon,
- Mr Green, Theatre practitioner
- Ms Johnson, Scrub nurse

C. Record of anatomical abnormalities and organ injury

Details of anatomical abnormalities, organ injury to be recorded by both retrieving and implanting surgeon at the time of retrieval/transplantation:

- No damage
- Mild, not affecting transplantation
- Moderate, if the organ requires surgical repair to allow it to be transplantable
- Severe, if the organ is untransplantable

[NB: If initially graded as "moderate", but subsequently the damage had a significant impact on the recipient's health, then the recipient centre should formally report this.]

- Indicate whether the organ was physically injured or whether damage was because the organ perfused badly during cold perfusion.
- Indicate whether the organ suffered physical injury:
  - prior to retrieval (e.g. during a road traffic accident)
  - or due to surgical injury during the retrieval
  - or during transport between centres
  - or during back table preparation at the recipient centre
  - or during implantation at the recipient centre
- If the organ was physically damaged or poorly perfused before it was sent to the recipient centre, was this recognised and reported by the retrieving surgeon?

D. Reasons for non-use of an organ

Declined without attempt at retrieval due to

- Unsuitable donor
- Poor-quality graft
- Other

Declined following surgical exploration due to

- Poor quality graft
- Graft injury found during the retrieval process
- Poor perfusion
- Malignancy
- Unable to place the graft due to:
- No suitable recipients
- Prolonged ischaemia
- Other specified
- Failure to retrieve
- Retrieval centre unable to mobilise a retrieval team
- Donor becomes too unstable before retrieval team can reach donor hospital

E. Outcome measures

- Primary non-function
- Liver and heart:
  – No evidence that the organ ever functioned
  – Death or re-transplantation.
- Kidney
  – No evidence that the organ ever functioned with need for permanent dialysis post-transplant.
- Pancreas
  – No reduction in insulin requirements post-transplant.
  – Primary non-function
- Liver: Peak AST/ALT > 2000 IU/l
- Kidney: Need for temporary post-operative dialysis within the first seven days.
- Cardiothoracic: Need for device support.

30 day patient and graft survival using risk-adjusted funnel plots for each organ type.

Appendix 11. 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 :	
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 ...	

Acirculatory (donor) WIT = ET = ... min

Absolute (donor) WIT = ... min

Total (donor) WIT = ...min

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 12. 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
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 13. 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 transplanations
4	Catastrophic/ extreme	Death	OR	System destroyed – need to rebuild	OR	All transplantations cancelled

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

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: 30 January 2016.

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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The transplantation of organs offers major therapeutic benefits and improvements to quality of life and is, in many cases, the only life-saving treatment for end-stage organ failure. The most critical factor remains the supply of organs for transplantation, but only organs recovered following strict quality and safety standards are likely to function satisfactorily. Careful evaluation of donors is essential to minimise the risk of transmission of infections or malignancies. Furthermore, since human organs can currently only be derived from the body of a person, strong ethical principles need to be associated with their use.

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