

Guide to the quality and safety of tissues and cells for human application

1st Edition

The Guide to the quality and safety of tissues and cells for human application is published by the Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM).

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Page layout and cover: EDQM

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ISBN 978-92-871-7639-4
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Printed at the Council of Europe

Foreword and acknowledgments

Founded in 1949, the Council of Europe is the oldest and largest of all European institutions and now numbers 47 member states¹. One of its founding principles is that of increasing co-operation between member states to improve the quality of life for all Europeans.

Within this context of inter-governmental co-operation in the field of health, the Council of Europe has consistently selected ethical problems for study. One of the most important of these ethical issues relates to the non-commercialisation of human substances, i.e. blood, organs, tissues and cell.

Transplant medicine and transplantation have progressed during recent decades in a way nobody would have imagined years before. As with organs, the demand for some transplantable tissues far outweighs the available supply. This has critical results, considering that human cells and tissues for transplantation can save lives or restore essential functions. For example, a corneal graft can restore sight in corneal blindness, having skin available for a traumatic burn can be critical for patient survival and the transplantation of haematopoietic stem cells can cure congenital or acquired diseases, including some leukaemias.

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.

Human cells and tissues for transplantation represent a special class of basic healthcare products, as well as being the potential starting material for much more complex biotechnology products in the future. As with all transplanted material of human origin, they carry risks of disease transmission, which must be controlled by the application of scrupulous donor selection and testing criteria and comprehensive quality systems.

Since 2002, the European Committee (Partial Agreement) on Organ Transplantation of the Council of Europe (CD-P-TO) has been publishing the *Guide to the safety and quality assurance for the transplantation of organs, tissues and cells*. This Guide deals with different aspects of the transplantation process, from risk assessment to disease transmission. During the last revision process, it became evident that the fields of organ transplantation and tissue and cell transplantation have different safety and quality provisions and concerns, thereby justifying the existence of two different guides. Therefore, the CD-P-TO has decided to separate the existing guidance into two new guides; one that deals with organs and the other with tissue- and cell-specific requirements. This 1st edition of the *Guide to the quality and safety of tissues and cells for human application* collates updated information to provide transplant professionals with a useful overview of the most recent advances in the field. To increase safety for recipients of tissues and cells, it is essential that professionals involved in identifying potential donors, transplant co-ordinators managing the donation process, procurement units, tissue establishments processing and storing tissues and cells, inspectors auditing these establishments and end users have easy access to this information.

This Guide has been divided into two parts. Part A contains general requirements applicable to all establishments involved in the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells. Part B contains specific guidelines and requirements for the different tissue and/or cell types. The general guidelines of Part A also apply to tissues that have not been included in Part B of the present edition because they are less commonly used (e.g. parathyroid tissue, neural tissue, etc.). Use of the word “must”

indicates mandatory compliance and alignment with European Directives, whereas use of the word “should” indicates recommended compliance. In addition, unless otherwise stated, the guidelines apply only to tissues and cells intended for clinical use or transplantation (including insemination and fertilisation). Tissues and cells used for “basic” research do not fall under the scope of the present Guide.

This Guide has been the work of many people. The work has been co-ordinated by the Centro Nazionale Trapianti (CNT; tissues) and Agence de la Biomédecine (ABM; cells), but a number of experts must be acknowledged for their contributions and efforts and in the discussions on various parts of this Guide. In particular, Deirdre Fehily (Italy) has put enormous amounts of energy, time, expertise and dedication into making sure the 1st edition of this Guide is a reality. Some other experts should be specifically acknowledged, including:

Anna Vilarrodona i Serrat, Spain
Boryana Avramova, Bulgaria
Carl-Ludwig Fischer-Fröhlich,
Germany
Carolina Stylianou, Cyprus
Catherine Faucher, France
Christian Chabannon, France
Efstratios Chatzixiros, Italy
Eliana Porta, Italy
Eliisa Lukk, Estonia
Elisa Pianigiani, Italy
Elba Agustí i Rovira, Spain
Esteve Trias, Spain
Fewzi Teskrat, France
Fiorenza Bariani, Italy
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Romania
Ruth M. Warwick, United
Kingdom
Scott A. Brubaker, United States
of America
Utku Ates, Turkey

These experts contributed to different aspects of the book and did a tremendous job in reviewing the literature and extracting knowledge from numerous international guidelines, collaborative projects and diverse publications and websites with the aim of ensuring accessibility to all this information.

Special thanks should be given to the European Commission, in particular to Ioana-Raluca Siska, who ensured the current text remained aligned with European Directives and made available the results from the European Union-funded projects EQSTB, EUSTITE, EuroGTP and SOHO V&S.

Several professional organisations, especially the American Association of Tissue Banks (AATB), the European Association of Tissue Banks (EATB) and the Joint Accreditation Committee-ISCT & EBMT (JACIE), should also be thanked for sharing their experience and knowledge.

Finally, the scientific Secretariat and editorial team at the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, in Strasbourg should be acknowledged: Marta López Fraga, Scientific Officer responsible for the transplantation activities at the Council of Europe and Ahlem Sanchez, John O'Brien, David Crowe and Isabelle Bylinski for their work on the administrative and editorial aspects of this publication. 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.

All this has been a great combined effort, with extensive discussions dedicated towards the common goal of increasing safety, efficacy and quality in tissue and cell donation and transplantation. The final result is this Guide, which constitutes a common European standard, based on the long-standing expertise and knowledge of the EDQM.

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Chapter 1. Introduction

1.1. Scope and purpose of this Guide

We are entering a new age of medical and biotechnological progress. Medical procedures that were unimaginable a generation ago are a reality today. One aspect of the recent and rapid advances in biological and medical research is that human tissues and cells are being used in an increasing variety of new ways. Many of these developments, such as advances in transplantation therapy, have unquestionable benefits, but using human tissues and cells in different ways also raises questions of safety, quality and efficacy and presents new ethical dilemmas.

Tissue from one deceased donor may be transplanted into as many as 100 people. Tissue transplants range from life-saving treatments (for example, in the treatment of catastrophic burns) to quality-of-life improvements.

Some tissues are used practically unaltered from the condition in which they were removed from the donor. Deceased donor corneas, for example, are used to restore sight, heart valves replace damaged ones and extend life, tendons and ligaments may be used for the treatment of sporting injuries or to repair degenerative defects, and skin can be employed to cover major burns or support the healing of ulcers. Other tissues, however, are processed into products that are almost unrecognisable as bodily material. Skin, for example, may be cut into conveniently-sized dressings, incorporated into sprays or gels, or de-cellularised for use in various surgical procedures. Bone can be processed into hundreds of different products and distributed via a global medical market for use in orthopaedics (general and oncology),

sports medicine and craniofacial/maxillofacial, dental and neurosurgery. Cellular components of bone may be removed entirely and even the calcium may be removed to promote incorporation and tissue regeneration. Bone allografts may be precision cut and sized, and bones can also be supplied in soft, pliable or injectable form. If a deceased individual has consented to the use of any part of their body for the treatment of others (or their relatives have authorised this after his/her death), many tissues can be put to use to fulfil this wish; bone, heart valves, skin, corneas, ligaments, cartilage, connective and adipose tissue, glands and nerves can all be used for therapeutic purposes.

While many tissues may only be donated after death, some may be provided by living donors, as long as this does not endanger the donor's life. Amniotic membrane from the placenta, gametes and ovarian tissue, parathyroid tissue and skull bone are all given by living persons. In addition, many types of haematopoietic stem cells are donated during life. Some examples are bone marrow, peripheral blood stem cells and umbilical cord blood. Additionally, heads of femurs removed during an operation to replace a hip joint and heart valves from patients receiving a heart transplant are sometimes processed and "recycled".

This is the 1st Edition of the Council of Europe *Guide to the quality and safety of tissues and cells for human application*. This Guide has two main objectives:

- The first is to provide sound information and guidance for all professionals involved in donation, banking, transplantation and other clinical applications of tissues and cells, in order to optimise the quality and minimise the risks of these complex procedures. Human cells and tissues for clinical applications represent a special class of basic essential healthcare products, as well as being the potential starting material for much more complex biotechnology products in the future. As with all transplanted material of human origin, they carry risks of disease transmission, which must be controlled by the application of scrupulous donor selection criteria (including testing) and comprehensive quality systems. The idea behind this Guide is to help

professionals on a practical level by providing generic guidance that will help improve the rate of successful clinical application of tissues and cells.

- Secondly, this Guide provides ethical principles and guidelines to be considered for the donation and transplantation of tissues and cells.

The field of tissue and cell donation and banking is now highly regulated in many countries. In the European Union (EU), four specific directives describe the requirements and these have been transposed into the national legislation of the 28 EU member states. This guide refers to those requirements where appropriate, 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 beyond.

According to the World Health Organization (WHO) Aide-Mémoire on tissue and cell donation and transplantation [1], National Health Authorities are responsible for ensuring that tissue and cell donation, banking and transplantation are appropriately promoted, regulated and monitored in the interests of patient safety and public transparency. More specifically, they are responsible for making sure that:

- an appropriate legislative/regulatory framework is in place;
- national/international practice standards have been defined;
- there is inspection/authorisation of screening, testing, procurement, processing, storage and distribution, imports and exports;
- there are programmes for vigilance and surveillance of adverse outcomes;
- there is monitoring and reporting of donation, processing, storage, distribution and import and export activity.

In this Guide, the term Health Authority is used throughout to refer to the body which has been delegated the responsibility for these activities on a national or regional basis by their government. Other

terms, such as Regulatory Authority, Regulatory Agency or, in the EU, Competent Authority, are equivalent to it.

Human tissues and cells also play a key role in medical research. In clinical trials of new medicines, for example, vital information about the effects of the medicine on an individual can be obtained from samples of tissues or cells and other materials provided by research participants. However, tissue is also used much more widely in medical research, from early drug “discovery” (such as using human tumour samples to discover possible targets for treatment) to later clinical development where samples may be used to identify which sub-groups of patient populations respond best to a new medicine. Additionally, current research is developing artificial tissue that should alleviate the shortage of tissues available for transplantation. These forms of “basic” research using human tissue still have an ultimately therapeutic goal in mind. However, as important as all these possibilities are, this Guide will only cover tissues and cells used for current therapeutic purposes.

Finally, a glossary of terms is provided in the Appendices.

This book 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) and the Ad hoc Tissues and Cells Expert Group (see Appendices). Unless otherwise indicated, “member states” applies to member states of the Council of Europe.

For matters dealing with the use of organs and blood or blood products, see the Council of Europe *Guide to the quality and safety of organs for transplantation* and *Guide to the preparation, use and quality assurance of blood components* [2], respectively.

1.2. Brief history of tissue and cell transplantation and banking

The best documented accounts of early transplants deal with skin transplantation, though the success or failure of these procedures has not been well documented. The first reliable account is that of the

Indian surgeon Sushruta in the 2nd century BC, who used auto-grafted skin transplantation for a nose reconstruction (rhinoplasty). Centuries later, the Italian surgeon Gasparo Tagliacozzi performed successful skin auto-grafts, but he consistently failed with allografts, offering the first suggestion of rejection centuries before that mechanism could possibly be understood. He attributed it to the “force and power of individuality” in his 1596 work *De Curtorum Chirurgia per Insitionem*. Orthopaedic surgeons refer to the origin of their discipline as 1668 when Job van Meekeren reported on the grafting of bone from a dog’s skull to correct a defect in a soldier’s cranium. It was not until 1869 that the first completely documented fresh human skin allograft was performed by the Swiss surgeon Jacques Reverdin.

The first successful human corneal transplant, a keratoplastic operation, was performed in 1905 by Eduard Zirm at Olomouc Eye Clinic (Czech Republic). Pioneering work in the surgical technique of transplantation was made in the early 1900s by the French surgeon Alexis Carrel, together with Charles Guthrie, who developed techniques for suturing arteries and veins. Their skilful anastomosis operations and new suturing techniques laid the groundwork for later transplant surgery and Alexis Carrel won the 1912 Nobel Prize in Physiology or Medicine for his work in the field. Major steps in skin transplantation occurred during the First World War, notably through the work of Harold Gillies in Aldershot, UK. Among his advances was the tubed pedicle graft, which maintained a fleshy connection from the donor site until the graft established its own blood supply.

Bone is the oldest tissue transplant on record and the most common tissue transplanted today. The first bone transplant recorded in modern times occurred in Scotland in 1878 when Sir William Macewen removed an infected humerus from a 12-year-old boy and replaced it with three allografts from an amputated tibia from another child with rickets. In 1907, Erich Lexer in Berlin developed a procedure to remove a whole knee joint from an amputee in one operating room and to transport the “warm” graft to an adjacent operating room for immediate transplant into the recipient. Five years later, Alexis Carrel’s work predicted the storage of tissues for future transplantation

and surgeons began to use bones and developed their own bone banks. These pioneers included Inclan in Cuba, Bush, Wilson and Hibbs in the USA, Hult working in Sweden, Judet in France, and Klen in what was then Czechoslovakia. Most of these early bone banks were simply refrigerators and, later, freezers, but greater sophistication was developed by bone banks in Leeds (UK), Berlin, Athens and Warsaw. When long-term freezer storage of long bones became feasible, limb-sparing surgery using this type of bone allograft to avoid amputations in the treatment of malignant skeletal tumours became popular. Burwell (UK), Parrish and Mankin (USA) and Ottolenghi (Argentina) published their results. The orthopaedic profession realised that if very large segments of bone could be transplanted successfully, smaller segments could also be used. This resulted in a very large increase in the use of bone allografts. Tissue storage methods were further developed during the 1950s by Hyatt at the US Navy Tissue Bank in Bethesda, Maryland, where they adapted methods of lyophilisation from the food preservation industry and applied the process to the preservation of bone and skin, which could then be easily stored, transported and reconstituted for use when needed. This method of preservation allowed bone to be easily stored and transported without any electrical or mechanical requirements and, to date, has had a profound effect on the availability and use of bone allografts. By the close of the 1990s, the use of musculoskeletal tissue allografts (i.e. bone, cartilage and soft tissue) had become commonplace in many clinical areas. Similarly, the first deceased donor eye bank was established in Odessa using eyes (packed in storage medium in glass containers) sent by rail from a Moscow trauma centre.

The first recorded cardiac valve transplantation was performed by Gordon Murray in Toronto who implanted an aortic allograft in the descending thoracic aorta to relieve aortic insufficiency in 1956. The first orthotopic transplantation of the aortic valve was performed by Donald Ross in London in 1962 and independently by Brian Barratt-Boyes in Auckland, New Zealand, a few weeks later. Pulmonary and mitral valves were first used as allografts in the succeeding years with the pulmonary autograft operation being first performed in 1967.

After the atomic bomb explosion in Japan, ending World War II, many scientists began to explore ways of protecting humans from irradiation. The first experiments were performed in mice and later in dogs by E.D. Thomas. As early as 1956, the idea that bone marrow transplants might exert a therapeutic effect against malignancies was proposed by Barnes and Loutit who observed an anti-leukaemic effect of transplanted spleen cells in experimental murine models. In 1959, the first human bone marrow transplants gave proof of concept that infusions of bone marrow could provide haematological reconstitution in lethally-irradiated patients with acute leukaemia. E.D. Thomas transplanted two patients with advanced acute lymphoblastic leukaemia with a syngeneic graft after high-dose total body irradiation; the grafts were successful but the patients died a few months later of relapse. G. Mathé administered allogeneic bone marrow for the treatment of several patients who had suffered accidental irradiation exposure and most survived with autologous reconstitution. In 1965, Mathé was the first to describe long-term engraftment of sibling bone marrow, thereby demonstrating chimerism, tolerance and an anti-leukaemic effect. Although the transplant itself was successful, the patient eventually died of varicella with chronic graft versus host disease (GvHD). In 1970, M. Bortin reported 203 transplants performed between 1958 and 1968, with only three patients alive at the time of the report. The major causes of death were graft failure, GvHD and relapse. Following these disappointing results, few centres persisted and the number of transplants declined sharply. Major progress came from the discovery of the HLA system by J. Dausset and J.J. Van Rood. Selection of HLA-identical siblings as bone marrow donors diminished the risk of rejection and GvHD. Using animal models, R. Storb and E.D. Thomas developed the model of total body irradiation for conditioning (in dogs) and the use of methotrexate for GvHD prevention. In mice, G. Santos showed that the use of cyclophosphamide could add immune suppression to the myeloablation of total body irradiation. He was also the first to use busulfan instead of total body irradiation. In 1989, the first successful cord blood stem cell transplant was performed to treat a child with Fanconi's anaemia with

cells from an unrelated donor. The first unrelated bone marrow registry was established in London, in 1973, by Shirley Nolan, whose son was diagnosed with Wiskott Aldrich syndrome. Following this first donor recruitment drive, the number of bone marrow and peripheral haematopoietic stem cell donors has increased all over the world, with more than 18 million donors now registered and including 500,000 cord blood donors [3].

Transplantation of pancreatic islets has been performed in humans since 1990 [4], but it was not until 1999 that the first successful transplant of pancreatic islets, using the so-called “Edmonton Protocol”, was performed by James Shapiro [5]. European centres became active around the same period, but their transplant recipients had complications of Type I diabetes that could not be managed with insulin injections. The advantage of the Edmonton Protocol was that it allowed restoration of the fine-tuned regulation of glucose metabolism through appropriate insulin production by the transplanted islets. In 2005, the first living donor pancreatic islet transplant from a 56-year-old woman to her 27-year-old diabetic daughter resulted in the transplanted cells producing insulin within minutes after transplantation.

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

Since 1987, through its activities in the field of organ/tissue transplantation, the Council of Europe has contributed actively to the implementation of high standards for the protection of public health and for the promotion of human rights and dignity. Nowadays, these transplantation activities are steered and co-ordinated by the *European Committee on Organ Transplantation* (CD-P-TO) [6]. The CD-P-TO was established following the Third Conference of European Health Ministers in Paris in 1987 on the Ethical, Organisational and Legislative Aspects of Organ Transplantation. This Committee is composed of internationally recognised experts from Council of Europe member states, observer countries, the European Commission, the WHO,

representatives from the Committee on Bioethics of the Council of Europe (DH-BIO) [7] and several other non-governmental organisations. Their activities are co-ordinated by the scientific Secretariat. In 2007, the Secretariat with responsibility for activities related to organ, tissue and cell transplantation was transferred to the European Directorate for the Quality of Medicines & HealthCare (EDQM) [8] of the Council of Europe. This Directorate is a key European organisation involved in the harmonisation, co-ordination, standardisation, regulation and quality control of medicines, blood transfusion, organ transplantation, pharmaceuticals and pharmaceutical care, consumer health, cosmetics and food packaging.

1.4. Recommendations and regulations in the field

1.4.1. Council of Europe

Within the framework principle of sharing knowledge through international co-operation, the Council of Europe and the CD-P-TO and its predecessors have established widely recognised recommendations and resolutions in the field of transplantation, covering ethical, social, scientific and training aspects of organ, tissue and cell donation and transplantation [9]. 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) [10] 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) [11], signed in Paris on 15 December 1958, aims to provide mutual assistance in respect of the supply of therapeutic substances of human origin.

The *European Agreement on the exchange of tissue-typing reagents* (European Treaty Series, No. 84) [12], signed in Strasbourg on 17 September 1974, lays the groundwork for the development of mutual assistance in the supply of tissue-typing reagents and establishment of joint rules between the signatory parties. The signatory parties undertake to make reagents available to other parties who are in need of them, by the most direct route, subject to the condition that no profit is made on them, that they must be used solely for medical and scientific purposes and are free of import duties. The Additional Protocol (European Treaty Series, No. 89) [13], opened for signature on 24 June 1976, which entered into force on 23 April 1977, provides for the accession of the European Community to this Agreement:

The *Oviedo Convention: Protection of human rights and dignity of the human being with regard to the application of biology and medicine* (European Treaty Series, No. 164) [14], signed on 4 April 1997, which entered into force on 1 December 1999, is the first legally binding international text designed to preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances. The Convention's rationale is that the interests of human beings must come before the interests of science or society. It lays down a series of principles and prohibitions concerning bioethics, medical research, consent, rights to private life and information, organ transplantation, public debate, etc. It specifically establishes the prohibition of financial gain from a part of the human body.

This latter Convention was further extended 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) [15], which was opened for signature on 24 January 2002 in Strasbourg and entered 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 or her integrity and other rights and fundamental freedoms with regard to transplantation of organs and tissues of human origin.

The Council of Europe *Convention on action against trafficking in human beings and its Explanatory Report* (European Treaty Series, No. 197) [16], opened for signature in Warsaw on 16 May 2005, which entered 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* [17], 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 rationale of the study is the prohibition of making financial gains from the human body or its parts.

Other major resolutions and recommendations in the field of tissues and cells include:

- Resolution (78) 29 on *harmonisation of legislations of member states relating to removal, grafting and transplantation of human substances* [18];
- Recommendation No. R (94) 1 of the Committee of Ministers to member states on *human tissue banks* [19];
- Recommendation No. R (98) 2 of the Committee of Ministers to member states on *provision of haematopoietic progenitor cells* [20];
- Recommendation Rec(2004)8 of the Committee of Ministers to member states on *autologous cord blood banks* [21].

The Council of Europe also produces other guidelines, including this 1st Edition of the *Guide to the quality and safety of tissues and cells for human application*, the 5th Edition of the *Guide to the quality and safety of organs for transplantation* and the 17th edition of the *Guide to the preparation, use and quality assurance of blood components*.

1.4.2. World Health Organization

In 1987, the 40th World Health Assembly, concerned by the trade for profit in human organs, initiated the preparation of the

1st WHO *Guiding Principles on Transplantation*, endorsed by the Assembly in 1991 in resolution WHA44.25 [22]. These Guiding Principles have greatly influenced professional codes and practices, as well as legislation, around the world for almost two decades. After a consultation process that took several years, the 63rd World Health Assembly adopted resolution WHA63.22 [23] on 21 May 2010, which endorsed the updated WHO *Guiding principles on human cell, tissue and organ transplantation* [24] and called on WHO member states to implement the guiding principles, to promote voluntary and unremunerated donation, to 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 [25] 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”. Subsequently, the *Declaration of Istanbul on organ trafficking and transplant tourism* [26] was adopted in 2008, as an initiative of The Transplantation Society (TTS) and the International Society for Nephrology (ISN). The 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, it leads inexorably to inequity and injustice and should also be prohibited. Organ trafficking, transplant tourism and transplant commercialism were defined by the Declaration, providing principles of practice based on those definitions. The Declaration of Istanbul distinguishes transplant tourism from 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 (1) it involves organ trafficking and/or transplant commercialism or (2) if 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.

Robust bi-directional donor-recipient traceability is a prerequisite to achieving effective vigilance and surveillance worldwide. For this reason, Resolution WHA63.22 [23] also urged WHO member states to collaborate in collecting data, including adverse events and reactions, in addition to the 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 adverse incident information for the purposes of improving safety and efficacy [27].

As a result of resolutions WHA57.18 and WHA63.22 (which requested that global data on the practices, safety, quality, efficacy and epidemiology of transplantations be collected in WHO member states which have transplantation programmes), an international transplant watchdog was set up as a collaborative initiative between the Spanish Organización Nacional de Trasplantes (ONT) and the WHO, termed the *Global Observatory on Donation and Transplantation* [28]. The universal availability of these data is recognised as a prerequisite for global improvements in demonstrating transparency, equity and compliance, and for monitoring systems in countries. Additionally, 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.

Finally, the WHO has published two Aide-Mémoires specifically for the field of tissue and cell donation and transplantation [29, 30].

1.4.3. European Union

Article 168 of the *Treaty on the Functioning of the European Union* [31] (previously Article 152 of the *Treaty of Amsterdam*) requires the EU to

establish high quality and safety standards for the use of blood, organs and other substances of human origin, such as tissues and cells.

Acknowledging that the transplantation of human tissues and cells is an expanding medical field that offers important opportunities for the treatment of disease, the EU aims for a common approach to the regulation of tissues and cells across Europe.

The EU Tissue and Cells Directives created a benchmark for the standards that must be met when carrying out any activity involving tissues and cells for human applications. The Directives also require that systems be put in place to ensure that all the tissues and cells used in human applications are traceable from donors to recipients.

The EU legislation for tissues and cells includes four Directives: the parent Directive 2004/23/EC [32] that provides the framework legislation, and two implementing Directives 2006/17/EC [33] and 2006/86/EC [34] that detail more technical requirements. The new Directive 2012/39/EU [35] amends Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells and 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 [36].

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 applies to the donation, procurement, testing, preservation, storage and distribution of human tissues and cells intended for human use. It also relates to manufactured products derived from human tissues and cells intended for human use. In the case of products made industrially from tissues and cells (which, in the EU, fall under Regulation 1394/2007 on advanced therapy medicinal products [37]), the Directive only applies to donation, procurement and testing.

Quality and safety standards for human organs intended for transplantation are laid down in Directive 2010/53/EU and the Commission-implementing Directive 2012/25/EU laying down information procedures for the exchange between EU member states of human organs intended for transplantation [38].

The EU Directives dictate that EU member states must encourage voluntary and unpaid donations of tissues and cells and must endeavour to ensure that the procurement of tissues and cells is carried out on a non-profit basis. Promotion and publicity activities in support of the donation of human tissues and cells with a view to offering or seeking financial gain or comparable advantage are not allowed. The EU Directives also provide clear mandates as regards the consent of donors and the anonymity of all data collected, and instructs EU member states to adopt measures to ensure data security and prevent unauthorised modifications to files and records.

These Directives do not cover research using human tissues and cells (e.g. *in vitro* research or research in animal models) and do not interfere with the decisions of EU member states on the use or non-use of any specific type of human cells, such as germ cells or embryonic stem cells.

The European Commission has supported EU member states in their efforts to implement the EU Tissue and Cells Directives by providing funding for several projects under the Programme of Community Action in the Field of Health [39]:

- **EQSTB** (European Quality System for Tissue Banking) focused on four main work packages: (i) Identification of the key requirements for tissue banking; (ii) Development of a registry to support exchange of tissues; (iii) Provision of training programmes, both online and face-to-face, to fulfil the needs of tissue establishment professionals and (iv) Development of an audit model and audit guide for tissue establishments, with recommendations for tissue establishments and guidance for auditors.
- **EUSTITE** (European Standards and Training in the Inspection of Tissue Establishments) [40] developed guidance and training courses for EU Competent Authorities on the inspection of tissue establishments and on vigilance for tissues and cells used in transplantation and in assisted reproduction. The guidance document served as a basis for the guidelines on the

implementation of inspection and control measures in the field of human tissues and cells included in Commission Decision 2010/453/EU of 3 August 2010.

- **POSEIDON** (Promoting Optimisation, Safety, Experience sharing and quality Implementation for Donation organisation and networking in unrelated haematopoietic stem cell transplantation in Europe) provided recommendations for improvements in the safety of unrelated haematopoietic stem cell transplantation, for the optimisation of human stem cell donation policy, and for promoting equal access to this therapy throughout the EU.
- **EUROCET** [41] is a platform that was initially funded by the European Commission and is now maintained by the Italian National Transplant Centre. It is a publicly accessible registry of tissue establishments and Competent Authorities for tissues and cells in the EU and it collects and publishes annual activity data on donation, processing and human applications of tissues and cells.
- **EuroGTP** (European Good Tissue Practices) [42] developed a Good Tissue Practices Guide and Personnel Training Guidelines for tissue establishments regarding recovery, processing and preservation of tissues, in order to ensure that all tissue establishments guarantee the highest level of quality and safety of tissues for transplantation. EuroGTP has provided a crucial basis for much of the technical content of this Guide. A strong collaboration between the European Association of Tissue Banks (EATB), which will update and maintain the GTPs as their own standards, and the Council of Europe will be maintained to ensure consistency and development in the light of the most up-to-date scientific knowledge.
- The project **SOHO V&S** (Vigilance and Surveillance of Substances of Human Origin) [43] addressed the harmonisation of terminology and documentation both relating to adverse events and reactions, and aimed to find a consensus on how

information should be exchanged between EU member states, the European Commission and third countries to enhance efficient management of incidents involving cross-border distribution of tissues and cells. The project drafted important guidance documents for the EU competent authorities, concerning the detection and investigation of suspected illegal and/or fraudulent activity related to tissues and cells, the communication and investigation of serious adverse events and reactions associated with human tissues and cells, as well as the vigilance and surveillance in the field of assisted reproductive technologies. The project also prepared a guidance document for healthcare professionals on vigilance and surveillance of human tissues and cells. A training model for Competent Authorities in the investigation and management of vigilance and surveillance of tissues and cells was also provided.

These projects have strengthened collaboration among health authorities and between these health authorities and the professional associations in the area of tissue/cell transplantation, allowing continuous input from field practice into the regulatory framework.

1.5. Differences between tissue and organ transplantation

Progress in the medical sciences has made it possible to effectively transplant human cells and tissues from one person into another. Cornea and musculoskeletal tissues are the most commonly transplanted, outnumbering organ transplants more than tenfold. Transplantation of tissues such as corneas, cardiovascular tissues, bone, tendons and skin are all well-established therapeutic techniques. Skin allografts are a life-saving procedure in severe burns and some of the other tissue transplants described above offer major therapeutic benefits to a wide range of patients. Indeed, demand is rapidly increasing for bone transplantation, particularly for secondary revision of hip replacement operations, as well as for skin treatment of severely burned

patients. Successful transplantation, even when not acutely life-saving, offers recipients major improvements in their quality of life.

The main differences between organ and tissue transplants are summarised in Table 1.1.

Table 1.1. Main differences between organ and tissue transplants

Organs	Tissues
Usually life-saving.	Tissue use is usually not life-saving, but life-enhancing.
Donor pool is small.	Donor pool is larger.
Time to implantation is usually measured in hours and the organs cannot be preserved for future use.	Time to implantation can be measured in days or years, depending on the tissue and the preservation method applied.
Donor can only supply a small number of recipients.	One donor's tissues can be used to transplant many patients. Thus, donor selection failures can impact many recipients.
Cannot be sterilised or exposed to robust decontamination processes.	Tissues and cells can often be subject to decontamination/sterilisation methodologies.
Often the only therapeutic option, with exceptions such as kidneys where dialysis can provide a sub-optimal solution while waiting for transplantation.	Alternative treatments are usually available, but may be less clinically effective.

Due to the above differences, selection criteria for tissue donors can often be more stringent than for organ donors.

Haematopoietic progenitor cells fall somewhere between organs and tissues in this comparison. They are usually intended for life-saving procedures and are transplanted on a one donor to one recipient basis. However, they can be processed to some extent, though not sterilised, and they can be stored for extended periods. Where bone marrow is donated by an unrelated donor for a specific recipient and transplanted without freezing, the situation is very analogous to organ

transplantation. In contrast, when cord blood is donated to a public cord blood bank, stored for years and possibly selected later for transplantation for a matching recipient, the situation is more analogous to tissue banking.

Other cells, like keratinocytes and chondrocytes, are closer to tissues in that they are life-enhancing and can be supplied by one donor to many recipients.

1.6. Benefits and risks of transplantation

Although patient-derived auto-grafts, as well as synthetic materials, are sometimes used to replace damaged tissues, donor-derived allografts are often preferable or even necessary as the only life-saving therapeutic option. A successful engraftment results in the donor tissue integrating and functioning as a part of the recipient's own body.

In practice, the decision to transplant any donor-derived tissues or cells will always be based on a clinical assessment of the risk versus the benefit to the patient, taking any alternative potential therapies into consideration. This is because any transplantation carries not only the risk of the operative procedure itself, but also of donor-related 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 recipient should be considered. In both cases, the potential benefits of the transplant procedure should outweigh the risks. Transparent communication and good collaboration between Health Authorities, tissue establishments and clinicians treating patients are vitally important in any donation process.

Some of the most widely used tissues and cells and the benefits for the transplanted recipients are listed in Table 1.2.

Table 1.2. Most widely used tissues and cells and the benefits for the transplanted recipients

Tissues and Cells	Function	Benefits for the recipient
Bones	Support the body and protect vital organs.	Used to repair or stabilise the spine and other bones damaged from degeneration, trauma, cancer or birth defects. Bone is also used in oral surgery and in the filling of bone cavities or other areas where bone mass has been lost.
Haematopoietic stem cells (bone marrow, peripheral blood stem cells and cord blood)	Give rise to platelets, leucocytes and erythrocytes.	Used for the treatment of haematological malignancies and genetic and autoimmune diseases.
Corneas/eyes	Corneas allow light to enter the eye. Sclera is the white of the eye which provides structure and support.	Indicated for visual problems caused by deterioration of the front part of the ocular globe. If whole eyes are donated, the corneas can be used in transplants for corneal blindness and the sclera can be used for oral grafts in dental procedures or in the treatment of glaucoma.
Fascia	Fibrous tissue that covers muscles.	Used to repair tendons, muscle, ligaments and deformities.
Heart valves	Direct the flow of blood in the heart.	Used for patients with valve defects, especially in children.
Pancreatic islets	Containing Langerhans cells, which are responsible for the production of insulin.	As an alternative to pancreatic transplants.
Pericardium	Protective lining around the heart.	Used for <i>dura mater</i> replacement in brain surgery.

Tissues and Cells	Function	Benefits for the recipient
Placenta/Amniotic membrane	Transfers oxygen and nutrients from the mother to the fetus.	The amniotic membrane is used in burns, to reduce surface inflammation, scarring and pain in surgical applications, in certain types of ulcers and in eye surgery.
Veins and arteries	Provide a structure for the flow of blood through the body.	Replace blood vessels that are damaged by disease, trauma or prolonged dialysis treatment. Also used in bypass surgery to re-route blood flow.
Skin	Protects the body against injury, infection and dehydration.	Used for the treatment of burn patients, certain types of ulcers, abdominal wall repairs and reconstructive or plastic surgery.
Tendons	Attach muscle to bone.	For use in joint injuries.

As regards the risks associated with tissue and cell transplantation, Article 6 of the *Additional Protocol to the Convention on human rights and biomedicine concerning transplantation of organs and tissues of human origin* clearly establishes that:

“...all professionals involved in organ or tissue transplantation must take all reasonable measures to minimise the risks of transmission of any disease to the recipient and to avoid any action which might affect the suitability of an organ or tissue for implantation.”

Careful evaluation of the donor medical case history, travel history, behavioural risks and history of malignancies are necessary in order to keep the risk of transmission of infections or malignancies to the recipient as low as possible. This is discussed in Chapter 4.

Only tissues and cells recovered, processed, stored and distributed within well-controlled quality management systems of donation, processing, storage and distribution are likely to function satisfactorily and to reach an acceptable level of safety. The donor selection criteria and the processing and preservation conditions are crucial parameters

that need to be tightly controlled. Therefore, any organisation involved in these processes should implement a comprehensive quality management system. Management commitment and support are essential for the development, implementation and monitoring of a quality system in order to ensure continuous improvement. All staff should understand the importance of quality and their role in achieving it consistently.

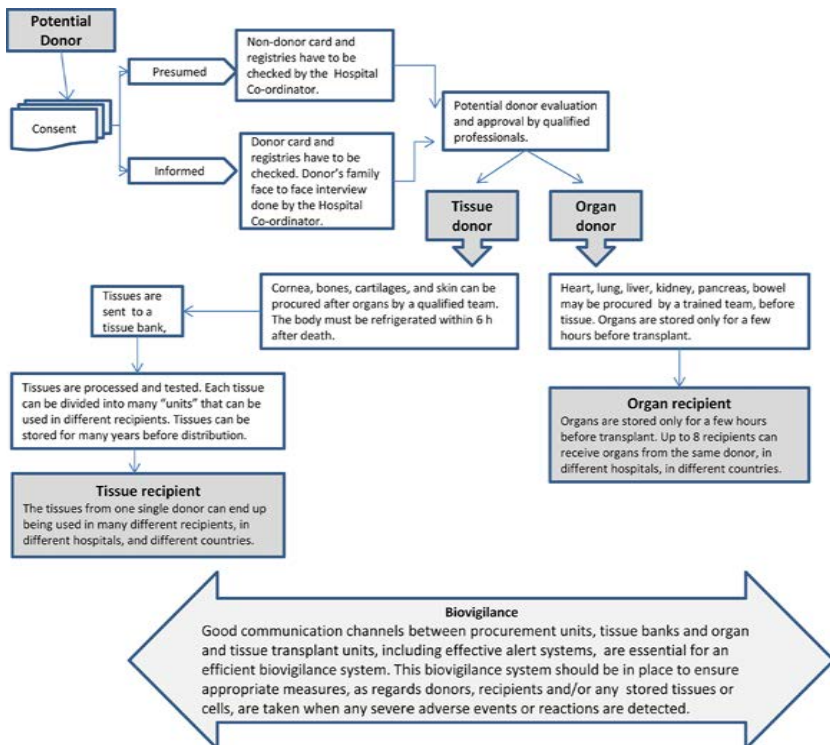
In summary, transplantation of tissues or cells can be greatly beneficial for a patient, but it is not without risk. In exceptional cases, a tissue and cell donation that does not meet all the necessary safety or quality requirements may be used for transplantation into a particular patient. This may occur, for instance, where the transplant is likely to be life-saving and alternative options for treatment of that patient have a poor prognosis. Patients contemplating any transplant should discuss the risks and benefits of any surgery or therapy with their physicians and make the decision that is best for them.

1.7. The process of tissue and cell donation and transplantation

Tissue and cell donation and transplantation continue to be fast-moving fields and such rapid developments bring their own challenges. These challenges include the control of all crucial technical activities and services (removal, transportation, processing, preservation, quality control and storage) that enable tissues and cells to be removed from one body and transferred to another body, the reimbursement of expenses and service charges, the safeguards from exploitation or misuse (e.g. formal requirements for consent from the potential donor before material may be taken) and the complex chain of intermediaries in the process of donations and transplantation, including both people and institutions.

The complex network of interactions that underlie the many different ways in which human bodily material may be provided by one person for the benefit of others is summarised in Figure 1.1.

Figure 1.1. Complex links between deceased tissue and organ donors and recipients



It is appropriate to conceptualise the entire process in terms of flows. Transplants can only take place if trained professionals are available to talk to the family of the potential deceased donor, if the hospital where the donor has died has the necessary infrastructure in place to remove the tissues within a given timeframe, if appropriate transport services exist in order to remove the tissues in an adequate manner, if surgeons are available to carry out transplantation of tissue into the recipient, etc.

The histories of the many different forms of tissue banking highlight the increasingly complicated and interconnected ways in which one person's tissues and cells may be used to help others. The central role

played by tissue establishments in modern medicine, in providing material for treatment and for research, highlights the complicated networks that may now connect the sources and recipients of donated bodily material, and the many intermediaries involved in processing the material, to facilitate its use by the clinical user.

Centralised management of tissue and cell donations would be the ideal scenario. Nevertheless, tissues and cells can be provided from both public organisations and private businesses; though co-operation between tissue establishments is often relatively limited. National and international efforts have focused on “best practice” for tissue establishments without usually providing a mechanism for comprehensive, nationwide sharing of donated material. In the meantime, a human tissue and cell supply industry has evolved internationally, with multiple providers competing in a market driven by, among other things, biotechnology and pharmaceutical companies. Thus, the flows involved between the original “source” or “donor” of the material, the amount of processing of the material involved and the commercial nature of some of those transactions are becoming ever more complex.

It is important to emphasise how any consideration of policy surrounding donation must increasingly take into account the complex flows and multiple intermediaries involved in the process [44]. Such awareness highlights the central role inevitably played in the donation and subsequent use of bodily material by organisations and organisational structures. For example, in the creation of professional roles such as donation and consent “co-ordinators” and the extent to which they are expected to maximise opportunities for donation, in how these professionals approach potential donors and form relationships with them, in how well one part of the system links with another and where responsibility is seen to rest, and in the way professionals in different fields interact and co-operate with one another. It also points to added complexities in the form of legal agreements, liabilities and obligations that may arise where donated material is transformed, banked or otherwise handled as a commodity by successive intermediaries.

The increasing possibility of using many forms of bodily material to benefit others in medical treatment has brought about increased pressure in member states to meet demand. There is a continual need to recruit new tissue and cell donors in order to maintain an adequate supply. Shortages of supply may affect particular sub-groups of the population more than others because of the need to match material according to immunological criteria or age. “Demand” for material is inherently variable; as scientific developments make more treatments possible, the demand for that treatment is likely to increase, and the development of alternatives may lead to reduced 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 is exacerbated in situations where the requirement for a high degree of matching between donor and recipient calls for ethnic minority recruitment and international collaboration. However, at the same time, it may imply a lack of consideration of the human nature of the source of the material. It is important to emphasise when using these impersonal terms that we are talking about people and people’s lives, on both sides of the equation.

1.8. Tissue banks, biobanks and tissue establishments

A “tissue bank” is a term commonly used to describe an establishment that collects and stores human tissues for either medical research or a medical application/transplantation.

The increased use of cells/tissues for transplantation and for research calls for terminology which will help to distinguish between establishments which collect and store cells/tissues for each of those purposes. Within Europe, the terms currently in use are tissue establishments and biobanks, respectively.

The term “biobank” is regularly used for repositories storing human biological samples for use in research. Presently, there is not an internationally-agreed definition of biobank, but the term is generally used for organised collections of human biological material (blood, tissues, cells, other body fluids, DNA, RNA, etc.) and associated information stored for one or more research purposes. In its glossary, the Organisation for Economic Co-operation and Development (OECD) defines a biobank as “a collection of biological material and the associated data and information stored in an organised system, for a population or a large subset of a population” [45]. Several other definitions, as used in various EU legislation/guidelines, are available on the website of the EU-funded project PRIVILEGED (Privacy in Law, Ethics and Genetic Data) [46].

In the USA, the term “biorepository” is preferred to biobank. For example, according to the glossary of the National Cancer Institute, a biorepository is:

“a facility that collects, catalogues, and stores samples of biological material, such as urine, blood, tissue, cells, DNA, RNA, and protein, from humans, animals, or plants for laboratory research. If the samples are from people, medical information may also be stored along with a written consent to use the samples in laboratory studies” [47].

The term “tissue establishment” became widely used in Europe following publication of the EU Tissues and Cells Directive 2004/23/EC, which defines it as “a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells”. The Directive does not cover research using human tissues and cells, so tissue establishments are concerned only with tissues and cells intended for human applications.

In the USA, the American Association of Tissue Banks (AATB) uses the term tissue bank for “an entity that provides or engages in one or more services involving tissue from living or deceased individuals

for transplantation purposes. These services include assessing donor suitability, recovery, processing, storage, labelling, and distribution of tissue” [48].

As the biobanking field is continuously evolving, and tissue establishments may become interested in collecting samples for research purposes, the terminology should also be refined to reflect these changes in the future.

In the current Guide, it was agreed to use the term tissue establishment and its definition in accordance with Directive 2004/23/EC.

1.9. Quality and safety

High quality, safe and efficacious procedures are essential for donors and recipients alike. The long-term outcomes of tissue and cell donation and transplantation should be assessed for the living donor, as well as the recipient, in order to document benefit and harm.

The level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, must be maintained and optimised on an on-going basis. This requires implementation of quality systems including traceability and vigilance, with adverse events and reactions reported both nationally and for imported/exported human products.

Optimising the outcome of tissue and cell transplantation entails a rules-based process that encompasses clinical interventions and *ex vivo* procedures from donor selection through to long-term follow-up. Under the oversight of health authorities, transplant programmes should monitor both donors and recipients to ensure that they receive appropriate care, including information regarding long-term risks and benefits. As mentioned before, evaluation of information regarding the long-term risks and benefits is essential to the consent process and for adequately balancing the interests of donors as well as recipients. The benefits to both must outweigh the risks associated with donation and transplantation. Donors should not be permitted to donate in clinically hopeless situations.

Locally organised donation and transplant programmes are encouraged to participate in national and/or international transplant registries. All deviations from accepted procedures that could increase the risk to recipients or donors, as well as any untoward consequences of donation or transplantation, should be reported to and analysed by responsible health authorities.

Transplantation of human material that does not involve long-term medical care of the recipient may not require active, long-term follow-up; though traceability should be ensured for the anticipated lifetime of the donor and the recipient. Internationally agreed means of coding to identify tissues and cells used in transplantation are essential for full traceability.

1.10. Ethical issues

Human tissues and cells can only be derived from the body of a person – hence the ethical challenges associated with their use. The range of materials described in this Guide makes explicit the very different circumstances under which a person can donate. The person providing the material may be living or deceased, the material may be used almost immediately or stored for long periods of time, the material may be used unprocessed or heavily processed, etc. Whatever the case, handling and disposal of human tissues should be carried out in a manner that shows respect for fundamental rights and for the human body.

Ethical standards of all aspects of tissue and cell donation and transplantation have to conform to the *Oviedo Convention on Human Rights and Biomedicine* (1997) [14], the *Additional Protocol on Transplantation of Organs and Tissues of Human Origin* (2002) [15] and to the *European Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells* [32]. Other important guidelines to observe from an ethical point of view are *Committee of Ministers Resolution (1978) 29 on harmonisation of legislation of member states relating to removal, grafting and transplantation of*

human substances [18], the WHO *Guiding Principles on human cell, tissue and organ transplantation* [24] and the *Declaration of Istanbul on organ trafficking and transplant tourism* [26].

Any action in the field of tissue and cell transplantation should be carried out in accordance with professional obligations and standard procedures.

A very wide range of tissues may be donated for transplantation. While many of these tissues may only be donated after death, some may be provided by living donors. Tissue donated for transplantation after death is governed by the same ethical principles as organs; it enters a common pool to be used according to need and its use cannot be directed to a particular individual. Cells, such as bone marrow, can be donated by a living person dedicated for transplant to another specific person but, in general, this will not be the case and the donated tissue will be for general use. For deceased tissue donation, the dead-donor rule, which states that patients must be declared dead before the removal of any vital organs or tissues for transplantation, must be strictly respected [49].

1.10.1. **Consent**

The *Oviedo Convention* states that an intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person must make a free choice in the absence of any undue influence and 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.

The *Additional Protocol to the Convention on human rights and bio-medicine concerning transplantation of organs and tissues of human origin* further expands these provisions for the specific case of donation and transplantation. This is explained in detail in Chapter 4.

Tissues must not be removed from the body of a deceased person unless that person has been certified dead in accordance with the national law and consent or authorisation has been obtained. The

removal 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 mistrust of the healthcare system, is one of the reasons why people are reluctant to donate bodily material. This may be associated with concerns about consent; both 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) and that additional material may be taken without explicit consent. Values such as honesty and trust are central in both the professional and personal relationships when donation of bodily material takes place. Therefore, it is of vital importance that the limits of the consent are clearly established, explicit and scrupulously respected.

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

In summary, all donation and transplantation programmes are dependent upon the goodwill and voluntary donation of relevant material from donors to continue their activity. 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 resultant physical harm from the use of transplantable tissue for human application will be reduced.

1.10.2. Conflicts of interest

To avoid any potential conflict of interests, physicians determining the death of a potential donor should not be directly involved in the tissue or cell procurement from the donor or subsequent transplantation procedures, nor should they be responsible for the care of any intended recipient of such tissues or cells.

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.

1.10.3. Financial aspects of donation and transplantation

Discussions around how best to increase supply of human tissues and cells often focus on questions of donor motivation, i.e. how individuals may best be encouraged to donate different forms of bodily material. 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. This motion is reiterated in the *Additional Protocol* to that Convention, which also clearly states in its Article 21 that the human body and its parts must not, as such, give rise to financial gain or comparable advantage. The aforementioned provision does 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 or tissues from living persons.

In summary, voluntary unpaid donation, long promulgated as the only ethical basis for donation of bodily material, should continue to play a central role in the donation process. Payments to donors of tissues or cells should cover only reasonable expenses and should not act as an inducement. Rewarded gifting is unacceptable.

Physicians and other health professionals should not engage in transplantation procedures, and health insurers and other payers should not cover such procedures, if the cells or tissues 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 cells or tissues by means of advertisement or public appeal may be undertaken in accordance with domestic regulations. However, advertising the need for availability of cells or tissues with a view to offering or seeking financial gain or comparable advantage for the donor, or their next of kin where the individual is deceased, should be prohibited. Brokering that involves payment to such individuals or to third parties should also be prohibited.

Tissue establishments storing and supplying fresh human tissue have developed largely in response to the increasing demand for supplies of human tissue for therapy and research. Tissues and cells should be supplied on a procurement cost basis and no payment should ever exceed the justifiable fee for the services rendered. Professional bodies should ensure that their guidelines reflect their members' responsibilities in the acquisition and supply of human tissue. Tissue establishments should operate as professional organisations on a non-profit-making basis and not as commercial organisations.

The allocation of tissues and cells should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified and transparent.

In accordance with the *Oviedo Convention*, human body parts should not be displayed in connection with public entertainment or art.

1.10.4. Equal access to transplantation

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, as is the importance of trust in these systems. An example of such organisational aspects includes that, whenever a person dies in circumstances where donation is a possibility, this possibility should be raised with their family.

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. Except in the case of directed donations, tissues must be allocated only among patients in conformity with transparent, objective and duly justified rules according to medical criteria. The persons or official bodies responsible for the allocation decision must be designated within this framework.

As proposed in the latest Report from the Nuffield Council on Bioethics [50], the role of the state with respect to donation should be understood as one of stewardship; actively promoting measures that will improve general health (thereby reducing the demand for some forms of bodily material) and facilitating donation. Such a stewardship role should extend to taking action to remove inequalities that affect disadvantaged groups or individuals with respect to donation.

1.10.5. **Anonymity**

The identity of the donor and the recipient should, except in the case of donation between family members, be maintained in strict confidentiality in order to prevent abuse and to protect the families of the donors and the recipients and their families from feelings of anxiety associated with emotional involvement, obligation to return favours, guilt, etc.

1.10.6. **Transparency**

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 are always protected.

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) in order to minimise harm to donors or recipients.

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Chapter 2. Quality management

2.1. Introduction

This chapter outlines the general principles of quality management systems that should be applied in all stages, from the identification of a potential donor through processing and storage of the tissues or cells to the final preparation for clinical application to the patient. Quality of tissues and cells is achieved through compliance with requirements at three different levels:

- The legal framework that provides the overall context in which the donation, procurement, testing, processing, storage, distribution and import/export activities for tissues and cells are performed.
- The quality management system that is a tool to ensure that tissues and cells consistently comply with the technical and legal requirements.
- The technical requirements specific to each type of tissue or cell that ensure quality, safety and efficacy, as detailed in Part B of this Guide.

A tissue establishment must implement a Quality Management System (QMS) that covers the scope of all of its activities. The following non-exhaustive list of standards and legal instruments provides tools to support a tissue establishment in the construction of a robust and efficient programme:

- The International Organization for Standardization (ISO) requirements, as addressed in the ISO 9000 Quality Management System family of standards. ISO standards have been developed

to assist organisations of all types and sizes to implement and operate effective quality management systems. ISO 9001:2008 on quality management system requirements is particularly relevant to tissue and cell processes.

- Good Tissue Practices for European tissue banks were developed by the EU-funded project EuroGTP, which aimed to agree harmonised practices and techniques across Europe and to increase the know-how and the level of competence of tissue establishment personnel. Much of the guidance developed in this project has been incorporated in the chapters of this Guide.
- EU Guidelines for Good Manufacturing Practices (GMP) provide specific guidance for the preparation of medicinal products, but much of their content is also relevant for tissue and cell procurement, processing, storage and distribution.
- Directive 2004/23/EC, which sets the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, and its associated technical directives provide key elements to be included in the tissue establishment QMS; these requirements are legally binding in EU member states.
- FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration.
- Net-FACT International Standards for Cord Blood Collection, Processing and Release for Administration.

2.2. Applying quality management in donation and banking of tissues and cells

Quality is the responsibility of all personnel involved in the process of providing tissues and cells for clinical application. A systematic approach to quality management should be implemented and maintained throughout the entire process. A good quality system should address quality management under the following headings:

- a. Personnel and organisation

- b. Premises, equipment and materials
- c. Contractual arrangements
- d. Documentation and record keeping
- e. Quality control
- f. Quarantine and release
- g. Process validation
- h. Traceability
- i. Complaints
- j. Investigation and reporting of non-conformance, adverse events and reactions
- k. Recall
- l. Self-assessment, internal and external audit
- m. Quality risk management
- n. Fiscal and continuity planning
- o. Tools for continuous quality improvement.

2.3. Personnel and organisation

There must be sufficient, suitably qualified personnel to carry out all tasks in compliance with quality and safety requirements. Tasks and responsibilities must be clearly defined, understood and documented. All personnel should have clear, documented and up-to-date job descriptions, signed by them. There should be an organisational chart that describes the hierarchical structure of the organisation with clear delineation of responsibilities and lines of reporting.

2.3.1. Key personnel

Key personnel in each organisation involved in the process (from the initial donor selection stage to the final delivery of tissues and cells) should include an identified person who is responsible for all activities carried out in their organisation, along with a documented delegate who takes over this responsibility in their absence. For those countries

that are members of the EU, the Responsible Person (RP) in a tissue establishment must meet qualification criteria defined in Directive 2004/23/EC. Each relevant organisation should also have an identified medical specialist/adviser, who may or may not be the RP. The processing and quality control functions should be independent to ensure the efficient and reliable evaluation of processes. The Quality Assurance function may be under the responsibility of an individual different from the RP, Head of Processing, Head of Quality Control or may be a role assigned to one of these individuals. In any case an adequate and independent audit system should be implemented.

2.3.2. Training

Personnel should receive initial and continued training appropriate to the duties assigned to them. Training methods should be documented and training records maintained. The effectiveness of training programmes should be monitored by regular assessment of the competency of personnel. Personnel should also be trained in quality principles relevant to their duties and in the broad ethical and regulatory framework in which they work. When applicable, personnel should have relevant knowledge of microbiology and hygiene and should be constantly aware that microbial contamination of themselves, donors, recipients and tissues and cells should be avoided. The training programme should include mid- to long-term training plans, be adequately resourced and target all the personnel that might be involved in any activities within the scope of this Guide, irrespective of the routine or occasional nature of the activity.

2.3.3. Safety issues for healthcare workers involved in transplantation

Personnel carrying out tissue and cell procurement and processing activities are exposed to a risk of infection to a similar degree as operating theatre personnel. In some cases, donors will not have been fully tested at the time of procurement or initial processing and, even where they have been tested, a residual risk of infection by untested agents remains. Standard universal precautions should be applied to

protect personnel from these risks. Documented procedures should be in place describing the actions to be taken if an individual is directly exposed to the blood or tissues of a donor or their donation (e.g. needle-stick injury). These procedures might include accelerated and extended testing of the donor, rapid testing of the staff member, with prophylaxis for the transmissible agent(s) where appropriate.

2.3.4. Safety issues for tissues or cells handled by personnel with bacterial or viral infections

Personnel involved in procurement and processing of tissues and cells might also pose a risk to the quality and safety of the tissues and cells if they themselves are infected with a transmissible agent. Organisations should have documented policies describing the requirements for health screening of personnel and for individuals to inform the organisation, in a confidential manner, if they have accidentally exposed tissues or cells to risk of contamination.

2.4. Premises, equipment and materials

Premises and equipment must be designed, located, constructed, adapted and maintained to suit the operations to be performed. Their layout and design must aim to minimise the risk of errors and permit operations to proceed in an orderly sequence, and should allow effective cleaning and maintenance in order to avoid contamination and cross-contamination.

2.4.1. Premises

Suitable, quiet premises should be available for confidential interviewing of living donors or the families or friends of deceased donors.

Facilities where tissues or cells are procured should meet appropriate grades of air quality and cleanliness. The appropriate standard of cleanliness will depend on the type of tissues or cells being procured, the degree of exposure of the tissues or cells during the procurement process and the decontamination or sterilisation processes that will

subsequently be applied to the tissues or cells during processing. Most operating theatres are now environmentally monitored and have qualified air systems that make them suitable for the procurement of tissues that are not subsequently sterilised. Other types of facilities, such as mortuaries, may also be adequate for the procurement of certain types of tissues, but they should be assessed for suitability on a case-by-case basis. Further guidance on facilities for tissue and cell procurement is given in Chapter 6 and in Part B of this Guide.

Premises should include adequate dedicated areas that allow the “first in, first out” principle for critical consumables and reagents to be respected. In this context, “critical” means those consumables and reagents that come in contact with the tissues or cells or influence the quality/safety of the tissues and cells directly (e.g. an additive) or indirectly (e.g. donor testing kits). These areas should allow for adequate segregation of those in quarantine and those released for use. They should be temperature mapped and monitored where appropriate.

Storage conditions for tissues and cells should be controlled and monitored. Where certain conditions are critical to maintenance of the required properties of the tissues or cells, appropriate alarms should be in place to indicate when conditions are approaching, or fall outside, predefined limits. Standard operating procedures (SOPs) should define the actions to be taken in response to alarms. Storage requirements apply equally to interim storage of tissues and cells prior to transport to a processing facility. Further guidance on requirements for storage is given in Chapter 7 and in Part B of this Guide.

Processing facilities should be dedicated to this activity and should be designed, qualified and monitored to ensure that air quality is appropriate for the process being carried out. An international standard should be followed in full to achieve the appropriate air quality (e.g. *Rules governing medicinal products in the European Union*.

Volume 4: EU guidelines to good manufacturing practice or ISO 8573-1).

For tissue establishments in the EU, there must be Grade A with a surrounding environment of at least Grade D (GMP classification). Many national requirements are more stringent, requiring Grade B and C backgrounds for certain processes or tissue or cell types. Processing

and storage facilities should be cleaned according to a schedule and procedure that has been validated to achieve the required level of cleanliness and all cleaning procedures should be documented.

More specific guidance on requirements for processing facilities is given in Chapter 7 and in Part B of this Guide.

2.4.2. Equipment

A list or register of equipment that might influence the quality or safety of the tissues or cells should be maintained. All equipment on this list must be designed, qualified and maintained to suit its intended purpose and minimise any hazard to donors, recipients, operators or to the quality and safety of the tissues and cells. A validation plan should indicate when and how critical pieces of equipment should be qualified and re-qualified as necessary. Equipment should be selected that permits effective cleaning. All equipment with a critical measurement function should be calibrated to a traceable standard, according to a planned schedule. Maintenance, monitoring and cleaning should also be carried out according to a schedule and documented in equipment log-books.

2.4.3. Materials

A controlled list should be constructed of all materials and consumables that come into contact with the tissues or cells or that influence the quality or safety of the tissues or cells. Detailed specifications for these critical reagents and consumables should be documented. Only materials from qualified suppliers that meet the documented specifications should be used. When indicated, manufacturers should provide a certificate of compliance for every lot/batch of materials supplied. Batch acceptance testing or checking of each delivery of materials should be performed and documented before release for use in tissue or cell procurement or processing. Equipment and materials should conform to international standards and EU and national licensing arrangements, where these exist.

Inventory records should be kept for traceability and to prevent use of materials after their expiry date. Each batch of critical reagents or consumable should be traceable to the respective tissue and cell procurement or processing session in which they were used.

Apparent deviations in the quality and/or performance of equipment and materials should be investigated and documented promptly. The outcomes of these investigations should be reported in a timely manner to the RP who should consider and approve the corrective and preventive actions to be implemented. For relevant deviations, a notice should be sent to the manufacturer and, where appropriate, reported to the Health Authority.

Further guidance on reagents and materials used in tissue and cell processing is provided in Chapter 7.

2.5. Contractual arrangements

Where steps influencing the quality or safety of tissues or cells, i.e. critical steps, are carried out by a third party, there must be a contract or Service Level Agreement in place that describes the roles and responsibilities of all parties for maintaining the quality chain and the quality requirements for the service provided. Agreements should allow for on-site audits of contracted third parties to confirm their compliance to expectations. An example of an expectation is that if a supplier changes specifications for equipment or reagents they provide to a tissue establishment, or if they substitute an item for the usual one ordered, they must first be certain that these changes are acceptable to the tissue establishment.

In EU member states, tissue establishments must establish written agreements with a third party each time an external activity takes place that influences the quality and safety of tissues and cells processed in co-operation with a third party. They must keep a complete list of these agreements and make them available at the request of Competent Authorities.

Agreements should be dated, reviewed and renewed on a regular basis.

Written agreements should be in place for at least the following service suppliers:

- a. testing laboratories (including donor, tissue and environmental testing);
- b. procurement teams that are independent from a tissue establishment;
- c. transport companies;
- d. suppliers of equipment, consumables and reagents;
- e. suppliers of services such as tissue and cell storage, processing or sterilisation;
- f. end users of tissues and cells;
- g. any service provided by an organisation in another country.

2.6. Documentation and record-keeping

Documentation must enable all steps and all data relating to the quality and safety of the tissues and cells to be checked and traced, from the donor to the 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 for critical information exchange, audio recordings may be useful. Donor documentation in general and donor referral records in particular must be subject to the same controls.

Documentation should be version-controlled and include at least the following items:

- a. a quality manual;
- b. specifications for materials and reagents;
- c. approved SOPs for all activities that influence the quality or safety of the tissues or cells, including the management of the quality system itself;
- d. identification of risks and a risk mitigation plan;

- e. records on the performance of operations, including processing records;
- f. records of complaints, audits and non-compliances;
- g. training and competency records of personnel;
- h. qualitative and quantitative specifications for tissues and cells;
- i. key performance indicators for tissues and cells.

Documents, including SOPs and forms, should be approved by appropriate and authorised persons and should be part of a document control system that ensures only the current version of the document is in use. The system for distribution of controlled documents should ensure that all relevant personnel have access to the correct version.

A documented system for change control should be in place that controls changes to premises, equipment, processes, personnel and any item that may impact the quality and safety of the tissues and cells. This change control system should link the rationale for change with the approval/rejection of the change, the criticality of the change with respect to the quality and safety of the tissues and cells, the impact of the change on the tissue establishment as a whole, the validation requirements of the proposed change and any training requirements.

Records should be legible and indelible and should not be handwritten, except for those situations where data must be entered in this way. Any alterations made to a record should be dated and signed. Documentation should be retained according to national requirements. Processing records should be maintained for all critical steps, and they should be dated and signed by the personnel responsible for carrying out the activity. All quality control tests and checks should be documented. Any deviations from the standard documented procedures should be recorded and reviewed and corrective action should be documented.

The QMS must define the period of time for which documents will be retained. In the EU, quality system documentation including raw data must be retained for 10 years and traceability documentation for 30 years after use or expiry of the tissues and cells. Data can be stored

on paper, electronically or on microfilm. International and national regulations on data protection have to be respected. Personnel should only have access to those categories of data for which they are authorised. See Chapter 10 for further guidance on computerised systems, including requirements for their validation.

Quality specifications should be prepared for each type of tissue and cell graft; these should be the basis for quality control testing and product release.

2.7. Quality control

Quality control refers to those activities, such as verification steps, sampling and testing, which are used to ensure that materials, processes and the final product meet the required specifications. Internal quality control in a laboratory includes the use of positive, weakly positive or negative control samples as appropriate. External quality assessment (sometimes also called proficiency testing) involves analysis of unknown samples and evaluation of the results by a third party. Quality control of critical functions can be performed using audit techniques that include a sampling plan.

Guidance on specific quality control tests for specific types of tissues and cells is provided in Part B of this Guide.

2.8. Quarantine and release

All tissues and cells should be stored with an unambiguous quarantine status until all quality control tests and checks have been conducted and results reviewed by the individual responsible for release. Release of tissues and cells may be conducted in two steps, one that confirms compliance of the donor with defined acceptance criteria, which is usually performed by clinical personnel, and one that confirms compliance of the tissue itself, its characteristics, processing and storage, with those criteria defined in the product specification. The latter is usually performed by quality assurance personnel.

2.9. Process validation

The processes applied to tissues and cells should be validated to demonstrate that they do not have detrimental effects on the required characteristics of the product and that they meet any claims on the label, e.g. sterilisation. Any change to a process should be assessed for impact on the status of the validation of that process.

Process validation studies must be conducted on typical processing scale batches. The number of batches used will depend on the variability of the process, the complexity of the process, the variability in the required characteristics of the particular tissues and cells and the experience of the technicians, but will usually include at least three consecutive batches.

Detailed guidance on process validation is provided in Chapter 7.

2.10. Traceability

Full traceability of donations from donor to recipient and of all materials, reagents and equipment that come into contact with tissues and cells is fundamental to recipient safety. Detailed guidance is provided in Chapter 11.

2.11. Complaints

All complaints should be documented, carefully investigated, and managed in a timely manner. The complaints procedure should take into consideration complaints from:

- a. living donors or the families of deceased donors;
- b. personnel;
- c. third party health professionals;
- d. clinical users, including those in another jurisdiction;
- e. patients.

A mechanism for categorising, tracking and trending complaints should be in place and should be readily available for audit.

2.12. Investigation and reporting of non-conformance, adverse events and reactions

Examples of non-conformance include deviations from SOPs, errors and accidents. Non-conformance might result in an adverse reaction in a living donor or in a recipient and should therefore link to the vigilance reporting system. There should be an SOP in place which defines how the organisation manages non-conformance and a log of all the instances of non-conformance that are investigated, including detailed documentation of the investigation, root cause analysis and corrective or preventive actions taken. A categorisation of cases of non-conformance depending on criticality with respect to the quality and safety of tissues and cells is a useful tool for prioritising corrective actions. Procedures should be in place to identify appropriate corrective and preventive actions to be taken and to inform the relevant authorities as appropriate. Reporting of errors and incidents in a non-punitive context should be encouraged to help achieve improvements in practice. Tracking and trending of non-conformance should be performed to identify common failures and identify areas for concern.

Serious adverse events and reactions should be reported through a vigilance system. For detailed guidance on vigilance of tissues and cells see Chapter 12.

2.13. Recall

An effective written procedure must be in place for recalling defective tissues or cells or those suspected as not meeting required quality or safety requirements. This written procedure must encompass the need to agree and document any corrective and preventive actions that may be necessary. The actions should be communicated to the end user, where appropriate. Further guidance on recall is provided in Chapter 12.

2.14. Self-assessment, internal and external audit

Auditing is an essential tool for ensuring compliance with the quality system and for supporting continuous quality improvement.

Internal audits should be scheduled and conducted in an independent way by designated, trained and competent persons. Internal audits are normally performed by the organisation's quality assurance personnel.

External audits are performed by independent bodies, often designated as approved/competent authorities or ISO certifying bodies, and are required for certification, accreditation and licensing purposes.

External audits provide an opportunity for critical review by experts unfamiliar with the systems in place locally. They can provide an excellent opportunity for systems improvement.

All audits should be documented and recorded. Clear procedures are required to ensure that the agreed corrective and preventive actions are undertaken appropriately. These actions and their completion should be recorded.

2.15. Quality risk management

The procurement, testing, processing, storage and distribution of tissues and cells should be subjected to comprehensive risk assessment to allow identification of those steps where quality system controls should be greatest and where validation of procedures is necessary. A "process flow" diagram listing all relevant steps, processes, reagents, tests and equipment can form the basis for the assessment exercise.

Risk assessment should include an estimation of the severity of any identified hazard (source of harm) and an estimation of the probability that the hazard will result in harm. Probability should be based on evidence and experience whenever possible.

Risk mitigation strategies should be developed to protect the tissues and cells, the donor and recipient, personnel and the process itself, as well as other processes being undertaken in proximity to it. The degree of control within the quality system should be related to the degree of risk associated with each step in the process.

Risk assessment should refer to current scientific knowledge, should involve appropriate technical expertise and should be related to the protection of the patient. The level of effort, standardisation and documentation of the risk control process should be aligned with the estimated risk level.

Risk assessment should be repeated and documented whenever a critical process is changed.

Risk assessment is also an essential tool for making important decisions, particularly when departures from normal procedures are under consideration. Examples would include:

- a. selection of a donor where full compliance with the normal criteria are not met, but the donation has a particular clinical value and the risk can be mitigated sufficiently to justify the departure from normal procedures;
- b. exceptional release of non-complying tissues or cells on the basis that the potential benefits for the recipient and the lack of availability of alternatives outweigh the risks;
- c. retention or discard of tissues and cells in storage following the introduction of new procedures or tests that imply higher levels of safety or quality;
- d. eligibility determination where certain test results are reactive, e.g. EU Directive 2006/17/EC Annex 2 requires further investigations with a risk assessment when anti-HBc is positive and HBsAg is negative and where a donor is reactive for a Treponema-specific test;
- e. prioritisation of a list of corrective actions following an audit or inspection, or prioritisation of quality improvements in general.

The most commonly applied risk assessment methods are FMEA (Failure Mode and Effects Analysis) and FMECA (Failure Mode, Effects and Criticality Analysis). Both methods estimate severity and probability, but FMECA also includes a factor for detectability, taking into consideration that those hazards that are more easily detected

represent a lower overall risk. FMECA allows the estimation of a Risk Priority Number (RPN) for the ranking of identified risks.

Guidance on quality risk management is provided in Part III Q9 of the *Rules governing medicinal products in the EU, Volume 4: EU Guidelines for good manufacturing practice for medicinal products for human and veterinary use* [1], where a number of well-established risk assessment methodologies are listed. The inclusion of this new section in GMP guidance reflects the current thinking that risk management should be an integral part of quality management.

2.16. Continuity planning

General quality management responsibilities include budgetary/fiscal oversight and contingency planning to ensure that essential services for patients are not interrupted. Each organisation in the chain from donation to distribution and biovigilance of tissues and cells should have a continuity plan in place that details how procurement services, donated tissues and cells and all associated documents will be maintained in the event that activities must temporarily be suspended or permanently ceased. Usually this plan will include a mutual agreement (Service Level Agreement or contract) with another organisation for the transfer of tissues or cells, documentation and services in these circumstances.

2.17. References

1. EudraLex, Volume 4 EU Guidelines for Good Manufacturing Practices – Medicinal products for human and veterinary use <http://ec.europa.eu/health/documents/eudralex/vol-4/>.

Chapter 3. Packaging and labelling

3.1. Introduction

Ensuring the traceability of all tissues and cells from the donor to the recipient is a responsibility shared by procurement centres, tissue establishments and organisations responsible for human application. All these stakeholders participate and contribute to actively safeguarding, in a continuous manner, the tracking of the stages tissues and cells go through. Accurate tracking of tissues and cells allows reliable data to be scientifically assessed for potential risks to the donor, to the procurement and processing operations and to the storage, transport and clinical use of donated material. Traceability is addressed in depth in Chapter 11. An essential aspect of ensuring accurate traceability is clear and complete labelling at all stages. The system of donor and recipient identification must be aligned with the tissue and cell packaging and labelling system in such a way that a correlation between the grafts, the source and the recipients exists at all times.

Labels must be attached to packaging that has been validated to demonstrate that it maintains the required properties of the tissues and cells and ensures integrity. This chapter addresses good practices in packaging and labelling at all stages from donation to implantation.

3.2. General

Packaging and labelling operations must be considered an integral part of tissue establishment activities and must be included in the training of personnel and specified in all relevant procedures.

Although this chapter establishes specific recommendations for packaging and labelling for the procurement and processing phases, they should equally apply to intermediate phases, such as in-process steps, where all materials, containers, equipment and unfinished tissues and cells must be adequately identified at all times. Additionally, tissues and cells obtained and/or processed for research purposes should be clearly identified as such on their packages and labels (e.g. FOR RESEARCH USE ONLY or NOT FOR CLINICAL USE).

The following generic requirements must be respected:

- a. Premises for the packaging and labelling of tissues and cells must be suitably laid out so as to avoid mix-ups or cross-contamination.
- b. Labelling and packaging operations must be designed to prevent any cross-contamination or mix-ups.
- c. Simultaneous operations must be avoided or adequate measures should be taken to avoid cross-contamination or mix-ups.
- d. Primary packaging and labelling of the tissue or cells must be performed in a qualified environment that must be specified in standard operating procedures.

For EU member states, the requirements for packaging and labelling of tissues and cells are detailed in Annex IV of Directive 2006/17/EC and Annex II of Directive 2006/86/EC.

3.3. Tissue and cell packaging

Packaging includes all operations, including primary and secondary packaging, which procured or processed tissues and cells undergo in order to become starting, in-process or finished grafts. The packaging aims both to protect the graft and to present it to the operator (for starting or in-process packaging) or to the clinical user (for final packaging) in a suitable manner. The type of graft and its intended use will determine the requirements needed to perform a packaging operation in a safe manner. Special consideration must be made for the primary packaging that will be in direct contact with the graft. In this case, the

materials and the conditions under which packaging takes place must be carefully specified, assessed and approved before use. Processing facilities must establish and document validated packaging protocols.

Packaging must ensure the integrity and maintain the sterility of the contents of the primary container. Storage containers must be appropriate for the type of tissue or cells, the temperature and type of storage method and the intended application. They must withstand sterilisation (where this is to be applied), not produce toxic residues during storage and be adequately robust to remain intact when handled during transport. Each tissue or cell container must be examined visually for damage or evidence of contamination before distribution for clinical use.

3.4. Tissue and cell labelling

Written procedures must be established and followed to ensure correct labelling. Each labelling phase for all tissues or cells must be documented. Material must be labelled during all phases of procurement, processing, storage and distribution. Labelling must be clear, legible and indelible.

Prior to labelling a unit of donated or processed material, the container must be inspected for evidence of impurities, defects, broken seals or contamination that could compromise the quality, integrity or safety of the tissue or cells.

The labels attached to the tissue and cell containers should both identify and describe the contents. The description should characterise the graft and reflect key aspects with regards to its maintenance and use. Standard nomenclature and standard international units of measurement must be used to describe tissues and the processing they have undergone. The identification should provide information on traceability that links the graft to the tissue establishment of origin and ultimately the donor. When tissues or cells are to be distributed internationally, language barriers should be considered and information translated or coded to enable understanding.

For autologous or directed donations, the name and/or identifier of the intended recipient must be included in the label.

Further guidance on traceability and coding is provided in Chapter 11.

The production of labels must be controlled. When applicable, reconciliation of labels that have been edited, used and/or returned/rejected must be performed according to written procedures. All excess labels containing quality or traceability information must be destroyed or maintained in a secure manner, when necessary, to prevent mix-ups. Obsolete unused labels must be destroyed according to written procedures.

It is highly recommended to perform labelling and packaging at the same time, in a continuous process, to reduce the risk of mix-ups or cross-contamination. Before application to the container, printed labels must be carefully examined to ensure that the information they contain conforms to the corresponding tissue or cells. The results of this examination should be documented at identified critical stages. Labels must be designed to adhere firmly to the container under all anticipated storage and transport conditions. The label applied by the facility must not be removed, altered or obscured. A sufficient area of the container must remain uncovered to permit inspection of the contents, whenever possible.

For processing of batches that include large numbers of individual final units, a representative printed label should be included in the processing batch record.

3.5. Sample and documentation labelling

All key blood and tissue samples for testing or archiving and all related documents must also be labelled in a legible, indelible manner that ensures traceability to the donor and the associated donations. A record of the time and place the sample was taken must be included on the label.

3.6. Packaging and labelling materials management

The selected packaging material must be able to withstand the storage temperature requirements (ambient temperature, refrigeration, freezing or cryopreservation) needed to preserve the required characteristics of the tissues or cells and, if applicable, the biological function. Additionally, the shipping container must be able to maintain this environment for an appropriate amount of time during transport. Primary packaging and transport containers used for tissues and cells should be “qualified,” and they must be suitable for use with biological materials (see Chapter 2). Selection of packaging, or a combination of packaging systems, should result in a sealed environment that prevents leaks.

As a general rule, labels should be machine-printed for clarity. They should be printed with ink that does not run or otherwise become unreadable when exposed to water or other liquids. Labels must maintain integrity and remain attached at the temperatures at which the containers will be stored.

The management of packaging and labelling materials must include the following:

- a. there must be written specifications for all packages and labels used for tissues and cells;
- b. there must be documented procedures describing the receipt, identification, quarantine, sampling, examination and/or testing, release, and handling of packaging and labelling materials;
- c. a validation study must be done to document the suitability of containers and labels for their intended purpose.

3.7. Primary packaging and labelling for procurement operations

Primary packaging refers to the materials that are intended to come into direct contact with the tissues and cells and are therefore considered as “critical”. Selected materials should not leach harmful

chemicals, they should be capable of being sterilised by a safe method if appropriate, and be sealable and leak-proof.

The following specific requirements must also be respected:

- a. Each tissue must be packed separately in sterile packaging as soon as possible after procurement. Double or even triple packaging should be used as a general rule.
- b. The package should be placed in a suitable container to ensure the preservation of the tissues and cells and to provide physical protection for the recovered human material during transportation. It is essential that the container remains sealed until the graft is received by the tissue establishment.
- c. As a minimum, the primary or secondary package must be labelled with a unique identifier or code and the type of tissue or cells. Where the size of the package permits, the following information should also be included on the label:
 - i. date of donation (and time, where possible);
 - ii. applicable hazard warnings;
 - iii. description of any additives (if used);
 - iv. in the case of autologous donation, the label must state **FOR AUTOLOGOUS USE ONLY**;
 - v. in the case of directed donation, the label must identify the intended recipient;
 - vi. if applicable, the fluid in which the tissues or cells are preserved.

If any of the information listed above cannot be included on the primary package label, it must be provided in accompanying records inside the transport container.

3.8. Secondary packaging and labelling for procurement operations

When secondary packaging is used after procurement, it should respect the same requirements as those established for primary

packaging (see section 3.7). If labels with the required information are not attached to the primary packaging they should be attached to the secondary packaging which should be closed and sealed.

3.9. Outer container packaging and labelling for procurement operations

When tissues or cells are shipped from the procurement site to the tissue establishment (rather than taken by the tissue establishment team or procurement team), the transport container must be labelled with:

- a. HUMAN TISSUE or HUMAN CELLS and HANDLE WITH CARE;
- b. the name, address and telephone number of the procurement organisation from which the package is being sent and a contact person in the event of problems;
- c. the name, address and telephone number of either the tissue establishment (and a person to be contacted to take delivery of the container) or identification information regarding the clinical team responsible for receipt of the container if the tissues or cells are being transported for immediate application;
- d. the date and time of shipment and identification of any refrigerant used (e.g. wet ice);
- e. specifications concerning conditions of transport relevant to the quality and safety of the tissues and cells (such as DO NOT DELAY, KEEP COOL, KEEP UPRIGHT);
- f. in the case of viable cellular products, the warning DO NOT IRRADIATE;
- g. when cells or tissue are known to be from a donor that has tested positive for a relevant infectious disease, the warning BIOLOGICAL HAZARD;
- h. specifications concerning storage conditions (such as DO NOT FREEZE);

- i. in the case of an autologous donor, the indication FOR AUTOLOGOUS USE ONLY;
- j. any other applicable hazard warnings.

3.10. Procurement package insert

It is recommended that documentation sent with procured tissues or cells to a tissue establishment indicates, where applicable, that they are in a state of “quarantine” so that it is clear that a final review regarding their release for distribution and use has not been completed. See Chapter 6 for full guidance on the requirements for procurement documentation.

3.11. Primary packaging and labelling for finished tissues and cells

Primary packaging and labelling refers to the materials that will come into direct contact with the tissues and cells, and the requirements in this regard are as described in section 3.7. The graft expiry date will be determined by the properties of the tissues and cells, but also by the integrity and stability of the packaging and labelling materials, among other factors.

The primary tissue/cell container label must provide:

- a. identification number or code and lot or batch number, where applicable (see Chapter 11);
- b. type of tissues and cells;
- c. identification of the tissue establishment;
- d. expiry date;
- e. in the case of autologous donation, the indication FOR AUTOLOGOUS USE ONLY, together with the identification of the donor/recipient;
- f. in the case of directed donations, the label must identify the intended recipient;

- g. when tissues and cells are known to be positive for a relevant infectious disease marker, the package must be marked as BIOLOGICAL HAZARD;
- h. if applicable, product modifiers, manipulations and additives used.

The following information must be provided either on the label or in accompanying documentation:

- a. description (definition) and, if relevant, dimensions of the tissue or cell product;
- b. morphology and functional data, where relevant;
- c. date of distribution of the tissue/cells;
- d. biological determinations carried out on the donor and results;
- e. storage conditions required;
- f. instructions for opening the container or package and any required manipulation/reconstitution;
- g. expiry dates after opening/manipulation;
- h. instructions for reporting serious adverse reactions and/or events;
- i. presence of potential harmful residues (e.g. antibiotics, ethylene oxide);
- j. if applicable, the fluid in which the tissue is preserved;
- k. any other applicable hazard warnings.

3.12. Secondary packaging and labelling for finished tissues and cells

Secondary packaging and labelling refers to materials that are not intended to come into direct contact with the tissues and cells. Special consideration must be taken when primary and secondary packaging and labelling are designed to be kept together until the moment of use. If secondary packaging is not sterile, it should be clarified in the package instructions that the outside of the primary package is

also not sterile and should not be placed within the sterile field during clinical application.

The information in section 3.11 should be included on a label on the secondary packaging if, for some reason (such as the size or material of the primary packaging), it cannot be included on the primary packaging.

3.13. Outer container packaging and labelling for finished tissues and cells

When tissues or cells are shipped for distribution purposes, every transport container must be guaranteed to maintain the conditions needed for the specific tissue or cell type.

For transport, the shipping container must be labelled with at least the following information:

- a. identification of the source tissue establishment, including an address and telephone number;
- b. identification of the destination organisation, including an address and telephone number;
- c. a statement that the package contains human tissue or cells and the warning **HANDLE WITH CARE**;
- d. where living cells are required for the function of the graft, such as stem cells, gametes and embryos, the warning **DO NOT IRRADIATE** must be added;
- e. recommended transport conditions (e.g. **KEEP COOL**, **KEEP UPRIGHT**);
- f. safety instructions for the method of cooling (where applicable);
- g. any other applicable hazard warnings.

3.14. Package insert for finished tissues and cells

A package insert refers to the complementary information associated with a graft that it is not feasible to place on labels. Critical

information for the clinical user must be provided, including the following:

- a. Date of distribution.
- b. A statement that the tissues or cells are suitable for transplantation following all required disease screening and testing.
- c. Instructions for proper storage, and thawing where appropriate, must accompany all tissues and cells. They should address graft preparation, handling and reconstitution where appropriate.
- d. Inserts should also contain the following information:
 - i. a statement limiting use of the material to specific health professionals;
 - ii. a statement that the material is intended for single use in one patient only;
 - iii. any applicable hazard warnings;
 - iv. instructions for opening the package and/or container, and for reconstitution or any other preparation of the contents (if appropriate);
 - v. the expiry time (if applicable) of the tissue or cells following reconstitution;
 - vi. a statement, if applicable, that the tissue or cells may not be sterilised or re-sterilised;
 - vii. recommended storage conditions;
 - viii. a statement that it is the responsibility of the end user to maintain the tissue or cells in appropriate storage conditions prior to transplantation;
 - ix. special instructions as appropriate, e.g. DO NOT FREEZE;
 - x. a statement if known sensitising substances are present (including type of antibiotics and preservatives added during processing that might be present as residues);

- xi. a statement that adverse reactions potentially attributable to the tissue or cells will be reported promptly to the tissue establishment;
- xii. a statement that it is the responsibility of the recipient hospital or other material storage and distribution facility, or the clinician, to maintain recipient records for tissue tracking and post-transplantation follow-up.

Chapter 4. Identifying potential donors, consent and evaluation

4.1. Donor recruitment/detection

The evolution and success of transplantation medicine in recent years has increased the need for the availability of tissues and cells. Donor recruitment, an area that requires constant effort and increasing public awareness and education, is a challenging task. National, as well as local, events to disseminate information to the public are considered an important tool in donor recruitment. Although both living and deceased donors are potential sources of tissues and cells, there are differences in which type of tissues or cells can be obtained from these two categories of donors. Donation of tissue from deceased persons often includes bone, soft tissue (fascia, tendons, ligaments), skin, corneas, heart valves and/or vessels; but specific cells from certain tissues may also be processed for clinical use (e.g. mesenchymal stem cells from bone, skin or adipose tissue). The bodies of deceased donors must be treated with respect and efforts should be made to restore the appearance of the body after removal of any tissue. Living donors can provide replenishable cells such as haematopoietic stem cells and gametes, but they can also donate tissue such as bone when a femoral head is removed during hip replacement surgery (where a prosthesis replaces the femoral head).

Although living donors are usually part of a registry and may or may not be called to donate (e.g. haematopoietic stem cell donors), deceased donors may have also registered but can also be identified if they have not declared their intention to donate tissues during their

life. The persons responsible for procurement co-ordination should develop a system to identify deceased persons that are not listed in any donor registry so as to offer the opportunity for donation, which may lead to increased availability of tissue allografts for patients who need them. In addition, hospitals should have mechanisms to identify potential tissue donors that could also be potential organ donors. In the event that a health facility does not have the means to manage a potential tissue donor, or is not licensed to procure bodily material according to local regulations, a local network should be in place that directs these potential donors to a hospital facility that qualifies and acts as a procurement centre. The information required for screening deceased consenting and “undeclared intention” donors should be retrieved from available medical records via an interview with the medical staff treating them (attending physician, general practitioner, nurse) and from relevant information provided by the donor’s relatives or other knowledgeable persons. To detect and select a potential deceased donor, a number of selection criteria need to be taken into consideration and these criteria are discussed in this chapter.

4.2. Donor identification and consent/authorisation

The *Oviedo Convention on Human Rights and Biomedicine* (1997) sets out the requirements for consent for any medical intervention, including the removal of tissues and cells from living and deceased donors for the purposes of transplantation into a recipient. It is important that all those who retrieve, receive, process, store and transplant donated tissues and cells are able to assure themselves that consent, in accordance with local requirements, is in place. Tissues and cells must only be used for the activities for which consent has been given. It is not lawful to use donated tissues/cells for other purposes.

The *Additional Protocol on Transplantation of Organs and Tissues of Human Origin* (2002) also prohibits organ and tissue trafficking. The prohibition of financial gain from the human body or its parts requires that consent must be voluntary, without any incentives or inducements to donate or to give consent for donation. It follows that the

process of donation must not create any obligation on the part of the donor or the recipient. This prohibition does not prevent payments for compensation due to loss of earnings during the donation procedure and payment for legitimate medical and technical services as part of the removal, processing and storage of tissues.

Procurement of human tissues or cells must be authorised only after all mandatory consent or authorisation requirements in force in the member states concerned have been met. Before the procurement proceeds, an authorised person should confirm and record that consent for the procurement has been obtained in accordance with national legislation and how and by whom the donor has been reliably identified.

Since living and deceased donors differ in some respects they are dealt with separately below.

4.2.1. The living donor

4.2.1.1. The consent process

A person can agree to donate tissues and cells for human applications only when they are alive and have the capacity to consent. The consent or authorisation process must ensure that consent is given by the appropriate person (the donor him/herself or their legal guardian, or an official body, as mandated by national legislation), i.e. it must be valid. The scope and duration of consent must be stated explicitly and the donor must be able to withdraw consent at any time.

The *Oviedo Convention* provides protection for those who do not have the capacity to give consent, such as minors or legally incompetent persons. A general principle of consent under these circumstances is that the person should, as far as possible, take part in the consent or authorisation procedure. In the case of a minor, their opinion should be taken into consideration in proportion to their age and their level of maturity. The recipient must be a brother or sister of the donor and the potential donor should not object to the donation. There are also specific instances, defined in local law, where donation can take place

if authorisation is given in writing by a person or body specified by law, which in turn has also been approved by a Health Authority.

For consent to be valid, it must be given voluntarily by a person who has been provided with the relevant information and has the capacity to consent. The donor must be aware of the types of tissues/cells to be removed, any associated risk to the donor, the purpose or use to which the tissues/cells will be put, whether or not the tissues/cells are to be processed and stored and whether the tissues/cells are likely to be exported to other countries. The discussion on consent should be conducted in a suitable environment and the donor must be given the opportunity to ask questions. The donor should be informed that tests will be carried out to detect any transmissible infections that might pose a risk to the recipient and what would happen in the event of a positive result. It is important that the person who seeks consent from the donor has received specific training in seeking consent, is sensitive to the needs of the donor and is able to answer questions about the donation and transplantation process.

It is advisable to seek written consent. Documented consent can then be made available to the tissue establishments that receive the material for processing and storage. This will help to assure establishments that consent has been duly given. If verbal consent is obtained, it must be clearly documented or recorded.

For example, donor consent to any apheresis procedure should imply documented counselling. The counsellors should act as advocates for the donor and should not in any way be involved with the recipient or be part of the receiving transplant team. Counselling must be unbiased, non-directed and objective.

Counselling should include detailed information, but be provided in a manner that is understandable to the donor. The purpose of the donation, its voluntary and non-remunerated aspect, a description of the procurement procedure, information on any substances (including autologous transfusion) that might be administered, types of medical and laboratory assessment, as well as after-care and follow-up should all be included in the counselling. The issue of potential

adverse reactions and events due to the procedure should also be openly discussed. The donor should be reassured that protocols for the protection of medical and donor data are in place according to local regulations.

If, during the medical or laboratory health check of the donor, there are observations that exclude the donor from the procedure, these should be discussed with the donor and they should be advised on how to proceed if any further actions need to be taken. If, however, there are findings that do not exclude the donor, but are considered important for the recipient (e.g. a haemoglobinopathy trait carrier haematopoietic stem cell donor), the transplant centre should also be informed. All results from the evaluation should be made readily available to the donor.

The donor should also be informed of his/her right to withdraw from the procedure and also the consequences, if any, of withdrawal for the recipient, for example, if a haematopoietic stem cells recipient has already begun a preparatory regime to receive the HSC.

4.2.2. The deceased donor

In the case of deceased donors, countries use either the explicit (“opt-in”) system or the presumed (“opt-out”) system of consent. The system of presumed consent has been credited with helping to increase the number of donations. However, other measures, such as effective identification of potential donor policies and changes to procedural infrastructures, have also had a large impact on increasing donations.

4.2.2.1. Explicit or opt-in system of consent

The opt-in system requires each individual or, their relatives once the person has died, to make a conscious choice to donate tissues and cells. As in the case of living donors, consent must be given by the appropriate person and the discussion on consent must cover the scope, duration and the fact that consent can be withdrawn.

Appropriate consent must be considered in terms of the person who gives consent and depends on local legal requirements. For example, the Human Tissue Act 2004, which applies to England and Northern

Ireland, requires that consent for removal of tissue from a deceased donor is given by the person when they were alive or, after their death, by their legally-authorised representative or a “person in a qualifying relationship to the deceased”. Furthermore, the Act prescribes a hierarchy of qualifying relationships (ranked from highest to lowest: spouse of partner, parent or child, brother or sister, grandparent or grandchild, niece or nephew, stepfather or stepmother, half-brother or half-sister, followed by a long-standing friend) and states that consent should be obtained from the person ranked highest in the hierarchy.

An individual can make their wish to be a tissue donor known during their lifetime by joining their national organ/tissue donor registry. In some countries, those who apply for a passport or driving licence also have to state whether or not they are willing to donate tissues and cells after death. These documents can then be used to determine whether or not the person wished to be a tissue donor. A person can also express their wish not to be a donor. Once a person is deceased, any objection to donation made by the person during their lifetime must be respected.

4.2.2.2. Presumed, deemed or opt-out system of consent

In this system, a person is presumed to have given consent to donate tissues and cells if they have not stated their wish to opt out of becoming a donor. There are several countries with presumed consent policies including Spain, Italy, France, Belgium, Austria and Singapore. These opt-out systems were introduced in order to help meet the short-fall in organs, tissues and cells available for transplantation. For example, surveys of potential donors in the UK have shown that, whilst 90% of the population support organ donation, only 28% are registered as donors.

4.2.2.3. Hard and soft legislative systems for consent

The legislative systems for consent incorporate either a “hard” (or “strong”) donation law where the views of the deceased’s relatives are not actively sought or a “soft” (or “weak”) donation law where the views of relatives are taken into consideration. In the case of a weak/

soft donation law, relatives have the right to veto the donation. There is a potential for conflict when the family's wishes are considered, as different family members may have different views that have to be reconciled. It is important to communicate with families in a sensitive manner as they need to continue to be engaged in the donation process so that information on the lifestyle of the donor, recent travel, etc., can be obtained in order to determine the risk to any tissue/cell recipients.

4.3. Data protection and confidentiality

The confidentiality and protection of all information regarding the donor, as well as the recipient, is considered of utmost importance so as to preserve public faith in the procurement and transplantation systems. Local regulations should be in place to ensure that any information on each individual donation is regarded as confidential by all personnel involved.

Security measures should be in place for data protection of the identity of the donor as well as the recipient. Such measures should ensure that there are no unauthorised data additions or deletions to donor files and should prevent unauthorised access to this information. Standard operating procedures (SOPs) should be in place to resolve discrepancies in the data.

A system for the assignment of unique codes to the donor, donation procedure and donated material, as well as the recipients, which can be linked in a traceability system, should be in place (see Chapter 11).

In the EU, Directive 95/46/EC on data protection applies to personal data processed throughout all activities from donation to transplantation of tissues and cells.

4.4. Donor evaluation

4.4.1. General

Evaluation of any candidate for donation includes the thorough collection of clinical and personal information to determine risks associated with a variety of transmissible diseases (viral, bacterial, mycobacterial, fungal, parasitic and prion-associated), as well as obtaining the donor's medical history to assist in the assessment of the quality of the tissues/cells that may be procured. This critical step of properly screening a potential donor is an important factor in providing safe cells or tissues for transplantation (i.e. tissues/cells that will not transmit disease and will function in the recipient as expected). Standard operating procedures must be in place for acquiring all the data necessary to make an informed decision regarding the suitability of each donation.

Generally, a donor's medical history and behavioural risk evaluation begins with collecting specific information regarding:

- a. cause of death (deceased donation);
- b. current clinical information;
- c. personal information, including:
 - i. social and sexual behaviours
 - ii. exposure events, including travel or residency
 - iii. previous diagnosis of disease conditions
 - iv. relevant family history, where indicated.

All available information obtained during initial screening should be taken into account prior to donor clearance for procurement. Additionally, any indication regarding the need to perform more specific donor testing should be based on an analysis of the identified risks. The importance of the accuracy and completeness of this information must be understood, and the sources used to obtain the information should be reliable.

There are special considerations for evaluating a paediatric donor and these are explained in section 4.4.4 below².

4.4.2. Medical history and behavioural risk evaluation

Relevant clinical as well as personal information about the donor's current and past history regarding certain risks must be collected for any donation event and documented by trained and competent persons authorised to perform these functions. This information should be obtained immediately before donation or as close as possible to the date of donation.

4.4.2.1. Cause of death

The cause of death (COD) is important and can indicate if the deceased donor had, or is suspected of having, a transmissible disease, or it can point to other concerns regarding tissue quality, including contamination. If the COD is unknown, donation cannot be permitted because the death may have been due to a disease that could be transmitted to cell/tissue recipients. If the COD is related to an active systemic infection, such as bacteraemia, sepsis or viraemia, the donor cannot normally be accepted for donation. The only exception is the cornea, which is avascular and can be stored in culture medium and subsequently tested for contamination. If the aetiology of an active infection cannot be established, the donor is not a suitable candidate for donation. Communication with the physician or medical staff caring for the patient is necessary if there are any questions regarding the patient's clinical history; specifically relating to events leading to death. These healthcare providers may know if there was a suspicion of sepsis or another infectious disease at the time of death, which may not have been well-documented in the records.

There can be a risk for the transplantation process associated with certain causes of death. For example, if the patient overdosed on non-prescribed drugs, this can increase the risk of an infectious disease

2 For EU member states, the selection criteria for both deceased donors (including additional exclusion criteria for deceased children donors) and living donors of tissues and cells are specified in Annex I of Directive 2006/17/EC.

due to risky behaviour associated with the use of recreational drugs. However, this risk should be evaluated on a case-by-case basis and can be mitigated by collecting reliable information. If ingestion or exposure to a toxic substance caused death, or if death was due to high voltage electrocution, the quality of some tissue/cell types can be affected and may cause harm to recipients if those tissues/cells are used for transplantation. The COD may also indicate the presence of massive trauma, which can preclude tissue procurement. For example, crushing injuries to the abdomen or limbs, a fall from a great height or massive internal and/or external trauma from being struck by a vehicle may preclude the ability to provide safe tissues due to overwhelming bacterial or fungal contamination caused by such an event. A death due to drowning requires scrutiny, including evaluation of the type of water, how long the body was submerged, whether the drowning was witnessed, the time of year and the water temperature. This information is necessary to assess the risk of contamination by water-borne micro-organisms. For example, donation of skin from a victim of drowning may not be possible due to gross contamination of the tissue that cannot be resolved. In all such cases, a visual examination of the body by procurement staff may be necessary during early, initial screening if adequate information regarding the condition of the body cannot reliably be obtained verbally.

4.4.2.2. Current clinical information

If a potential donor appears eligible after initial screening, available records should be obtained, reviewed and evaluated as soon as possible. The types and extent of records that are available can vary, depending on whether death occurred within or outside a healthcare facility. If death occurred in a healthcare facility, the following records may have been produced and, if so, should be obtained and reviewed:

- a. emergency room and emergency medical transport (ambulance) records, if applicable;
- b. admission records, progress notes, physician's orders/notes and nursing observations;

- c. laboratory test results (microbiology, chemistry, haematology, virology, urinalysis, toxicology and/or pathology);
- d. transfusion and infusion information (to be used for haemodilution evaluation, see Chapter 5);
- e. X-rays;
- f. surgical records (review for additional transfusions and infusions that may have taken place and any biopsy reports);
- g. records of consultations, such as psychiatry, infectious disease, neurological, orthopaedic, oncology, rheumatology, etc.;
- h. discharge summary or death record (assess whether an autopsy is planned).

Direct communication with the attending physician or the medical staff caring for the patient is recommended as it often provides valuable information. Specific inquiries should be made regarding any concern for the patient having an active infection or a communicable disease. An extensive hospitalisation in the donor's medical history can increase the risk of them having acquired a nosocomial infection, as seen in patients that have undergone prolonged ventilator-assisted breathing.

Abnormal, unexpected or unusual results from medical tests performed during admission should be scrutinised, such as from microbiological cultures, biopsy results or haematological evaluations (e.g. very low, abnormally high or a sudden substantial drop in the white blood cell count; a cell differential evaluation, which describes an unusual alteration in the morphology of white or red blood cells). The presence of certain cells and cell counts can indicate active infection. If a series of Complete Blood Counts (CBCs) are available, they should be reviewed for suspicious trends and sudden changes. If a review of blood culture results was requested, then the reason for requesting it should be investigated.

If death occurred outside of a healthcare facility, the following records may be available and, if so, they should be located and reviewed:

- a. police records, if available;

- b. medical examiner or coroner records;
- c. extended care facility records (assisted living facility);
- d. funeral home records.

A thorough review of all available records is recommended. In some cases records might be known to exist, but are not readily available. Ideally all records should be viewed before tissue procurement begins but, if this is not possible, they must at least be reviewed by a responsible person prior to release of the tissues/cells for transplantation.

Relevant information from the records must be transferred and documented on transplantation forms or, if allowed, photocopied or recorded. The transplantation records must fully and accurately reflect the relevant information gained from reviewing these records and from discussions with medical or other personnel. Transferring information from records to a new document carries the risk of transcription or interpretation errors. These steps must be performed by well-trained, competent staff from the procurement organisation or tissue establishment.

4.4.2.3. Personal information

A risk assessment interview must always be performed with living donors or, in the case of a deceased donor, with a knowledgeable person(s) who can give personal information to help determine eligibility for donation. No donation of tissues from a deceased donor should ever proceed without this personal interview, regardless of any other sources of information used, such as autopsy reports, etc. A donor risk assessment interview questionnaire is a critical medical record and must be developed and referenced in the tissue establishment's policy and procedures manual. It must cover all relevant risks associated with medical history, as well as transmissible disease history, sexual and behavioural history, travel history and, if relevant, family history.

The interview should be held in private and should be carried out just prior to donation or as soon as possible before or after procurement. It can comprise a multitude of questions concerning the risk

for transmissible diseases or factors that could influence cell/tissue quality. When interviewing a person representing a deceased donor, care must be taken during this interview to consider their emotional state. However, this should not over-ride the need to properly screen the donor for relevant risks. Answers from such interviews can reveal risk information not found in available medical records. In order to obtain complete and honest answers, as well as to avoid misunderstandings about the objective of certain questions of a private nature, a clear explanation of why they are needed in order to ensure the quality and safety of the tissues and cells should be provided. Interviews can be conducted as a conversation between the interviewer and interviewee to facilitate this objective. Interviewees should be informed that they can ask questions when they do not understand the information being sought or if they feel that there is an issue that the interviewer has not asked about.

The interviewer representing the tissue establishment or procurement organisation should have appropriate training and the resources available to be able to properly answer any questions the interviewee may have. The interviewee should know the donor well enough to be considered as an acceptable representative and be instructed to answer the questions to the best of their knowledge. The interviewee should not simply be the most readily available person. Although a family member may seem appropriate, another individual may be able to provide better, current information. Thus, the donor's sexual partner, girlfriend/boyfriend, current housemate, care-giver or a close friend should also be considered as potential interviewees. It is important to assess whether the selected interviewee has known the donor for a recent period of significant length. Selecting an interviewee that currently lives with the candidate for donation may be preferable because they may be able to offer the best, current, behavioural risk information.

The interviewer must be capable of deciding whether the interviewee is sufficiently knowledgeable or if another person should be sought.

The interview should be conducted using terminology that can be easily understood by the general public. Interviewers should avoid

using medical terms when possible and short, direct questions are the best way to ensure that the questions are understood. An example of a donor risk assessment questionnaire (together with a framework document for its rationale, both provided by NHS Blood and Transplant, UK) is available in Appendix 4.

4.4.2.3.1. Social and sexual behaviours

Behavioural risk is evaluated to determine donor suitability and should include an inquiry into the following histories that could increase the risk for a transmissible disease such as HIV or viral hepatitis:

- a. sexually-transmitted disease – increased risk if recent occurrence, especially for genital ulcerative disease (syphilis, gonorrhoea, herpes);
- b. high-risk sexual behaviour in the past 12 months, including having sex:
 - i. in exchange for money or drugs;
 - ii. with a person from a high-risk region for endemic disease (HIV-1 Group O, HTLV-I);
 - iii. with an intravenous or intranasal drug user;
 - iv. with a recipient of certain human clotting factor concentrates;
 - v. with someone that has tested positive for HIV, HBV or HCV, or with a person with clinically active symptoms;
 - vi. involving frequent changes of sexual partners;
- c. incarceration (prison or a juvenile correctional facility);
- d. history of tattoos, body piercing or acupuncture in the last 4 months when it is not known that only sterile instruments or procedures were used;
- e. intravenous or intranasal drug use.

4.4.2.3.2. Exposure events, including travel or residency

Exposure events that increase the risk of acquiring a communicable disease can occur at any time during life. This includes accidents, certain medical therapies and travel to or residency in an area endemic for certain diseases.

Events that can increase transplant-related risk and affect donor eligibility include:

- a. recent bite from an animal suspected of having rabies;
- b. occupational or other exposure to a toxic substance in amounts sufficient to affect tissues/cells and affect transplantation outcome (e.g. ethylene glycol);
- c. receipt of a live vaccination within the last 4-6 weeks;
- d. exposure to someone else's blood when that person was known to be infected with HIV, HBV or HCV;
- e. sharing a residence with someone who has HBV or clinically-active HCV (in the past 12 months);
- f. chronically transfused with blood or blood products (concern is raised if the administration of blood or blood products occurred many years ago, before adequate disease screening tests became available);
- g. transfused in the UK;
- h. risk of transmission of diseases caused by prions (e.g., people diagnosed with Creutzfeldt-Jakob disease, or variant Creutzfeldt-Jakob disease, or having a family history of non-infectious Creutzfeldt-Jakob disease; people with a history of rapid progressive dementia or degenerative neurological disease, including those of unknown origin; recipients of hormones derived from the human pituitary gland, such as growth hormones, and recipients of grafts of cornea, sclera and *dura mater*, and persons that have undergone undocumented neurosurgery where *dura mater* may have been used.) For variant Creutzfeldt-Jakob disease, further precautionary measures may be recommended;

- i. receipt of a xenotransplant. The risk is due to possible exposure to endogenous retroviruses [3].

New and emerging diseases, including those that have spread to a new geographical area, can pose a significant challenge when screening donors for risks of communicable disease due to travel history. Professionals responsible for donor selection should be vigilant regarding surveillance of changes to the global movement of infectious disease risks. In Europe, regular monitoring of the Rapid Communication reports originating from the Eurosurveillance [4] website is recommended, as well as actively seeking information to assess the epidemiological status of diseases in the areas where a donor has lived or travelled. Questions that assess this risk should be included in the donor risk assessment questionnaire to be posed to the donor or the donor's representative. The risk of transmission of an infectious agent through procurement of tissues or cells from a donor who may have visited an affected area should be balanced by considering the likelihood of a transmission occurring. Regional risks can vary. Some new or emerging diseases that should be considered are: dengue fever, yellow fever, malaria, Chagas' disease, tuberculosis, plague, Chikungunya virus, West Nile virus (WNV), Q fever, antibiotic-resistant diseases, variant Creutzfeldt-Jakob disease (vCJD) and HIV-1 Group O.

In 2012, ECDC in collaboration with the European Commission organised an expert consultation on priority-setting for risk assessment of communicable diseases transmissible through substances of human origin (blood, tissues and cells, and organs) [5]. It was determined that arthropod-borne diseases posed the most urgent threat. West Nile fever, dengue, Chikungunya virus, malaria, Chagas' disease and leishmaniasis were identified as "urgent threats", whereas Usutu virus fever, tickborne encephalitis and babesiosis were not seen as urgent threats. ECDC will use this priority list as a basis for developing comprehensive, review-based risk assessments in 2012, which will be available on the ECDC website.

4.4.2.3.3. Previous diagnosis of disease

Disorders that should be evaluated in potential donors to determine if they qualify for donation can include histories related to:

a. Malignancy

Donors with malignancies must be carefully evaluated as there are some instances when they can be regarded as suitable donors; their suitability as donors depends on the type of malignancy and the type of tissue to be donated.

In general, malignancy can be considered an absolute exclusion criterion, except for primary basal cell carcinoma, *in situ* carcinoma of the cervix and some appropriately evaluated grade I and II primary tumours of the central nervous system according to the WHO classification (see Table 4.1) [6]. It is important to properly evaluate malignancy gradation in the central nervous system (CNS), including a complete histological exam and not just a simple biopsy, taking into account possible heterogeneity of the mass.

Donors with malignant diseases can be evaluated and considered for cornea donation except for retinoblastoma, haematological neoplasm and malignant tumours of the anterior segment of the eye.

When an accurate risk assessment (on an individual basis) of the type of malignancy, course/recurrence, treatment, effect on the type of tissue to be recovered and the processing characteristics can be performed by a qualified and well-trained medical director, exceptionally, some malignancies can be accepted. For EU member states, malignancies should be considered absolute exclusion criteria.

It is important to evaluate conditions such as cirrhosis or a serious gastrointestinal disorder that could show an increased the risk of malignancies.

Table 4.1. WHO grading of tumours of the CNS neoplasias

From Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization, *Classification of Tumours of the Central Nervous System*. IARC, Lyon, 2007.

	I	II	III	IV
Astrocytic tumours				
Subependymal giant cell astrocytoma	*			
Pilocytic astrocytoma	*			
Piloxyoid 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				
Gangliocytoma	*			
Ganglioglioma	*			
Anaplastic ganglioglioma			*	
Desmoplastic infantile astrocytoma and ganglioglioma	*			
Dysembryoplastic neuroepithelial tumour	*			
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 neurohypophysis	*			
Pituitaryoma	*			
Spindle cell oncocytoma of the adenohypophysis	*			

b. Neurological disorders or symptoms

In general, neurological disorders of unknown origin can be considered absolute exclusion criteria:

- i. degenerative or demyelinating disease or a disorder of unknown aetiology involving the central nervous system;
- ii. Diagnosis of dementia without a confirmed primary cause that is acceptable for donation, unless there has been a gross and microscopic examination of the brain to rule out prion-associated disease. If dementia has a primary cause, like dementia of vascular origin, donation can be accepted;
- iii. any suspicion of prion-associated disease (CJD, vCJD), such as rapid progressive dementia;
- iv. a history of chronic, systemic autoimmune disease that could have a detrimental effect on the quality of the tissue to be retrieved.

c. Auto-immune disease (evaluate the effect on the quality of the tissue to be recovered).

d. Genetic disease (evaluate the effect on the quality of the tissue to be recovered).

e. Systemic infection. Donors with systemic infection, which is not controlled at the time of donation (including bacterial diseases, systemic viral, fungal or parasitic infections, or significant local infection in the tissues and cells to be donated), should be excluded. Donors with bacterial septicaemia may be evaluated and considered for eye donation, but only where the corneas are to be stored by organ culture to allow detection of any bacterial contamination of the tissue.

f. History of bacterial and protozoic diseases that can lead to chronically persistent infections, including tuberculosis,

brucellosis, leprosis, melioidosis, Q fever, chlamydiosis, salmonellosis and tularaemia. In this regard, specific attention should be paid to tick/arthropod-borne diseases such as borreliosis, bartonellosis, rickettsiosis, trypanosomiasis, leishmaniasis, babesiosis and ehrlichiosis. The risk of transmitting these infectious agents with specific tissues has to be assessed and negative effects for the recipients have to be excluded.

- g. Conditions that may increase the risk of infection, including:
- i. diabetes;
 - ii. prolonged, high-dose steroid therapy;
 - iii. malnourishment;
 - iv. chronic respiratory diseases/conditions.

The receipt of medication and other therapies must be evaluated to determine donor suitability, due to risk of a weakened immune system. Consider:

- i. anti-rejection drugs (organ transplant recipient);
- ii. corticosteroids (long-term, high-dose therapy can mask a current viral infection);
- iii. radiation and/or chemotherapy (can also weaken tissues near the target area).

Recent history of vaccination with live attenuated virus should be evaluated as a potential risk of transmission.

If it is known that the potential donor was excluded or deferred from donating blood by a blood collection establishment, and the specific reason for deferral cannot be discovered, the donor may be considered ineligible for tissue donation.

Some medical conditions can adversely affect specific tissues which, if recovered, processed and made available

for transplantation, may result in unfavourable outcomes for the tissue recipients. This risk is evaluated on a case-by-case basis and for specific tissue types. For example, a potential donor with multiple known conditions related to a high risk for cardiovascular disease may not qualify as a suitable donor of cardiac tissue (heart valves, cardiac conduits, etc.) or vascular tissue (arteries, veins); a person with skin disease may not be suitable for skin donation; someone with a metabolic bone disease may not be an appropriate donor of musculoskeletal tissues; or a person with a collagen disorder should not be a donor of soft tissues or tissues comprised of that type of collagen (tendons, ligaments, fascia lata, cardiovascular tissues). Donor age may play a role in the decision-making process, as well as donor weight (minima or maxima).

Part of the responsibilities of the tissue establishment's Quality Management team is to properly characterise the allografts they provide for transplantation. The minimum specifications that allografts should meet in order to be deemed suitable for use should be described in policies and procedures, and donor qualification should form the basis of how those specifications are consistently met [7].

4.4.2.3.4. Relevant family history

If a blood relative of the donor was definitively diagnosed by a physician to have CJD, then the donor may have a small, genetic pre-disposition to this disease if their relative's CJD did not have an iatrogenic cause. Deceased donors having a family history of non-iatrogenic CJD should be excluded.

The risk associated with HTLV-1 in a donor may be higher if the donor or his parents originated from a high prevalence area.

4.4.3. Physical evaluation of donors

The physical evaluation of a deceased donor must be performed prior to procurement and includes looking for the presence of any signs on the body that might indicate there could be risk for a transmissible disease. This examination must be documented and, together with a donor's medical history, behavioural risk information and the results of donor testing, used to determine the suitability of a donor. A sample tissue donor physical assessment form provided by the American Association of Tissue Banks can be found in Appendix 5.

Risks to look for should include signs of:

- a. Systemic disease:
 - i. active malignancy (suspicious skin lesions);
 - ii. malnutrition, multiple deformities.
- b. Bacterial or viral infection:
 - i. recent receipt of a live vaccination (vaccination site infection, scabs, lesions);
 - ii. recent receipt of a tattoo, body piercing or acupuncture where non-sterile instruments were used (shaved area, redness, swelling, scabbing may require further investigation to assess risk);
 - iii. skin lesions such as a rash, petechiae, skin ulcers, blue/purple or gray/black lesions, shingles;
 - iv. oral lesions such as ulcers or thrush;
 - v. enlarged lymph node(s);
 - vi. jaundice, icterus, hepatomegaly.
- c. High-risk behaviour (related to HIV infection or viral hepatitis):
 - i. injectable drug use (non-medical injection sites);

- ii. inspection of tattoos (for hidden injection sites, also to assess extent and location of the tattoo);
 - iii. genital or skin lesions or trauma indicative of a sexually-transmitted disease (e.g. evidence of anal intercourse, insertion trauma, peri-anal or herpetic lesions, syphilitic chancres or other lesions).
- d. Trauma:
- i. fractures, avulsions, lacerations or abrasions that may affect (contaminate, compromise integrity) the tissue to be recovered;
 - ii. internal trauma that can cause cross-contamination between cavities, e.g. injury to the bowel, penetrating or crushing injuries.
- e. Cleanliness of the body:
- the condition in which the body is found (this can also relate to increased risk for contamination/cross-contamination).
- f. Scars (surgical, scarification):
- if findings do not match the donor's history, further investigation may be required.

Every donor (adult or child) must be thoroughly examined following established protocols, covering the anterior and posterior aspects of the body as well as an inspection of body cavities. A donor's excessive weight cannot compromise the requirement to perform a thorough assessment. No finding suggestive of possible risk should be left unresolved.

For living donors, a physical examination should be performed to ensure safety of donors and recipients according to the specific requirements of the particular type of tissue or cell donated. This examination should be performed in the context of a clinical evaluation that includes both an interview and a physical examination.

4.4.4. Considerations for evaluation of paediatric donors

Special screening considerations are required for paediatric donors. If the child is 18 months old or younger, or has been breastfed in the 12 months prior to death, the birth mother should be evaluated for risks associated with HIV, HBV, HCV and HTLV. Other diseases that can be transmitted vertically from mother to foetus may also be relevant, such as malaria or Chagas' disease. Special testing may be needed if a risk is deemed relevant. Since a child's immune system is only in development, protective antibodies may not yet have been produced against an infection, thereby increasing the risk of hidden infections in child donors.

In the EU, Directive 2006/17/EC stipulates that children aged under 18 months born to mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests.

Child donors must be screened with as much diligence as adult donors. The physical assessment must not be overlooked or shortened simply because the donor is a child. Although risk associated with sexual activity may not seem relevant, infectious disease risk associated with child abuse (sexual) is possible, so examination of the genital and peri-anal regions are recommended.

4.5. References

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Chapter 5. Donor testing

5.1. Introduction

The use of tissues and cells for human application can result in unintentional disease transmission. However, such events can be prevented by scrupulous donor evaluation, including testing of each donor close to the time of donation in accordance with established good practice. The risk can be substantially reduced by appropriate donor sample testing, but adequate controls must be in place to ensure that test results are accurate. Controls include:

- a. selecting a qualified laboratory that will perform testing following good laboratory practice;
- b. ensuring the validity of any donor blood specimen collected for infectious disease testing;
- c. use of appropriately validated infectious disease tests;
- d. providing well-written standard operating procedures (SOPs) and training for all personnel involved in collection and labeling of donor samples, for sample storage and transport, and for technical staff performing testing and reporting results, as well as for those receiving and interpreting them.

These are vital elements of a tissue establishment's "quality system" and a responsible person must keep informed of advances in testing technology for infectious disease (e.g. third- and fourth-generation antigen and antibody tests, Nucleic Acid Amplification Technique (NAT), etc.).

5.2. General

Tissue establishments must ensure that all donations of human tissues and cells are subjected to those biological tests mandated by national legislation³.

SOPs should be in place that define the criteria for acceptance or rejection of tissues and cells based on those test results.

Documented measures must be taken by tissue establishments that receive tissues or cells from another country or that distribute tissue or cells to another country to ensure that the donor testing requirements of the destination country are met. Evidence should also be available to show that any laboratory used for testing of donor samples has been authorised by the appropriate authority to perform such testing.

5.3. Quality of donor samples

Manufacturers of infectious disease testing kits typically publish specific sample requirements for each sample. Personnel of procurement organisations and tissue establishments involved in collecting, storing or testing donor samples must be aware of these requirements to ensure optimised test performance. If inadequate or adulterated samples are provided and tested, test results may not be valid, which increases the risk of donor-related infectious disease transmission.

Donor-related conditions that could affect the quality of a test specimen must also be taken into account. Infectious disease test results may be invalidated by haemo- or plasma-dilution if a qualified, pre-transfusion or pre-infusion sample is not available (see section 5.3.2). Haemolysis can also affect test results.

The ability to detect antibodies against viral agents can be impaired if the donor has received immunosuppressive treatment. In this case,

3 In EU member states, Annex II of Directive 2006/17/EC, amended by Directive 2012/39/EU, stipulates the mandatory laboratory tests and the general testing requirements for both living and deceased donors of tissues and cells.

NAT tests can prove valuable because detection of nucleic acids is not affected by immunosuppressive therapy. The underlying condition requiring immunosuppression will demand further assessment as it in itself may constitute an independent reason for deferral. If any of these donor-related conditions exist, they must be documented in the donor record and evaluated by a responsible person prior to release of tissues or cells for clinical application.

5.3.1. Sample collection (sample type, tubes, labelling, time-limits and handling)

All personnel involved in any stage of the testing process must be fully trained. Microbiological testing must be carried out on the donor's serum or plasma according to the test kit manufacturer's specification. Testing must not be performed on other fluids or secretions, such as aqueous or vitreous humour, unless validation has been performed to ensure test validity on that sample. In the case of a neonatal donor (i.e. 1 month of age or less), the required tests should be carried out using a blood sample from the donor's birth mother.

Donor sample collection and manufacturer's test instructions must be followed regarding:

- a. the type of collection tube (no anti-coagulant or a specific anti-coagulant) required for the test being performed;
- b. sample storage and transport conditions post-collection, which can include centrifugation and/or separation within time-limits or specimen refrigeration/freezing;
- c. testing required to be performed within a specified timeframe post-collection.

To ensure traceability at every stage of the testing process, all donor samples must be identified with a permanently affixed label that contains information or references that link the sample and the laboratory test results to the donor. The date and time when the sample was drawn must be accurately documented. It is recommended that at least 2 donor identifiers, such as the donor's full name, date of

birth, and/or medical record number be used. In the case of a sample from a deceased donor, the label or associated documentation should also include some identification of the person who collected it and a description of the site on the donor's body the sample was taken from (e.g. cephalic vein, femoral artery, subclavian artery, superior vena cava, etc.). It is good practice for the identity of all donor samples to be confirmed by a second person from the procurement team, and this confirmation process should be documented [1]. If any donor blood samples were drawn before death, they can be qualified for use, but there must be assurance that the patient identifier used for any such specimen is confirmed as coming from the donor by appropriate labeling so mix-ups do not occur (i.e. performing critical communicable disease testing on the wrong patient) [1]. Other donor identification methods can be used, if validated, to ensure traceability [2]. Specimens of blood, serum or plasma collected at different times must not be mixed together for testing (e.g. a serum or plasma sample must not be physically combined with another serum or plasma sample collected at the same or a different time).

For obvious safety reasons, the collection of donor blood for infectious disease testing must always occur as close as possible to the donation event. Personnel collecting, or otherwise obtaining, donor blood samples to be used for this critical testing must consider factors that could influence sample degradation and cause false-negative or false-positive test results, e.g. time of sample collection, temporary storage conditions.

Proper handling of any donor blood sample after it is collected is necessary to ensure that testing protocols can meet the required specifications. For example, when a blood sample is collected in a tube containing an anti-coagulant, this liquid or powder requires that a completely filled tube be gently mixed by slowly inverting the tube 5 to 10 times immediately after collection [3].

After collection, specimen handling by personnel can include centrifugation and/or separation of the serum or plasma from red cells within specific time-limits. Additionally, specimen storage and/or transport conditions can involve refrigerating or freezing the plasma

or serum aliquot. Specific instructions from the test kit manufacturer must be followed and can differ among tests [1]. In all cases, qualified transport containers and validated shipping procedures must be used when sending donor samples to a testing laboratory.

The facility receiving any donor sample for testing should have SOPs in place to define sample acceptance or rejection criteria based on collection, storage and transport conditions. The testing facility must document acceptance or rejection of the sample and should share this sample status in a timely manner with a responsible person at the procurement organisation or tissue establishment.

5.3.1.1. **Deceased donor**

In the case of a deceased donor, blood samples should be obtained prior to death or, if not possible, within 24 hours after death. Samples can be used that were collected up to 7 days prior to death, but sample storage parameters must be reviewed to ensure such samples remain qualified for use according to the manufacturer's instructions for the specific testing kit. It is important to collect blood samples without untoward delay after death to avoid sample characteristics that could cause false-positive test results (e.g. partial haemolysis) or that could lead to its rejection for testing (e.g. complete haemolysis). Delays in donor sampling have been shown to increase the incidence of red cell haemolysis, and other substances can appear in non-circulating blood due to growth of micro-organisms and release of enzymes (including by-products of tissue and cell death) [1].

5.3.1.2. **Living donor**

In the case of living donors, blood sampling should be obtained at the time of donation or, if not possible, within 7 days of the donation. For practical reasons, collection of a sample from an allogeneic bone marrow stem cell or peripheral blood stem cell donor can occur within 30 days prior to donation, taking into account that re-testing at the time of donation will be informative, but without there being a point-of-return when irreversible measures for pre-conditioning of the recipient had been initiated.

5.3.2. Haemodilution assessment

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 blood, testing of donor blood collected post-transfusion or post-infusion may not be valid due to haemo- or plasma-dilution of the donor and, thus, of any samples taken from the donor. An assessment of the extent of the donor's dilution that might render any test result invalid includes the use of a formula (algorithm) to calculate dilution of the donor's original circulating blood volume (and circulating antigen and/or antibody levels, if present). Examples of when a haemodilution calculation may need to be performed include:

- a. **ante-mortem** blood sample collection: if blood, blood components and/or colloids were administered in the 48 hours *preceding blood sampling*, or if crystalloids were infused in the hour *preceding blood sampling*;
- b. **post-mortem** blood sample collection: if blood, blood components and/or colloids were administered in the 48 hours *preceding death (circulatory arrest)*, or if crystalloids were infused in the hour *preceding death (circulatory arrest)*.

Refer to Appendix 6 for an example of a commonly-used formula to assess the donor's potential haemo- or plasma-dilution that can be applied when the donor has lost blood. Adaptations of the algorithms may be needed for body sizes outside the normal adult range. Allowances may be needed for very large, very small or paediatric donors. In brief, a donor's total plasma volume (TPV) and total blood volume (TBV) are estimated by calculations based on the donor's body weight, then direct comparisons are made to amounts of recent transfusions and/or infusions that were administered prior to circulatory arrest or prior to collection of the blood sample, whichever occurs first [1]:

- a. estimate TPV of donor (weight in kg $\times$ 40 mL/kg);
- b. estimate TBV of donor (weight in kg $\times$ 70 mL/kg);

- c. calculate total blood (mL) received in last 48 h (A);
- d. calculate colloids (mL) received in last 48 h (B);
- e. calculate crystalloids (mL) received in last 1 h (C);
- f. add B + C and compare to TPV (fluid volumes are compared);
- g. add A + B + C and compare to TBV (mass/fluid volumes are compared);
- h. does either comparison show > 50% dilution? If not, the blood sample qualifies and can be used for infectious disease testing.

Although not normal practice, a tissue establishment may accept tissues and cells from donors with plasma dilutions of more than 50%, but only if each required test has been properly validated for use with a diluted test specimen. In such cases, performing NAT tests for HIV, HBV, and/or HCV may be more appropriate.

It should be noted that donor blood can be diluted if the analyte is drawn in close proximity to an infusion or transfusion intravenous line, even if the donor is not haemo- or plasma-diluted. Samples should be drawn from the opposite side of the body in relation to the site of infusion.

5.4. Testing laboratories

To meet high expectations for quality and safety, all infectious disease testing required for deceased and living donors must be carried out by qualified testing centres (laboratories) that are accredited, designated, authorised and licensed for these activities according to the regulations of the relevant Health Authority and, ideally, should participate in external quality assessments.

If additional biological assays are performed for a donor of hematopoietic stem cells, the laboratory used should be accredited and participate in an appropriate external quality assessment programme [3].

Tissue establishments can perform these testing protocols themselves or have a written agreement with any laboratory that performs donor infectious disease testing on their behalf. Tissue establishments should

evaluate and select a testing laboratory on the basis of their ability to comply with regulatory requirements and any other specific expectations of the tissue establishment (e.g. time-sensitive availability of test results). The tissue establishment should assess the laboratory's qualifications, and also the test kits and procedures the laboratory intends to use. There must be evidence that good laboratory practice is being followed and that personnel are appropriately trained and experienced in the relevant testing procedures. To ensure a consistent level of competence and performance, audits of the testing laboratory(ies) should be undertaken periodically by the tissue establishment or by qualified external experts as part of the tissue establishment quality system.

5.5. Tests to be performed

The donor screening tests selected must be validated and used in accordance with current scientific knowledge. Where CE-marked testing kits are available, they must be used. As a minimum requirement, the following biological tests must be carried out on the donor's serum or plasma according to the manufacturer's instructions for each test kit [2]:

- a. HIV 1 and 2 – anti-HIV-1 and anti-HIV-2 (antibodies to HIV-1 and HIV-2);
- b. Hepatitis B⁴ – HBsAg and anti-HBc;
- c. Hepatitis C – anti-HCV (antibody to hepatitis C virus);
- d. Syphilis⁵ – a treponemal-specific test or a non-specific treponemal test can be used.

4 When anti-HBc is positive and HBsAg is negative, further testing is necessary to determine the donor's hepatitis status. This will usually involve anti-HBs and/or NAT for HB. In these circumstances, a risk assessment must be performed and documented by the tissue establishment's Responsible Person, who will determine donor eligibility and tissue release for clinical use. This also applies when cell or tissue distribution occurs from procurement directly to the clinical team responsible for human application or for direct use.

HTLV-I antibody testing must be performed for donors that have lived in, or originated from, high-prevalence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas [2].

The minimum testing requirement for infectious agents is antibody detection. In the absence of NAT, testing the mother of donors 18 months old or younger, or who have been breastfed within the 12 months prior to donation, is necessary.

5.5.1. Additional tests

Since NAT tests are more sensitive and deceased donors cannot be re-tested after six months, consideration should be given to additionally performing NAT testing for HIV, HBV and HCV on deceased donors. Donor history of deceased donors may also be less reliable.

With regard to additional testing for donors originating from high-prevalence areas for specific diseases or whose sexual partners or parents originate from such areas, refer to existing international scientific evidence such as that provided by the European Centre for Disease Prevention and Control [4]. Additional testing that may be considered, depending on the donor's history and the characteristics of the tissues or cells donated, include: ABO group, RhD (D antigen), HLA (human leukocyte antigen), diagnostic tests for malaria, West Nile virus NAT, antibodies to CMV, toxoplasma antibodies, antibodies to EBV (Epstein-Barr virus) or antibody to *Trypanosoma cruzi* (the infectious agent for Chagas' disease) [2].

- 5 A validated testing algorithm must be applied to exclude the presence of active infection with *Treponema pallidum*. A non-reactive test for syphilis, whether a specific or non-specific test is used, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a treponemal-specific (confirmatory) test is non-reactive. A donor whose specimen is reactive for a treponemal-specific test requires a thorough risk assessment by a Responsible Person to determine donor eligibility for their donation to be released for clinical use.

5.5.2. Re-tests of samples from living donors (allogeneic use)

For living donors, initial infectious disease testing is performed at the time of donation or up to 7 days after donation when this is not possible. However, in the case of bone marrow and peripheral blood stem-cell collection, blood samples must be drawn for testing within the 30 days prior to donation. Minimum testing requirements are the same as for deceased donors; although there are some additional considerations because the donor is available for more testing and infectious disease test kits are typically optimised for testing samples from living donors and because there may be additional infectious risks pertinent to the profoundly immunosuppressed recipients of bone marrow or similar types of graft.

Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. Under such circumstances, donor sampling for initial testing can occur up to 30 days prior to and 7 days post-donation. If samples from a living donor undergo serology testing and then are additionally tested by NAT for HIV, HBV and HCV, re-testing after an interval is not required. Re-testing is also not required if processing includes an inactivation step that has been validated for the viruses concerned.

5.5.3. Testing of autologous samples

In the case of autologous living donors (where the tissues or cells removed will be stored or cultured and transplanted back into the donor), it is necessary to perform the same serological tests as for allogeneic donors. If an autologous donor's blood sample has not been appropriately tested or if a test is positive for a relevant infectious disease, this will not necessarily prevent the tissues or cells, or any product derived from them, from being stored, processed and re-implanted in the autologous donor. However, this is only the case if appropriate storage can provide isolation/segregation to ensure there is:

- a. no risk of cross-contamination with other stored allografts;

- b. no risk of contamination with adventitious agents;
- c. avoidance of mix-ups due to misidentification (see Chapter 3).

SOPs based on risk analysis must be in place to define the acceptance and rejection criteria for these contaminated tissues and cells.

5.6. Reporting and documentation of test results

Tissues and cells must be held in “quarantine” until such time as the requirements relating to donor testing have been completed. With this in mind, donor infectious disease testing should be performed and reported without delay. Reporting methods must be used that link the donor’s unique identifier to the test results, whilst also keeping the donor anonymous to third parties. Data security measures are required, as well as safeguards against any unauthorised additions, deletions or modifications to donor test results. There must be no unauthorised disclosure of infectious disease test results.

Arrangements between the testing laboratory and the tissue establishment, or the clinical team responsible for use of the donated tissues or cells, should include agreed methods for the reporting of test results to ensure mix-ups are avoided and prevent misinformation. Laboratories and tissue establishments must have policies relating to the management of donor test results that may be pertinent to family members and other contacts of the donor or have public health implications.

Reporting procedures should ensure that accurate, rapid and verifiable results are provided. In addition, there must be a system in place to ensure prompt alerts, using an immediate notification system, when a positive infectious disease test result occurs. Other precautionary measures regarding reporting may include [5]:

- a. where manual systems are still used (although they are not recommended), virology analysis reports should be cross-checked to ensure that the transcription of test results has been confirmed by two independent assessors;
- b. using computerised procedures for the transfer of test results from laboratory equipment to the laboratory data-processing

- management system (e.g. medical records) to eliminate the need for manual transcription of data;
- c. using clearly-interpretable, computerised graphic symbols to highlight positive results;
- d. including the titre of antibodies and/or the related positivity threshold next to the viral negative/positive result;
- e. the use of formal laboratory reporting structures and accreditation or certification pathways in order to improve quality standards;
- f. use of widely-recognised international units of measurement.

5.7. Archived samples

If any donor sample remains after all required testing has been completed, it is desirable to freeze and store aliquots of serum and/or plasma. Therefore, archive samples may be used for a number of purposes; for example, look-back into a new infectious agent, development of more accurate or new tests, or for use when investigating a report of a serious adverse reaction in a recipient of cells or tissue. A documented risk assessment, approved by the tissue establishment's Responsible Person, should be performed to determine the fate of all stored tissues and cells following the introduction of any new donor test that could reasonably be considered to affect safety or quality.

5.8. References

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Chapter 6. Procurement

6.1. Introduction

To ensure high standards of quality and safety during the procurement process for cells and tissues, it is recommended that a quality system be in place in the procurement organisation or the tissue establishment undertaking the process. This quality system must guarantee adequate training of all personnel involved, as well as complete standard operating procedure (SOP) documentation for all stages of the process. Control measures must be undertaken by procurement professionals to reassure the public that appropriate quality and safety parameters are in place to ensure a high level of health protection.

The procurement of human tissues or cells can only take place after mandatory donor consent or authorisation requirements have been satisfied, as described in Chapter 4. Tissues and cells must also be packaged and labelled correctly (see Chapter 3), and then transported to the tissue establishment or clinical team for direct use, in accordance with established requirements.

Chapter 2 details the quality management expectations regarding personnel, facilities, equipment, materials, procedures, and documentation. Additional considerations focused on procurement activities are detailed in this chapter. Chapters in Part B of this Guide describe the requirements for procuring specific tissues such as ocular, amniotic membrane, skin, cardiovascular or musculoskeletal tissues, or when obtaining haematopoietic stem cells, or tissues and cells for use in advanced therapies.

6.2. Personnel

Procurement activities must be performed by personnel with appropriate qualifications, training and experience. This includes successful completion of a comprehensive technical and/or clinical training programme involving the specific cell or tissue types to be procured. Persons performing any procurement event must be made aware of the risks, as well as the potential consequences, if procurement policies and procedures are not followed as directed in SOPs and according to the relevant legislation. To promote compliance with donor selection criteria and procurement procedures, the tissue establishment (or the procurement organisation) must have a written agreement with each person, clinical team or organisation involved in performing procurements, as well as those collecting critical information used in donor selection. The written agreement must include descriptions of expectations and responsibilities related to quality and safety measures, as well as any additional regulatory requirements. A written agreement is not necessary for personnel employed by the tissue establishment (or procurement organisation) responsible for these steps; although expectations and responsibilities pertaining to procurement must appear in their job description. Staff must also undergo a comprehensive training programme, including the broader ethical, legal and regulatory context of their work.

6.3. Facilities, equipment and materials

6.3.1. Facilities

Procurement activities must be authorised by the Health Authority(ies). Each procurement event must take place in an appropriate facility, following technical procedures (see section 5.4. Procedures) that minimise bacterial or other contamination of procured tissues and cells. For reasons of privacy and control of contamination, access to the area where procurement takes place must be restricted, especially during the performance of procurement steps. Donation of

tissues and cells by living donors must take place in an environment that ensures their health, safety and privacy.

It is highly recommended that the facility where procurement takes place:

- a. is of adequate size regarding floor space and work-tops that will be used;
- b. is appropriately located to ensure cleanliness and privacy;
- c. is furnished with sufficient light fixtures;
- d. is in a good state of repair;
- e. is free of pests;
- f. provides a sufficiently clean or cleanable environment that will not contribute to contamination of the cells or tissues during procurement activities.

Prior to procurement, steps to minimise the potential for contamination must include cleaning all working surfaces with an approved disinfectant. The procurement area must also be cleaned appropriately post-procurement and this involves proper disposal of all bio-hazardous waste and sterilisation of all re-usable instruments. If a tissue establishment (or procurement organisation) uses the general cleaning services of the facility to clean and/or sterilise the operating room as well as surgical instruments, the procedures used by them must be inspected/validated.

It is recommended that the procurement area meet the criteria of a standard operating room:

- a. ancillary areas used for preparation or entry to the procurement area should be reserved for this use and be cleaned according to a procedure that minimises the risk of introducing contamination;
- b. rooms used for changing clothes, for preparatory washing (forearm and hand scrubbing) and personal hygiene should be easily accessible and appropriate for the number of procurement personnel;

- c. rooms provided with plumbing and drainage systems should not directly communicate with procurement or equipment storage areas.

When this is not possible, a risk assessment must be performed.

If the tissue establishment has its own procurement area, whenever possible, a controlled environment (such as exist in hospital operating rooms) should be used. The environmental control system should ensure at least a Grade D classification of the procurement area “at rest” (if the area is not classified, a validated cleaning methodology must be applied). It should provide comfortable and safe working conditions (in terms of temperature and humidity), and have filtered ventilation with pressure gradients that direct air to circulate from the cleanest area in the room to areas of the lowest level of cleanliness. To qualify these controls, annual environmental and operational qualification procedures can be performed (e.g. filter integrity testing, air exchange and pressure measurements, airborne particle counts, temperature and humidity measurements). Instrumentation used for such measurements must be properly maintained and calibrated, and used according to the manufacturer’s instructions.

When procurement of tissues or cells must occur outside of a designated procurement area (such as in a mortuary, a funeral home or, for a living donor, in their residence or hospital room), a secure, enclosed space must be prepared to limit potential environmental contamination.

6.3.1.1. Processing at the procurement stage

The requirements for procurement and processing are often confused. Requirements for procurement are typically less stringent than for processing. As a result, some organisations attempt to bypass processing requirements by performing processing during procurement. In all cases, processing must be performed under strict processing requirements, even if it is performed simultaneously with procurement. Processing includes cutting, shaping, cleaning, sizing and packaging.

In any setting, microbiological safety during the procurement of cells or tissues must be considered. Due to specific contamination control and other quality assurance requirements (described in more detail below and in Chapters 2 and 13-19), simultaneous performance of “processing” steps during the procurement phase, or in the procurement area, is not recommended. The strict environmental controls (i.e. air quality Grade A where tissue and cells are exposed to the environment during processing steps) and monitoring requirements expected for “processing” cannot be met by the sites where procurement usually takes place (i.e. an operating room or an area of less stringent control). If processing at the site of procurement is unavoidable, its duration and extent should be limited to the minimum necessary, and an air quality Grade A environment (surrounded by, at least, air quality Grade D) for the processing steps is desirable. Records supporting the qualification of the processing site must be available for inspection. If this level of control is not possible, an in-process (active) environmental monitoring method should be used; preferably, active air monitoring using a viable particle counter and culturing method or, as a minimum control, microbiological settle plates can be used. Sample cultures of the cells or tissues procured should also be taken and a properly validated culture method must be used (see Chapter 2). Ultimately, the procurement environment, if it is also used as a processing environment, must be specified and must achieve the quality and safety required for:

- a. the type of tissues and cells procured;
- b. the various tissue and cell processing steps that will be used (e.g. none, exposure only to antibiotics, a validated inactivation method or a validated sterilisation method);
- c. the planned human application (as well as consideration of the immune status of the recipient, if applicable).

Selection of the use of less than optimal conditions must be supported by a written justification and must be authorised by the Health Authorities.

6.3.2. Equipment and materials

Materials (e.g. disposables and reagents) and equipment (e.g. instruments, devices, packaging, containers) used during procurement must be managed in accordance with standards and specifications and with due regard for relevant national and international regulations, standards and guidelines for the intended use of the donated tissues and cells (see Chapter 2). Qualified sterile instruments, CE-marked devices (where available) and sterile disposable materials (e.g. drapes, gloves, fluids, etc.) must be used for tissue and cell procurement. Instruments or devices must be of good quality, validated or specifically certified (e.g. surgical grade) for procurement use and they must be maintained in good working order to ensure successful procurement. This must include visual inspections and scheduled calibration of devices with a measurement function. Routine annual maintenance inspections (qualification procedures) of equipment used for procurements are encouraged and a re-qualification assessment is advised whenever repairs or modifications have occurred. Procurement personnel must receive appropriate training, supported by records, on the proper use of equipment.

The use of disposable instruments for procurement is recommended, whenever feasible. When re-useable instruments are utilised, compliance with a validated cleaning, disinfection and sterilisation process for removal of infectious agents must be routinely used and these steps should be supported by documentation for each event. A system must be in place that allows tracing of “critical” equipment and materials to each tissue or cell procurement using them and to the donor.

In EU member states, critical reagents and materials must meet documented requirements and specifications and, when applicable, the requirements of Directive 93/42/EEC concerning medical devices (1) and Directive 98/79/EC on *in vitro* diagnostic medical devices (2).

Personnel conducting procurement activities must be provided with personal protective equipment (clothing) appropriate for the type of procurement. Usually, this will extend to being scrubbed and involves

wearing a sterile gown, sterile gloves, a face shield and a protective mask.

Approved materials necessary for reconstruction of a deceased donor's body must be provided to allow this step to be completed effectively.

6.3.2.1. Packaging, containers and labelling

Immediately following procurement, tissues and cells must be packaged so as to minimise the risk of environmental contamination and be appropriately labelled to ensure traceability. Guidance for this critical step is provided in Chapter 3 for all stages of the donation process, from procurement to distribution.

6.4. Procedures

Technical SOPs for procurement must be in place, based on the requirements of Health Authorities, the recommendations laid out in this Guide and the expectations of the tissue establishment or end user needs. These SOPs verify the correct steps to be taken for each stage of procurement and, indeed, all stages of the donation and transplantation process. Procedures that ensure contamination control must be used, such as use of sterile techniques, material and equipment (like those used during surgical procedures on patients). Personnel conducting the procurement must be appropriately gowned and gloved and should wear protective masks (see section 6.3.2). Periodic review of technical SOPs by a responsible person must be performed and updates may be necessary due to scientific and technical progress. Procedures must be authorised and appropriate for the type of donor and the type of tissue or cells procured and must be standardised.

SOPs must be readily accessible so that procurement personnel can follow the required steps, including:

- a. verification of the donor's identity and what constitutes evidence of donor (or donor's family) consent or authorisation (see Chapter 4);

- b. assignment and proper use of a unique identifier/code (see Chapter 11);
- c. knowledge of selection (risk) criteria required for donor assessment, including physical examination of the donor (see Chapter 4);
- d. knowledge and assessment of the laboratory tests required for donor acceptance (see Chapter 5);
- e. steps that minimise the risk of microbiological contamination during procurement (see this Chapter, Chapters 2 and 13-19);
- f. procurement steps that protect properties of the tissue and cells required for clinical use (see this Chapter and Chapters 13-19);
- g. for deceased donation, how to reconstruct the donor's body so it is as similar as possible to its original anatomical appearance;
- h. considerations for packaging, labelling and transportation of procured tissues or cells to the tissue establishment or, in the case of direct distribution, to the clinical team responsible for their human application or direct use (see this chapter and Chapter 3);
- i. considerations for collecting, packaging, labelling and transporting donor blood or fluid samples to the laboratory for testing (see this chapter and Chapters 3 and 5);
- j. procedures that protect the safety of the living donor (see Chapters 14 and 18-20).

Additionally, the tissue establishment (or procurement organisation) is expected to have procedures in place to notify, without delay, other tissue establishments or the Health Authority of all relevant available information regarding:

- a. knowledge of deviations from approved procedures that occurred or that are suspected to have occurred, and/or
- b. any serious adverse reaction in a living donor that may influence the quality and safety of the tissues and cells procured.

To minimise the risk of tissue or cell contamination by procurement personnel who may be infected with a transmissible disease, policies and procedures must be established and followed to address this risk. Additional procedures and policies that minimise the risk of microbiological contamination during procurement must be considered, including:

- a. the maximum number of personnel permitted to be present during procurement must be defined and respected;
- b. preparation of the donor's skin must follow the recommended standards of practice used for surgical patients and must occur at the beginning of procurement using an appropriate anti-microbial agent designed for this purpose;
- c. the procedure for skin disinfection should account for the elimination of bacterial spores as well as vegetative micro-organisms and therefore include suitable disinfectants, their concentrations and durations of exposure;
- d. before use, materials and equipment to be used must be visually inspected by procurement personnel to ensure they meet specifications (e.g. sterile, seals not broken, equipment functioning as expected, etc.);
- e. for deceased donation, it is advisable to procure tissue before the autopsy takes place but, if this is not possible, detailed procedures must be written to address the increased potential for contamination when procurement takes place after autopsy.

Procedures must be written to accommodate procurement steps that protect certain properties of the tissue and cells required for their ultimate clinical use. These are described more fully in Part B of this Guide (tissue-specific chapters), but generally include:

- a. procurement time-limits (after death): the general rule is 24 hours if the body has been refrigerated in the first 6 hours after death or 15 hours if the body has not been refrigerated;
- b. preservation of important anatomical structures and other tissue or cell characteristics;

- c. temperature requirements during storage and transport to the next destination;
- d. avoidance of delays in transport due to time-limits in place for processing after procurement.

Efforts should be made to ensure that procurement procedures do not substantially affect funeral arrangements or other formalities. If this is not possible, the donor's family must be informed at the time of consent. Timely, effective communication with all parties involved can help to meet expectations in regard to delays, as well as aesthetic considerations when tissues are procured from areas of the body that may be visible if funeral proceedings are planned (e.g. face, neck, arms, etc.).

Tissue establishments (or procurement organisations) must have a procedure that addresses retention of records (i.e. archived procurement records) (see Chapters 2 and 10).

6.4.1. Temporary storage and transport

Critical parameters related to maintaining environmental conditions (e.g. temperature, sterile packaging) must be controlled during temporary storage and transport of recently procured tissues/cells. Records to demonstrate compliance with specified storage conditions must be created and maintained.

Temporary storage must provide clearly separate and distinguishable areas for tissues and cells that remain in quarantine. In order to prevent mix-ups or cross-contamination, physically separate areas or storage devices or secured segregation within a storage device or unit (i.e. refrigerator, freezer) must be allocated and prominently labelled (with, for example, the term QUARANTINED). Temporary storage areas or units for tissues and cells must be monitored (and alarmed, if necessary) and checked to ensure expected environmental requirements are being met.

Transport of recently procured tissues and cells should occur without delay using an approved courier. The courier or transportation service must maintain records of pick-up and delivery, as well

as the container's contents, so that the package is fully traceable. The procedures, materials and equipment used by procurement personnel to package and transport recently procured tissues and cells must be approved or provided by the tissue establishment or the clinical team who will receive them.

Evidence of the integrity of packages and their contents upon arrival at their destination must be documented and reported to the procurement organisation.

6.5. Documentation

Since procurement is a critical activity, descriptive documentation of the steps taken, the materials and equipment used, and identification of the personnel involved must be recorded and made available. Such records must be clear and legible, protected from unauthorised amendments, retained and readily retrievable throughout a specified retention period, and in compliance with data protection legislation. Procurement records must be as detailed as necessary to facilitate traceability, providing a complete history of the work performed and be capable of linking the records to the particular donor and tissue and cells procured. When tissues and cells are to be sent across national borders, consideration of possible language barriers should be addressed and a common language agreed upon for all donor-, tissue- and cell-related documentation.

A unique identifier (e.g. a donation number for a donation event and/or a donor identification number) must be allocated to the donor as well as the procured tissues and cells (see Chapter 11). This coding must be in place to ensure an effective and accurate system capable of tracking tissues throughout all handling stages, including an identifiable link to the procurement steps. For each donor, there must be a record containing the donor's identity (i.e. first name, family name, date of birth, gender). If a mother and child (both living) are involved in the donation, records must indicate not only the name and date of birth of the mother, but also the name (if determined) and date

of birth of the child. This coded data should be entered in a register maintained for this purpose.

Before the procurement of tissues and cells may proceed, an authorised person must confirm and record:

- a. that consent for the procurement has been obtained in accordance with local laws, and
- b. how and by whom the donor has been reliably identified.

To ensure that all steps are traceable and verifiable, the tissue establishment (or procurement organisation) must produce a report, recorded at the time of procurement, which must be forwarded without delay to the destination (including the clinical team responsible for human application or direct use in the case of living donors). This procurement report, at a minimum, must contain:

- a. donor identification data (first name, family name, date of birth and gender, as well as how and by whom the donor was identified);
- b. the environmental conditions of the procurement facility (location or description of the physical area where procurement took place);
- c. a list of observations during the physical examination of the donor's body (for a living donor, only when such an examination is justified);
- d. a description and identification of procured tissues and cells, including samples for infectious disease testing;
- e. the identification of the person who is responsible for the procurement session, including their signature;
- f. date, time (where relevant, start and end times) and location of procurement;
- g. SOPs used, including notes describing any incidents that occurred during procurement;

- h. type, volume, manufacturer and the lot/batch/serial number of reagents, additives and tissue/cell transport solution(s) used;
- i. the name and address of the tissue establishment or procurement organisation;
- j. the name and destination of the cells and tissues.

Additionally, for procurement of tissues or cells from a deceased donor, this report must contain:

- a. a sufficiently detailed summary of the events surrounding death;
- b. the date and time of donor death and tissue procurement (and, where relevant, start and end times) to facilitate determination of the time interval from death to procurement;
- c. the conditions under which the donor body was kept prior to procurement (whether or not the donor body was cooled or refrigerated and, where appropriate, the time when cooling or refrigeration began and ceased);
- d. if possible, whether procurement took place before or after autopsy and whether or not an autopsy is planned;
- e. when applicable, a description of other tissues and cells from the same donor sent to different tissue establishments, including their identification;
- f. if possible, information regarding the reconstruction of the donor's body.

If procurement from a living donor involves a directed donation, the recipient's identification must be documented to avoid any confusion.

Chapter 7. Processing and storage

7.1. Introduction

Processing means all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human application. Storage occurs at various stages from procurement to clinical use and must be controlled and documented to ensure that the required properties of the tissues or cells are maintained during storage and that cross-contamination or loss of traceability is avoided.

The opportunity to process tissues and cells brings great advantages. The aims of processing include:

- a. facilitating and optimising clinical utilisation by dividing a donation into multiple ready-to-use grafts;
- b. preservation of the required properties of the biological material, making extended storage for future use possible;
- c. reducing the risk of disease transmission or adverse reactions by removing those elements that are not necessary for the success of the transplant and the inactivation of microbes or even sterilisation in circumstances where cell viability is not required.

Processing includes a range of activities such as, but not limited to, cutting, grinding, shaping, centrifugation, soaking in antibiotic or anti-microbial solutions, sterilisation, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing and cryopreservation.

Although it brings great benefits, processing can also introduce risks. The potential risks include microbial contamination from the environment or cross-contamination from other tissues or cells, mix-ups in identification or labelling errors or having a detrimental impact on those characteristics of the tissues or cells that render them clinically effective. For these reasons, all the necessary steps must be performed within a comprehensive quality management system, must be documented in standard operating procedures (SOPs) and must be thoroughly validated to demonstrate that the quality and efficacy of the final product has not been compromised and that contamination or cross-contamination have not been introduced during processing.

This chapter provides generic guidance on tissue and cell processing. Further, more specific, guidance is provided in Part B of this Guide.

7.2. Acceptance criteria (reception at the tissue establishment)

Each tissue establishment must have a documented policy and specifications against which each consignment of tissues and cells, including donor blood samples, are verified. These must include the technical requirements and other criteria considered by the tissue establishment to be essential for the maintenance of acceptable quality. When the procured tissues or cells arrive at the tissue establishment, there must be done a documented verification of the consignment must be completed which cover the transport, including the transport conditions, packaging, labelling and associated documentation and samples (including blood), to ensure that they meet the requirements and the specifications of the receiving establishment (and in EU countries requirements of Annex IV of Directive 2006/17/EC.)

Upon receipt of the documentation, the procurement report and shipping record (if the donation was transported by a third party) should be cross checked with the contents of the package.

The packaging and tissues and cells received and any accompanying samples should be examined to ensure that they have not been damaged in transit.

The following should be checked and recorded:

- a. no evidence of unauthorised opening or manipulation exists;
- b. no signs of damage that might result in the deterioration of tissues/cells or storage problems;
- c. transport and storage temperature;
- d. identification of the donor (donation number);
- e. description of the tissue or cells;
- f. procurement report including procurement date and time;
- g. purpose of tissue/cells (i.e. for transplant/research);
- h. status of the tissue or cells (e.g. quarantine);
- i. associated samples (including blood).

The tissue establishment must ensure that the tissue and cells received are quarantined and stored in a defined, separated and adequate location and under appropriate conditions until they, along with the associated documentation, have been inspected or otherwise verified as conforming to requirements. The acceptance or rejection of received tissues or cells must be documented.

The data that must be registered at the tissue establishment include:

- a. consent/authorisation, including the purpose(s) for which the tissues and cells may be used (i.e. therapy/transplant, education or research, or both therapeutic use and research/education) and any specific instructions for disposal if the tissues or cells are not used for the purpose for which consent was obtained;
- b. all required records relating to the procurement and donor history (see section 6.5);
- c. for allogeneic donors, a properly documented review of the complete donor evaluation against the appropriate selection criteria by an authorised and trained person;

- d. in the case of cell cultures intended for autologous use, documentation of the possibility of medicinal allergies (such as to antibiotics) of the recipient.

The review of relevant donor/procurement information and thus acceptance of the donation needs to be carried out by specified/authorised persons.

The tissue establishment must have documented procedures for the management and segregation of non-conforming tissues or cells, or those with incomplete infectious disease test results, to ensure that there is no risk of contamination of other tissues and cells being processed, preserved or stored.

The tissue establishment should sign an agreement that defines the responsibilities of each party in the transport of the tissues/cells to the tissue establishment if the material is not being transported by their own personnel. Such transportation should be direct, without intermediate stops when possible, to ensure the safety and maintenance of the temperature conditions of the tissues and cells.

Quality control checks of procurement and transportation methods should be regularly reviewed by tissue establishments to ensure that the integrity of tissues or cells and storage temperatures are maintained during procurement and transit.

7.2.1. Coding

Tissue establishments must ensure that human tissues and cells are correctly identified at all times. Upon receipt of the tissues and cells, the tissue establishment should assign a unique identification code to the material if this has not already been done at procurement. This code can then be extended to identify the different products and batches of tissues or cells obtained during processing and storage (for further information on traceability, see Chapter 11).

Tissues and cells should be labelled at all stages of processing and storage (see Chapter 3 for further guidance on labelling). The label must include at least the following information:

- a. unique identification;
- b. identification of the tissue establishment;
- c. type and characteristic of the product;
- d. batch number, if applicable;
- e. recipient name, if applicable.

The coded data must be entered in a register maintained for the purpose.

7.3. Processing

7.3.1. General

Tissues and cells should be appropriately processed and preserved for clinical use. Tissue establishments must include all processes that affect quality and safety in their SOPs and must ensure that these processes are carried out under controlled conditions. The critical processing procedures must be validated (as described in Chapter 2) and must not render the tissues or cells clinically ineffective or harmful to the recipient. This validation may be based on studies performed by the establishment itself, or on data from published studies or, for well-established processing procedures, by retrospective evaluation of the clinical results for tissues supplied by the establishment.

Tissue establishments must ensure that the equipment being used, the working environment, process design, and validation and control conditions are in compliance with established quality and safety requirements⁶. Every step of processing must be performed under defined conditions to guarantee the quality of tissues and cells and the safety of staff and patients (see Chapter 2).

Before implementing any significant change in processing, the modified process must be validated and documented. The processing procedures must undergo regular critical evaluation to ensure that

⁶ In the EU, these requirements are laid down in Directive 2006/17/EU and 2006/86/EC. Other useful standards may be found in the EQSTB guidance.

they continue to achieve the intended results. Any modifications to the processes used in the preparation of tissues and cells must also meet the criteria laid down in the corresponding change control procedure. These criteria must cover all preparation methods, including transformation processes and media preparation, and the necessary equipment, material and additional therapeutic products used and the controls performed.

If processing is performed by a third party, it is recommended that a written agreement be put in place between the tissue establishment and the sub-contracted party.

Tissues and cells should be processed and stored according to currently accepted practice, based on the best available scientific evidence, and in compliance with the Quality Management System (see Chapter 2). The methods should be validated and specified in SOPs.

The recommended time-limits between procurement, processing and storage are described in the tissue/cell-specific sections of this Guide (see Part B). When appropriate, these maximum times from procurement (or cardiac arrest) until processing and storage must be defined. Procurement, processing and storage times must be documented in the tissue/cells records.

The reagents used in preservation and processing should be of an appropriate grade for their intended use and be sterile, if applicable, and comply with existing national regulations. Possible contamination of preservation fluid should be avoided and monitored by repeated testing for bacteria and fungi. The use of antibiotics during procurement, processing and preservation should be avoided if possible or at least be justified by the institution. Whenever possible, reagents used for procurement, processing and preservation should be approved for human use and should be CE marked. Reagents not approved for human use may be used if reagents or procedures that include the reagent have been approved by national authorities or have been established in medical literature to be acceptable for the purpose specified. The origin, characteristic conditions for storage (physical, chemical, microbiological) and expiry dates of reagents should be monitored

and recorded. Reagents should be used in a manner consistent with the instructions provided by the manufacturer.

7.3.2. Processing methods

Processing methods must not render the tissues or cells clinically ineffective or harmful to the recipient and should be designed to ensure both the safety and biological functionality of a prepared tissue/cell graft. Methods of processing should be validated (see the general text on validation in Chapter 2 and section 7.2.3 below).

Pooling of donors during processing must be avoided: the only exception being when it is the only way of providing a clinically effective graft.

7.3.3. Processing validation

In the EU, Directive 2006/86/EC allows for validation studies to be based on any of the following:

- a. studies performed by the establishment itself;
- b. data from published studies;
- c. for well-established processing procedures, retrospective evaluation of the clinical results for tissues and cells supplied by the establishment.

Where validation is based on studies performed by the establishment itself, reports should include at least the following elements:

- a. a validation plan that specifies the critical parameters to be assessed and the acceptable result thresholds for these parameters;
- b. a documented methodology;
- c. all results obtained, described clearly and with relevant interpretation;
- d. a signed declaration of validation acceptance or rejection by the Quality Manager or the Responsible Person.

Validation studies should be performed by applying “worst case” scenarios. The equipment used for validation studies should be fully qualified, and measuring devices should be calibrated to traceable standards. The validation experiments should be repeated at least three times, though this will depend on the degree of variability in the data, to ensure reliably repeatable results. For an example of a validation study, see Appendix 7.

Where validation is based on data from published studies, the relevant publications should be filed as part of the validation record. In this case, the tissue establishment should demonstrate that they can effectively reproduce the published process with the same results in their facility (operational validation). Copies of the relevant SOPs and the results of the operational validation should be provided to demonstrate that the process is equivalent to that applied in the published study(ies).

Where specific steps have been modified or adapted, separate validation should confirm that these changes have not invalidated the method. There should be a signed declaration of validation acceptance or rejection by the Quality Manager or the Responsible Person.

Where validation is based on retrospective evaluation of the clinical results for tissues or cells supplied by the establishment (i.e. for well-established processing procedures), data should be collected and analysed that includes the number of tissue or cell grafts implanted following processing by the method under consideration and the period of time during which these implantations occurred. It should be demonstrated that, where a vigilance system was already in place at the time, clinical users were informed of the procedure for reporting adverse reactions. There should be a signed declaration of validation acceptance or rejection by the Quality Manager or the Responsible Person.

The procedures used to prevent or reduce contamination during processing may vary, depending on the type of tissue and how it is processed. However, they should all be fully validated. Decontamination methods, such as antibiotic soaking, should be validated to

demonstrate effectiveness against a range of contaminants similar to those routinely found on the tissues or cells in question. Such studies should be designed to ensure that residual decontaminants (e.g. antibiotics) do not affect the validity of the microbial tests carried out on the product.

If the process includes a sterilisation or viral-inactivation step, site-specific validation studies should be completed to demonstrate the log reduction achieved by the process.

As technology progresses and if new validation methods become available, tissue establishments should prepare, validate and follow procedures to prevent contamination with Transmissible spongiform encephalopathy (TSE)-associated prions during tissue processing.

Subsequent to process validation and during routine processing, tissue establishments should monitor tissue and cell quality to ensure a state of control is maintained throughout the processing part of the product life-cycle. This will provide assurances for the continued capability of the process and controls to produce finished tissues and cells that meet the desired quality and to identify changes that may improve product quality or performance. Relevant process trends (e.g. quality of incoming materials or components, in-process and finished product results, cases of non-conformance and defect reporting) should be collected and assessed in order to verify the validity of the original process validation or to identify required changes to the associated controls.

Documentation and tracking of patient outcomes constitutes a critical element of on-going process verification. For new or significantly changed processes, a project of close clinical outcome monitoring should be agreed with clinical users.

7.3.4. Avoiding contamination and cross-contamination

Facilities for aseptic and clean, non-sterile processing should provide separate work areas with defined physical and microbiological parameters. Wherever appropriate, a validated pathogen inactivation/

reduction or terminal sterilisation protocol should be included in the process.

Processing should not change the characteristics of the tissues/cells so as to make them unacceptable for clinical use.

The specification of the air quality of the processing facilities should be decided on the basis of the particular type of tissue or cell and the processing method that is being applied. A number of criteria should be taken into consideration, as shown in Table 7.1. Where the risk of tissue or cell contamination during processing is high, and the chances of any contaminants being transferred to the recipient are high, a more stringent air quality specification should be adopted.

Table 7.1. Criteria to be considered in order to determine the air quality specifications of the processing facilities according to EuroGTP guidance

Criterion	Explanation
Risk of tissue or cell contamination during processing	Processes that are mostly “closed” (e.g. bone marrow cryopreservation, where the only exposure of the cells to the environment is when a spike is inserted to add cryoprotectant) need a less stringent specification than those that involve hours of open processing (e.g. bone and tendon graft cleaning and shaping).
Use of anti-microbials during processing	Some tissues, even though not terminally sterilised, can be exposed to various anti-microbial agents without compromising the characteristics required for clinical efficacy. Processes that include, for example, detergent washing, alcohol rinses, hydrochloric acid (HCl) treatment, imply less risk of transferring an environmental contaminant than those where cell viability is required and no anti-microbial agents can be applied, or the only anti-microbial step possible is soaking in antibiotics.
Risk that contaminants will not be detected in the final tissue or cell product due to limitations of the sampling method.	Where the only possibilities for final microbiological sampling are swabbing or testing of unrepresentative samples, the risk that environmental contaminants will be undetected is higher compared to processes where 10% destructive testing of final products can be performed.

Criterion	Explanation
Risk of transfer of contaminants at transplantation	Tissues that are minimally processed, cellularised, or containing blood, blood vessels and lipids are more likely to support microbial contaminants than those that are blood- and cell-depleted. Tissues or cells that are applied to small areas on the external surfaces of the body, or to areas that are minimally vascularised, are less likely to transmit infections than those that are infused into the blood stream or implanted into internal organs.

Processing facilities should be dedicated to this activity and should be designed, qualified and monitored to ensure that air quality is appropriate for the process being carried out. An international standard, such as the Good Manufacturing Practice (GMP) guidelines and/or ISO 8573-1:2010, should be followed in full to achieve the appropriate air quality. For tissue establishments in the EU, there must be Grade A with a surrounding environment of at least Grade D (GMP classification). Many national requirements are more stringent, requiring B and C for certain processes. Processing and storage facilities should be cleaned according to a schedule and procedure that has been validated to achieve the required level of cleanliness and all cleaning procedures should be documented.

Whichever classification is applied, facilities should have:

- a. floors, walls and ceilings of a non-porous material with smooth surfaces that are easily disinfected;
- b. temperature control;
- c. for sterile processing, air filtered through high-efficiency particulate air (HEPA) filters with an appropriate pressure differential between zones that can be documented;
- d. a documented system for monitoring temperature, air supply conditions, particle numbers and bacterial colony forming units (environmental monitoring, see below);
- e. a documented system for cleaning and disinfecting rooms and equipment;

- f. a documented system for gowning and laundry;
- g. adequate space for personnel and storage of sterile garments;
- h. access limited to authorised personnel.

The frequency of particle (viable and non-viable) monitoring should be based on a series of robust data, which demonstrates the normal variability for these parameters in the facility during typical operations. The greater the variability, the more frequent the monitoring should be. Warning and action levels must be established, with defined steps to be taken when those levels are exceeded.

The entry of personnel and materials to the processing facilities, transit and exit of personnel and material through the processing area and the rules of use and clothing to be worn in them should be established in order to:

- a. minimise the risk of tissue/cell contamination;
- b. reduce the environmental bioburden;
- c. protect the staff from biohazards.

A written procedure designed to eliminate potential contamination and/or cross-contamination from personnel and materials to tissues and cells should be in place.

The entry of personnel, tissues/cells and materials should be done through airlocks to avoid the direct flow of non-treated air into clean-rooms. Personnel gowning procedures should be validated to ensure that gowning materials and protocols are adequate and that the resulting microbial monitoring of the clothes is satisfactory. The materials and tissue/cell packages should enter the facilities using a validated procedure where the cleanliness level, according to the microbial load, conforms to the destination clean-room.

Only the minimum number of personnel required for efficient processing should enter processing areas. The need for additional persons to be present in processing areas should be taken into account during risk assessment when the procedure is being designed.

In order to avoid cross-contamination, the tissues from one donor should not come into contact, at any time during processing or

during storage, with tissues from another donor. Furthermore, grafts that must be processed further (e.g. lyophilisation, sterilisation, etc.) should be treated as a single donation. Each tissue should have a batch number that is also recorded in the processing records.

Processing techniques must be critically assessed at regular intervals to ensure that they always provide the desired results.

Non-conforming products must be identified and separated from compliant products. The fate of non-compliant products will be decided by the Responsible Person in charge of the tissue establishment.

7.4. Quality control

Tests and procedures should be performed to measure, assay or monitor processing, preservation and storage methods, equipment and reagents to ensure compliance with established tolerance limits. The evaluation of the quality controls performed on the tissues/cells should be established and each should be described in written procedures. The written procedures should at least include the test method, the sample size and the accepted criteria. The minimum evaluation requirements for each type of tissue/cells are described in the tissue/cell-specific (Chapters 13-19). The results of all tests or procedures should become part of the permanent record.

If in-process controls are performed in the processing area, they should be carried out so that there is no risk to the processing protocol itself.

In many cases, it is not possible to exclude the presence of contaminated material during processing because tissue originates from naturally contaminated parts of the body and disinfection is not 100% effective. The microbiological safety of tissues and cells is based on donor selection and minimisation of initial contamination, control and monitoring of contamination during the entire transplantation process, and validated methods of decontamination or inactivation during processing of tissues and cells, or sterilisation of non-viable tissues.

Microbiological controls have to be performed on the starting or incoming tissue. Testing methods should be able to detect relevant aerobic and anaerobic bacteria, as well as fungi, and have to take into account possible specific contaminations of the tissue, for instance, with difficult micro-organisms such as *Neisseria sp.* or *Mycobacterium sp.* Preferably, a representative sample of the tissue itself should be tested using appropriate media, incubation conditions and temperatures. Other suitable samples may be taken from transport or washing solutions. In-process testing should be performed at relevant processing steps; for instance, after a stage of decontamination or inactivation, or after washing or a change in storage solution. For in-process control tests, large amounts of spent storage solutions or cell-culturing medium, or other suitable sample material, should be used. When processing is controlled and validated to a high degree, in-process testing can be performed as monitoring controls on a determined percentage of batches. Where a percentage of a finished tissue batch is sacrificed for microbiological testing, this sample should include some tissue from the final stages of packaging. Whenever possible, a tissue or cell sample should be tested. In addition (or, in exceptional cases such as an exclusive sample), spent storage or culturing medium or final washing solutions can be used for testing with sample filtration. Every effort should be made to take representative samples. It is widely recognised that swabbing is not an effective method of tissue sampling and that small tissue samples are frequently not representative. Depending on the type of sample, membrane filtration and/or direct inoculation, either with an evaluation of the result based on macroscopic observation of turbidity or growth detection by automated culturing systems, can be applied. For preparations with a short shelf-life, rapid microbiological methods should be considered for testing of the sample itself or the microbiological culturing media after short pre-incubation of the sample. Tests for the detection of mycoplasmas should be performed as late as possible during the preparation process. If risk factors are present, it is desirable to perform additional tests for the detection of specific infectious agents. Sampling and testing methods

have to be validated to show the representativeness of the sample and the suitability of the selected methods.

Microbiological tests should focus on aerobic and anaerobic bacteria, as well as fungi. If risk factors are present, it is desirable to perform additional tests for the detection of mycoplasma.

Various procedures exist for securing microbiological control, such as decontamination by antibiotics, sterilisation, or any other physico-chemical methods. These procedures must be specifically adapted to the type of tissue or cells and should be validated in detail.

Most of the usual sterilisation procedures, such as gamma-irradiation, heat sterilisation or sterile filtration, are not applicable for tissue and cell preparations. If physico-chemical methods are intended to be applied, these procedures have to be adapted to the type of tissue or cells and should be validated. The effectiveness of a decontamination or inactivation procedure should be shown for relevant micro-organisms in the tissue or cell preparation itself and not only in an aqueous solution. Some micro-organisms may survive the antibiotic treatment, but are not detected by microbiological testing due to sampling error, and can recover when conditions change.

7.5. Packaging and labelling

Packaging and labelling are described in detail in Chapter 3.

7.6. Storage

Tissues and cells should be processed and stored according to currently accepted best practice, based on the best available scientific evidence and according to GMP and Good Laboratory Practice (GLP), as appropriate for tissues and cells.

Storage areas must be kept clean, with documented evidence of cleaning.

Currently used methods of tissue and cell storage include:

- a. storage in organ culture media at 31 °C (e.g. corneas);

- b. hypothermic storage (refrigeration) above 0 °C, but below + 10 °C;
- c. freezing with or without the use of cryoprotectants;
- d. storage at ambient temperature (for freeze-dried products).

7.6.1. Expiry date

In order to ensure the maximum safety and quality of tissues and cells, it is mandatory for EU member states to have a maximum storage time with an expiry date specified for each type of storage condition. The selected period should reflect, among other factors, possible deterioration of the required tissue and cell properties. When relevant for the type of tissue or cells, the time of procurement should also be indicated.

7.6.2. Risk assessment

A documented risk assessment, approved by the Responsible Person, must be undertaken to determine the fate of all stored tissues and cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step that enhances safety or quality.

7.6.3. Storage temperature

Refrigeration devices containing tissues/cells should be suitable for the use intended, and procedures for monitoring such devices should be validated so that tissues/cells are maintained at the required storage temperature. Regular monitoring and recording of temperature, together with suitable alarm systems, should be employed on all storage refrigerators, freezers and liquid nitrogen tanks (see Chapter 2).

7.6.4. Cross-contamination during storage

Every effort should be made to avoid cross-contamination of material stored in liquid nitrogen vessels. Frozen tissues must be double wrapped during storage. This is crucially important for storage with liquid nitrogen owing to the accumulation of microbial contaminants

in liquid nitrogen storage vessels. The seals and the material employed must be validated for their use at the designated storage temperature and the conditions of use to demonstrate that the packaging and labelling can retain their integrity under such conditions.

7.6.5. Quarantine

All human tissues/cells that are stored prior to determination of their suitability must be kept under quarantine. Quarantined tissues should be physically separated and visibly different (by labelling and/or packaging whenever possible, or by any other means, e.g., computerised systems) from released tissues.

An SOP must describe how to categorise quarantined and released product.

7.7. Release

Release is the act of certifying compliance of a specific tissue or batch of tissues with the requirements and specifications. Prior to any tissue being released, all relevant records including donor records, processing and storage records, and post-processing quality control test results must have been reviewed, approved and documented as acceptable by the Responsible Person according to the relevant local SOPs. There must be a SOP which details the circumstances, responsibilities and procedures for the release of tissues and cells.

At the time of release, donor records and tissue or cell processing records should be reviewed to ensure that the material is suitable for transplantation and implantation.

This will include:

- a. approval of donor eligibility by the responsible or designated person;
- b. review and approval of the processing and storage record;
- c. final inspection of both the label and container to ensure accuracy and integrity;

- d. results of screening tests on incoming material and in-process testing;
- e. specifications for final product release based on testing results used to determine final release (e.g. microbiology test results; if necessary and justified, release of the final product can be performed on a “negative-to-date” basis).

The items indicated in the processing and storage record should contain at least:

- a. the procurement file and/or the release statement of the person responsible for procurement;
- b. type of tissues and cells processed and/or stored;
- c. quantitative and qualitative description of tissues and cells processed, preserved and/or stored;
- d. date and time of each stage of processing and storage, the identification of persons responsible for each step and the identifying media and related products used (batch number and expiry date);
- e. status of tissues and cells at all stages of processing and storage (i.e. quarantine, released for therapeutic use, *in vitro* research, etc.);
- f. use of antibiotics, antibiotic composition and incubation period, if applicable;
- g. type and amount of media used;
- h. procedures and records concerning the processing of tissues and cells, if applicable;
- i. processing data (preparation, culture technique, incubation, treatment chemicals);
- j. data on techniques of decontamination, sterilisation or viral inactivation;
- k. results of specific quality testing, depending on tissue and cell type (e.g. HLA, histology, radiology results, tissue or cell viability, number of CD34 cells, etc.);

- l. procedures and records concerning the preservation of tissues and cell (e.g. cryopreservation, trace of the cooling curve, glycerolisation, lyophilisation) if applicable;
- m. date and time of storage;
- n. method of storage;
- o. storage temperature;
- p. expiry date;
- q. identification of tissues and cells, i.e. donor identification code plus product code.

Access to registers and data must be restricted to authorised persons. These records must be kept for a minimum of 30 years after clinical use or discard of the tissues and cells.

The person responsible for tissue or cell release should sign a statement, which specifies the fulfilment of all ethical, legal requirements and quality release criteria, thereby releasing the tissue/cells for storage in an inventory of tissues and cells that are available for transplantation, human application or research/educational use.

7.7.1. Exceptional release

In certain circumstances, tissues or cells may be distributed for transplantations that are not fully compliant with all safety and quality requirements. This must only occur in emergency situations or under special clinical circumstances. The decision must be based on a documented risk assessment and must be in conformity with national regulations. Exceptional release will occur only with the authorisation of the Responsible Person and does not preclude follow-up testing, donor screening and other quality assurance measures described in the SOPs.

7.7.2. Disposal of human tissues/cells

There must be a documented policy for discarding of tissues/cells that are unsuitable for clinical use. Records should include details of date and methods of disposal and reasons for discarding the material. The

material should be appropriately handled and disposed of in a manner compliant with local control of infection guidelines. Human tissue, cells and other hazardous waste items should be disposed of in such a manner as to minimise the hazards to the tissue establishment's personnel or the environment, and should be in conformity with applicable European, national and local regulations.

Disposal of human tissues should be carried out in a manner that shows respect for fundamental rights and for the human body.

Chapter 8. Distribution and import/export

8.1. Introduction

This chapter describes the requirements for distribution of tissues and cells and defines recommended controls for their import and export. The term “distribution” should be understood to mean transportation and delivery of tissues or cells intended for human applications. The entire distribution chain must be appropriately validated, including the equipment used, to ensure the maintenance of critical transport conditions. The terms “import and export” should be understood to include all processes and procedures that facilitate the entry or exit of tissues and cells to/from a single country. Import/export controls must ensure that the quality and safety of the tissues or cells are in compliance with this Guide.

Tissues and cells can be distributed by a tissue establishment:

- a. to a clinical facility where they will be applied, i.e. allocation;
- b. to another tissue establishment within the same country for local distribution;
- c. to a tissue establishment outside the country, i.e. export;
- d. from another country to a clinical facility or tissue establishment in the country, i.e. import.

For the movement of tissues or cells between countries that are within the EU, the legislation does not require import/export controls to be in place. However, several EU member states opt to apply more stringent requirements than those in the Directives and to consider

this movement in the same way as import/export involving countries outside the EU (referred to as “third countries”).

8.2. Transport

The choice of mode of transport should take into account any general regulations governing transportation of biological substances.

Critical transport conditions, such as temperature and time-limit, must be defined to ensure maintenance of the required tissue or cell properties. If the tissues or cells require specific environmental conditions, the capacity of the transport container to maintain the required environmental conditions, and the length of time that these conditions can be maintained by the transport container, should be determined by validation and documented. If liquid nitrogen is used to maintain very low temperatures, an automatic filling mechanism or a standardised manual procedure must be in place to ensure and document that an adequate level of liquid nitrogen is maintained during transport.

Containers/packages should be secured and appropriately labelled (see Chapter 3).

8.3. Allocation

The allocation of tissues and cells should be guided by clinical criteria and ethical norms. The allocation rules should be equitable, externally justified and transparent.

The procedures for distribution of tissues and cells by authorised tissue establishments must comply with the criteria laid out in the sections below.

It is mandatory for EU member states to have procedures in place for the management of requests for tissues and cells. The rules for allocation of tissues and cells to certain patients or healthcare institutions must be documented and made available upon request.

8.3.1. Visual examination

Packaged tissues or cells should be examined visually for appropriate labels, expiry date, container integrity and security and any evidence of contamination prior to being dispatched.

8.3.2. Medical competence

Distribution for clinical application should be restricted to hospitals, physicians, dentists or other qualified medical professionals and must comply with any national allocation regulations.

8.3.3. Documentation

The place, date and time of pick-up and delivery (including time zone where relevant) and identity of the person receiving the tissues/cells should all be recorded and maintained in the tissue establishment from which the tissues or cells are used.

In EU member states, if the transport is sub-contracted, a written agreement must be signed between the transporter and the tissue establishment to ensure that the required conditions will be maintained. This document must describe what should happen if the tissue or cells are damaged or lost during transportation.

Any transportation must be accompanied by a transport record that is attached to the package.

8.3.4. Recall and return procedures

An effective recall procedure must be in place in every tissue establishment, including a description of the responsibilities and actions to be taken in the case of a recall. This must include procedures for the notification of the relevant Health Authority(ies).

A documented system must be in place for the handling of returned products, including criteria for their acceptance into the inventory, if applicable.

8.4. Import and export

8.4.1. Underlying principles

The import and export of tissues should be guided by clinical need rather than by any financial considerations (i.e. profit-maximising practices). According to international conventions, neither the human body nor its parts may be sold for financial gain. Suppliers may apply a charge to cover their reasonable expenses in ensuring the quality and safety of tissues or cells. Public confidence and willingness to donate can be damaged by any kind of nefarious trading in donated material. For further guidance on the ethical aspects of tissue and cell supply and transplantation and the ethical aspects of consent, see Chapters 1 and 4.

Import and export between countries should be done only through legally authorised tissue establishments who have the competence to guarantee a sufficient level of quality and safety evaluation and to meet traceability requirements. They should be specifically authorised for:

- a. import and/or export of human tissues and/or cells intended for human applications;
- b. import and/or export of tissues or cells intended for the manufacture of medicinal products derived from human tissues and/or cells;
- c. import of procured human material intended for processing, storage or banking in a tissue or cell establishment in their country.

As general rules, if clinicians or healthcare facilities identify a need to import tissues or cells, they should organise this through a written agreement with a licensed tissue establishment in their own country. Third party agreements must specify the terms of the relationship and the relevant responsibilities, as well as the protocols to be followed to meet the required performance specifications.

8.4.2. Import

Tissue establishments that wish to import tissues or cells should be able to demonstrate that the need cannot be adequately met by comparable material available from sources within their country or that there is another justifiable reason for the import. They should also be able to justify the import in terms of accessibility, quality, speed of supply, risk of infection, quality of service, cost-effectiveness or scientific or research needs. They should ensure that any material intended for import is consistently sourced under the legal and ethical requirements of both their country and the exporting country. If the importing tissue establishment cannot satisfy itself that ethical standards are in place in the country of origin, the tissues or cells should not be imported.

The safety and quality characteristics of the tissues or cells to be imported should be equivalent to those in place within the importing country. Imports should only be accepted from countries that have established procedures to authenticate the legitimacy of exporters and the provenance of the donated material they supply. Exporters should be asked to provide evidence of compliance with the regulations that they are required to observe before any orders are placed with them.

Where an EU country imports from a non-EU country and the ultimate destination is a different EU member state, then the tissues or cells should fulfil the quality and safety requirements of both EU countries (i.e. with one EU country acting as the point of entry into the EU and the other as the final receiver of the tissue or cells).

Companies that act as distributors, often also carrying out import and export activities, have responsibilities equivalent to those of tissue establishments for ensuring the equivalent safety and quality requirements, for maintaining traceability and for having adequate vigilance systems in place. The fulfilment of these requirements implies having staff and expertise (including medical expertise) to evaluate donor selection criteria and reports of adverse incidents and reactions.

8.4.2.1. Routine importation

The importing tissue establishment should assess and document that the exporting tissue establishment complies with the quality and safety requirements laid down in this Guide. This includes respect for the fundamental ethical principles of consent, non-remunerated donation, anonymity and respect for public health. The evaluation should include at least the following:

- a. the general quality and safety systems at the exporting establishment, including organisational chart, staff training, facilities, processing methods, validation studies, traceability and biovigilance systems, licenses and accreditation (including lab certification/authorisation) and donor blood testing;
- b. a review of the safety and quality of individual dispatches of tissues or cells, i.e. confirmation of donor consent, confirmation of donor sample testing and their results, donor eligibility records, description of the tissue or cells, transportation arrangements, etc.

Potential language barriers should be considered and a common language agreed upon for all donor and tissue/cell-related documentation.

A Service Level Agreement or contract between the exporting and importing tissue establishments that clearly defines roles and responsibilities is a basic requirement. Agreed procedures for the transport of the tissues and cells from the country of origin to the tissue establishment in the importing country should form part of the contract and should specify the methods to be followed to ensure the maintenance of the required environmental conditions, of the package integrity and of compliance with agreed timeframes. Such transportation should be direct, without intermediate stops when possible, using an approved courier. The courier or transportation service must maintain records of pick-up and delivery, as well as the container's contents, so that complete traceability is ensured.

The agreement should specify how tissues and cells will be identified. Unique identifying codes should allow traceability and a formal and unambiguous identification of all tissues and cells.

Agreements between importing tissue establishments and suppliers in other countries should include provisions for the performance of audits at the exporting facility and should require that any changes to authorisation status be immediately communicated to the importing tissue establishment.

8.4.2.2. **“One-off” importation**

There may be cases where exceptional or “one-off” importation is necessary for a single patient. In these cases, the importing tissue establishment should ensure that there exists a documented evaluation of the safety and quality of the tissues or cells being imported. The importing tissue establishment should keep the documentation obtained from the exporting tissue establishment for the time period specified in national regulations (e.g. 30 years in EU member states).

8.4.3. **Customs clearance**

For clearance of Customs, all tissue and cells supplied from abroad require a clear description of the content of the consignment, its destination and intended use. It is important that frozen tissue and cells, which are usually packed in dry ice or stored in liquid nitrogen or in a dry shipper, must not be delayed at border crossings. Therefore, it may be expedient for the importer to inform Customs of a prospective consignment and any enquiries by Customs should be answered promptly. The agreement with the exporter should define responsibilities for meeting the cost of transport, refrigeration and/or storage at a Customs facility for any items that may be detained pending Customs enquiries.

8.4.4. **Acceptance at the establishment**

Each importing establishment should have a documented procedure and specifications against which each consignment of tissues and cells, together with its associated documentation, is verified for compliance

with the written agreement in place with the exporter. Any non-compliances should be reported to the exporter. Consignments should be examined for any evidence of tampering or damage during transport. Tissues and cells should be stored in quarantine in an appropriate secure location under defined conditions until such time as they, along with their associated documentation, have been verified as conforming to requirements. The acceptance or rejection of received tissues/cells should be performed and documented in line with the guidance in Chapter 7.

8.4.5. Export

Tissues or cells should not be exported if there is an unmet clinical need for the material in the country of origin. Exported material should be procured, used, handled, stored, transported and disposed of in accordance with the consent that has been given by the donor. Tissues and cells should only be exported to countries that have proper controls on the use of donated material. They should only be exported for the purposes for which they can lawfully be used in the country of destination and exporters should satisfy themselves beforehand that the human tissue and/or cells will be used for a *bona fide* clinical application or research.

Tissue establishments should ensure that the quality and characteristics of the tissues and cells to be exported are equivalent to those of the tissues/cells implanted in their own country and required in the country of destination.

8.5. International co-operation

For some transplant patients, including sensitised patients, it may be difficult to find a match within their own country. In these cases co-operation between countries is necessary and in some cases it may be necessary to identify suitable donors worldwide. International co-operation and exchange of tissues and cells is necessary to increase the chances of providing tissues and cells for patients in life-threatening

situations. For these reasons, it is important to ensure that there is good co-operation between organisations that allocate internationally. Registries should be in place for all imported and exported tissues and cells to ensure transparency in the process.

Chapter 9. End users

9.1. Introduction

Once tissues and cells arrive at a hospital or other clinical unit for application to a patient, the responsibility for maintaining the quality assurance chain is transferred to that organisation. This includes the need to maintain traceability, to store and handle tissues and cells correctly, to inform patients of the risks involved in the use of the material, and to detect, report and investigate adverse outcomes. The EU-funded project SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) considered these issues in a working group and is developing a guidance document for clinical users. Much of the text in this chapter has been adapted from drafts of that guidance document.

9.2. Appropriate use

The risk associated with the human application of tissues and cells is generally regarded as very low, particularly where the donated tissues and cells have been highly processed, blood and other cells have been removed or if it has even been terminally sterilised. However, the application of human substances always carries some risk. Adverse outcomes are rare, but viruses and bacteria have been transmitted by a wide range of tissue and cell types and transplants or grafts have failed for various reasons, often associated with the quality or safety of the tissues or cells provided for clinical use [1].

Physicians should always give careful consideration to the risks and benefits of treating a patient with substances of human origin and

consider the availability of alternatives before making a decision. Once the physician has decided that the application of substances of human origin is the most appropriate treatment option, all health professionals involved in treating the patient should be conscious of the exceptional nature of the health product being applied, i.e. as material donated altruistically for the benefit of patients in need, often in short supply and carrying some small and sometimes unpredictable risk for the recipient. Only the required amount should be ordered and wastage should be avoided.

9.3. Choosing a tissue or cell supplier

Before requesting tissues or cells from a particular tissue establishment, hospitals and clinics should establish that the supplying tissue establishment is working to appropriate standards of safety and quality. If the tissue establishment is within the EU, it should be able to provide an authorisation certificate from the appropriate Health Authority. This certificate should specify the types of tissues or cells and the general activities for which the centre is authorised. The centre should be regularly inspected by the Health Authority to confirm compliance with the legal requirements. In non-EU countries, tissue establishments should be asked to provide evidence of the quality and safety standards they follow and any independent quality accreditation or certification they may hold. Choosing appropriately authorised or certified tissue establishments helps to ensure that the donors of the tissues or cells have been appropriately tested and selected and that all the quality system requirements are in place for the processing, storage and distribution of the material. If a clinical entity has a large volume requirement for a particular type of tissue or cell, it may consider it appropriate to conduct a quality audit of the supplier.

It is good practice for tissue establishments to sign basic end-use agreements with hospitals and clinics before beginning to supply them with tissues or cells. The agreement should define responsibilities regarding traceability, appropriate use, disposal, adverse reaction and event reporting and investigation.

9.4. Receiving tissues or cells from other countries

When a hospital or clinic wishes to order tissues or cells from another country, it is good practice to ask a reliable local tissue establishment to locate and communicate with the tissue establishment abroad (within the EU it is a legal requirement that any imports from third countries are managed by authorised tissue establishments). The tissue establishments can liaise to ensure that equivalent standards of safety and quality are applied. For EU member states, any tissue establishment that is authorised in its own member state may provide tissues or cells directly to clinical units in other member states, although some member states have implemented more stringent rules (as allowed by these Directives) and do require formal import procedures to be followed, even when the material comes from another EU country. It is important to be aware of the national legislation in place for the importation of tissues or cells from another country.

9.5. Exceptional release

In exceptional circumstances, a clinical entity may agree with a tissue establishment that tissues or cells that do not meet the normal release criteria can be released and used in a specific patient on the basis of a risk/benefit analysis, taking into consideration the alternative options for the patient and the consequences of not providing the tissues or cells concerned. The risk assessment should be documented before acceptance of the exceptionally released material. The recipient patient's physician should work with the Medical Director of the tissue establishment in conducting the risk assessment and the risk/benefit analysis for their patient and the discussions and conclusions should be documented. The treating physician should sign his/her agreement with the exceptional departure from normal procedures where there is any risk implied for the recipient patient. The patient should also participate in, or at least be informed of, the decision process and the conclusions before giving consent.

9.6. Recipient consent

Although donors of tissues and cells are carefully selected and tested, an element of risk remains due to the exceptional nature of the material. In the context of these risks, however small, it is highly recommended that the patients who will receive a human tissue or cell graft be made aware of the facts and give their consent to the risks involved. The Notify Library database led by the World Health Organization and hosted by the Italian National Transplant Centre (www.notifylibrary.org) is a useful tool for accessing risk information for a particular type of tissue or cell. The information given to a prospective recipient should include at least the following:

- a. a description of any adverse outcomes that have been reported for the given type of tissue or cell transplant;
- b. an estimate of the frequency of the adverse outcomes described;
- c. information regarding alternative therapies.

Once the appropriate information has been provided, the patient should then sign a consent form that should include at least the following elements:

- a. confirmation that the risks associated with the transplant have been explained and the information has been understood; and
- b. acceptance of the risks in light of the potential benefits.

This consent form should be separate from the more generic consent to receive treatment or surgery.

9.7. Centralised v. decentralised management of tissues and cells

The most prevalent model for the management of tissues and cells in the hospital is that the material is delivered directly to the relevant department or operating theatre, i.e. a decentralised model. The great advantage of the decentralised model is that a specialist clinician is in control. However, maintaining traceability of tissues and cells is very

difficult in such a model and compliance with the requirements for storage and handling is also problematic. Centralised models greatly improve the ability to trace tissues and cells and can significantly improve inventory control and compliance with safety and quality standards. For these reasons, a centralised model for the receipt, short-term storage and traceability of tissues and cells for human applications is strongly recommended.

Regardless of the model applied for the management of human tissues and cells, all activities associated with receipt, storage, handling and follow-up should be incorporated into the existing Quality Management System of the hospital or clinic. The roles and tasks of officially designated persons should be clearly specified in standard operating procedures (SOPs).

9.8. Package insert/instructions and temporary storage before use

Once tissues or cells have been distributed by a tissue establishment for clinical use, appropriate storage and handling becomes the responsibility of the clinical unit. Instructions should be available in the package insert that accompanies the tissues or cells that describe the appropriate storage conditions and the proper handling procedures to be followed before clinical application. These instructions should be precisely followed. Where a specific storage temperature is necessary from receipt to clinical application, the storage device (fridge, incubator, etc.) should be regularly maintained and calibrated and should be secure, i.e. with restricted access. It should be dedicated to the storage of healthcare products. It should be ensured that during short-term storage, and before clinical application, the material is stored together with its associated documentation or the documentation should be clearly linked to the tissues or cells and easily accessible. The accompanying document should specify the presence of particular additives or reagents that may affect the recipient (e.g. antibiotics, allergens). This information should be taken into account. If there is no package insert accompanying the tissues or cells, they should not be used.

9.9. Inspection of the container, documentation and the tissues or cells

Before opening the container, or attaching an infusion device to a bag of cells, the label should be checked and compared to the description on the package insert, to confirm that the material is indeed what was ordered for the patient and what is shown on the label. The packaging and the tissue should be inspected for any signs of damage during transport. Where temperature during transport is critical, there should be confirmation that the required temperature was maintained during transport.

In the case of tissues, the graft should be examined once the container has been opened to confirm that the anatomical characteristics are as shown on the label (e.g. left v. right femur, aortic v. pulmonary heart valve).

Tissues to be used in surgery should be specified and their use documented in the surgical checklist.

9.10. Surplus or unused tissues or cells

It is not generally permitted to use tissue remaining from a clinical procedure in another patient; it should be discarded as clinical or anatomical waste, in accordance with national rules, or returned to the supplying tissue establishment for appropriate disposal. If, in particular circumstances, it is considered justifiable to use the remaining tissue in another patient, it should first be discussed with the Responsible Person at the supplying tissue establishment. Similarly, a single unit of tissues or cells should not be used in two separate patients and this will normally be specified in the package insert.

Tissues or cells provided to one clinical entity should not generally be sent to another entity for clinical use. Within the EU, this would be defined as “distribution” and it would require specific authorisation. Tissues or cells that are received and not subsequently used in one department of a hospital may be sent to a different department or operating theatre in the same hospital but, as a minimum, the supplying

tissue establishment should be informed of this. There may be nationally established rules for this scenario.

The documentation that accompanies the tissue/cells should specify whether they can be returned to the tissue establishment if not opened or used, e.g. if the patient is not well enough for surgery or surgery is cancelled for another reason. Most tissue establishments will not accept tissues that are returned under these circumstances. Those tissue establishments that do accept returned, unused and unopened tissues will have to confirm that the conditions for maintenance of the required tissue properties were continuously provided and documented and that the packaging was not tampered with.

9.11. Traceability

Coding and traceability are addressed fully in Chapter 11. In the EU, the unit or entity that uses tissues or cells for a human application is required to maintain traceability records from the point of receipt of the tissue until 30 years after clinical use or other final disposal. These records (mandatory in the EU) must include:

- a. identification of the supplying tissue establishment;
- b. identification of the clinician/end user/facility;
- c. type of tissues and cells;
- d. product identification;
- e. identification of the recipient;
- f. date of application.

Details of the tissue or cells applied should be in the recipient's hospital record and in the operating theatre log-book where they have been applied during surgery. Alone, this is not adequate to permit rapid re-tracing of patients who might be at risk from a particular donation or processing batch. Clinical entities should also have an electronic or paper "log" where all received, transplanted and discarded tissues or cells are recorded. This will allow quick and easy action in the case of a "recall" by the tissue establishment or the Health Authority or for

internal follow-up/review. Careful consideration should be given to where and how this log will be archived for the required period and the person(s) responsible for its safe storage should be clearly identified and documented.

Some supplier tissue establishments require clinical entities to return a traceability form or card providing details of the recipient for each graft supplied. A copy of the card should be retained in the recipient medical record. The details should be sufficient to unambiguously identify the recipient, i.e. at least three points of identification including a unique identifier. It should be noted that returning the card does not release the clinical entity from its responsibility to maintain the information to ensure traceability. Where cards or forms are returned to the supplier tissue establishment, the manner of documentation should adhere to national data protection regulations and should ensure that personal information is not visible or that the recipient's privacy is not compromised in any way.

9.12. Adverse events and reactions

Vigilance and Surveillance (V&S) are addressed in full in Chapter 12. Effective V&S relies heavily on all health professionals involved from procurement to transplantation, but particularly medical staff (including surgeons) involved in tissue and cell procurement activities that might be aware or informed of additional safety information on donors during their follow-up.

Serious adverse reactions (SARs) can be detected during and after donation in living donors or after transplantation in tissue or cell recipients. As adverse transplant outcomes might result from many diverse factors associated with the clinical procedure or the patient's underlying condition, clinicians might not consider the tissues or cells transplanted as a possible reason for the outcome. Tissue establishments that supply tissues and cells should encourage procurement organisations and clinical users of tissues and cells to always consider whether adverse outcomes might have been associated with any of the

stages from donation to clinical application so that similar occurrences might be prevented in the future.

For most types of well-established tissue and cell transplantation, detailed clinical outcome reporting by the clinical user to the tissue establishment is required only in those exceptional circumstances where there is an untoward serious adverse reaction. Routine clinical follow-up and reporting of tissue and cell recipient clinical progress is required for all highly-matched life-saving transplants, such as haematopoietic stem cell infusions or when novel tissue or cell processes have been applied or new types of tissues or cells are being transplanted. This routine clinical follow-up is not generally considered as part of vigilance.

Tissue establishments that supply tissues and cells should provide clinical user organisations with clear instructions on how to report SARs, preferably using standardised documentation. In general, suspected SARs should be reported by the clinical users to the tissue establishment that supplied the tissues or cells immediately, before it is confirmed or investigated in order to enable the tissue establishment to take appropriate precautionary actions to prevent harm to other patients and to involve the tissue establishment in the investigation process. As described further in Chapter 12, the clinician treating the recipient plays a critical role in the investigation of suspected SARs, together with the supplying tissue establishment.

9.13. Management of recalls and reviews

There are various reasons why a tissue establishment may recall tissues or cells that were distributed to a clinical entity. A recall may be related to the receipt of new information regarding the donor's medical or behavioural history that implies a risk of disease transmission risk or to the discovery of an error in processing or a fault or contaminant in a reagent or solution used in processing. It may be instigated by the tissue establishment or required by the National Authority.

When a tissue establishment issues a recall, it will be necessary to trace very quickly all the recipients of the particular batch (or donation) of tissues or cells implicated. The existence of a centralised log-book or electronic database of tissues/cells received with dates of use or disposal and identification of recipients will greatly facilitate conducting a recall. In many of the most significant cases of disease transmission arising from tissue/cell transplantation, it was not possible to trace the fate of some of the tissue grafts supplied for clinical use. This scenario could leave some patients at risk and without appropriate follow-up and treatment. In these situations, centralised management of tissues and cells in the clinical entity will facilitate effective action.

A review may be required as part of an investigation of the safety of particular tissues or cells that have been applied to patients in the past. It may require recalling patients for additional testing or other investigations. In this case, a central log-book or database of the tissues or cells supplied will also greatly facilitate the process.

9.14. References

1. Notify. Exploring Vigilance Notification for Organs, Tissues and Cells. Organs Tissues & Cells, 2011, November, 14, 3: Suppl.

Chapter 10. Computerised systems

10.1. Introduction

Computerised systems are playing an ever-increasing role in the management of business operations, including those related to healthcare. Reliance on such technology requires that these computerised systems be adequately validated. It is beyond the scope of this chapter to detail the full requirements for validation of computerised systems, but the primary reference documentation that is available is highlighted and the key requirements that tissue establishments should comply with are summarised.

10.2. Industry guidance for computerised system validation

The most common industry guide utilised for validation of computerised systems is that from the International Society for Pharmaceutical Engineering (ISPE) [1]. More specific guidance related to blood and tissues is available from the British Committee for Standards in Haematology [2].

10.3. Regulations governing computerised system validation

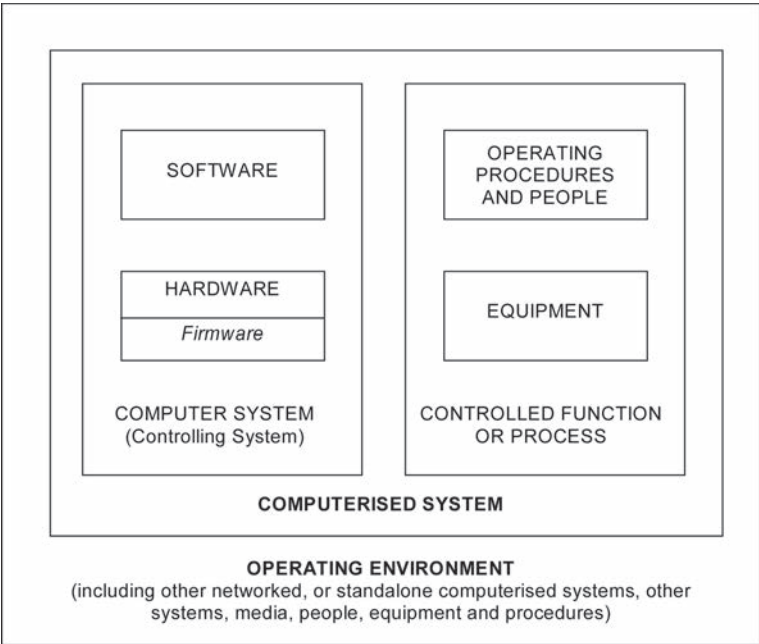
The regulation of computerised systems is well established in the pharmaceutical industry, with European Good Manufacturing Practices (GMP) [3] acting as the regulatory reference in Europe. The PIC/S [4] is also used by inspectors in the EU. As the pharmaceutical industry operates on a global scale, many European companies maintain compliance with the US Food and Drug Administration (FDA) [5].

10.4. Introduction to computerised systems

A computerised system is a set of software and hardware components that, together, fulfil certain functionalities. The computer application should be validated for its intended use and the IT infrastructure should be qualified [3].

PIC/S has expanded on this definition of a computerised system in their guidance to reference the fact that computerised systems can control functions and/or processes, and that such systems have to interact with their environment [4]. This can be represented diagrammatically as shown in Figure 10.1.

Figure 10.1. The relationships between the various components of a computerised system in its operating environment (from “PIC/S Good Practices for Computerised Systems in regulated GxP environments (PI 011-3, currently under revision)” [4])



Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process either [3].

The PIC/S document also lists the critical items that an inspector should consider during inspection and is a valuable tool for tissue establishments since it details the minimum requirements that should be in place [4].

10.5. Validation of computerised systems

Tissue establishments utilise a wide range of computer systems. As a minimum, there should be a catalogue of the hardware and software utilised on site. This list can include simple stand-alone computer systems that utilise a software package to track and trend data to fully integrated systems that control a range of processing steps and present data that allows release of tissues and cells for clinical applications. Computerised systems may also play a role in controlling the facility or ensuring environmental conditions (e.g. a Building Management System). The level of validation required for such systems depends on the criticality of the systems to the quality and safety of the tissues and cells. Thus, a criticality rating should be applied to all computerised systems in place. The level of validation of these critical systems is dependent on the type/category of software used. GMP and Good Automated Manufacturing Practice (GAMP5) provide examples of software categories and typical approaches to follow for each category (Table 10.1).

The approach of tissue establishments to computerised systems validation should be embedded within their Validation Policy or Validation Master Policy. This policy should include, as per PIC/S guidance:

- a. the identity of the computerised systems and interfaces that are subject to validation;

Table 10.1. GAMP categorisation of software and the examples of typical approaches to validation of such systems (modified from the International Society for Pharmaceutical Engineering (ISPE) [1])

Category	Description	Typical examples	Typical approach
Infrastructure software	- Layered software (i.e. upon which applications are built). - Software used to manage the operating environment.	- Operating systems - Database engines - Middleware - Programming languages - Statistical packages - Spreadsheets - Network monitoring tools - Scheduling tools - Version control tools	- Record version number and verify correct installation by following approved installation procedures - See the <i>GAMP Good Practice Guide: IT infrastructure control and compliance</i>
Non-configured	Run-time parameters may be entered and stored, but the software cannot be configured to suit the business process.	- Firmware-based application - COTS software - Instruments (see the <i>GAMP Good Practice Guide: Validation of laboratory computerised systems</i> for further guidance)	- Abbreviated life-cycle approach - URS - Risk-based approach to supplier assessment - Record version number and verify correct installation - Risk-based tests against requirements as dictated by use (for simple systems, regular calibration may substitute for testing) - Procedures in place for maintaining compliance and fitness for intended use

Category	Description	Typical examples	Typical approach
Configured	• Software, often very complex, that can be configured by the user to meet the specific needs of the user's business process. Software code is not altered.	• LIMS • Data acquisition systems • Scada • ERP • MRP II • Clinical trial monitoring • DCS • ADR reporting • CDS • EDMS • Building Management Systems • CRM • Spreadsheets • Simple human-machine interfaces Note: specific examples of the above system types may contain substantially customised elements.	• Life-cycle approach • Risk-based approach to supplier assessment • Demonstrate supplier has adequate QMS • Some life-cycle documentation retained only by supplier (e.g. design specifications) • Record version number and verify correct installation • Risk-based testing to demonstrate application works as designed in a test environment • Risk-based testing to demonstrate application works as designed within the business process • Procedures in place for maintaining compliance and fitness for intended use • Procedures in place for managing data

Category	Description	Typical examples	Typical approach
Custom	• Software custom-designed to suit business process.	• Varies, but may include: • Internally- and externally-developed IT applications • Internally- and externally-developed process control applications • Custom ladder logic • Custom firmware • Spreadsheets (macro)	• Same as for “Configured” above, but also: • More rigorous supplier assessment, with possible supplier audits • Possession of full life-cycle documentation (FS, DS, structural testing, etc.) • Design and source code review

DCS: Distributed Control System, DR: Design Review, DS: Design Specification, FS: Functional Specification, GAMP: Good Automated Manufacturing Practice, LIMS: Laboratory Information Management System, MRP-II: Manufacturing Resource Planning, PIC/S: Pharmaceutical Inspection Co-operation Scheme, PKI: Public Key Infrastructure, PLC: Programmable Logic Controller, QMS: Quality Management System, SCADA: Supervisory Control And Data Acquisition, URS: User Requirements Specification, COTS: Commercial off-the-shelf, CRM: Customer relationship management, EDMS: Electronic document management system, CDS: Client data system.

- b. a brief description of the validation strategies for different categories of computerised systems, as well as other validation activities;
- c. an outline of the protocols and related test procedures for all validation activities, including computer systems. The reporting requirements for documenting the validation exercises and related results should also be defined;
- d. the identity of key personnel and their responsibilities as part of the validation programme.

The approach to computerised systems must be controlled within the quality system of the organisation. Thus, there should be:

- a. a policy on coding practices;
- b. a policy for source code review;
- c. a system to control changes to computerised systems;
- d. appropriately trained staff or in-house expertise for computerised systems;
- e. appropriately contracted and controlled external contractors, where relevant;
- f. appropriate training for all staff that interact with computerised systems.

10.6. Security

Physical and/or logical controls must be in place to restrict access to computerised systems solely to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, and/or restricted access to computer equipment and data storage areas.

The extent of security controls depends on the criticality of the computerised system. The creation, changes to and cancellation of access authorisations must be recorded. Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data and the date and time such events occur [3].

10.7. Failure of the system

For computerised systems that support critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to enact alternative arrangements should be based on risk assessment and should be appropriate for the particular system

and the business process it supports. These arrangements should be adequately documented and tested [3]. Testing of these alternative systems and their ability to retrieve data should be assessed annually.

10.8. Electronic signature

Records may be signed electronically. According to Annex 11 of EU GMP [3], all electronic signatures are expected to:

- a. have the same impact as hand-written signatures within the boundaries of the company;
- b. be permanently linked to their respective record;
- c. include the time and date that they were applied.

10.9. Archiving

Data must be archived. This data should be checked for accessibility, readability and integrity. If changes are made to the system (e.g. new computer equipment or software), then the ability to retrieve archived data must be ensured and tested [3].

10.10. References

1. Good Automated Manufacturing Practice (GAMP) 5: A risk-based approach to compliant GxP computerised systems. International Society for Pharmaceutical Engineering (ISPE). Available at www.ispe.org/gamp-5.
2. The specification and use of Information Technology (IT) systems in blood transfusion practice. British Committee for Standards in Haematology. Available at www.bcsbguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dpage=1&dtype=Transfusion&sspage=0&ipage=0#gl.
3. European Good Manufacturing Practices. Annex 11 Computerised Systems. Available at http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm.

4. Good practices for computerised systems in regulated GXP environments. Pharmaceutical Inspection Convention /and Co-operation Scheme (PIC/S). Available at www.picscheme.org.
5. US FDA's Title 21 Code of Federal Regulation (CFR) part 11. Available at www.fda.gov/regulatoryinformation/guidances/ucm125067.htm.

Chapter 11. Traceability

11.1. Introduction

Transplantation of tissues and cells brings great benefits for patients. There are, however, rare but important risks associated with transplantation, including graft failure and donor-transmitted infections and malignancies. The concept of traceability has two main components: (i) it is the means to link a donor with a recipient, or multiple recipients, and (ii) it is the way to identify and link all the steps and procedures to which tissues or cells are subjected, together with their location and the equipment and materials used, before they reach the recipient. Traceability is essential to ensure rapid action to prevent harm, when links in the safety and quality chain are found to have been compromised. Apart from quality and safety, traceability is also crucial for ethical reasons, as it is the means by which legitimate donation with proper consent can be verified for every tissue or cell product.

Donor selection, procurement from the donor, and thorough processing, storage and distribution (transport) of tissues and cells involve many complex steps that determine the quality of the tissues and cells used for clinical application. Human errors, equipment failure, the use of inadequate written procedures or new risks that cannot be predicted may impact on the safety or quality of the tissues and cells at any of these stages, which could in turn increase the risk to recipients. In the case of deceased donors, procurement teams are provided with a medical history at short notice and additional information about the donor at a later stage may have implications for the safety and quality

of tissues procured from those donors. The use of defective equipment, poor quality consumables, contaminated solutions or defective testing kits may only come to light after the tissues and cells have been processed and transplanted. This means that traceability, from donation through to end use, is essential in order to determine which tissues or cells could potentially be affected by additional information or adverse incidents.

Tissue establishments must be able to locate and recall tissues and cells once they become aware of information that may have implications for their quality and safety. The time interval between detecting risks to the quality and safety of tissues and cells and preventing them from being used in patients has been referred to as the “traceability window period” [1]. Recalls can be due to improper donor evaluation, positive donor serology tests, tissue or cell contamination or infection in recipients of other tissues donated by an individual donor or to risks introduced during the processing or storage of the tissues or cells. The increasing global circulation of tissues and cells for transplantation, the fact that several tissue products can originate from one donor that can also donate organs, and the existence of international markets for equipment, consumables and additives adds to the need for robust systems of traceability.

Traceability underpins biovigilance (see Chapter 12). Within each tissue establishment, investigation of adverse events and reactions, and of deviations from standard methods, can only be carried out if a system of traceability is in place. Many establishments share practices, and effective investigations can help to improve shared practices and improve standards. Hence, in addition to biovigilance, ongoing quality improvement of procedures and practices relating to procurement, processing, donor testing, storage and distribution of tissues and cells also relies on good systems of traceability.

11.2. What is traceability?

Traceability is the thread that joins all the pieces of critical information together, from the moment that a potential donor is identified

until the moment when the tissues or cells are applied to the recipient or discarded. Robust systems must ensure secure identification of:

- a. the donor and all records associated with the donor and their medical and behavioural history;
- b. the donation (tissues or cells procured from the donor) and all records associated with the donation, processing, storage and distribution of the final products and all samples taken from the donor or from the donation for the purposes of testing for quality and safety;
- c. the recipient of the tissues or cells.

The following are key requirements of an effective traceability system:

1. The need for unique identification

At every stage in the pathway, from donor to recipient, each organisation holding tissues or cells must have records on the donor, the donation and donation samples and must ensure that they are uniquely identified and labelled within their own organisation. While uniqueness can be ensured without difficulty within one organisation, the risks of duplication are increased when tissues, cells, samples or records move from one organisation to another. For example, duplicate identifiers may result when samples are sent to a testing laboratory or when tissues or cells are sent to a hospital, as each receiving establishment may assign its own identifier. This risk can be eliminated if a global standard is used to identify samples or tissue products. Avoiding duplication of identifiers can involve including a tissue establishment or procurement organisation identifier as an element of the identification for the donor, donation or sample. Within the EU, the European coding system will help to address this need (see section 11.4).

2. Safe transfer of critical information

The traceability trail depends on the accurate transcription of critical identification information. Manual transcription errors cause breaks in the traceability path. The use of electronic

transfer of critical information (bar codes or other machine-readable codes) is recommended. If manual transcription is used, a double-blind entry system should be implemented.

3. Timeliness

When a risk is identified, it must be possible to trace all implicated products or all potentially affected recipients rapidly. A delay could result in harm to patients. Systems need to be quickly accessible, with efficient links between organisations in order to reduce the traceability window period.

4. Clarity of responsibilities at interfaces between organisations

It is essential that each organisation in the chain clearly understand its responsibilities for traceability. It is notable that in the high profile cases of viral transmission during transplantation that have been published, hospitals were often not able to trace all recipients [2].

5. Long-term secure record storage

For effective reviews, traceability data needs to be maintained for long periods of time. For example in the EU, all information related to traceability must be maintained for 30 years after transplantation or the expiry date of the tissues and cells. Data that is critical to the safety and quality of tissues and cells, including records of equipment used and materials such as consumables coming into contact with those tissues or cells, should be kept so as to ensure access to the data for at least 10 years after clinical use of the product, its expiry date or disposal. Organisations need to consider the impact of the obsolescence of technology and to ensure that records remain quickly accessible. There is a need for regular management review of data storage, with a pro-active approach to prevent obsolescence. The location of traceability records may change when organisations merge or if they cease activities relating to donor selection, donor testing, procurement, processing, distribution or transplantation. In such cases, there must be an effective link between the new location of the data and the previous location.

6. Traceability audits

Organisations must include audits of traceability from donor to recipient and vice versa as part of ongoing quality management. The traceability trail may encompass data stored in several organisations.

There must be a system to identify each procurement (or donation event), linking it to its associated donor and their record, each product prepared from that donation, the establishment which processes and stores the tissues/cells for transplantation, as well as the recipient of the donated material or its eventual disposal. All critical materials, equipment and reagents that have come into contact with the tissues or cells must also be traceable.

The EU definition of traceability is provided in the Glossary (Appendix 3) in this Guide.

11.3. What records must be traceable?

There must be a system of record-keeping relating to activities associated with tissues and cells. Records should describe procurement, donor testing, processing, storage, distribution and should include equipment used, materials such as consumables that have come into contact with those tissues/cells and the identity of the members of staff who were responsible for all critical activities from procurement until implantation or disposal.

Tissue establishments must ensure that data protection and confidentiality measures are in place in accordance with the data protection laws in the relevant country. Since many organ donors are also tissue donors, it is important that effective links be in place between organ procurement organisations and tissue establishments.

All records must be legible and indelible, protected from unauthorised amendments, stored securely and readily retrievable. Establishments should conduct regular audits of records to ensure that they are accurate and comprehensive. Good practice requires that amendments to written records are signed and dated. Computer records should be

maintained in a validated system (see Chapter 10) and there must be procedures to back up electronic records to prevent loss, corruption and unauthorised access and amendment. Records must be shown to be reliable and a true representation of the results. Records may be handwritten or transferred to another validated system, such as a computer or microfilm. Records should be maintained of equipment and consumables, including the lot numbers and expiry dates of additives, cryopreservatives and packaging materials used during procurement and processing. The tissue establishment should also retain temperature records, analyser print-outs and relevant environmental monitoring records for viable and non-viable particles. Where tissues and cells have been imported, it is important that tissue establishments ensure that the relevant information retained abroad remains accessible for as long as it may be required.

The records must be kept in an appropriate archive, which is acceptable to the Health Authority of each respective country.

11.3.1. Records of identification, donor tests and clinical evaluation of the donor

Records must contain at least the following:

Donor records

- a. donor identity;
- b. age, sex, medical and behavioural history of donor;
- c. outcome of physical examination for deceased donors;
- d. completed haemodilution formula, where applicable;
- e. consent/authorisation form;
- f. clinical data, laboratory test results and the results of any other tests carried out;
- g. for deceased donors, the results of the autopsy (if performed) or preliminary verbal report;
- h. for haematopoietic stem cell donors, the donor's suitability for the chosen recipient;

- i. for unrelated haematopoietic stem cell donations, where the organisation responsible for procurement has limited access to recipient data, the end user or his/her physician should be provided with the relevant donor data to confirm suitability.

Donor testing records

- a. date and time donor blood samples were taken (blood samples from deceased donors must be taken within 24 hours of death);
- b. date of receipt of the blood sample at the testing facility (in-house or at a contracted laboratory);
- c. record of each test kit used to test donor blood sample (i.e. manufacturer, lot number, expiry date);
- d. results of donor testing, including repeat testing if applicable.

11.3.2. Records of procurement of tissues and cells

The organisation undertaking procurement should produce a procurement report and provide it to the tissue establishment. The procurement report should contain at least:

Procurement report

- a. the identification of the tissue establishment receiving the tissues or cells;
- b. donor identification data (including how and by whom the donor was identified);
- c. description and identification of procured tissues and cells (including samples for testing);
- d. identification of the person who was responsible for the procurement session, including their signature;
- e. date, time (start and end, if relevant) and location of the procurement and standard operating procedure used;

- f. description of the physical area where procurement took place, including environmental conditions at the procurement site;
- g. for deceased donors, storage conditions of the cadaver, i.e. refrigerated (or not) and time of start and end of refrigeration;
- h. manufacturers and lot numbers of reagents and transport solutions used;
- i. any incidents that occurred during procurement.

11.3.3. Records of processing of tissues

The organisation undertaking processing should keep the following records:

Processing records (non-exhaustive list)

- a. tissues and cells received and evaluation of their suitability;
- b. standard operating procedures used to process the tissues and cells;
- c. equipment used during processing;
- d. records of consumables used during processing (manufacturer, lot number, storage conditions of consumables (if appropriate), expiry date);
- e. records of sterilisation or decontamination, if applicable;
- f. records of cryopreservation and freezing protocols, if applicable;
- g. records of environmental monitoring (temperature monitoring, microbial monitoring and particle counts as appropriate);
- h. records of product testing, including microbial testing;
- i. any incidents that occurred during processing.

11.3.4. **Records of storage and distribution of tissues and cells**

Organisations undertaking storage or distribution should keep the following records:

Storage records

- a. storage location and a transfer record if storage locations change;
- b. date placed in storage;
- c. date removed from storage;
- d. records of storage temperature;
- e. any incidents that occurred during storage.

Records of distribution/transport

When the tissues and cells are transported or distributed to hospitals or clinics for implantation, tissue establishments should keep the following records:

- a. name of party responsible for distribution;
- b. identification of the establishment, courier or individual who transported the tissues and cells at any stage between procurement and end use (implantation);
- c. packaging records (e.g. records of the dry shipper used);
- d. time and date of distribution of tissues/cells;
- e. time and date of delivery of tissues/cells;
- f. identification of the receiving establishment, clinician or end user/facility;
- g. any incidents that occurred during distribution.

11.3.5. **Records of end use of tissues and cells**

The medical facility applying or implanting the tissues or cells to recipients should keep the following records:

Records of end use

- a. identification of the supplier tissue establishment;

- b. identification of the clinician or end user/facility;
- c. type of tissues and cells;
- d. product identification;
- e. identification of the recipient;
- f. date of implantation;
- g. any incidents that occurred during implantation;
- h. any adverse reactions in the recipient.

In the EU, the medical facility applying the tissues or cells to the recipients must keep the above data for 30 years. Some national standards require the end users to provide the supplying tissue establishment with the details of the patient in whom the tissues or cells were transplanted. Whether this information is sent to the tissue establishment or not, it is essential that the end user maintain these records, as they are ultimately responsible for recording the fate of the tissues or cells.

11.4. European coding system

The EU tissue and cell Directives (European Directives 2004/23/EC – Articles 8, 25 and 2006/86/EC – Article 10) set out the requirement to develop a single European coding system to identify and label tissue and cell products so as to support traceability of tissues and cells in the EU. This requirement will become binding in 2014.

Each tissue product will be assigned a specific code, which will identify and describe that product. It will be possible to decode the information to obtain text that describes the tissue or cells and their origin via an on-line code translator. In a multi-lingual world, codes are more useful than readable text as they are unambiguous. The coding system used to identify and label tissues and cells will be developed so that it is compatible with any national or international system of coding used in EU member states. The code on the label attached to each product will be eye readable and there will also be the potential of making it machine readable in the future. The use of machine readable barcode labels will ensure the accuracy of records, as manual transcription

errors will not occur and the machine output can easily be entered into electronic databases. The plan will allow those countries that are already using national or international systems, such as ISBT 128 with a standard for barcoding and other forms of machine readability, to continue using those systems while incorporating the requirements of the EU code.

11.4.1. Management of the coding system

The EU Commission has contracted external service providers to help implement the coding system (see www.Eurocet128.org). A coding management system will be put in place both at national (e.g. update of the compendium of EU tissue establishments by the national competent authorities) and EU level (e.g. update of the compendium of tissues and cells products by the European Commission in collaboration with national competent authorities). The coding system will assign unique identifiers to tissue establishments and define a system of nomenclature to generically describe tissues and cells. Reference compendia composed of codes that apply to tissue establishments in the EU and each tissue and cell product are being developed. Since new tissue products will be continuously developed, the nomenclature will have to be regularly updated. There will be effective systems of communication to ensure that all stakeholders are kept informed of any updates. Both compendia will be publicly available, so the generic codes for the tissues and cells used by the EU member states may be also used by other interested countries.

The code for each product will be made up of 2 parts: a Donation Identification Number and a Product Identification Number (see Table 11.1).

Table 11.1. European coding system for tissues and cells

Donation Identification Number

ISO country identifier	Tissue establishment code	Unique donation number
2 characters (alphabetic)	6 characters (alpha/numeric)	13 characters (alpha/numeric)

Product Identification Number

Coding system identifier	Product code	Split number	Expiry date
1 character (alphabetic)	7 characters (alpha/numeric)	3 characters (alpha/numeric)	8 characters (numeric)

11.4.2. Donation identification

The coding system must identify each donation event since donors can potentially donate tissues and cells on several occasions, e.g. haematopoietic cells when alive and corneal tissue after death. The ISO country code (2 characters in length) will be used to identify the country where the donation or procurement took place. Each country will also allocate national codes (6 characters) for authorised tissue establishments (i.e. a tissue establishment code).

Each tissue establishment can, based on the donation identification system in place in their country, assign a unique number for the donation, which should be 13 characters in length. The number may be created locally or provided by the Health Authority or international organisation. Hence, taken together, these codes will ensure that each donation will have a unique Donation Identification Number that can be used to label each tissue product.

11.4.3. Product identification

Once the tissue/cells have been processed, the tissue establishment must label the final product with the Donation Identification Number

and a Product Identification Number. The Product Identification Number consists of the assigned product code (which depends on the system of nomenclature in use), a split number (if applicable) and the expiry date of the product.

Several systems of nomenclature are in use in the EU. Some EU member states prefer to use a generic or basic system, while others use a system of nomenclature that provides a more detailed description of the product. A flexible solution is to incorporate the different systems within the coding by using a character to identify which product nomenclature is in use. The mapping from this identification character to the specific product nomenclature will be maintained within the product compendium. The identification character will be followed by 7 characters, which will be assigned to the product based on the respective system of nomenclature.

EU member states that decide to use the generic system of nomenclature will be able to use an EU common list that assigns codes for each product type at a generic level. EU member states that decide to use more detailed product nomenclature can either use their own national codes or international product codes such as the ISBT (International Society Blood Transfusion) 128 system. For example, the generic code may represent a product type such as a tendon, whilst a more detailed code would include detailed product information, such as whether the tendon is whole, shaped, irradiated, etc.

The product code will be followed by the split number, which will have 3 digits, and the expiry date of the product in ISO standard format (yyyymmdd), which has 8 digits.

11.5. References

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2. Tugwell BD, Patel PR, Williams IT et al (2005) Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor. *Ann Intern Med* 143:648-654.

Chapter 12. Biovigilance

12.1. Introduction

This chapter provides guidance on the implementation of good Vigilance and Surveillance (V&S) practice by all those involved in the transplantation process, from donation, through banking, to clinical use and to the regulation of the field.

A programme of V&S is essential for ensuring quality and safety of tissues and cells for human application. While the quality system focuses on preventing errors and maintaining a consistent standard of agreed specification for tissues and cells released 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. These occurrences can be classified into adverse events, referring to process failures that might lead to harm in a recipient or a living donor, or adverse reactions, referring to adverse responses that have indeed occurred, including the transmission of a communicable disease, in a recipient or in a living donor. Therefore, an adverse event may or may not cause an adverse reaction. Similarly, an adverse reaction may or may not be related to an adverse event. The reporting of these incidences represents important learning opportunities that can help all procurement organisations, tissue establishments, cell therapy facilities and clinical users, and not just those involved in the incident in question, to improve their processes and to achieve higher levels of safety and quality [1, 2].

A Serious Adverse Event (SAE) is any untoward occurrence associated with the procurement, testing, processing, storage and distribution of

tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for the patient or which might result in, or prolong, hospitalisation or morbidity.

A Serious Adverse Reaction (SAR) is an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

In summary, an SAR is an incident where a living donor or recipient has been seriously harmed while an SAE is an incident that results in a risk of serious harm to a living donor or a recipient, although no harm has yet occurred. All Serious Adverse Reactions and Events (SAREs) should be reported by health professionals to ensure appropriate investigation and corrective and preventive actions.

Although adverse events may occur at all stages from procurement to distribution of tissues and cells, many of them are expected and not severe, and may be managed through the Quality Management System (QMS) of the tissue establishment. On the other hand, SAREs are rare and, therefore, there are significant benefits associated with consolidating V&S data on a regional, national or international scale.

12.2. Management and quality

As for other vigilance systems, vigilance activities in the field of tissues and cells should be considered and recognised at all levels of tissue establishments that are authorised for tissue and cell activities, beginning with the strategic and senior management levels. The organisation of the vigilance system, as well as the role of the various parties involved, should be defined and broadly communicated within the tissue establishment.

Health authorities are encouraged to draw up guidelines for tissue and cell vigilance systems, notification forms and examples of SAREs that should be reported. Appropriate communication and co-ordination

between procurement organisations, tissue establishments and transplantation centres are of utmost importance for an efficient vigilance system. Any organisations or bodies involved in tissue and cell activities, including clinical users, should have standard operating procedures (SOPs) in place that describe how to collect, report, investigate and communicate SARE notifications. The identification of a local co-ordinator, 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 tissue establishment level according to guidelines established by the Health Authority.

Relevant SOPs and the management of SARE data collection and investigation should be evaluated during the tissue establishment inspection process. The implementation of computerised, integrated systems for SARE data collection and management is encouraged.

12.2.1. Non-serious adverse events and reactions

While this chapter focuses on the detection, reporting and investigation of SAREs, all adverse incidents and non-compliances, including those with minor consequences, should be documented and regularly reviewed within the QMS of the tissue establishment. This allows trends to be monitored and actions to be taken to continuously improve quality and safety. One important role for the Health Authority is to define and inform tissue establishments and professionals of which adverse events and reactions should be notified to them through vigilance and which should be managed locally through the QMS of the tissue establishment.

12.2.2. Complaints

Complaints from any party (clinical users, donors, patients or third parties) should also be managed within the QMS. They should be acknowledged immediately and investigated. A formal acknowledgment 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.

12.3. Serious Adverse Reactions

An SAR has occurred when a patient or a living donor has been harmed in a significant manner by the process of donation or the human application of the tissues and/or cells. SARs must be detected, reported, investigated and assessed in terms of severity, frequency or probability of recurrence and imputability. Efficient systems for rapid quarantine or recall of unsafe tissues or cells must be in place, along with procedures for look-back where donors or recipients are found to have been exposed to a risk. Important learning outcomes from each SAR should be appropriately communicated to relevant stakeholders.

A number of clinical symptoms or situations suggest that an SAR might have occurred in a tissue or cell recipient and should therefore be seen as triggers for an adverse reaction report. Here are some examples of reportable SARs (*abbreviated descriptions in brackets*):

- a. suspected harm in living donor related to procurement (*Patient harm*);
- b. unexpected⁷ primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion) (*Infection from donor*);
- c. transmitted infection (viral, bacterial, parasitic, fungal, prion) possibly due to contamination or cross-contamination by an infectious agent in the procured tissues, cells or associated materials, between procurement and their clinical application (*Infection from infected/contaminated tissue/cells*);

7 In certain circumstances, clinicians may knowingly transplant an infective donation (e.g. a CMV-positive bone marrow donation). In these circumstances, patients should be informed about benefits versus additional risks and there should be specific follow-up. Clinical and biological monitoring, as well as prophylactic or pre-emptive treatment, should comply with existing recommendations or regulatory requirements, where they exist.

- d. hypersensitivity reactions, including allergy, anaphylactoid reactions or anaphylaxis (*Hypersensitivity*);
- e. malignant disease possibly transferred by the tissues or cells (donor derived, process-associated or other) (*Malignancy*);
- f. unexpectedly delayed or absent engraftment or graft failure (including mechanical failure) (*Failure*);
- g. toxic effects from tissues and cells or associated materials (*Toxicity*);
- h. unexpected immunological reactions due to tissue or cell mismatch (*Mismatch*);
- i. aborted procedure involving unnecessary exposure to risk, e.g. wrong tissue supplied, discovered after patient is anaesthetised and the surgical procedure has begun (*Undue risk*);
- j. suspected transmission of genetic disease (*Genetic abnormality*);
- k. suspected transmission of other (non-infectious) illness (*Other transmission*);
- l. other (*Other*).

12.3.1. Detection of SARs

Effective V&S relies heavily on all health professionals involved from procurement to transplantation, namely:

- a. medical staff (including surgeons) involved in tissue and cell procurement activities who might be aware or informed of additional safety information on donors during their follow-up;
- b. staff and personnel involved in tissue and cell procurement;
- c. clinical users who should be alert to adverse outcomes and be aware when such outcomes might be associated with the tissues or cells transplanted;
- d. any other tissue establishment staff involved in any procurement and transplant activities;

- e. other vigilance systems (e.g. material/device vigilance, pharmacovigilance, etc.), when issues of concern are detected that might impact on the safety of tissues or cells 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 SARs.

As adverse transplant outcomes might result from many diverse factors associated with the surgical procedure or the patient's underlying condition, clinicians might not consider the transplanted tissues or cells as a possible source of the outcome. Tissue establishments that supply tissues and cells should encourage procurement organisations and clinical users of tissues and cells to always consider whether adverse outcomes might have been associated with the donation process or the transplanted tissues or cells so that similar occurrences might be prevented in the future.

For most types of well-established tissue and cell transplantation, detailed clinical outcome reporting by the clinical user to the tissue establishment is required only in those exceptional circumstances where there is suspicion of an untoward SAR. However, reporting of the clinical progress of tissue and cell recipients to the tissue establishment might also be required for all highly-matched, life-saving transplants such as haematopoietic stem cell infusions or when novel tissue or cell processes have been applied or new types of tissues or cells are being transplanted. This routine clinical follow-up is not considered as part of vigilance.

Equally important is the need to detect donation complications (also considered as SARs) in living donors that might be associated with the donation process in some way. For example, SARs may be detected after stimulation treatment in living donors. Although long-term follow-up of living donors of tissues and cells is needed, it should be differentiated from vigilance. However, co-ordination between these activities should be encouraged.

12.3.2. Reporting SARs

12.3.2.1. Clinicians to tissue establishments

Tissue establishments that supply tissues and cells should provide clinical user organisations with clear instructions on how to report SARs, preferably using standardised documentation. In general, suspected SARs should be reported immediately by the clinical users to the tissue establishment that supplied the tissues or cells, before investigation or confirmation, to allow the tissue establishment to take appropriate precautionary actions to prevent harm to other patients and to involve the tissue establishment in the investigation process.

12.3.2.2. Procurement organisations to tissue establishments

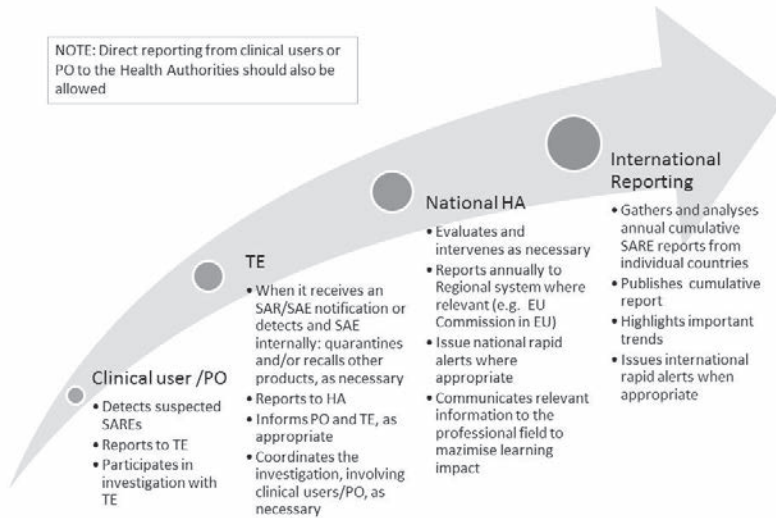
Similarly, health professionals and procurement organisations should report living donor SARs to the tissue establishment, even if the SAR is only suspected to be transplantation-derived, so that the broader implications for other centres, clinical users and patients can be considered without delay.

12.3.2.3. Reporting to regional/national programmes

Information regarding SARs in recipients or living donors must be reported by tissue establishments to the Health Authorities so that the benefits of consolidated data can be realised and the lessons learned can be shared (see Figure 12.1).

A “Severity Scale” can be used to decide whether a particular adverse reaction is an SAR that needs to be reported to the Health Authorities. The scale shown in Table 12.1 is the one used in the EU. It was proposed by the EU-funded project EUSTITE [3] for tissue and cell vigilance and is based on one used for haemovigilance. In the EU, all SARs that meet the descriptions of “Serious”, “Life-threatening” or “Death” must be reported to the Health Authorities.

Figure 12.1. Serious Adverse Events and Reactions reporting flow [5]



HA: Health Authority; EU: European Union; PO: Procurement Organisation; SAE: Serious Adverse Events; SAR: Serious Adverse Reactions; SARE: Serious Adverse Reactions and Events; TE: Tissue Establishment.

Table 12.1. Severity Scale for Serious Adverse Reactions

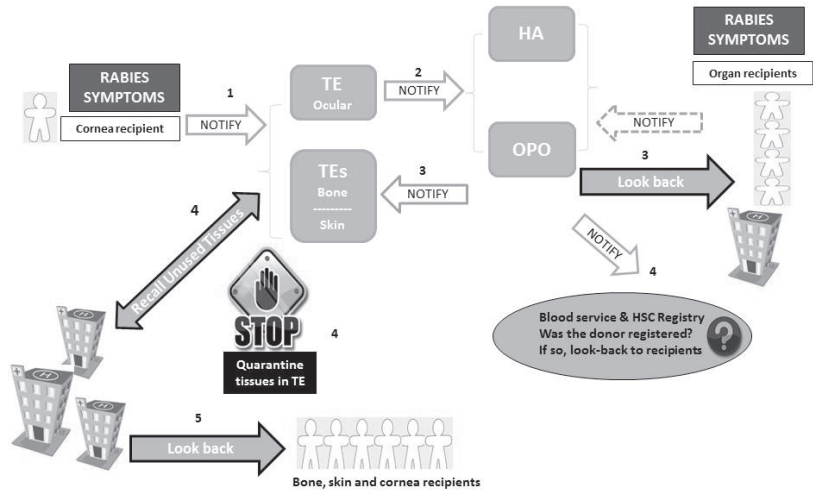
Severity	Comments
Nil	No harm, no risk, patient not informed as there was no risk of harm.
Non-serious	Mild clinical/psychological consequences. No hospitalisation. No anticipated long-term consequence/disability.
Serious	- Hospitalisation or prolongation of hospitalisation, and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following Assisted Reproductive Technologies (ART) with donor gametes or embryos.
Life-threatening	- Major intervention to prevent death or - evidence of a life-threatening transmitted infection or - birth of a child with a serious genetic disease following ART with donor gametes or embryos.
Death	Death

The tissue establishment is responsible for providing clinical user entities, procurement organisations and critical third parties with clear instructions, forms and guidance on how to notify SARs in accordance with the national or local requirements. SARs reporting and management should be incorporated within the tissue establishment's quality system, with one or more SOPs that describe the process for acknowledgment of notifications, investigation, follow-up on corrective and preventive actions and reporting to the Health Authorities. The procedures should enable rapid action to be taken by all affected organisations to protect the safety of recipients. This may involve tissue and cell quarantine, recall and look-back in patients who have already had implicated tissues or cells applied. These actions may need to be taken by organisations other than the one that received the original notification. For example, the organ procurement organisation

will play a central role where the donor was both an organ and tissue donor.

Figure 12.2 indicates a series of actions that might need to be taken in the case of a report of a suspected transmission from a deceased organ and tissue donor, highlighting that communication with other organisations that might need to quarantine implicated tissues or cells or conduct recalls or look-backs should be quick and effective.

Figure 12.2. Example of an adverse reaction involving quarantine, recall and look-back



HA: Health Authority; HSC: Haematopoietic Stem Cells; OPO: Organ Procurement Organisation; TE: Tissue Establishment.

Although SARs should generally be co-ordinated and centrally reported by tissue establishments at a national level, it is recommended that national V&S programmes allow direct reporting from clinical users or even patients to Health Authorities. This might occur where a clinician or a patient suspects that a tissue establishment is not working correctly or where they do not have confidence, for whatever reason, that the report will be fully investigated.

12.3.2.4. **International reporting**

Where SARs are detected in relation to tissues or cells that have entered international distribution channels, appropriate international collaboration should ensure that all of the stakeholders involved (clinicians, tissue establishments and Health Authorities) in each of the countries concerned are informed and participate, as necessary, in the investigation and follow-up actions.

EU member states are obliged to send an annual report of the SAREs they have received to the European Commission. Such international reporting allows for trend analyses on the basis of consolidated data.

12.3.3. **Investigating and assessing SARs**

SARs in tissue or cell recipients should be investigated by a team that includes both the clinician that transplanted the tissues or cells, the tissue establishment that provided them and, in more serious cases, the Health Authority in that country. 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 SAR. The investigation should focus on establishing the level of imputability, i.e. the extent to which the tissues or cells transplanted can be considered to have caused the SAR. Where there is suspicion of an infectious disease transmission, investigation will rely heavily on the availability of an archived sample of donor serum. It is 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.

The scale provided in Table 12.2, again developed by EUSTITE on the basis of the scale used in haemovigilance, and used in EU guidance to its member states, can be applied to describe the outcome of the imputability investigation. It is proposed that all adverse reactions be graded in terms of imputability. Grades might change in the course of an investigation and should generally be assigned at the point of initial notification and again at the completion of the SAR investigation. The evaluation of imputability should be based on scientific or clinical data. The European Centres for Disease Control (ECDC), the World Health Organization (WHO) or other sources of epidemiological and risk information may be able to support the process.

Table 12.2. Scale describing the possible outcomes of an imputability investigation

Imputability level		Explanation
NA	Not Assessable	Insufficient data for imputability assessment.
0	Excluded	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes.
1	Unlikely	Evidence clearly in favour of attribution to alternative causes.
2	Possible	Evidence is indeterminate.
3	Likely, probable	Evidence in favour of attribution to the tissues/cells.
4	Definite, certain	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells.

Certain SARs that have minor consequences for an individual donor or recipient might imply significant risk in a broader way. For example, an SAR in a donor that then receives wide publicity might discourage donation in general, putting patients at risk through an impact on the supply of tissues or cells generally. These broader implications can be assessed using a tool that evaluates both the broad

consequences and the probability of recurrence. An Impact Assessment tool was also developed by the EUSTITE project and can help both tissue establishments and health authorities to decide on the level of response that might be appropriate, depending on the impact score that is allocated for a specific incident (see Appendix 8).

12.4. Serious Adverse Events

Serious Adverse Events can occur at any moment from donor selection to clinical application.

12.4.1. SAE detection

For effective detection of SAEs, all relevant stakeholders must be aware of their responsibilities for identifying errors or unexpected results. This includes all staff in tissue establishments and procurement organisations, those working in organisations such as testing laboratories that provide “third party” services to tissue establishments and clinical users who may also detect errors at the point of clinical use. In European Directive 2006/86/EC, 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.

12.4.2. SAE reporting

Non-compliances with the quality system should be documented and investigated as part of the internal quality management system. On occasion, however, a particular non-compliance may be of such importance that it should be considered an SAE and reported through the vigilance system. According to European Commission instructions to EU member states for annual vigilance reporting, deviations from SOPs in tissue establishments (or other adverse events), which have implications for the quality and safety of tissues and cells, should

result in SAE reporting to the Health Authority when one or more of the following criteria [4] apply:

- a. inappropriate tissues or cells have been distributed for clinical use, even if not used;
- b. the event could have implications for other patients or donors because of shared practices, services, supplies or donors;
- c. the event resulted in a mix-up of gametes or embryos;
- d. the event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient-specific) allogeneic tissues or cells;
- e. the event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

12.4.3. Investigating and assessing SAEs

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 given in Appendix 8 can also be applied to SAEs to help reach a decision on the response required.

12.5. Vigilance co-ordination

Co-ordination between various systems of vigilance (e.g. medical device vigilance, pharmacovigilance) should be in place both at the local level (tissue establishment) and at the Health Authority level.

12.5.1. Rapid alerts

In some circumstances, a particular event or reaction requires rapid communication nationally or internationally to facilitate urgent action, such as a recall of products or critical materials or the quarantine of tissues or cells. Rapid alerts should only be issued in exceptional circumstances. The following criteria have been identified in the

SOHO V&S project [5] as triggers for rapid alerts within or between EU member states:

- a. SAE/SAR of a serious or potentially serious nature;
- b. potential risk to other individuals or other tissue establishments;
- c. wider public health implications;
- d. rapid intervention needed (preventive or corrective measures, urgent communication).

Within the EU, a system for Rapid Alerts (referred to as RATC, Rapid Alerts for Tissues and Cells) is managed by the European Commission and enables the Competent Authorities of the EU member states to rapidly share urgent information regarding risks to patients where that information has consequences in more than one EU member state. Since February 2013, this system was moved to a new secure Internet platform where all rapid alerts are generated and shared.

12.6. Vigilance communication

12.6.1. “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 feed-back to health professionals is critical to support continued SARE notification. All stakeholders, Health Authorities, tissue establishments and clinicians 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.

12.6.2. Vigilance experience and feed-back

Health Authorities and professional societies should publish the results of their programmes without identifying individual centres, hospitals or individual people. Those tissue establishments or hospitals 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 outcomes 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 [5]. 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.

12.7. 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 on particular epidemic agents, infectious diseases or new in vitro diagnostic techniques in the field of tissues and cells.

12.8. References

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Chapter 13. Specific ocular tissue requirements

13.1. Introduction

Ocular tissues are obtained from deceased donors and can be prepared into corneal grafts, anterior and posterior lamellar grafts and scleral tissue. Corneal grafts are mainly used in diseases of the stroma (loss of transparency due to scars or loss of the normal curvature as in keratoconus) and of the endothelium (Fuchs' dystrophy and re-interventions for endothelial decompensation of previous grafts). Lamellar transplant surgery has replaced full thickness grafting in most cases; anterior lamellar grafts can be used for treatment of stromal scars or stromal distortion, whereas posterior lamellar grafts are applied for degenerative diseases of the corneal endothelium.

The generic chapters of this Guide (see Part A) all apply to ocular tissue banking and must be read in conjunction with this chapter. For the following aspects, there are no additional requirements apart from those described in the generic chapters:

- a. Packaging and labelling (Chapter 3)
- b. Donor Testing (Chapter 5)
- c. Distribution and import/export (Chapter 8)
- d. End users (Chapter 9)
- e. Computerised systems (Chapter 10)
- f. Traceability (Chapter 11)
- g. Biovigilance (Chapter 12)

This chapter defines the additional specific requirements for ocular tissues.

13.2. Donor evaluation

13.2.1. Exclusion criteria for cornea donation

General

There are some additional exclusion criteria for the donation of ocular tissues and some of the exclusions applied to other tissues are not applicable for cornea donation as described below.

Donor age

Provided that corneas are examined to exclude those with inadequate endothelium density, no upper donor age limit needs to be set (it can be determined by the tissue establishment). The lower age limit is less certain. Due to their high plasticity, corneas from young donors are less suitable. Therefore, their use will depend on surgical demand.

Malignancies

Donors with a history of or suffering from retinoblastoma, haematological malignancies (e.g. leukaemia, lymphoma, multiple myeloma, etc.) or malignant tumour of the anterior segment or the fundus of the eye must be excluded from donation of ocular tissues. Donors with a history of or suffering from other malignant diseases may be considered for cornea donation.

Infections

Persons with significant localised infection (bacterial, viral, parasitic or mycotic) are excluded from donation of ocular tissues, including past ocular herpes infection.

Donors suffering from septic bacteraemia are excluded from the donation of ocular tissues other than corneas. Donors suffering from septic bacteraemia may be considered for cornea donation, provided that a representative sample of incoming material (adjacent scleral or other

surrounding tissue or material) was tested with an appropriate microbiological procedure before any treatment. Additionally, a sample has to be tested for microbial contamination during storage in a culture medium, applying a suitable method that allows the detection of potential bacterial or fungal contamination of the tissue. Donors colonised with multidrug-resistant bacteria should always be excluded.

Eye diseases

The following contra-indicate cornea donation:

- a. ocular inflammation (including known ocular involvement by systemic disease, e.g. sarcoidosis, rheumatoid arthritis);
- b. corneal disorders including keratoconus, keratoglobus and dystrophy;
- c. corneal opacity, scarring, pterygium or other superficial disorders of the conjunctiva or corneal surface that involve the central optical area of the corneal button.

Prior intra-ocular or anterior segment surgery

The following contra-indicate cornea donation:

- a. prior surgery that would prejudice graft outcome;
- b. receipt of a corneal, sclera or limbal allograft;
- c. refractive corneal surgical procedures, e.g. radial keratotomy, lamellar inserts, laser refractive surgery (photo-refractive keratectomy keratomileusis).

13.2.2. Exclusion criteria for other types of ocular tissue donation (e.g. sclera, limbal tissue, limbal cells)

- a. No upper donor age limit needs to be set. The lower age limit is less certain. Use of ocular tissue from young donors will depend on surgical demand.
- b. The donor evaluation criteria are the same as for general exclusion described in Chapter 4.

13.3. Procurement

13.3.1. *Post-mortem* time

The ocular tissues should be procured as quickly as possible after cardiac arrest, preferably within 24 hours, but some national and local standards allow procurement up to 48 hours after cardiac arrest.

13.3.2. Procurement team

Ocular procurement personnel must operate under aseptic conditions and must be appropriately clothed for the type of procurement to minimise the risk of contamination of the tissue to be removed and also of personnel. Usually, this requires hand disinfection, the wearing of sterile clothes and sterile gloves and the use of face masks or protective masks.

13.3.3. Procurement procedure

The donor eyes should be flushed with an appropriate sterile solution to remove debris, mucus and foreign matter from the cornea and conjunctival sac. An appropriate broad-spectrum antibiotic/anti-fungal solution may be used to further moisten the eyes. Either the whole eye (enucleation by excision of extraocular muscles and the optical nerve) or the corneoscleral disc by *in situ* excision can be procured using aseptic procedures. It is recommended to procure the cornea with a rim of scleral tissue.

13.3.3.1. Whole eye procurement

After enucleation, the bulbus should be placed in a fixed position in a moist chamber with an appropriate solution. Broad-spectrum antibiotics may be used to further minimise bacterial contamination.

13.3.3.2. Corneoscleral disc procurement

Peritomy should be performed to incise the conjunctiva in a circle as close to the limbus as possible, followed by sclerotomy 2-3 mm from the limbus. After excision, the corneoscleral disc should be immersed in an appropriate corneal storage solution.

13.3.3.3. **Scleral tissue procurement**

Scleral tissue should be recovered from the whole eye after enucleation.

13.3.4. **Reconstruction of the donor**

An appropriate prosthesis or other material suitable for this purpose must be used to restore the appearance of the donor. If necessary, the donor's eyelids should be closed by, for example, tissue glue.

13.4. **Receipt of procured tissue at tissue establishments**

Tissue should be transported to the tissue establishment as soon as possible after procurement or must be placed in the first processing solution directly after procurement. Whole eyes should be stored at temperatures between 1 and 10 °C until processing is due to begin. Corneoscleral discs (after *in situ* excision) for hypothermic storage (see section 13.4.3.1) should also be stored between these temperature limits, whereas corneoscleral discs obtained for organ culture should be stored in organ culture medium at temperatures between 10 and 38 °C. The maximum storage time for eyes in a moist chamber is 48 hours.

13.5. **Processing and storage**

13.5.1. **Processing facilities**

In selecting an appropriate air quality specification for ocular tissue processing, the criteria identified in Chapter 7 should be considered. Table 13.1 outlines those factors to be considered for ocular tissue processing.

Table 13.1. Factors influencing the specification of processing air quality for ocular tissue

Criterion	Explanation	Ocular tissue-specific
Risk of tissue or cell contamination during processing	Processes that are mostly “closed” (e.g. bone marrow cryopreservation, where the only exposure of the cells to the environment is when a spike is inserted to add cryoprotectant) need a less stringent specification than those that involve hours of open processing (e.g. bone and tendon graft cleaning and shaping).	Some hypothermic processing methods allow corneal tissue to be prepared and evaluated without exposure to the environment. Where the tissue must be exposed, the time of exposure is limited to a short period related to the evaluation of endothelium cells or lamellar preparation.
Use of anti-microbials during processing	Some tissues, even though not terminally sterilised, can be exposed to various anti-microbial agents without compromising the characteristics required for clinical efficacy. Processes that include, for example, detergent washing, alcohol rinses, HCl treatment, etc. imply less risk of transferring an environmental contaminant than those where cell viability is required and no anti-microbial agents can be applied or the only anti-microbial step possible is soaking in antibiotics.	Corneal tissue can be stored in preservation media that can contain certain antibiotics as well as markers that change colour when micro-organisms grow in them. Organ culture storage methods allow the visual examination of the medium for microbial growth.

Criterion	Explanation	Ocular tissue-specific
Risk that contaminants will not be detected in the final tissue or cell product due to limitations of the sampling method	Where the only possibilities for final microbiological sampling are swabbing or testing of unrepresentative samples, the risk that environmental contaminants will be undetected is higher compared to processes where 10% destructive testing of final products can be performed.	Sampling a piece of corneo-scleral tissue when it is freshly preserved is feasible, but the amount of tissue available is very small. If it is preserved in organ culture media, then the preservation solution should be submitted to culture media testing and control.
Risk of transfer of contaminants at transplantation	Tissues that are minimally processed, cellularised, or containing blood, blood vessels and lipids are more likely to support microbial contaminants than those that are blood- and cell-depleted. Tissues or cells that are applied to small areas on the external surfaces of the body, or to areas that are minimally vascularised, are less likely to transmit infections than those that are infused into the blood stream or implanted into internal organs.	Corneal tissue is not vascularised and so the risk of viral and bacterial transmission is low. If limbal tissue, sclera or other vascularised parts of the eye are transplanted, the risk is equivalent to other tissue types. Corneal tissue is used to replace corneas, which are exposed to the environment, and thus are easy to treat topically.

Taking the factors in Table 13.1 into consideration, it is appropriate that processing of corneas take place in a microbiologically- and climate-controlled environment (including temperature and humidity control, ventilation and air filtration), with validated cleaning and disinfection.

Within the EU, tissues that are exposed to the environment without a subsequent microbial inactivation process should be processed in environments with an air quality equivalent to those of Grade A, as defined in EU Good Manufacturing Practice (GMP), with a

background environment at least equivalent to EU GMP Grade D. Taking the factors described in Table 13.1 into account, it is reasonable to apply this minimum standard for cornea processing.

13.5.2. Cornea processing methods

The following methods for preparation of the cornea are accepted:

- a. excision of the corneoscleral button from enucleated whole eyes (at the processing area);
- b. excision of the corneoscleral button from the donor eyes *in situ*;
- c. lamellar tissue preparation of the corneoscleral button obtained through one of the two ways mentioned previously, using manual or automated methods or lasers;
- d. cryopreservation for long-term storage may be used for non-viable cornea tissue for tectonic grafting.

13.5.3. Cornea storage methods

Corneal tissue must be viable when transplanted. The following storage methods are established in eye banking practice:

- a. Hypothermic storage of the whole eye
The maximum recommended storage time is 72 hours between 1 and 10 °C for selected surgeries. An inspection of the endothelium is mandatory and cell loss during storage must be taken into account, except when the corneal tissue is designated for emergency or anterior lamellar grafting.
- b. Hypothermic storage of the corneoscleral disc in a corneal storage solution
The maximum storage time between 1 and 10 °C depends on the storage medium used (usually 7 days, see the manufacturer's instructions for the medium in use). It is recommended not to exceed the prescribed storage time. An inspection of the endothelium is mandatory and cell loss during storage must be taken into account, except for tissue designated for

emergency or anterior lamellar grafting. Instructions for surgical use, together with a recommendation for microbiological testing of the corneal storage medium and/or remaining scleral rim at the time of surgery, should be included.

c. Storage of the corneoscleral button by organ/tissue culture

It is recommended to keep the storage time as short as possible, with a maximum storage period of 5 weeks between 30 and 38 °C. It is at the discretion of the Responsible Person/Medical Director to prolong storage time, provided that documentation (evidence or validation of the procedure) is present to support this. An inspection of the endothelium is mandatory at the end of the storage period, except for tissue designated for emergency or anterior lamellar grafting.

Changes of storage medium using aseptic procedures during the storage period is at the discretion of the Responsible Person/Medical Director and depends on the indications of the manufacturer of the storage medium in use.

In order to retain its physiologic thickness, the cornea must be transferred up to a maximum of 6 days before transplantation into a solution with a high osmotic potential (i.e. a transport or deswelling solution) at a temperature between 15 and 38 °C. The recommended maximum storage time of 5 weeks includes storage time in a transport solution.

13.5.4. Sclera processing and storage

After removal of the corneoscleral button from the bulbus, the sclera is prepared using aseptic techniques by removing the remaining contents (vitreous, lens, iris, choroidal and retinal tissue) and annexes (remnants of muscles, conjunctiva). The tissue can also be cut into pieces.

Sclera can be stored (whole or in separately packed pieces) at ambient temperature (dehydrated in > 70% ethanol, in glycerin, fixed in formalin or freeze-dried), frozen or kept in a refrigerator between 2 and 8 °C (in a hypothermic storage solution, 70% ethanol or saline with

antibiotics). However, sclera can only be kept for a short period (up to 7 days) in hypothermic solutions or in saline with antibiotics in the refrigerator.

13.6. Microbiological testing

a. Organ culture storage method for corneas

A minimum storage period (not less than 3 days) is mandatory to allow for proper microbiological testing, thereby minimising the risk of contamination. The time period required to perform sensitive microbiological tests of the cornea in the storage medium is at the discretion of the Responsible Person/Medical Director. The efficacy of this quarantine period and the microbiological testing method should be evaluated and validated for the antibiotics being used in the storage media.

A second microbiological test is highly recommended at the time of terminal evaluation and transfer of the cornea into the transport medium.

Microbiological testing of storage media samples is mandatory; visual inspection of the medium alone for a change in colour or transparency is not adequate. However, the culture medium should be regularly inspected for cloudiness, which may indicate microbial contamination.

b. Hypothermic storage method for corneas

Due to the short time of storage, it is not possible to wait for the final result of sensitive microbiological testing of the culture medium. However, sampling of the culture medium one day after the start of the storage period, or just before delivery for clinical use, is recommended. The treating physician should be informed of a positive result as quickly as possible. Also, a recommendation to the surgeon to perform microbiological testing on the cornea storage medium or on remaining scleral rim at the time of surgery is recommended.

c. Sclera

A sensitive microbiological testing method must be applied before storage.

13.7. Quality control and cornea evaluation

Quality control tests on corneal grafts should consider at least the following minimum quality criteria:

- no evidence of microbiological growth (aerobic or anaerobic bacteria, yeast or fungi);
- endothelial characteristics (cell density and viability);
- morphology and integrity of the cornea layers;
- free visual area and diameter of the corneal button.

Depending on the specific use of the cornea, it is necessary to check and document the conditions of:

- the epithelium (if intended for a full-thickness graft, superficial or deep anterior lamellar graft, or a limbal graft), taking into account that the epithelium may detach or fall off during storage;
- the corneal stroma (if intended for a full-thickness graft or a superficial or deep anterior lamellar graft). Transparency of the corneal stroma is crucial;
- the endothelium, which is essential for maintaining corneal transparency (if intended for a full-thickness graft or a posterior lamellar graft).

a. Macroscopic inspection

Without optical instruments, the donor eye must be inspected *in situ* for corneal transparency and corneal pathology such as:

- abnormalities of the external globe;
- signs of previous surgery of the anterior segment;
- epithelial abrasions, retention of excessive orbital tissue or laceration of the globe;

- epithelial defects;
 - stromal opacities. A mild arcus senilis with a defined clear zone is acceptable. The minimal diameter of the clear zone is at the discretion of the Responsible Person/Medical Director;
 - abnormal corneal shape (keratoconus, micro- or megalocornea);
 - condition of the anterior chamber (shape, evidence of blood);
 - abnormalities, such as the pterygium extending to the optical zone.
- b. Slit lamp evaluation
- Slit lamp examination (before decontamination and dissection) is highly recommended, but not mandatory. It facilitates exclusion of any visible or pathological changes of the epithelia or stroma (e.g. scars, oedema, significant arcus, striae, epithelial defects, endothelial guttae or disease, polymegethism, pleomorphism, infiltrates or foreign bodies).
- c. Microscopic evaluation of the endothelial cells of the cornea
- Examination by one of the following methods is necessary:
- Specular microscopy
 - The appearance of the endothelial cells with specular microscopy varies with temperature, type and time of preservation and media used. Evaluation of corneas at ambient temperature is recommended.
 - Transmitted light microscopy (bright field, phase-contrast)
- For ease of cell counting, induction of swelling of the inter-cellular space with a hypotonic solution is necessary in order to make the endothelial cells visible. The use of a vital stain (e.g. trypan blue) may help to identify dead cells (necrotic/apoptotic) and denuded Descemet's membrane.

An endothelial cell density of less than 2,000 cells/mm², moderate to severe signs of polymegathism and pleomorphism, signs of significant cell loss during organ/tissue culture or the presence of dead cells are generally considered as contraindications for long-term graft survival.

Chapter 14. Specific amniotic membrane requirements

14.1. Introduction

Human amniotic membrane (hAM) is the innermost, semi-transparent layer of the foetal membranes formed by a single layer of cuboidal, epidermis-like cells that are attached to a thick basement membrane and an avascular stromal matrix consisting of scattered fibroblasts in a collagen scaffold.

It has some unique properties. Clinical and experimental data has shown [1-5] that hAM facilitates the proliferation and differentiation of epithelial cells, maintains the original epithelial phenotype, promotes goblet cell differentiation, reduces scarring and vascularisation and lacks immunogenicity. Collagen type I, III, IV, V and VII, laminin and fibronectin have been identified in the amniotic basement membrane and stroma. The presence of a rich extracellular matrix and collagen endows the stroma with anti-inflammatory properties, which arise from the entrapment of inflammatory cells, the presence of various growth factors and the inhibition of proteinase activity and decreased lipid peroxidation. In addition, it has anti-adhesive and anti-bacterial activities, along with the ability to modulate stromal scarring. It also protects wounds and reduces pain. Moreover, hAM epithelium produces various growth factors such as Interleukin 6 (IL-6) and 8 (IL-8). These characteristics have led to the use of hAM in clinical practice; mainly in the treatment of ophthalmology, but also to encourage epithelialisation in burns, as a temporary or long-term wound dressing,

as graft material over skin ulcers to replace mucosa, in arthroplasty and intra-abdominal and reconstructive surgery.

The generic chapters of this Guide (see Part A) apply to hAM banking and must be read in conjunction with this chapter. For the following aspects, there are no additional requirements apart from those described in the generic chapters:

- a. Packaging and labelling (Chapter 3)
- b. Donor Testing (Chapter 5)
- c. Distribution and import/export (Chapter 8)
- d. End users (Chapter 9)
- e. Computerised systems (Chapter 10)
- f. Traceability (Chapter 11)
- g. Biovigilance (Chapter 12)

This chapter defines the additional specific requirements for hAM.

14.2. Donor evaluation

Amniotic membrane could be contaminated by normal vaginal flora during normal vaginal delivery. Therefore, it should be obtained under aseptic conditions following elective caesarean section after a full-term pregnancy. If the hAM was obtained during vaginal delivery, different sterilisation procedures can be applied (e.g. heat-dried and air-dried amniotic membrane sterilised by gamma irradiation).

The recommended donor age is between 18 and 45 years.

14.2.1. Specific exclusion criteria

Pathologies of the female genital tract or other diseases of the donor or unborn child that might present a risk to the recipient include:

- a. significant local bacterial, viral, parasitic or mycotic infection of the genital tract, especially amniotic infection syndrome;
- b. gestational diabetes of the donor;
- c. (known) malformation of the unborn/newborn;

- d. premature rupturing of membranes;
- e. endometritis;
- f. meconium ileus.

Individual tissue establishments may have additional exclusionary criteria.

14.3. Procurement

14.3.1. Procurement facility and procurement team

Amniotic membranes are usually collected from living donors by medical staff at a gynaecological clinic after caesarean section. Staff performing the procurement must be dressed appropriately for the procedure so as to minimise the risk of contamination of the tissue to be removed and any hazard to themselves.

14.3.2. Storage and transport after procurement

Procured foetal tissue should be stored at appropriate temperatures to maintain their characteristics and biological functions.

The storage and transport time of procured foetal membranes should be kept as short as possible (the recommended maximum time is 24 hours) and a temperature of 2 to 10 °C should not be exceeded.

The foetal membranes should be placed in a sterile receptacle containing a suitable transport medium. The sealed organ bag should then be placed inside an adequately labelled sterile container to be transported to the tissue bank. Individual tissue establishments should validate the composition of the transport medium and determine if an antibiotic cocktail is required.

The temperature during transport to the tissue establishment must be monitored and recorded. Temperature stability and reliability should be guaranteed by the container or mode of transport used, or in cases of unexpectedly high or low environmental temperatures, a temperature recording unit should be enclosed in the container that records temperature in, at least, half-hourly intervals.

14.4. Processing and storage

14.4.1. Receipt of procured placenta at the tissue establishment

The procured foetal membranes can either be:

- a. stored at a temperature range of 2 to 10 °C (e.g. in the refrigerator). The refrigerator temperature should be monitored and permanently recorded. In this case, processing should be carried out no later than 48 hours after procurement. If the process is intended to maintain amnion cell viability, then it is recommended that the cell nutrient medium be changed in a climate-controlled environment shortly after receipt of the donated material;
- b. stored at a temperature lower than –60 °C (ultra-low-temperature freezer).

14.4.2. Processing facilities

In selecting an appropriate air quality specification for hAM processing, the criteria identified in Chapter 7 should be considered. Table 14.1 outlines those factors to be considered for hAM processing.

Table 14.1. Factors influencing the specification of processing air quality for hAM

Criterion	Explanation	Skin-specific
Risk of tissue or cell contamination during processing	Processes that are mostly “closed” (e.g. bone marrow cryopreservation where the only exposure of the cells to the environment is when a spike is inserted to add cryoprotectant) need a less stringent specification than those that involve hours of open processing (e.g. bone and tendon graft cleaning and shaping).	During processing, amniotic membranes are necessarily exposed to the processing environment for extended periods during dissection, sizing and evaluation of their characteristics.
Use of anti-microbials during processing	Some tissues, even though not terminally sterilised, can be exposed to various anti-microbial agents without compromising the characteristics required for clinical efficacy. Processes that include, for example, detergent washing, alcohol rinses, HCl treatment, imply less risk of transferring an environmental contaminant than those where cell viability is required and no anti-microbial agents can be applied, or the only anti-microbial step possible is soaking in antibiotics.	Soaking in antibiotics is the only anti-microbial step possible for cryopreserved amniotic membrane. It is important to validate the antibiotic solution and to list the microorganisms that are acceptable pre-decontamination. Glycerolised amniotic membranes or lyophilised amniotic membranes can be exposed to more robust decontamination or sterilisation processes. Therefore, the processing environment is not as critical for those amniotic membrane types but the process should be validated and the maximal acceptable bioburden should be defined in order not to overly restrict the decontamination process.

Criterion	Explanation	Skin-specific
Risk that contaminants will not be detected in the final tissue or cell product due to limitations of the sampling method	Where the only possibilities for final microbiological sampling are swabbing or testing of unrepresentative samples, the risk that environmental contaminants will be undetected is higher compared to processes where 10% destructive testing of final products can be performed.	Sampling of amniotic membrane for microbiological analysis following antibiotic soaking is not extensive; typically a very small percentage is sampled. However, the storage medium can also be sampled.
Risk of transfer of contaminants at transplantation	Tissues that are minimally processed, cellularised, containing blood, blood vessels and lipids are more likely to support microbial contaminants than those that are blood- and cell-depleted. Tissues or cells that are applied to small areas on the external surfaces of the body, or to areas that are minimally vascularised, are less likely to transmit infections than those that are infused into the blood stream or implanted into internal organs.	Although not vascularised, amniotic membrane can support microbiological contaminants and has transmitted bacterial and viral agents. Amniotic membrane is mostly used for ophthalmologic purposes. However, other indications are burns, skin ulcers, arthroplasty and in intra-abdominal and reconstructive surgery. These patients can also develop immunosuppression by various mechanisms and, despite recent advances in therapy, have a high risk of death from infections.

Taking the factors from Table 14.1 into consideration, it is appropriate that processing of hAM allografts should take place in a bacteriologically- and climate-controlled environment (including temperature and humidity control, ventilation and air filtration), with validated cleaning and disinfection. For cryopreserved hAM where less bacterial inactivation is possible, a particularly clean and well-controlled environment is required.

Within the EU, tissues that are exposed to the environment without a subsequent microbial inactivation process (e.g. cryopreserved viable skin) should be processed in environments with an air quality equivalent to those of Grade A, as defined in EU Good Manufacturing Practice (GMP), with a background environment at least equivalent to EU GMP Grade D. Many national requirements for hAM processing environments are more stringent, requiring EU GMP Grade C or B as a background, which might be more appropriate for processing tissues prone to tissue contamination due to extensive manipulation or processing phases at ambient temperature and that are not followed by a terminal sterilisation step.

14.4.3. Processing methods

Procured hAM can be processed to facilitate longer storage periods until transplantation in suitable patients. The methods used should be up-to-date and validated. Tissue establishments tend to use different graft processes, according to their own standard operating procedures (SOPs) and mandatory regulations.

The foetal membranes should be rinsed several times, and the amnion and chorion should be mechanically separated and blood residues should be removed according to a documented standard operating protocol. The amnion should be placed on a suitable carrier membrane (e.g. nitrocellulose membrane) if it needs to be divided into smaller pieces.

Maximum storage durations should be specified in all cases. There are several methods of hAM preparation and preservation (see below).

14.4.3.1. Cryopreservation

Amniotic membrane can be cryopreserved in a medium with cryoprotectant using an appropriate container (bags or cryovials) and transferred to liquid nitrogen tanks (vapour phase, -140°C).

However, if the hAM is stored in sterile glycerol medium, the storage temperature is usually below -60°C .

If stored at higher temperatures, the process should be validated, taking into account the quality of the tissues over time.

14.4.3.2. Heat-dried amniotic membrane

The tissue is dried overnight in an oven at 40 ± 2 °C, then sterilised using 25 kGy gamma irradiation. Since the membrane loses many of its biologic properties due to the high temperature, hAM preserved in this way is typically used as a biologic dressing for the management of burns.

14.4.3.3. Air-dried amniotic membrane

After the amniotic membrane is separated and washed in sterile conditions, it is air-dried overnight in a laminar flow hood. It can then be sterilised using gamma irradiation and packaged. Although high temperatures are not applied using this method, some properties of the amnion are lost or altered due to dehydration. Amniotic membrane prepared in this way can be used for wound dressings.

14.4.3.4. Lyophilised (freeze-dried) amniotic membrane

The amniotic membrane can be cut into pieces and rapidly frozen at -50 to -80 °C. Then it is vacuum-dried using a freeze-drying device. Water in the tissue is extracted through sublimation until a final water content of 5-10% is attained. The tissue can then be sterilised using gamma irradiation and packaged. This type of preparation induces minimal changes in the properties of the amniotic membrane and the product can be stored at ambient temperature. Lyophilised amniotic membranes should be transported at ambient temperature. This type of preparation is mainly used for the management of wounds.

14.4.3.5. Preservation in cold glycerol

Glycerol has long been used as a cryoprotective agent. Due to its high osmotic potential, it can extract interstitial water from the amniotic membrane. Typically, 80% glycerol is used to dry the amniotic membrane, which can then be preserved at 4 °C for a long time, although it loses some of its biologic properties. Amniotic membranes preserved in this way are used as dressings for burns.

14.4.3.6. Antibiotic impregnated amniotic membrane

After separation, the amniotic membrane is placed overnight in an antibiotic solution composed of five different types of wide-spectrum antibiotics and an anti-fungal agent and then frozen at -80°C . The resultant amniotic membrane is suitable for the management of infected wounds by providing an appropriate concentration of antibiotics to the wound surface.

14.5. Quality control

During procurement and preservation of hAM, a reliable macroscopic examination of the donor placenta should be performed to exclude visible pathological changes.

Samples for detecting aerobic and anaerobic bacteria and fungal cultures should be obtained from the transport/storage medium, the rinsate from washings of the membrane, or from pieces of the membrane, before placing it in antibiotic solutions and before packaging. A microbiological method for the detection of bacteria and fungi should be applied that is validated as effective for the types of contaminants that occur on this tissue.

14.6. Distribution

For cryopreserved hAM, distribution temperatures between -60°C and -85°C should be maintained, for example using dry ice. Transport temperatures of cryopreserved human amniotic membrane above -60°C are to be strictly avoided to ensure the stability of the product and maximum safety for the recipient. The tissue establishment must ensure that all storage processes are performed under controlled conditions.

Lyophilised amniotic membrane can be stored and distributed at ambient temperature. Foetal membranes preserved in cold glycerol should be transported under cold temperatures between 2 and 10°C .

Chapter 15. Specific skin requirements

15.1. Introduction

Donor skin grafts can play a critical role in the treatment of severely burned patients by acting as skin replacement, a vehicle for dermal tissue to guide repair in a more physiological manner, or as a means of reducing scarring, maintaining body homeostasis and controlling pain. For these reasons, it is considered the treatment of choice for substantial loss of skin tissue, such as in cases of severe burns for which it acts as a life-saving therapy. Homologous skin is also considered to be an excellent biological dressing for the treatment of other types of skin loss such as venous ulcers, decubitus ulcers, toxic epidermal necrolysis (Lyell's syndrome), surgical wounds and congenital epidermolytic skin disorders. In these cases, skin grafts promote re-epithelisation, shorten healing time, control pain and may protect important structures such as tendons, bones, cartilage and nerves.

These factors explain the constant demand for skin allografts by burns centres, and reconstructive and vascular surgery units, where the capacity of these bio-products to “take” and integrate into the wound bed are exploited.

The shortage of homologous skin grafts has promoted the development of skin-replacement products and many research groups have focused on biomaterials for skin substitution in wound healing. In the last 30 years, a huge number of biological and synthetic skin/dermal substitutes have been developed with the aim of producing an artificial skin that is able to replace human skin completely, but an ideal skin substitute has not yet been realised. A further logical

development of this research involves the use of stem cells to repopulate the dermal matrix and reproduce “physiological” skin.

The generic chapters of this Guide (see Part A) all apply to skin banking and must be read in conjunction with this chapter. For the following aspects, there are no additional requirements apart from those described in the generic chapters:

- a. Packaging and labelling (Chapter 3)
- b. Donor Testing (Chapter 5)
- c. Distribution and import/export (Chapter 8)
- d. End users (Chapter 9)
- e. Computerised systems (Chapter 10)
- f. Traceability (Chapter 11)
- g. Biovigilance (Chapter 12)

This chapter defines the additional specific requirements for skin.

15.2. Skin-specific donor evaluation

15.2.1. Skin inspection

In addition to the standard physical examination described in Chapter 4, the donor’s skin must be inspected in a particular manner prior to skin procurement. Skin should be checked for multiple or dysplastic naevi, dermatitis, local infections, ectoparasites or rashes. The results must be recorded and taken into account before initiating the final release of the tissue.

15.2.2. Skin-specific exclusion criteria

In addition to the donor exclusion criteria described in Chapter 4, there are some specific conditions that exclude skin donation. The list of selection criteria for donors is based on a risk analysis related to the use of the tissue on patients, i.e. to minimise the risk of transfer of diseases to the recipient and to ensure the appropriate quality of the skin

for optimal functional results. The following conditions contraindicate skin donation:

- a. auto-immune dermatoses;
- b. systemic connective tissue diseases;
- c. diseases affecting the dermis (dermal mucinosis, nephrogenic fibrosing dermopathy, porphyria);
- d. mechanical or microbial damage to the skin;
- e. burns at the location on the body where skin is to be procured;
- f. toxicity of the skin as a result of the presence of toxic agents or poisons;
- g. presence of possible melanomas;
- h. systemic infections, which at the time of donation are not under control.

The following relative contraindications for skin donation should be considered on a case-by-case basis:

- a. extensive lacerations or scars;
- b. skin diseases with extensive involvement, such as psoriasis, eczema or nodules;
- c. relevant ulcers, decubitus, pyoderma or mycoses;
- d. skin disorders interfering with procurement or aesthetically not acceptable for patients (e.g. extensive tattoos);
- e. diabetes for > 10 years with complications.

15.2.3. Skin-specific procurement procedures

It is recommended to refrigerate the body prior to procurement in order to obtain suitable tissue, reduce skin contamination and facilitate skin procurement due to the harder consistency of the subcutaneous tissue. Procurement from living donors can also be performed in patients undergoing abdominoplasty who consent to tissue donation.

Skin from living donors having abdominoplasty operations is procured to obtain full-thickness skin grafts (1-3 mm). The area is

prepared by depilation and disinfection. The tissue can be processed for de-epidermisation and cryopreservation or lyophilisation.

15.2.4. Skin-specific post-mortem time

Skin can be procured up to 24 hours after death if the body is cooled or refrigerated within 6 hours of death. If the donor body was not refrigerated after death, then procurement should be completed within 15 hours of death.

15.3. Skin procurement

15.3.1. Skin-specific procurement team

Skin procurement teams should consist of at least two people, operating under aseptic conditions and appropriately clothed for the type of procurement. In the case of multi-tissue procurements, the order in which the tissues are removed should be standardised and pre-defined and, in the case of multiple procurement teams, should be agreed between the teams beforehand so that risks of cross-contamination between tissues are minimised. Procurement teams should follow an effective and validated donor disinfection procedure, which can significantly reduce the microbial positivity rate of processed skin samples. Studies show that whether the skin procurement is performed before or after bone procurement, the contamination rate of skin is no different if the procurement process is controlled and standardised [1].

15.3.2. Skin procurement procedure

The skin is procured under aseptic conditions after adequate shaving of the donor areas and appropriate pre-operative disinfection of the skin to remove the transient and reduce the resident microbial flora. A standardised procedure should be established for skin disinfection by the tissue organisation and allocated to all procurement sites.

The procedure should guarantee the elimination of bacterial spores as well as vegetative micro-organisms. Therefore, suitable disinfectants,

such as povidone iodine or peracetic acid, should be chosen. Their concentrations and the durations of exposure should also be evaluated.

A local sterile field using sterile drapes must be used prior to procurement to effectively reduce microbial contamination. Skin grafts are cut by electric or battery-operated dermatomes from areas of the body that are typically not exposed, particularly from the posterior trunk and the lower limbs. Graft thickness usually ranges between 200 and 800 microns and each graft should be cut as long and homogeneously as possible.

15.3.3. Reconstruction of the skin donor

For aesthetic reasons and with a view to a respectful reconstruction of the donor, it is not acceptable to take skin from the neck, face and other typically exposed areas of the body that might be visible when people pay their last respects to the donor. Once the tissue has been procured, non-leaking garments should be used to prevent seepage.

15.3.4. Procurement documentation

The organisation responsible for the skin procurement must produce a procurement report to be provided to the tissue establishment. In addition to the generic requirements defined in Chapter 6, it must contain a description and identification of the procured skin (including samples for testing).

15.3.5. Skin transportation to the tissue establishment

The skin layers must be packaged immediately after procurement in a suitable transport medium in sterile, sealed, refrigerated containers that are adequately labelled to ensure traceability (see Chapter 3). Storage at low temperatures prevents proliferation of most bacteria and fungi and maintains viability. The temperature of the package during transport to the tissue establishment must be monitored and be between 2 and 10 °C.

15.3.6. Receipt of procured skin at the tissue establishment

The recovered skin should be transferred to the tissue establishment as soon as possible after procurement or should be put in an initial processing fluid directly after procurement. After the skin has been received by the tissue establishment, processing of the skin should commence within 72 hours of procurement having taken place. Prior to processing, the skin should be kept in a refrigerator, in a physiological medium with sufficient buffering capacity. It is recommended that the cell nutrient medium be changed in a climate-controlled environment shortly after receipt of the skin grafts.

15.4. Skin processing

The recovered skin is processed to allow longer storage periods until transplantation in suitable patients. The methods used must be in line with current state-of-the-art and validated procedures (see Chapter 7). Different tissue establishments apply specific preparation processes according to their own standard operating procedures (SOPs) and any applicable local authorisations.

15.4.1. Processing facilities

In selecting an appropriate air quality specification for skin processing, the criteria identified in Chapter 7 should be considered. Table 15.1 outlines those factors to be considered for skin processing.

Table 15.1. Factors influencing the specification of processing air quality for skin

Criterion	Explanation	Skin-specific
Risk of tissue or cell contamination during processing	Processes that are mostly “closed” (e.g. bone marrow cryopreservation where the only exposure of the cells to the environment is when a spike is inserted to add cryoprotectant) need a less stringent specification than those that involve hours of open processing (e.g. bone and tendon graft cleaning and shaping).	During processing, skin is necessarily exposed to the processing environment for extended periods.
Use of anti-microbials during processing	Some tissues, even though not terminally sterilised, can be exposed to various anti-microbial agents without compromising the characteristics required for clinical efficacy. Processes that include, for example, detergent washing, alcohol rinses, HCl treatment, imply less risk of transferring an environmental contaminant than those where cell viability is required and no anti-microbial agents can be applied, or the only anti-microbial step possible is soaking in antibiotics.	Soaking in antibiotics is the only anti-microbial step possible for cryopreserved skin. Glycerolised skin or lyophilised skin can be exposed to more robust decontamination or sterilisation processes, so the processing environment is not as critical for those skin types.

Criterion	Explanation	Skin-specific
Risk that contaminants will not be detected in the final tissue or cell product due to limitations of the sampling method.	Where the only possibilities for final microbiological sampling are swabbing or testing of unrepresentative samples, the risk that environmental contaminants will be undetected is higher compared to processes where 10% destructive testing of final products can be performed.	Sampling of skin for microbiological analysis following antibiotic soaking is not extensive; a very small percentage is typically sampled.
Risk of transfer of contaminants at transplantation	Tissues that are minimally processed, cellularised, containing blood, blood vessels and lipids are more likely to support microbial contaminants than those that are blood- and cell-depleted. Tissues or cells that are applied to small areas on the external surfaces of the body, or to areas that are minimally vascularised, are less likely to transmit infections than those that are infused into the blood stream or implanted into internal organs.	Although not vascularised, cryopreserved skin can support microbiological contaminants and has transmitted bacterial and viral agents. Although skin is placed on the external surface of the body, it is mostly used for severely burned patients whose own skin barrier is no longer functional. These patients usually develop immunosuppression by various mechanisms and, despite recent advances in therapy, have a significant risk of death from infection.

Taking the factors from Table 15.1 into consideration, it is appropriate that processing of skin allografts takes place in a bacteriologically- and climate-controlled environment (including temperature and humidity control, ventilation and air filtration), with validated cleaning and disinfection. For cryopreserved skin, a particularly clean and well-controlled environment is required.

Within the EU, tissues that are exposed to the environment without a subsequent microbial inactivation process (e.g. cryopreserved

viable skin) should be processed in environments with an air quality equivalent to those of Grade A, as defined in EU Good Manufacturing Practice (GMP), with a background environment at least equivalent to EU GMP Grade D. Many national requirements for skin processing environments are more stringent, requiring EU GMP Grade B or C as a background, which might be more appropriate for processing tissues prone to tissue contamination due to extensive manipulation or processing phases at ambient temperature and that are not followed by a terminal sterilisation step.

15.4.2. Skin decontamination and preservation

After being received by the tissue establishment, skin is decontaminated and processed into fresh, glycerol-preserved, cryopreserved or lyophilised skin allografts, according to the procedures of the tissue establishment. Skin grafts to be cryopreserved are processed immediately after receipt in order to maintain cell viability. Skin allografts can also be processed as de-epidermised dermis. All human tissues intended for transplantation are processed into specimens appropriate for clinical use. Processing must not change the physical properties of the tissue so as to make it unacceptable for clinical use. All processes must be validated in accordance with the guidance in Chapter 2. Compliance of processing standards with published guidelines ensures adherence to generally accepted quality standards. The maximum shelf-life of tissue grafts under each type of storage condition should be specified.

15.4.3. Skin graft sizing

Skin allografts can be cut into specific sizes or can be cut to the actual size required for the skin grafts. Skin grafts may be provided as meshed or non-meshed grafts.

The graft's rough edges should be trimmed and, typically, a rectangular shape is measured with a ruler or callipers. The linear dimensions and the area of each skin graft must be recorded, as too must the location of origin (e.g. leg, back, abdomen). The grafts should then be packaged in appropriate sterile packages.

15.4.4. **Glycerol-preserved skin allografts**

This method was developed [2] to maintain skin allografts without freezing, using an increasing series of glycerol concentrations (50%, 70% and 85%). Glycerol-preserved allografts (GPA) are a de-vitalised skin graft, which is considered a safe product due to the anti-bacterial/anti-viral properties of high concentrations of glycerol. The glycerol solutions used should be sterile and of high quality (e.g. see European Pharmacopoeia monograph *Glycerol 85 per cent (0497)*).

15.4.5. **Fresh skin allografts**

This is a method for the storage of viable skin allografts which maintains their structural integrity for short periods of time (days to weeks). Fresh skin can be stored in a refrigerator.

15.4.6. **Cryopreserved skin allografts**

Cryopreservation of skin allografts necessitates rapid processing phases at low temperatures in order to maintain cell viability. Inappropriate storage compromises the potential to restore normal metabolic activity and, thus, physiological functioning after transplantation.

Cryoprotectants such as glycerol or dimethylsulfoxide (DMSO) can adversely affect cell viability. Cell viability should be assessed both by qualitative (histomorphology and/or immunochemistry) and quantitative methods. A controlled (refrigeration curve) and validated refrigeration procedure is recommended. Cryopreservation between -60 and -80 °C is a method for medium-term (months) preservation of viable skin allografts. Viable skin allografts can be stored in liquid or vapour nitrogen for longer periods (years).

15.4.7. **Lyophilised skin allografts**

This is a method for the storage of non-viable skin allografts. Lyophilised skin can be kept at ambient temperature. A maximum limit for residual moisture should be defined.

15.4.8. De-epidermised dermis

This is a method to lower the antigenicity of the skin graft. Full-thickness skin is aseptically processed to remove the epidermis and cells that can lead to tissue rejection and graft failure. The result is an intact acellular matrix of dermis that can be cryopreserved or lyophilised.

15.4.9. Sterilisation of skin allografts

When tissue viability is not required or where skin tests positive for microbiological contaminants, it can be sterilised by gamma-irradiation. Research has shown that 25 kGy irradiation of deep-frozen skin in radio-protective solutions sterilises the tissue without histomorphological or physical alterations compared to normal cryopreserved skin [3].

15.5. Quality control

15.5.1. Microbiological testing of skin

It is recommended to perform microbiological testing prior to the start of processing and on post-processed samples of skin in cryoprotectant (without antibiotic) for each anatomical area. Specimens should be obtained directly from the site that has been processed and placed in a specimen container labelled with the anatomical area (back, leg, etc.). These specimens should be sent for destructive culturing to check for bacteria and fungi. Acceptance criteria regarding the presence of microbial contaminants in processed tissues should be defined in advance and reported in written procedures. Specimens contaminated by critical pathogens, such as *Clostridium*, should be discarded without corrective actions in order to remove potentially unsuitable tissue from the transplantation process.

Processing facilities should have a robust quality control/assurance programme that has a validated process to eliminate or reduce potential pathogens that may cause disease transmission. This should include evaluation of the bacteriologic bio-burden (for pre-processing

and in-processing samples to evaluate contamination), validated bacteriologic and/or virucidal washes and/or treatments, final product testing for microbiological contamination using destructive testing and a final review of screening/testing by the Responsible Person of the tissue establishment prior to release of the tissues for transplantation.

15.5.2. Skin allograft distribution

As skin allografts are considered a life-saving therapeutic material, tissue establishments should have a written procedure for allocation of the grafts based on clinical priority criteria. Distribution of skin grafts for transplantation should be restricted to hospitals, tissue establishments, physicians, dentists or other qualified medical professionals in compliance with any national regulations.

15.6. References

1. Pianigiani E, Ierardi F, Cuciti C et al. Processing efficacy in relation to microbial contamination of skin allografts from 723 donors. *Burns*. 2010;36(3):347-51.
2. Mackie DP. The Euro Skin Bank: development and application of glycerol-preserved allografts. *J Burn Care Rehabil* 1997;18:s7-9.
3. Rooney P, Eagle M, Hogg P, Lomas R, Kearney J. Sterilization of skin allograft with gamma irradiation. *Burns* 2008; 34:664-673.

Chapter 16. Specific cardiovascular requirements

16.1. Introduction

Cardiovascular tissues can be procured from deceased heart-beating and non-heart-beating and from living donors (in the case of a patient undergoing a heart transplant when the indication for their transplant procedure is not a valvular disease). Cardiovascular tissues that can be donated and transplanted include valves (aortic, pulmonary and mitral), arteries and veins.

Due to the greater resistance to infection of allografts compared with synthetic materials, the current most important clinical indication for adults is the replacement of infected valves (endocarditis) and the replacement of infected vascular prostheses. For valve replacement in newborns and young patients, human valves are usually transplanted to repair congenital malformations. They are the preferred option as they avoid the need for long-term anti-coagulant therapy (as required for the mechanical alternative) and do not tend to calcify as rapidly (as do the xenograft alternatives). In the case of arterial tissues, peripheral re-vascularisation and arterial patches for repair of congenital malformations are the most common indications.

The future of cardiovascular tissue banking is to develop new procedures, such as valve and vascular de-cellularisation, to allow re-cellularisation with cells from the recipient, either *in vitro* before implantation or *in vivo* after the tissue implant. Tissue engineering (i.e. combining synthetic materials with de-cellularised human matrices),

and other advanced therapy procedures, represent important technical improvements in the future for cardiovascular tissue banking.

The generic chapters of this Guide (see Part A) all apply to cardiovascular tissue banking and must be read in conjunction with this chapter. For the following aspects, there are no additional requirements apart from those described in the generic chapters:

- a. Packaging and labelling (Chapter 3)
- b. Donor Testing (Chapter 5)
- c. Distribution and import/export (Chapter 8)
- d. End users (Chapter 9)
- e. Computerised systems (Chapter 10)
- f. Traceability (Chapter 11)
- g. Biovigilance (Chapter 12)

This chapter defines the additional specific requirements for cardiovascular tissue.

16.2. Donor evaluation

16.2.1. Contra-indications specific for cardiovascular tissue

The following exclusion criteria are specific to cardiovascular tissue donation:

- a. cardiac valvulopathy of the aortic and pulmonary valves, with moderate to severe incompetence (the vessels can still be acceptable);
- b. aortic dissection (detachment of the intima and adventitia);
- c. direct (open) and massive traumas in the procurement area;
- d. Marfan's syndrome;
- e. freezing of the body;
- f. bacterial or fungal endocarditis.

Other conditions to be evaluated as part of the donor selection process are:

- a. chronic alcoholism with myocardial dilatation;
- b. epilepsy, both presumed (in case of recent onset and not fully investigated) and being treated;
- c. pneumonia in previous days without evidence of effective treatment;
- d. previous cardio-surgical interventions on the tissue to be procured.

Common practice is to procure vessels from donors below 55 years and heart valves from donors below 65 years. However, some centres are validating the extension of these limits.

16.3. Procurement

16.3.1. Procurement team

The cardiovascular procurement teams should consist of at least 2 people. They should work under aseptic conditions, and be scrubbed, gowned in sterile clothing, and wear sterile gloves, face shields and protective masks.

16.3.2. Procurement procedure

For heart valve procurement it is important, whenever possible, to procure the ascending aortic artery (including the supra-aortic trunks and the pulmonary artery with the complete bifurcation) together with the heart.

For vessel donors, the maximum possible length of the recovered vessel should be maintained, avoiding iatrogenic lesions during manipulation, and collateral branches should be cut at 2-3 mm from the arterial wall.

16.3.3. Tissue transportation to the tissue establishment

Common practice is to place procured tissues in a crystalloid transport solution with the possible addition of nutritional or osmotic elements (e.g. Betzler, Hank's medium, albumin) and/or antibiotic solutions and packaged in at least two sterile packaging layers after procurement.

For donors of organs, valves and vessels, it is convenient to package the heart and the vascular segments in different containers.

This package should then be placed in another container that ensures a temperature between 2 and 10 °C and protects the recovered tissues during transport.

16.3.4. Procurement documentation

The organisation responsible for procurement must produce a procurement report to be given to the tissue establishment. In addition to the generic requirements defined in Chapter 6, this report must contain a description and identification of the recovered material (heart, arteries, veins, valves, etc.).

16.4. Processing and storage

Procured cardiovascular tissues can be processed to facilitate longer storage periods and to reduce microbial contamination.

In order to ensure tissue quality, it is essential that the time between cardiac arrest and cryopreservation be as short as possible. Cardiovascular tissue should be procured within 24 hours after death if the body has been refrigerated in the first 6 hours after death or within 15 hours after death if the body has not been refrigerated. Time from procurement of the heart to dissection and disinfection should not exceed 24 hours.

Processing of cardiovascular tissues includes dissection and evaluation of minimum functional requirements, incubation with antibiotics and, in some cases, anti-mycotics, cryopreservation and storage. The duration and temperature of antibiotic treatment and the composition

of antibiotic cocktails should be defined by each tissue establishment, with prior evaluation of the initial tissue bioburden (i.e. before the tissue comes into contact with an antibiotic solution) and following a validation of the effectiveness of the cocktail against the most common microbes likely to contaminate the tissues.

The methods used must be in line with current state-of-the-art and validated procedures (see Chapter 7). Different tissue establishments apply specific preparation processes according to their own standard operating procedures (SOPs) and in line with relevant local authorisations.

16.4.1. Processing facilities

In selecting an appropriate air quality specification for cardiovascular tissue processing, the criteria identified in Chapter 7 should be considered. Table 16.1 outlines those factors to be considered for cardiovascular tissue processing.

It is vital that the processing of cardiovascular allografts take place in a microbiologically and physically controlled environment with temperature control, ventilation and air filtration, and with validated cleaning and disinfection. Taking the factors from Table 16.1 into consideration, cardiovascular tissue should be processed in optimal environments with an air quality of Grade A (EU GMP Guidelines) with an adequate background environment. For EU countries, the background must be at least Grade D (EU GMP), but given the risks associated with the processing, testing and implantation of cardiovascular tissues, it is recommended that a Grade B background environment (EU GMP) be provided.

Table 16.1. Factors influencing the specification of processing air quality for cardiovascular tissue

Criterion	Explanation	Skin-specific
Risk of tissue or cell contamination during processing	Processes that are mostly “closed” (e.g. bone marrow cryopreservation where the only exposure of the cells to the environment is when a spike is inserted to add cryoprotectant) need a less stringent specification than those that involve hours of open processing (e.g. bone and tendon graft cleaning and shaping).	During processing, heart valves and vessels are exposed to the processing environment for extended periods during dissection, sizing and evaluation of their characteristics.
Use of anti-microbials during processing	Some tissues, even though not terminally sterilised, can be exposed to various anti-microbial agents without compromising the characteristics required for clinical efficacy. Processes that include, for example, detergent washing, alcohol rinses, HCl treatment, imply less risk of transferring an environmental contaminant than those where cell viability is required and no anti-microbial agents can be applied, or the only anti-microbial step possible is soaking in antibiotics.	Heart valves and vessels are exposed to antibiotics, and in some cases, anti-mycotics, with a typical decontamination period of 24 hours. It is important to validate the effectiveness of the antibiotic cocktail and to list the micro-organisms that can be accepted pre-incubation as this method is not very effective compared to more robust methods that can be applied to other tissues.

Criterion	Explanation	Skin-specific
Risk that contaminants will not be detected in the final tissue or cell product due to limitations of the sampling method.	Where the only possibilities for final microbiological sampling are swabbing or testing of unrepresentative samples, the risk that environmental contaminants will be undetected is higher compared to processes where 10% destructive testing of final products can be performed.	Sampling of a piece of myocardium or a discarded vessel for microbiological analysis does not ensure a representative sample for analysis. Storage media or rinsates from washings should also be sampled to make this evaluation more effective.
Risk of transfer of contaminants at transplantation	Tissues that are minimally processed or cellularised, or containing blood, blood vessels and lipids are more likely to support microbial contaminants than those that are blood- and cell-depleted. Tissues or cells that are applied to small areas on the external surfaces of the body, or to areas that are minimally vascularised, are less likely to transmit infections than those that are infused into the blood stream or implanted into internal organs.	Cardiovascular tissue is vascularised and can support and transmit microbiological contaminants, bacterial and viral agents. Cardiovascular tissue is used in open surgery in well-vascularised areas and frequently to replace infected tissue (endocarditis). If it is contaminated, the risk of serious infection is considerable.

16.5. Cryopreservation and storage in liquid nitrogen

Cardiovascular tissues can be cryopreserved by using a controlled rate freezer and following a validated protocol. During the cryopreservation process, the parameters of the freezing cycle must be recorded, as well as any inconsistencies that might have occurred during the operation. After cryopreservation, the frozen tissues can be transferred to a temperature-monitored liquid nitrogen tank and stored either in

the vapour phase of liquid nitrogen (between -140°C and -150°C) or immersed in the liquid nitrogen itself (between -170°C and -190°C). Some tissue establishments use ultralow temperature electric freezers working below -135°C . Cardiovascular tissue can be stored in liquid nitrogen (vapour phase or liquid) for up to 5 years. Longer storage periods should be validated.

16.6. Cardiovascular tissue thawing

Thawing, the removal of the cryoprotective medium (dilution) and re-establishment of the isotonic state of the vascular allograft are of critical importance in order to guarantee the integrity of the cryopreserved tissue. The record that accompanies the cryopreserved tissue must contain the detailed protocol of thawing, dilution and tissue reconstitution that was performed, together with a comprehensive list of the materials used.

16.7. Quality control

It is recommended that the quality control tests on cardiovascular grafts should consider the following minimum quality criteria:

- a. non-reactive results for the mandatory virology markers;
- b. functional competence. It should be noted that fenestrations within the margins of the lunulae are very often not a pathological finding. Provided the coaptation of the graft is ensured by adequate sizing, marginal fenestrations should not induce valve regurgitation either in the short- or long-term. Large fenestrations, particularly when they are in opposing cusps, should constitute a rejection criterion;
- c. good morphology (no fissures, congenital defects, no/minimal calcification, etc.). Only small calcifications in the distal wall of the aorta, where they are most likely not to interfere with graft functioning, can be accepted; although information on their size and location must be clearly reported to the clinical user;

- d. anatomical suitability, i.e. accurate length of conduit and diameter of annulus. Special attention should be paid to achieving an accurate measurement of the diameter of the annulus to avoid overstretching; this is particularly critical for the pulmonary valve;
- e. intact tissue matrix structure.

Cardiovascular allografts must be microbiologically sampled and cultured for aerobic and anaerobic bacteria, as well as fungi and yeasts, according to European Pharmacopoeia criteria, before antibiotic and, where relevant, anti-mycotic incubation.

Microbiological analyses should be performed on:

- a. the transport medium at the beginning of the processing procedure;
- b. the sub-valvular (aortic and pulmonary) myocardial tissue and vessels before antibiotic incubation;
- c. a final sample of each graft after antibiotic/anti-mycotic incubation and rinsing, but before final packaging.

The result of the microbiological control, performed according to European Pharmacopoeia criteria, of the final sample must be negative, otherwise the tested heart valve or vessel must be discarded.

Table 16.2 suggests a list of micro-organisms which, if detected in any cardiovascular tissue culture, even if detected only prior to decontamination, requires that the tissue be designated as unsuitable for clinical use.

Table 16.2. Suggested list of contaminants that should result in tissue discard if detected at any stage of processing

<i>Clostridium</i> sp. (notably <i>C. perfringens</i> or <i>C. tetani</i>)
<i>Enterococcus</i> sp.
<i>Flavobacterium meningiosepticum</i>
<i>Klebsiella rhinoscleromatis</i>
<i>Listeria monocytogenes</i>
<i>Neisseria gonorrhoeae</i>
<i>Nocardia</i> sp.
<i>Pseudomonas aeruginosa</i> or <i>P. pseudomallei</i>
<i>Staphylococcus aureus</i> (MRSA)
<i>Salmonella</i> sp.
<i>Shigella</i> sp.
<i>Streptococcus pyogenes</i> (Group A)
<i>Aspergillus</i> sp.
<i>Candida</i> sp.
<i>Mucor</i> sp.
<i>Penicillium</i> sp.
Other yeasts and fungi
<i>Mycobacteria</i> sp.

This means, for example, that detection of *Enterococcus* sp. in a pre-antibiotic aortic myocardium sample, with a negative result in all other samples (e.g. transport medium, post-decontamination aortic sample and before final packaging), should result in rejection of all cardiovascular tissue from this donor.

16.8. Cardiovascular allograft distribution

Transportation of cardiovascular tissues can be carried out using dry-shipping containers (vapour phase nitrogen between -140°C and

–150 °C). This allows re-storage of the tissues in the liquid or vapour phase of nitrogen without affecting the expiry date. If the tissue is to be re-stored at –80 °C, then the expiry date must be reduced to a maximum of 6 months. If dry ice is used for transportation of the vascular allograft, the tissue should not be returned to liquid or vapour phase nitrogen tanks, but must be re-stored at –80 °C and the expiry date reduced to a maximum of 6 months. Once cardiovascular tissues have been thawed, they cannot be re-frozen.

Transport temperatures above –60 °C for cryopreserved cardiovascular tissues are to be strictly avoided to ensure the stability of the product and maximum safety for the recipient. The receiving tissue establishment must ensure that all packaging and distribution processes have been performed under controlled conditions.

Chapter 17. Specific musculoskeletal requirements

17.1. Introduction

Musculoskeletal tissues can be procured from deceased heart-beating and non-heart-beating donors and from living donors (e.g. in the case of a patient undergoing hip or knee prosthesis surgery), and include bones, ligaments, tendons, meniscus, cartilage and other soft tissues (e.g. fascia lata). The current indications for the implantation of musculoskeletal tissues are, but are not limited to, tumour surgery, prosthesis replacement, filling where there is bone loss, fractures, malunion, bone fusion (spine and limbs), and ligament and meniscus replacement. The future of musculoskeletal tissue banking is focused on the following areas:

- a. to develop new preservation methods to maintain the biological properties of the grafts;
- b. to develop new procedures such as de-cellularisation or cell therapy to improve graft incorporation in recipients.

The generic chapters of this Guide (see Part A) all apply to musculoskeletal tissue banking and must be read in conjunction with this chapter. For the following aspects, there are no additional requirements apart from those described in the generic chapters:

- a. Packaging and labelling (Chapter 3)
- b. Donor testing (Chapter 5)
- c. Distribution and import/export (Chapter 8)
- d. End users (Chapter 9)

- e. Computerised systems (Chapter 10)
- f. Traceability (Chapter 11)
- g. Biovigilance (Chapter 12).

This chapter defines the additional specific requirements for musculo-skeletal tissue.

17.2. Donor evaluation requirements

17.2.1. Physical evaluation

The donor's body must be inspected before starting the procurement procedure to check for contraindications. The entire body should be checked for the presence of bone or joint deformities, open fractures or surgical scars. The results must be recorded and taken into account during the procurement and processing phases, as well as before the final release of the tissue.

17.2.2. Specific contra-indications for musculoskeletal tissue

In addition to the general exclusion criteria described in Chapter 4, screening of musculoskeletal tissue donors should be conducted for the following disorders and age limits:

1. Bone, cartilage, osteoarticular grafts, tendons, meniscus and fascia lata:
 - a. history of osteo-arthritis;
 - b. metabolic bone diseases (osteoporosis, osteopetrosis, Paget's disease, etc.);
 - c. ingestion of cyanide or heavy metals (mercury, gold, etc.);
 - d. local bacterial, viral, parasitic or mycotic infection;
 - e. systemic lupus erythematosus;
 - f. polyarteritis nodosa;
 - g. sarcoidosis;

- h. evidence of local trauma (e.g. open fracture).
- 2. In addition to the contra-indications of point 1 above, iatrogenic or degenerative tears or lesions detected during procurement of cartilage, meniscus, tendons and osteoarticular grafts contraindicate the use of the tissue.
- 3. Donor age limits differ for different kinds of musculoskeletal tissues. These limits may be revised upon performance of a validation study. Some countries have national guidelines or requirements but, in their absence, the following age limits, for male or female donors, are recommended:
 - a. for bone; a lower age of 15 years (6-15 years for paediatric donors). No upper age limits except when the bone is to be used for structural support, in which case younger donors are normally preferred;
 - b. for tendons and fascia lata: 15-65 years;
 - c. for osteo-articular grafts, cartilage, meniscus: 15-45 years.

17.3. Procurement

17.3.1. Procurement from deceased donors

Limiting the number of members of the procurement team can be critical to minimising the contamination rate of tissues during procurement [1].

Staff must have the experience, education and training necessary to procure tissues, including significant anatomical knowledge to accurately obtain not only the regular tissues recovered (femur, patellar ligaments, etc.), but also specially requested materials (e.g. whole elbow). The musculoskeletal tissue procurement team should work under aseptic conditions, and be scrubbed, gowned in sterile clothing and wear sterile gloves, face shields and protective masks.

It is important to define the functions of the different members of the team for the procurement process to avoid cross-contamination.

The musculoskeletal tissues must be procured after appropriate pre-operative disinfection of skin to reduce the transient and reduce the resident microbial flora. A local sterile field using sterile drapes must be used prior to procurement to effectively reduce microbial contamination.

The musculoskeletal tissues most frequently procured from deceased donors are:

- a. long bones of the lower limb;
- b. femur;
- c. tibia and fibula;
- d. iliac crest or hemi-pelvis;
- e. long bones of the upper limb;
- f. humerus;
- g. ribs;
- h. fascia lata;
- i. Achilles tendon;
- j. patellar tendon;
- k. menisci.

17.3.2. Reconstruction of the deceased donor

Once tissues have been procured from a deceased donor body, it must be reconstructed to maintain its original anatomical appearance.

For aesthetic reasons and with a view to a respectful reconstruction of the donor, a wooden or plastic replica bone approximating the size of the donated bone may be used to replace the procured bone. The incised muscles, subcutaneous tissue and skin should be sutured. The use of sutures and other materials suitable for cremation should be considered.

17.3.3. Procurement from living donors

Musculoskeletal tissues/cells can also be procured from living donors. The following are some examples:

- a. patients having a hip replacement procedure can donate the femoral head that is being replaced by the prosthesis;
- b. cranial flaps removed during neurosurgical procedures can be stored for autologous grafting when it is impossible to immediately replace the craniotomy flap due to a brain oedema;
- c. cartilage can be used for producing autologous chondrocyte cultures for application in the same patient.

17.4. Processing and storage

The procured musculoskeletal tissue should be transferred to the tissue establishment as soon as possible.

17.4.1. Processing facilities

In selecting an appropriate air quality specification for musculoskeletal tissue processing, the criteria identified in Chapter 7 should be considered. Table 17.1 outlines those factors to be considered for musculoskeletal tissue processing.

It is important that processing of musculoskeletal allografts take place in a bacteriologically- and climate-controlled environment, including temperature and humidity control, ventilation and air filtration, with validated cleaning and disinfection. Where these grafts are not destined for terminal sterilisation, the need for an optimal processing environment is critical to the safety of the graft.

Table 17.1. Factors influencing the specification of processing air quality for musculoskeletal tissue

Criterion	Explanation	Musculoskeletal specific
Risk of tissue or cell contamination during processing	Processes that are mostly "closed" (e.g. bone marrow cryo-preservation where the only exposure of the cells to the environment is when a spike is inserted to add cryo-protectant) need a less stringent specification than those that involve hours of open processing (e.g. bone and tendon graft cleaning and shaping).	During processing (including cutting, shaping, cleaning, grinding, etc.), musculoskeletal tissue is necessarily exposed to the processing environment for extended periods. Environmental conditions are not as critical during freeze-drying if the tissues are packaged during the freeze-drying procedure.
Use of anti-microbials during processing	Some tissues, even though not terminally sterilised, can be exposed to various anti-microbial agents without compromising the characteristics required for clinical efficacy. Processes that include, for example, detergent washing, alcohol rinses, HCl treatment, imply less risk of transferring an environmental contaminant than those where cell viability is required and no anti-microbial agents can be applied, or the only anti-microbial step possible is soaking in antibiotics.	It is possible to soak musculoskeletal tissue in antibiotics just after procurement and before initial packaging or during processing, but these do not penetrate the tissue and can only inactivate surface contaminants. Blood and marrow removal, washing and similar preservation methods have been shown to be effective for reducing or eliminating contamination with micro-organisms. Bone can be terminally sterilised by gamma-irradiation or treated with a series of washes and chemical treatments that, together, achieve an equivalent degree of sterility (see section 17.3.3).

Criterion	Explanation	Musculoskeletal specific
Risk that contaminants will not be detected in the final tissue or cell product due to limitations of the sampling method	Where the only possibilities for final microbiological sampling are swabbing or testing of unrepresentative samples, the risk that environmental contaminants will be undetected is higher compared to processes where 10% destructive testing of final products can be performed.	Sampling of complete structural fragments of bone or tendon is limited to taking small and unrepresentative analytes or to swabbing. Tests can be done by immersion of the tissue in culture medium after processing or by filtering and culturing wash solutions. For bone that is processed to small pieces or ground, representative samples can be taken for culturing. For terminally sterilised bone, sampling is not an issue as the process is validated to achieve a certain sterility assurance level.
Risk of transfer of contaminants at transplantation	Tissues that are minimally processed, cellularised, or containing blood, blood vessels and lipids are more likely to support microbial contaminants than those that are blood and cell depleted. Tissues or cells that are applied to small areas on the external surfaces of the body, or to areas that are minimally vascularised, are less likely to transmit infections than those that are infused into the blood stream or implanted into internal organs.	Musculoskeletal tissue that has not been thoroughly marrow-depleted during processing is fully vascularised and the risk of transmission of viral and bacterial agents exists. Musculoskeletal tissue is used in open and well-vascularised surgeries, sometimes linked to replacement of a prosthesis, where a significant risk of infection exists.

Within the EU, tissues that are exposed to the environment without a subsequent microbial inactivation process should be processed in environments with an air quality equivalent to those of Grade A (as defined in EU Good Manufacturing Practice (GMP)), with a background environment at least equivalent to Grade D (EU GMP).

Many national requirements are more stringent, requiring Grade B (EU GMP) as a background, which may be more appropriate for the processing of bone and tendons that are prone to tissue contamination due to extensive manipulation and that have processing phases at +37 °C that are not followed by a terminal sterilisation step. Bone that is destined for terminal sterilisation can be processed in a Grade C environment.

17.4.2. Musculoskeletal graft processing

There are various methods of bone processing applied by individual tissue establishments. Allogeneic and autologous bone allografts from living donors are processed in the same manner as for tissues from deceased donors. Between processing steps, musculoskeletal tissues can be stored at -40 °C, though it is better to store at -80 °C or, for short periods, to keep on dry ice.

Musculoskeletal grafts from different donors must not be pooled during processing.

Processing of bone and other musculoskeletal tissue generally involves the removal of extraneous tissues (muscle attachments and the periosteum), blood and lipids using physical debridement, high pressure water rinses, mechanical agitation and/or ultrasonic processes. The protocols for these steps can vary between tissue establishments.

More specific procedures can be applied to musculoskeletal grafts, such as a demineralisation technique. This consists of reducing the calcium content of bone grafts in order to expose the bone morphogenetic proteins that provide the osteo-inductive capability of the graft, thereby improving its incorporation in the recipient.

17.4.3. Sterilisation or decontamination of musculoskeletal tissues and cells

For sterilisation and decontamination, a wide range of procedures can be used. Sterilisation procedures should ensure that no viable organisms are present in the sample after sterilisation. The term Sterility Assurance Level (SAL) represents the expected probability

of a micro-organism surviving on an individual unit of product after exposure to a sterilisation process. SAL 10^{-6} has been established as the standard for medical devices and indicates that there is a probability of one chance in a million of one unit of product being contaminated with a single organism after a sterilisation process.

17.4.3.1. **Sterilisation**

- Radiation sterilisation

Both gamma rays and accelerated electron beams can be used for sterilisation processes. No specific dose can be recommended as this depends on multiple factors associated with the individual process. However, it should be noted that higher doses can reduce the biomechanical strength of the bone. Doses used for gamma ray sterilisation range from 17 to 35 kGy and are established after calculation of the initial bioburden of the tissue. The irradiation process must always be documented.

- Ethylene oxide sterilisation

Although an effective sterilant, ethylene oxide is no longer recommended for tissue processing due to the risks of residuals that might be mutagenic.

17.4.3.2. **Decontamination**

- Chemical decontamination

There are many chemicals that can be used as decontaminants or that have an inactivating effect on specific pathogens (e.g. paracetic acid, iodophors, ethanol, etc.). The effectiveness of these agents on certain types of tissue must be validated. It is important that the chemicals used be mentioned in the documentation that accompanies the grafts, particularly if it is possible that traces of these products or their by-products remain in the tissue.

- Antibiotic decontamination

Antibiotics may be used to decontaminate musculoskeletal tissue. The effectiveness of each antibiotic cocktail should be

validated and documented. The use of an antibiotic decontamination procedure might be the only method of microbial inactivation possible for grafts where cell viability is required.

17.4.4. Storage

Each type of storage condition should specify the maximum shelf-life for the tissue, as well as any exclusions for specific graft types (e.g. tendons should not be freeze-dried). Maximum storage periods should be established by tissue establishments using validation studies.

17.4.4.1. Preservation and storage in freezers

Preservation and storage of musculoskeletal tissues (including cancellous, cortico-cancellous and cortical bone, ligaments and tendons) by freezing is a common method applied. There is limited scientific evidence to justify particular temperature limits, but the practice of storing up to 5 years at or below -40°C is common and many banks store below -70°C . Storage at higher temperatures, e.g. -20°C , is usually applied for shorter periods of up to 6 months.

17.4.4.2. Cryopreservation

Cryopreservation is a process whereby tissues are preserved by cooling to temperatures of approximately -196°C (i.e. the boiling point of liquid nitrogen). The process starts with controlled cooling to -80°C . This method is suitable for the preservation of some cell viability in cartilage. It is used for osteochondral bone grafts and for cartilage, although some centres also use it for other types of musculoskeletal tissue. Cryoprotectants (e.g. glycerol, DMSO) are added to the medium to prevent the ice crystal formation that destroys cells. The storage time under these conditions should not exceed 5 years.

17.4.4.3. Preservation and storage at ambient temperature

All kinds of lyophilised musculoskeletal allografts can be stored at ambient temperature up to 5 years.

An important limitation is the integrity of the packaging material to ensure microbiological safety and to prevent rehydration during storage.

17.5. Quality control

Quality control tests on musculoskeletal grafts should take at least the following minimum quality criteria into account:

- a. morphology and integrity of the musculoskeletal grafts;
- b. shape and a size of the graft;
- c. residual moisture in lyophilised grafts (the maximum level to be defined according to validation studies);
- d. osteo-inductive activity (*in vivo* or *in vitro*) in demineralised bone (usually demonstrated by validation rather than testing of every batch);
- e. sterilisation indicators;
- f. no evidence of microbiological growth.

During procurement or prior to processing, microbiological samples should be collected to establish the initial contamination levels of tissues to assist in making a decision during quarantine regarding the release of procured material for further processing. These microbiological tests are also important as controls during the procurement procedure.

Samples for microbiological analysis should also be collected before packaging of the final product. Possible sampling techniques for microbiological testing include:

- a. swabs;
- b. destructive methods (e.g. biopsy or sacrificing a proportion of ground tissue);
- c. collection of the last portion of the fluid used for washing of the tissue graft for subsequent analysis, usually following filtration.

17.6. References

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Chapter 18. Assisted reproductive technology requirements

Assisted reproductive technology (ART) is a general term referring to methods used to achieve pregnancy by artificial or partially artificial means, involving the manipulation and banking of reproductive tissues and cells. Reproductive tissues and cells include oocytes, ovarian tissue, embryos, sperm and testicular tissue.

These methods are primarily used to treat infertility, but can also be proposed to fertile couples for genetic reasons (gamete donation or pre-implantation genetic diagnoses) to avoid the birth of a child with a particular genetic condition or to couples who have specific communicable diseases, e.g. HIV infection, to reduce the risk of infection when a pregnancy is desired. Single women and lesbian couples can also benefit from ART, in accordance with national laws and regulations.

Banking of reproductive tissues or cells can also be an important tool for the preservation of fertility in patients who are undergoing treatment for cancer.

Different ART techniques can be used such as intrauterine insemination (IUI), *in vitro* fertilisation (IVF), intracytoplasmic sperm injection (ICSI) and cryopreservation of fertilised eggs or embryos, gametes and/or germinal tissue. These procedures may be carried out with gametes, fertilised eggs or embryos belonging to the couple being treated or donated by non-partner donors, where national legislation permits this.

The development of this field of medicine requires functioning ART centres that collect, test, manipulate, inseminate or transfer and store human reproductive tissues and cells. These establishments, as is

the case with other types of tissue establishments referred to in this Guide, should follow strict ethical, quality and safety principles, all of which are intended to prevent disease transmission and enhance clinical performance. Legal safety and quality requirements for the field of ART have been developed and are mandatory for EU countries (Directives 2004/23/EC, 2006/17/EC and 2006/86/EC).

In recognition of the importance and the specificity of ART as a component of the large and heterogeneous field of tissue and cell therapy, dedicated safety and quality standards along with ethical guidance should be elaborated. This will be included in the 2nd edition of the *Guide to the quality and safety of tissues and cells for human application* (due in 2015).

Chapter 19. Specific haematopoietic stem cells requirements

19.1. Introduction

Haematopoietic stem cell transplantation represents one of the most widely used forms of cell therapy; in part, because haematopoiesis represents the best-known biological model of somatic stem cell and tissue differentiation. Following the first case reports half a century ago, the procedure rapidly established itself as a life-saving treatment for a variety of malignant diseases. Haematopoietic stem cell transplantation also has a role when the haematopoietic tissue is functionally damaged by congenital or acquired disorders such as severe congenital immune deficiencies or severe acquired aplastic anaemia. More recently, the use of autologous haematopoietic stem cell transplantation in combination with immuno-suppressive agents has been evaluated for patients with certain auto-immune diseases. In its main field of application, i.e. as a component of the treatment of patients with poor-risk or advanced malignancies, it is now well established that allogeneic haematopoietic stem cell transplantation exerts its beneficial effects through the recognition of residual tumour cells in the recipient by donor-derived immune effectors. Thus, allogeneic haematopoietic stem cell transplantation represents one of the rare forms of clinically useful, immune cellular therapies. Limits to the use of these therapeutic procedures are their intrinsic toxicity, dominated by (though not limited to) graft versus host disease (GvHD); an immune disorder in which donor-derived immune effectors recognise and harm the host's normal tissues such as skin, gut and liver.

The field has developed tremendously in the past half-century in developed countries, and now many emerging countries are establishing allogeneic and autologous haematopoietic stem cell transplantation programmes. The field has integrated medicinal and technical innovations, including the use of new immuno-suppressive agents, the use of different sources of haematopoietic stem cells, such as bone marrow, mobilised peripheral blood and cord blood, the procurement of cells from unrelated donors, and much improved supportive care for recipients. Several other biotechnological advances, including stem cell selection, immune effector activation and stem cell expansion have become available. However, these advances have only entered clinical practice to a limited extent, and procurement of haematopoietic stem cell transplantation remains relatively unchanged. Hospitals that care for recipients often obtain autologous or allogeneic cell products (which are regulated differently from other medicinal products) from hospital-based or blood establishment-based collection and processing facilities that are located in their immediate vicinity. Each of these facilities works on a typically small to medium scale. Given the high rate of international exchange of donated haematopoietic stem cell material, harmonisation of the practices in this field would be of great benefit.

19.2. Donor screening

Haematopoietic stem cells for transplantation are obtained from living donors; either from the recipient patient in the case of autologous transplantation or from an allogeneic donor with matching human leukocyte antigen (HLA). Allogeneic donors can be related or unrelated to the intended recipient. In the case of an unrelated donor, collection can be from either healthy volunteer donors or through cord blood donations that are stored and delivered by cord blood banks. ABO major- and minor-incompatible haematopoietic stem cell transplantation is possible.

Haematopoietic stem cells can be obtained from a variety of autologous or allogeneic sources that include bone marrow, peripheral

blood stem cells and cord blood. The same quality standards apply for autologous or allogeneic donations.

19.3. Collection

Severe events in donors after allogeneic hematopoietic stem cell donations can occur and so there must be careful training of clinicians caring for donors and there must be appropriate follow-up of donors [1-5].

19.3.1. Bone marrow

Bone marrow harvesting is an aseptic process that should be undertaken in an operating theatre by appropriately trained personnel. Special attention should be paid to the training of clinicians in bone marrow collection and after-care of the donor and to vigilance and surveillance of donors as well as of recipients. Provisions for counseling of donors and their routine post-donation follow-up must be provided.

Bone marrow for therapeutic use is obtained through multiple punctures, usually of the posterior iliac crests. When absolutely necessary, the anterior iliac crests can also be used. The sternum is not recommended for purposes of bone marrow collection. Punctures are usually performed under general anaesthesia and epidural anaesthesia may be considered. A donor pre-anaesthesia visit is mandatory before cell collection. The maximum volume of donation should not exceed 20 mL/kg donor weight. This limit may be exceeded if the collection is undertaken in the operating room, but only if continuous monitoring of donor clinical and biological parameters guarantees donor safety and expert anaesthetic staff are present using appropriate fluid replacement therapy.

A 24-hour blood component donor support protocol, including the provision of CMV antibody-negative (or equivalent), irradiated and leukocyte-depleted blood components, should be available. However, blood transfusion in allogeneic donors should be avoided whenever

possible. Autologous red blood cell donation pre-harvest can be considered, but should take account of potential iron deficiency induction as the time scale from final donor selection to harvest can be short. When autologous blood is taken, it must be taken in a collection facility that meets applicable national/international requirements. Donors must be appropriately monitored and treated for iron deprivation after haematopoietic stem cells collection as part of their routine care and follow-up.

19.3.2. Peripheral blood stem cells

19.3.2.1. Peripheral blood stem cells

Peripheral blood stem cells (PBSC) should be collected in a therapeutic apheresis facility by personnel who have appropriate experience in care for haematology or oncology patients, PBSC mobilisation and therapeutic apheresis. Special attention should be paid to paediatric patients and the special circumstances pertaining to apheresis in young patients, whose weight (usually less than 20 kg) places them at risk of haemodynamic changes, both on commencement and during the procedure. The same applies to small adults.

Mobilisation of PBSC prior to autologous collection is ensured by the administration of various types of mobilisation regimens, for example rhG-CSF, or a combination of agents or other single agents may be needed if the patient fails to mobilise their PBSC. Circulating levels of CD34⁺ cells guide commencement of apheresis. The total number of collected CD34⁺ cells in one or several consecutive apheresis protocols is the criterion that usually decides when cell collection (and mobilisation treatment) should cease. The number of cells required will vary with the size of the patient/recipient. Collection centres should have protocols to determine what cell numbers are optimally needed to be collected, taking into account the patient's well-being during and after the collection, as well as their needs as a future recipient.

Cell mobilisation is initiated using rhG-CSF prior to allogeneic donation from healthy adult donors. Donors must be informed about the expected side-effects of the mobilisation protocol, and how they

can be mitigated. Some Health Authorities do not permit the use of rhG-CSF in paediatric donors and so other collection strategies may be employed such as bone marrow donation.

The target collection number of CD34⁺ cells should be set prior to starting apheresis. The target will vary for autologous and allogeneic donations and will depend on clinical need and regulations, as well as best available clinical practices. For example, the European Pharmacopoeia monograph for *Human haematopoietic stem cells* (2323) requires an autologous stem cell product to contain at least 2×10^6 CD34⁺ cells/kg recipient weight.

In addition to optimising the collection of CD34⁺ progenitors, the process should ensure that collected cell products are minimally contaminated with mature cells that could compromise subsequent processing steps or contribute to the occurrence of side-effects in recipients.

19.3.2.2. **Allogeneic blood mononuclear cells (“Donor-lymphocyte infusions” or DLI)**

Infusion to the recipient of donor-derived immune effector cells representing a component of blood mononuclear cells is an effective prophylaxis and treatment for tumour relapse in recipients of allogeneic transplantation with haematopoietic chimerism. In this case, the same donor whose PBSC or bone marrow was collected for allogeneic transplantation undergoes a second or subsequent collection of leucocytes by apheresis without mobilisation. The collected cell product then undergoes minimal manipulation prior to infusion of the mixture of immunocompetent cells to the recipient. The infused cell dose is measured by flow cytometry and expressed as CD3⁺ lymphocytes per kg of recipient weight.

Whenever possible, peripheral veins allowing for sufficient blood flow should be used for venous access to facilitate the collection of DLI; pre-donation evaluation of the quality of peripheral venous access should be carefully performed by appropriately qualified personnel. Placement of central catheters should be performed only when placement of a peripheral catheter by appropriately trained personnel

has failed; again, it should be performed by an appropriately trained specialist and should consider placement in the location that is associated with the lowest frequency of complications. Placement of central venous catheters in unrelated donors may not be allowed by national registries. Donors should be informed of potential complications associated with catheter placement (including pain, bleeding, thrombosis and infection). Due consideration should be given to the safety of the donor in the placement of central venous catheters.

There must be a pre-established procedure for quick access to an intensive care unit and human and equipment resources for immediate resuscitation, should an accident occur during the collection procedure.

19.3.3. Cord blood

The Council of Europe has been studying the issue of cord blood donation for a number of years and has always been concerned about the proliferation of private cord blood banks dedicated to the collection and storage of cord blood for autologous use. This concern resulted in the adoption of Recommendation Rec (2004) 8 of the Committee of Ministers to member states on autologous cord blood banks and its Explanatory Memorandum [6], which recommends that member states only allow the establishment of cord blood banks for altruistic and voluntary cord blood donation. The recommendation also states that the promotion of cord blood donation for autologous use and the establishment of cord blood banks for autologous use should not be supported by member states or their health services. Where autologous cord blood banks are established, the promotional material or information provided to families must be accurate, and fully informed consent to cord blood storage must be obtained. Autologous cord blood banks must clearly inform parents about the differences between the different medical objectives of autologous and allogeneic donations and about the uncertainties relating to the medical applications of autologous cord blood preservation. In any case, autologous cord blood banks must meet the same quality and safety standards as for allogeneic cord blood donation and banking.

Umbilical cord blood can be obtained at birth from fully-informed women who have previously consented to allogeneic donation (including related donations), following normal delivery of a healthy baby. No modification in delivery practices, with a view to increasing the volume of cord blood collected, is allowed. Collection after caesarean delivery is possible, provided that the baby and mother are well. Collection should be performed only by trained staff. Because the collected cell number is a critical parameter used by transplant teams to select umbilical cord blood, it is important that blood volume collection be maximised within the confines of not interfering with normal delivery practices. Traceability of the collected cell product from the mother and the newborn must be ensured by personnel that collect the blood. Systems to allow reporting on the health of the mother and newborn subsequent to donation of umbilical cord blood are part of the umbilical cord blood banking process.

19.4. Processing of minimally-manipulated haematopoietic cell products

Processing of minimally manipulated haematopoietic cell products is intended to provide appropriate conditions for product preservation and storage or to improve the risk-benefit ratio of autologous or allogeneic haematopoietic stem cell transplantation [7, 8]. It does not affect the main biological properties of the collected cell product, which is to support the Marrow Re-populating Ability (MRA) and the establishment of haematopoietic chimerism in a myelo-ablated or immuno-suppressed recipient.

19.4.1. Volume reduction

Volume reduction is either a preparatory step to further processing (including cryopreservation and storage) or a means to reduce the volume of the infused cell product and, thus, prevent recipient side-effects relating to volume overload in the transplanted patient. Various centrifugation-based techniques can be used. Cell loss associated with volume reduction must be evaluated and expected recoveries defined.

19.4.2. Red blood cell depletion

Red cell depletion is a critical step in cases where there is major ABO incompatibility between a donor and a recipient in the allogeneic setting (HLA identity does not preclude the existence of major or minor ABO incompatibility). Various techniques for blood cell depletion are available, including buffy-coat centrifugation or apheresis cell separation. The efficiency of the technique must be monitored by measuring the residual content of red cells and whether this value falls below the maximum accepted level (usually 0.2 mL/kg). Similarly, the cell and progenitor loss associated with such procedures must be evaluated and expected recoveries must be defined.

19.4.3. Plasma removal

Plasma removal represents a critical step in cases with minor ABO incompatibility between allogeneic donor and recipient setting (HLA identity does not preclude the existence of major or minor ABO incompatibility). The necessity of donation plasma removal in case of minor ABO incompatibility can be judged using a titration of anti-A and anti-B antibodies in the recipient during the period that precedes the collection of the donation, taking into account seasonal fluctuations for these biological measurements (the usual threshold is 1/32, depending on the technique used). Plasma removal is usually performed by centrifugation of the collected cell product. The cell loss associated with such procedures must be evaluated and expected recoveries must be defined.

19.4.4. Cryopreservation and thawing

Cryopreservation is systematically used in the autologous setting and by cord blood banks that prospectively collect and store umbilical cord blood. In the allogeneic PBSC or marrow setting, cell collection from the donor is usually synchronised with the administration of a conditioning regimen to the recipient and these types of allogeneic donations are usually infused to the recipient within hours of the donation's collection. However, an increasing proportion of allogeneic

bone marrow or PBSC is being cryopreserved for logistical reasons such as a donor living far from the transplant centre, international exchange of donations, professional constraints, and unforeseen changes in transplant schedules.

Cryopreservation must be conducted in an appropriate environment, with the aim of recovering the maximum possible proportion of living cells upon thawing. Cells must be cryopreserved at -80°C or below (i.e. in ultra-low temperature freezers or in liquid/vapour phase nitrogen), with sufficient and suitable cryoprotectant, and with a controlled freezing protocol. Cryoprotectants prevent ice crystal formation in cells as they freeze. The most commonly used cryoprotectant is dimethyl sulfoxide (DMSO), which can be combined with hydroxy ethyl starch (HES).

19.4.5. Cell selected products

Several clinically applicable immuno-affinity methods for positive selection of $\text{CD}34^{+}$ cells have been developed. A limited number of CE-marked automated instruments are available to capture $\text{CD}34^{+}$ cells from bone marrow, PBSC or umbilical cord blood on the large scales needed for clinical transplantation. The use of such medical devices requires specific training for personnel involved in these procedures.

19.4.5.1. T-cell depletion in the allogeneic setting

T-cell depletion prevents or reduces the occurrence of GvHD following allogeneic transplantation from related or unrelated donors, but is rarely used for HLA-identical transplantation from living donors or from umbilical cord blood. This is because the advantages of reducing GvHD are offset by associated increases in relapse rates and graft failures. Indications for T-cell depletion remain limited to specific forms of allogeneic transplantation, such as from haplotype-mismatch donors and following myelo-ablative conditioning regimens. In these situations, it is important that T-cell depletion is as extensive as possible. Accurate determination of the residual T- and B-cell content is mandatory. The highest acceptable dose of residual T-cells must be defined in advance by the medical team in charge of the recipient

(usually 1×10^4 CD34⁺ cells/kg of recipient weight) and their guidance sought if the set objective is not met.

19.4.5.2. Tumour cell depletion in the autologous setting

Autologous tumour cells collected with normal haematopoietic stem cells may contribute to post-transplant relapse, but this has not been firmly established on the basis of clinical and biological observations. A definitive advantage for tumour-purging of autologous grafts has not been demonstrated by clinical trials. The use of CD34⁺ cell selection devices for this purpose has been practically abandoned but, if a transplant team decides to use such a procedure, then tumour cell depletion should be as extensive as possible and then accurate determination of the residual tumour cell content is crucial, using either immuno-histochemical techniques, flow cytometry or molecular biology techniques.

19.4.6. Depletion of allo-reactive immune effectors

Total T-cell depletion is associated with both positive (i.e. GvHD prevention) and negative (i.e. prolonged immuno-suppression) consequences that prevent its adoption in routine clinical practice. Other specific procedures evaluated by clinical trials include depletion of activated and allo-reactive T-cells (i.e. those that can be identified by the expression of the CD25 T-cell receptor subunit). Removal of CD25 T-cells can be done using immuno-selection devices similar to those routinely used for CD34⁺ positive cell selection. It is important that T-cell depletion be as extensive as possible. Therefore, accurate determination of the residual T- and B-cell content is critical. The highest acceptable dose of residual allo-reactive T-cells must be defined in advance by the medical team in charge of the recipient and their guidance sought by the collection team if this objective cannot be met.

19.4.7. Production of virus- or fungus-specific immune cells

Prolonged immuno-suppression is a hallmark of allogeneic haematopoietic stem cell transplantation and the clinical consequences are

the development of opportunistic and often life-threatening infections in many recipients.

Adoptive transfer of immune effectors targeting the most frequently encountered opportunistic infectious agents is possible with different techniques. Currently, the most widely employed technique is immuno-selection of T-cells secreting IFN-gamma after exposure and activation with specific peptides. If such cell products are to be administered to recipients of allogeneic transplantation, the specifications of the cell products must be defined prior to processing and compliance or non-compliance with these specifications must be documented. Processing must be performed and supervised by appropriately trained personnel.

19.5. Product specification, quality controls and release criteria

19.5.1. Biological information needed to confirm donor suitability and recruitment

All clinical and biological information pertaining to donor identification, screening and recruitment must be kept, along with all information pertaining to processing and distribution. This information must remain as a permanent part of the production and release file.

Details on the nature of such information and the procedure to obtain it are provided in Chapters 3 and 4 of this Guide.

19.5.2. Safety controls

Detection of transmissible infections is performed through donor screening (using microbiological and other testing, as required by national, European and international guidance and regulations) and through microbiological testing of samples obtained at the different stages of cell collection, processing and distribution.

Detection of donor transmissible diseases other than occult pre-neoplastic or neoplastic diseases or other disorders is through donor

screening, using medical questionnaires, physical examination and biological testing, as necessary.

The proportion of the various sub-populations of leukocytes in the collected cell product must be measured. High numbers of mature cells such as granulocytes may negatively impact on several subsequent processing steps, and may contribute to recipient side-effects at re-infusion.

Removal of red blood cells from ABO-incompatible allogeneic cell products through specific processing procedures must be documented when relevant, as must the removal of T-cells or other immune effectors from allogeneic cell products through specific processing procedures.

The removal of tumour cells from autologous cell products using specific processing procedures must also be documented where appropriate.

19.5.3. Quality controls (including potency assays and markers)

The Total Nucleated Cells (TNC) remains a widely-used measure for evaluating the quality of collected bone marrow. The cell dose for recipients is usually expressed in TNC/kg of recipient weight. In addition, nucleated cell counts are largely used as in-process controls to document that technical procedures have been appropriately conducted in the processing facilities (i.e. procurement of TNC following plasma removal, volume reduction, red blood cell depletion, etc.).

The proportion of cells of the erythroblastic lineage may be high in umbilical cord blood and must be documented. CD34⁺ cell counts are used as a surrogate marker for haematopoietic stem cells, both in the peripheral blood of individuals undergoing mobilisation regimes and in the collected cell product, whether from apheresis following mobilisation or from umbilical cord blood donation. The value of CD34⁺ cell counts for assessing the MRA of bone marrow is less well established; in part, due to the near abandonment of autologous bone marrow transplantation and the decrease in the proportion of allogeneic haematopoietic stem cells transplantation performed with bone

marrow. CD34⁺ cell counts are usually measured by flow cytometry, using monoclonal antibodies that recognise one or several epitopes on the human CD34 membrane antigen. It is recommended to use diagnostic kits rather than a combination of reagents. Diagnostic kits include all the necessary reagents to produce a measure of the percentage and absolute number of CD34⁺ cells in biological samples, and ensure that detected CD34⁺ cells are alive and belong to the progenitor cell compartment (as opposed to pro-erythroblasts). Use of a single-platform, rather than a dual-platform, minimises errors in calculating cell counts. As an example, the ISHAGE (ISCT) algorithm provides a robust and reproducible gating strategy to measure CD34⁺ cells.

Potency assays for cell products used for autologous or allogeneic transplantation rely on the detection of colony forming units (CFU) in clonogenic assays, using semi-solid media. These functional tests are hampered by the delay required to produce results (usually two weeks). Thus, the results are usually only available long after a non-cryopreserved cell product has been transplanted in an allogeneic recipient. Clonogenic assays are hampered by poor intra- and inter-laboratory reproducibility. This particular issue could be improved by using commercially-available and standardised culture media and by participation in proficiency testing and external quality assessment schemes. It remains to be demonstrated that the recent introduction of image analysers can further improve the situation. CFU-GM (colony-forming units: granulocyte/monocyte) numbers can be interpreted in two ways: the absolute number of clonogenic progenitors per kilogram of recipient weight can be used as a surrogate marker for MRA (but this has largely been supplanted by CD34⁺ cell counts), or the frequency of CD34⁺ cells that form colonies in culture can be used to provide additional information about the functionality of the graft. In the latter case, a policy should be defined to deal with cases where CD34⁺ cells clone at a low frequency. Some national regulations and guidelines define in which context CFU-GM measurements are mandatory. As a minimum, it is recommended that CFU-GM measurements should be performed during inspections and proficiency testing

exercises in order to demonstrate the ability of the cell therapy facility to produce functional haematopoietic stem cell products.

19.5.4. Release criteria

The cell processing facility, along with its clinical counterparts, must define which safety and quality controls serve as release criteria. It must also define which criteria must be strictly met and which ones may lead to documented waivers. Specific instructions should be established in the cell facility on how to deal with the recipient, donor and stem cell products throughout the donation and processing and issue stages and all the way through to transplantation.

19.6. Packaging and labelling

Packaging is designed at all steps with two objectives: to protect the cell product and to protect personnel and the environment. The primary packaging must be made of a biologically compatible material. Cryopreservation requires that low-temperature-resistant packaging is used, which can also withstand contact with liquid nitrogen.

Labelling must unambiguously identify the donor, the intended recipient, the cell product and its nature as well as the additives used and the conditions under which the product is to be stored and distributed. Following procurement, the donor identifier should be on the 'transit' label when tissues are distributed to the tissue establishment for processing. The recipient must be identified (but not the donor) when tissues are distributed for end use. In all cases there must be an audit trail to the donor.

International standards for labelling now exist (e.g. ISBT 128, European coding system, etc.) and must be used in order to promote consistency, traceability, aid international exchanges and facilitate vigilance and surveillance.

19.7. Storage and distribution

Storage must be done in conditions that minimise the risk of cross-contamination.

Conditions for temporary storage must be defined for each type of cell product and for each of the stages of the process, from collection to pre-processing and post-thawing, etc.

The cryogenic system used for long-term storage must be continuously monitored and processes must be in place to detect failures in the system such as temperature rises and changes in the level of liquid nitrogen.

Internal and external transport must be controlled. Transportation within the same institution (i.e. from the collection facility to the processing facility or from the processing facility to the transplant ward, etc.) must be defined by standard operating procedures. When service providers are used for transportation of a fresh or cryopreserved cell product, the conditions by which the service is delivered must be established and regularly audited by the cell processing facility, which remains responsible for the delivery of the cell products. This includes appropriate training of the personnel in charge of transportation.

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Chapter 20. Advanced therapy medicinal products

20.1. Introduction

Substances of human origin represent a special category of therapeutic treatments, most of which are well established in medical practice. Depending on how those substances are preserved, processed or transformed and their intended use, they can be considered “traditional” replacement tissues and cells, such as those described in the other tissue- and cell-specific chapters of this guide or, where the degree of manipulation is considerably greater, as a separate category of products requiring additional quality and safety measures that address a higher level of risk. In the EU, the latter products are referred to as “Advanced Therapies” and include engineered tissues, cultured cells and gene therapy products.

Defining the borderline between “traditional” tissues and cells and “advanced therapy” products is not always easy as there is a spectrum in the complexity and scale of cell or tissue manipulation. Whereas the tissues and cells discussed in the previous chapters are obtained from the donor and submitted to isolation, preparation and preservation processes, the tissues and cells described in the current chapter are subjected to more substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. Whether the product is considered “traditional” or “advanced”, the principles of quality, safety and traceability described in this Guide from donation and testing through to supply for clinical application

and biovigilance apply. The focus remains to provide a safe and effective therapy for patients, whatever their classification.

20.2. Legislative frameworks

In EU member states, current legislation differentiates between traditional tissues and cells and Advanced Therapy Medicinal Products (ATMP), with the latter regulated as medicinal products (Regulation 1394/2007) [1] requiring full GMP conditions and Centralised Marketing Authorisation by the European Commission prior to distribution. Through this legislation, ATMPs are a new class of medicinal product in the EU, produced by engineering somatic cells or tissues or by transferring a gene into cells. A similar regulatory approach has been adopted in the USA where products that are “more than minimally manipulated” are regulated in a more stringent manner compared with traditional human cell and tissue products. Some ATMPs are defined as such because they involve transplantation/injection/administration of cells to be used in the recipient for a function that is different from what it was in the donor.

ATMPs can be produced by authorised hospital departments or by pharmaceutical or biotechnology companies that have obtained a European marketing authorisation. However, the hospital exemption rule offers an opportunity for tissue establishments, hospital or academic departments within a member state to supply cells or tissues for preparing ATMPs, on the basis of an individual prescription and for treating patients within the national border. This “hospital exemption” recognises the importance of offering single patients possible beneficial treatments. Currently, several “advanced therapy” products being used in the EU are provided under the hospital exemption rule; only two ATMPs have so far been authorised for industrial production. As per the data in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database, analysed during the period 2004-2010 [2], the investment effort within Europe in the clinical development of Advanced Therapies has been focused on somatic cell therapy (about 75%) using dendritic cells, hematopoietic blood stem cells

(homologous and non-homologous use) and mesenchymal stromal cells, with the rest being tissue-engineered products and treatments with gene therapy medicinal products.

20.3. Special safety considerations when culturing cells

The inclusion of cell expansion as a criterion that describes “substantial manipulation” has meant that some relatively well-established laboratory procedures now fall under the advanced therapy definition, although they are generally cultured/prepared within a hospital.

Autologous keratinocyte cultures for burned patients are an example of a cultured cell product that has been successfully applied in clinical practice since 1981 [3]. The culture of limbal cells is similar in terms of processing complexity and, for the ophthalmic surgeon, a traditional keratoplasty is not very different to one that is enhanced by the application of stem cells from the corneal limbus. Many other ATMPs are currently provided for patients without centralised marketing approval as medicines administered in a clinical trial setting, such as mesenchymal stromal cells and dendritic cells [4].

If allogeneic cells are greatly expanded in number and intended for use in multiple recipients, the procedures applied must reflect the potential for generating high titres of infectious agents during the culture period and, hence, greater risks of cross-infection between different cell lines and transmission to recipients. The degree of microbiological testing, beyond the mandated minimal testing described in Chapter 5, should reflect the increased size of the population at risk of any disease that might be transmitted by the cells. In these circumstances, additional testing of the cultured cells for infectious agents should be considered.

While disease transmission is not an additional concern for cultured autologous cells, culturing or ex vivo activation of a single or mixed-cell population might induce substantial functional changes in the biological properties of the resulting processed cell product. Thus, expansion and culture conditions should be defined in order to control the number of cellular duplications and to achieve an adequate

balance between number of passages and duplications. The validation of the preparation process with respect to maintaining genetic stability and the relevant biological properties, as well as avoidance of malignant transformation, should be performed. Quality control testing and inspection during production and prior to release should normally include cell viability, cell identity and testing of biological activity to ensure that each batch of cultured cells meets the specification of the product.

A specific safety issue when culturing human cells is the use of materials of animal origin, such as media or growth factors. Specification and verification of the source and method of preparation of the material is required. Culture media and other reagents derived from animals must be evaluated for the risk of contamination with micro-organisms, particularly viruses and agents of transmissible spongiform encephalopathies (TSE). Documentation must be obtained that demonstrates the application of appropriate quality assurance measures by suppliers of media of animal origin, including origins and veterinary certificates for the animals used in the preparation of the material (e.g. bovine serum albumin). Certificates must be supported by audit trails for collection, pooling, shipping and final formulation by the third party supplier. The use of raw materials, culture media, reagents and processing materials that come along with a TSE certificate from the European Directorate for the Quality of Medicines & HealthCare (EDQM) minimises the risks of infection from TSE.

For further guidance on cell culture, please refer to the report on the second ECVAM Task Force on Good Cell Culture Practice [05]

20.4. Combining cells with biological or synthetic matrices

In some circumstances, cultured cells will be combined with synthetic or biological matrices to provide the mechanical support and required shape of a replacement tissue. The matrix material must be evaluated for compatibility with any cells used and should be sterile unless there is a well-documented justification for not sterilising the

material. Reference should be made to the Medical Devices regulations for products that contain non-viable materials of animal origin or synthetic materials as matrices. De-cellularised human tissues are often considered the optimal matrix for immediate transplantation, with subsequent re-cellularisation *in vivo*, or for *in vitro* cellularisation with autologous cultured cells.

20.5. Processing environments

Advanced therapy products containing viable cells cannot undergo terminal sterilisation and some virus removal/inactivation steps are not always technically possible. For this reason ATMPs must be produced under fully aseptic conditions applying the facility requirements of GMP (Grade A in a background of Grade B).

20.6. Clinical use and follow-up of novel processes

The intended use and purpose of a novel advanced therapy product must be fully described with a comprehensive list of the qualitative and quantitative characteristics and with defined limits, where possible, that demonstrate the safety of the product. Full clinical trials in compliance with Directive 2001/20/EC are required to obtain a marketing authorisation in the EU. The decision to use an advanced therapy product, particularly a novel one that is not yet licensed in the EU, or that is produced in a non-EU country, involves a quality, safety and clinical judgement and a formal regulatory approval based on the evaluation of residual risks inherent in the product that have to be balanced against the anticipated clinical benefits of the procedure. It is therefore necessary for products to be assessed in relation to legally-defined standards of safety, quality and effectiveness, so that clinicians may take clinical decisions on the basis of relevant and sufficient information on residual risks. Recipients should be followed-up with rigorous documented monitoring of safety, clinical performance and effectiveness (e.g. infection, morphology, function, proliferation, persistence, immunotoxicity and efficacy). Where the relevant legislation

requires vigilance reporting through pharmacovigilance systems, any adverse outcomes related to the donation, procurement or testing of the donor should be communicated to the relevant Health Authorities.

20.7. References

1. Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:pdf>.
2. Romaldas Maciulaitis, Lucia D'Apote, Andrew Buchanan, Laura Pioppo and Christian K Schneider Clinical development of Advanced Therapy Medicinal Products in Europe: evidence that regulators must be proactive. *Mol Ther.* 2012 Mar;20(3):479-82.
3. O'Connor NE, Mulliken JB, Banks-Schlegel S, Kehinde O, Green H. Grafting of burns with cultured epithelium prepared from autologous epidermal cells. *Lancet* 1981;1:75-8.
4. Lowdell MW and Samuel E. Processing of Cells for Transplantation. In: *Tissue and Cell Processing an Essential Guide*. Eds: Fehily D, Brubaker S, Wolfenbarger L and Kearney JN. Wiley Blackwell 2012.
5. Coecke, S., Balls, M., Bowe, G., Davis, J., Gstraunthaler, G., Hartung, T., Hay, R., Merten, O.-W., Price, A., Shechtman, L., Stacey, G.N. and Stokes, W., (2005), *Guidance on Good Cell Culture Practice. A report of the second ECVAM Task Force on Good Cell Culture Practice*, ATLA, 33: 1-27.

Appendix 1. General reference documents used

The experts who developed the chapters in this Guide incorporated principles and specific text from many regulatory, professional and scientific publications. The following are the most important reference documents used:

- Guide to the quality and safety of organs for transplantation. Council of Europe, 5th edition 2013, available at <http://www.edqm.eu/en/EDQM-Publications-Blood-TransfusionOrgan-Transplantation-Guides-1131.html>
- Guide to the preparation, use and quality assurance of blood components. Council of Europe, 17th edition 2013, available at <http://www.edqm.eu/en/EDQM-Publications-Blood-TransfusionOrgan-Transplantation-Guides-1131.html>
- 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 at http://www.edqm.eu/site/booklet_rec_res_organ_transplantationpdf-en-30783-2.html
- Convention for the Protection of Human Rights and Fundamental Freedoms, available at <http://conventions.coe.int/treaty/en/treaties/html/005.html>

- 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 at <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>
- Council of Europe (2002) Additional protocol to the Convention on Human Rights and Biomedicine, on Transplantation of Organs and Tissues of Human Origin, available at <http://conventions.coe.int/Treaty/en/Treaties/Html/186.htm>
- Council of Europe Convention on action against trafficking in human beings and its Explanatory Report, available at http://www.coe.int/T/E/human_rights/trafficking/PDF_conv_197_trafficking_e.pdf
- 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 http://www.edqm.eu/medias/fichiers/Joint_Council_of_EuropeUnited_Nations_Study_on_tra1.pdf
- World Health Organization (2010) WHO guiding principles on human cell, tissue and organ transplantation, available at http://www.searo.who.int/LinkFiles/BCT_WHO_guiding_principles_organ_transplantation.pdf
- Aide-Mémoire on Key Safety Requirements for Essential Minimally Processed Human Cells and Tissues for Transplantation, available at <http://www.who.int/entity/transplantation/AM-SafetyEssential%20HCTT.pdf>
- Aide-Mémoire on Access to Safe and Effective Human Cells and Tissues for Transplantation; World Health Organization, available at <http://www.who.int/entity/transplantation/AM-HCTTServices.pdf>

- Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF>
- Directive 2006/17/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF>
- Directive 2006/86/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, available at http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025en00320050.pdf
- Directive 2012/39/EU amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:327:0024:0025:EN:PDF>
- EudraLex, Volume 4. *EU Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use*, Annex 1 Manufacture of Sterile Medicinal Products, 2008, available at http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf
- EudraLex, Volume 4 *EU Guidelines for Good Manufacturing Practices Medicinal products for human and veterinary use* <http://ec.europa.eu/health/documents/eudralex/vol-4/>

- European Commission, Operational Manual for Competent Authorities on inspection of tissue and cell procurement and tissue establishments, Version 1.0, available at http://ec.europa.eu/health/blood_tissues_organ/docs/manual_en.pdf
- Commission Decision 2010/453/EU of 3 August 2010 establishing guidelines concerning the conditions of inspections and control measures, and on the training and qualification of officials, in the field of human tissues and cells provided for in Directive 2004/23/EC of the European Parliament and of the Council <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do>
- Medical products containing viable human cells – Application of risk management and requirements for processing practices; ISO/FDIS 13022:2012
- Guide of Recommendations for Tissue Banking. EQSTB Project co-funded by the European Commission, 2007.
- Outputs of the EU-funded project *European Good Tissue Practices (EuroGTP)* including the guidance document, 2011, available at <http://EuroGTP.com>
- Outputs of the EU-funded project *European Union Standards and Training in the Inspection of Tissue Establishments (EUSTITE)* including the Vigilance Tools and Guidance, the Final Vigilance Recommendations and the Inspection Guide (2006 to 2009), available at <http://www.notifylibrary.org/content/eustite>
- Outputs of the EU-funded project *Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)* including the draft Vigilance Guides for Competent Authorities and for Clinical Users of tissues and cells (2010 to 2013), available at <http://www.notifylibrary.org/content/soho-vs>

- Notify. Exploring Vigilance Notification for Organs, Tissues and Cells. Organs Tissues & Cells, 2011, November, 14, 3: Suppl. More information available at <http://www.transplant-observatory.org/SiteCollectionDocuments/glorenotify.pdf>
- 5th Edition FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, 2012, available at http://www.factweb.org/forms/store/ProductFormPublic/search?action=1&Product_productNumber=621
- Guidelines for the Blood Transfusion Services in the UK. 2007, available at <http://www.transfusionguidelines.org.uk/index.aspx?Publication=RB>
- Human Tissue Authority (UK) Code of Practice 5: Disposal of Human Tissue, 2009, available at <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code5disposal.cfm>
- Human Tissue Authority (UK) Code of Practice 8: Import and export of human bodies, body parts and tissue Disposal of Human Tissue, 2009, available at <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code8importandexport.cfm>
- Report from the Nuffield Council on Bioethics Human bodies: donation for medicine and research, available at http://www.nuffieldbioethics.org/sites/default/files/Donation_full_report.pdf
- 13th Edition of the Standards for Tissue Banking of the American Association of Tissue Banks, 2012.

- United States Food and Drug Administration (FDA). 21 CFR 1271 HCT/Ps Good Tissue Practices, available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271>
- Principles of Cell Collection and Tissue Recovery, Gillan H, Pamphilon D, Brubaker S, in *Tissue and Cell Processing: An Essential Guide*, eds. Fehily D, Brubaker S, Kearney JN, Wolfinger L, Wiley Blackwell Publishing, 2012

Appendix 2. Acronyms

AATB	American Association of Tissue Banks	DMSO	dimethyl sulfoxide
Ab	antibodies	DR	design review
anti-CMV	antibody against cytomegalovirus	DS	design specification
anti-EBV	antibody to Epstein-Barr virus	EATB	European Association of Tissue Banks
anti-HBc	antibody to hepatitis B core antigen	EBV	Epstein-Barr virus
anti-HCV	antibody to hepatitis C virus	EC	European Commission
anti-HIV-1	antibody to HIV-1	ECDC	European Centre for Disease Prevention and Control
anti-HIV-2	antibody to HIV-2	EDMS	Electronic document management system
ART	assisted reproductive technology	EDQM	European Directorate for the Quality of Medicines and HealthCare
ATMP	advanced therapy medicinal products	EMA	European Medicines Agency
BM	bone marrow	EudraCT	European Union Drug Regulating Authorities Clinical Trials
CA	competent Authority	EU	European Union
CBC	complete blood count	FDA	Food and Drug Administration (US)
CD-P-TO	European Committee (Partial Agreement) on Organ Transplantation of the Council of Europe	FS	functional specification
CDS	client data system	GAMP	good automated manufacturing practice
CE (marked)	Conformité Européenne or European Conformity marking	GLP	good laboratory practice
CFU	colony forming units	GMP	good manufacturing practice
CJD	Creutzfeldt-Jakob disease	GTP	good tissue practice
CMV	Cytomegalovirus	GvHD	graft versus host disease
CNS	central nervous system	hAM	human amniotic membrane
COD	cause of death	HBc	hepatitis B core antigen
COTS	commercial off-the-shelf	HBsAg	hepatitis B surface antigen
CRM	customer relationship management	HBV	Hepatitis B virus
DCS	distributed control system	HCTT	human cells and tissues for transplantation
DH-BIO	Committee on Bioethics of the Council of Europe	HCV	Hepatitis C virus
		HES	hydroxy ethyl starch

HIV	Human Immunodeficiency Virus	SARE	severe adverse reactions and events
HLA	human leukocyte antigen		
HTA	Human Tissue Authority (UK)	SCADA	supervisory control and data acquisition
HTLV	Human T-lymphotropic virus		
ICSI	intra-cytoplasmic sperm injection	SOP	standard operating procedure
IL	interleukin	TBV	total blood volume
ISPE	International Society for Pharmaceutical Engineering	TE	tissue establishment
IUI	Intra-uterine insemination	TNC	total nucleated cells
IVF	<i>in vitro</i> fertilisation	TPV	total plasma volume
ISBT	International Society of Blood Transfusion	TSE	transmissible spongiform encephalopathy
LIMS	Laboratory information management system	URS	user requirements specification
MRA	marrow repopulating ability	vCJD	variant Creutzfeldt-Jakob disease
MRD	matched related donor	V & S	vigilance and surveillance
MRP-II	manufacturing resource planning	WHO	World Health Organization
NA	not assessable	WNV	West Nile virus
NAT	nucleic acid amplification technique		
OECD	Organisation for Economic Co-operation and Development		
ONT	Organización Nacional de Trasplantes (Spain)		
PIC/S	pharmaceutical inspection co-operation scheme		
PLC	programmable logic controller		
PO	procurement organisation		
PKI	public key infrastructure		
QC	quality control		
QMS	quality management system		
RhD	rhesus D antigen		
rhG-CSF	recombinant granulocyte-colony stimulating factor		
RP	responsible person		
SAE	severe adverse event		
SAL	sterility assurance level		
SAR	severe adverse reaction		

Appendix 3. Glossary

Acceptance criteria The standards required to satisfy quality and safety expectations and ensure a acceptable quality and safety of the final product.

Advanced therapy medicinal product A medicinal product that is either a gene therapy medicinal product, a somatic cell therapy medicinal product, a tissue engineered product, or a combined advanced therapy medicinal product (which are medicinal products incorporating cells and medical devices or actively implantable medical devices).

Adverse event Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells.

Adverse reaction An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells.

Allogeneic Refers to cells and tissues donated by one person for clinical application to another person.

Allograft Tissues or cells transplanted between two genetically different individuals of the same species. The term is synonymous with the term homograft.

Amniotic membrane The innermost layer of the placental membrane; it surrounds the foetus during pregnancy.

Apheresis Medical technique in which peripheral blood of a donor or patient is passed through an apparatus that separates out one particular constituent and returns the remaining constituents to the donor or patient.

Assisted reproductive technology Methods used to achieve pregnancy by artificial or partially artificial means. This includes, but is not limited to, *in vitro* fertilisation, intra-cytoplasmic sperm injection, cryopreservation of gametes and/or embryos and intra-uterine insemination.

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.

Autologous Refers to cells or tissues removed from a patient for subsequent clinical application to themselves.

- Banking** Processing, preservation, storage and distribution of tissues and cells for therapeutic and/or research purposes.
- Barcode** An optical machine-readable representation of data relating to the object to which it is attached.
- Batch** A defined quantity of starting material, packaging material or product processed in one process (or series of processes) so that it can be considered to be homogenous.
- Best practice** A method or technique that has consistently shown results superior to those achieved with other means and that is used as a benchmark.
- Biobank** A collection of biological material and the associated data and information stored in an organised system for a population or a subset of a population.
- Bioburden** Total number of viable micro-organisms (total microbial count) on tissues or cells or on the environment, usually measured before the application of a decontamination or sterilisation process.
- Bone** The hard, rigid form of connective tissue constituting most of the skeleton of vertebrates composed primarily of calcium salts. There are two types of osseous tissue that form bones: cortical bone (the compact bone of the shaft of a bone that surrounds the marrow cavity) and cancellous or trabecular bone (typically occurs at the ends of long bones, proximal to joints and within the interior of vertebrae. Cancellous bone is highly vascular and frequently contains bone marrow).
- Bone marrow** Tissue at the centre of large bones. It is the place where new blood cells are produced. Bone marrow contains two types of stem cells: haematopoietic (which can produce blood cells) and stromal (which can produce fat, cartilage and bone).
- Cell** The smallest transplantable and functional unit of living.
- Cell culture** The result of *in vitro* cell growth.
- Clean area/environment** An area with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.
- Compatibility testing** Testing for the presence or absence of recipient antibodies to HLA-antigens and to blood group antigens present on the cells, tissues or organs for transplantation.
- Competent Authority** See Health Authority.
- Computerised system** A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.
- Consent to donation** Legally valid permission or authorisation for removal of human cells, tissues and organs for transplantation.
- Cord blood** Blood collected from placental vessels and umbilical cord blood vessels after the umbilical

- cord is clamped and/or severed as a source of haematopoietic stem cells.
- Cord blood bank** A specific type of tissue establishment where haematopoietic stem cells collected from the placental and umbilical cord blood vessels are processed, cryopreserved and stored. It may also be responsible for collection, testing or distribution.
- Cornea** The transparent dome-shaped anterior portion of the outer covering of the front of the eye; it covers the iris and pupil and is continuous with the sclera.
- Critical** Potentially having an effect on the quality and/or safety of (or having contact with) cells and tissues.
- Cross-contamination** Unintentional transfer of micro-organisms and/or other material from one donation or processing batch to another.
- Culture/cell expansion** *In vitro* proliferation of retrieved cells for the purpose of transplantation.
- Deceased donor** A person declared as dead according to established medical criteria and from whom cells, tissues or organs have been recovered for the purpose of transplantation. The possible medical criteria are:
- Deceased Heart Beating Donor (Donor after Brain Death): a donor who is declared dead and diagnosed by means of neurological criteria.
 - Deceased Non-Heart Beating Donor (Donor after Cardiac Death) (NHBD): a donor who is declared dead and diagnosed by means of cardio-pulmonary criteria.
- Decontamination** See Disinfection
- Deviation** Departure from an approved instruction or established standard.
- Direct use** Any procedure where tissues/cells are donated and used without any banking/storage.
- Disinfection** A process that reduces the number of viable micro-organisms, but does not necessarily destroy all microbial forms, such as spores and viruses.
- Distribution** Transportation and delivery of cells or tissues intended for human application, after they have been allocated.
- Disposal (of tissue/cells)** The act or means of discarding tissues and cells.
- Donor** A person, living or deceased, who is a source of cells or tissues for the purpose of transplantation.
- Donor evaluation** The procedure of determining the suitability of a potential donor, living or deceased, to donate.
- Donor selection** See Donor evaluation.
- End user** A healthcare practitioner who performs transplantation procedures.
- Error** A mistake or failure to carry out a planned action as intended or application of an incorrect plan that may or may not cause harm to patients.
- Exceptional release** The distribution for clinical use of a unit of cells and/or tissue that does not fully comply with the defined safety

and quality criteria for release. The release is justified by a specific clinical need where the benefit outweighs the risk associated with the non-compliance.

Expert Individual with appropriate qualifications and experience to provide technical advice to a Health Authority inspector.

Expiry date The date after which tissues or cells are no longer suitable for use.

Export The act of transporting human bodies, body parts, cells or tissues intended for human application to another country where they are to be further processed or used.

Facility Refers to a physical building or part of a building.

Fascia A layer of fibrous connective tissue that surrounds muscles, groups of muscles, blood vessels and nerves, which binds some structures together, while permitting others to slide smoothly over each other.

Final product Any tissue or cell preparation intended to be transplanted or administered after the final release step.

Follow-up Subsequent evaluation of the health of a patient, living donor or recipient, for the purpose of monitoring the results of the donation or transplantation, maintenance of care and initiating post-donation or post-transplantation 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.

Good laboratory practice Set of principles that provides a framework within which studies are planned, performed, monitored, recorded, reported and archived by laboratories conducting testing of all kinds.

Good manufacturing practice A standard applied internationally for the safe manufacture of medicinal products. Although the processing of tissues and cells is not normally regulated under medicinal manufacturing legislation, many of the principles of GMP can usefully be applied to tissues and cells for human application.

Haematopoietic stem cells Primitive haematopoietic cells capable of self-renewal as well as maturation into any of the haematopoietic lineages, including committed and lineage-restricted progenitor cells, unless otherwise specified and regardless of tissue source. May also be referred to as *Haematopoietic Progenitor Cells*.

Haemodilution Dilution of serum or blood samples used for laboratory investigations due to infusions and transfusions.

Health Authority In the context of this Guide, the body that has been delegated the responsibility for ensuring that tissue and cell donation, banking 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 EU, Competent Authority, are equivalent to it.
- Heart valve** One of the four structures within the heart that prevent backflow of blood by opening and closing with each heartbeat. They include two semilunar valves (the aortic and pulmonary), the mitral (or bicuspid) valve, and the tricuspid valve. They permit the flow of blood in only one direction.
- Human application** The use of tissues or cells on or in a human recipient and extra-corporeal applications.
- Human error** A mistake made by a person rather than being caused by a poorly designed process or the malfunctioning of a machine such as a computer.
- Human cells and tissues for transplantation** Material containing or consisting of human cells and/or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples include, but are not limited to, musculo-skeletal tissue (bone, cartilage, meniscus), skin, soft tissue (tendons, ligaments, nerves, *dura mater*, fascia lata and amniotic membrane), cardiovascular tissue (heart valves, arteries and veins), ocular tissue (corneas and sclera), bone marrow, HSCs derived from peripheral and cord blood, stem cells from any tissue and reproductive cells/tissues.
- Identification of tissues and cells** The act of labelling tissues and cells in order to uniquely designate their origin, use or destination.
- Import** The act of bringing tissues or cells into one country from another for the purpose of transplantation.
- Imputability** An assessment of the probability that a reaction in a donor or recipient may be attributed to the process of donation or clinical application or to an aspect of the safety or quality of the cells or tissues applied.
- Incident** A generic term for an adverse reaction or event.
- Incident reporting** (*adverse event reporting, serious/critical incident reporting*) A system in a health-care organisation for collecting, reporting and documenting adverse occurrences impacting on patients that is inconsistent with planned care, e.g. medication errors, equipment failures, violations.
- Informed consent** A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to donate, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure.
- In-process control** Checks performed during processing in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specification. Control of the environment or equipment may also be regarded as a part of in-process control.
- Inspection** On-site assessment/control of compliance with the local/national regulations for tissues and cells, performed by officials of the Health Authority(ies).

Labelling Includes steps taken to identify packaged material by attaching the appropriate information to the container or package so they are clearly visible through the immediate carton, receptacle or packaging.

Living donor A living person from whom cells or tissues 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:

- 1st degree Genetic relative: Parent, Sibling, Offspring.
- 2nd degree Genetic relative: Grandparent, Grandchild, Aunt, Uncle, Niece, Nephew.
- Other than 1st or 2nd 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.

Lyophilisation A controlled dehydration process typically used to preserve a perishable material or to make the material more convenient for transport.

Manipulation Preparation of retrieved tissues or cells to make them suitable for transplantation. In the context of haematopoietic stem cell processing, this is an *in*

vitro procedure that selectively removes, enriches, expands or functionally alters the cells.

Malignancy The presence of cancerous cells or tumours with a tendency to metastasise potentially resulting in death.

Medicinal product Any substance or combination of substances presented as having properties for treating or preventing disease in human beings, or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Musculoskeletal Tissues that are part of the skeletal and/or muscular system such as muscles, bones, cartilage, tendons and ligaments which function in support and movement of the body.

Non-compliance Failure to comply with accepted standards, requirements, rules or laws.

Next of kin A person's closest living blood relative or relatives.

Opt-in donation system A method for determining voluntary consent where only those who have given explicit consent are donors.

Opt-out donation system A method for determining voluntary consent where anyone who has not refused donation is a donor.

Organ Differentiated and vital 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.
- Package insert** A document included in the packaging of a distributed tissue or cell product that includes important information for the end users on handling, storage, traceability and adverse outcome reporting and, in some cases, on the product's properties or characteristics.
- Packaging** All operations, including filling and labelling, which a tissue or cell product has to undergo in order to become a finished product.
- Packaging material** Any material employed in the packaging of tissues or cells, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
- Pericardium** A double-walled sac that contains the heart and the roots of the great vessels.
- Placenta** An organ that connects the developing foetus to the uterine wall to allow nutrient uptake, waste elimination and gas exchange via the mother's blood supply.
- Pooling** The physical contact or mixing of cells or tissues from two or more donors in a single container. The use of any shared space during processing, such as laminar flow cabinets or freeze-dryer chambers, also implies pooling.
- Preservation** The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.
- Primary packaging** Any material employed in the packaging of tissues and cells, excluding any outer packaging used for transportation or shipment, intended to be in direct contact with the graft.
- Procedures** Description of the operations to be carried out, the precautions to be taken and measures to be applied that relate directly or indirectly to the process from donation to transplantation.
- Processing** All operations involved in the preparation, manipulation, preservation and packaging of cells or tissues intended for human application.
- Procurement** A process by which tissue or cells are made available for banking or clinical use. This process includes donor identification, evaluation, obtaining consent for donation, donor maintenance and retrieval of cells, tissues or organs.
- Procurement organisation** A health-care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues or cells.
- Quality** The degree to which a set of characteristics fulfils requirements.

Quality assurance Describes the planned and performed actions to provide confidence that all systems and elements that influence the quality of the product are working as expected, both individually and collectively.

Quality control The part of quality management focussed on fulfilling quality requirements. In terms of preparation, it is concerned with sampling specifications and testing and, for the organisation, it relates to documentation and release procedures, which together ensure that the necessary and relevant tests have actually been carried out and that materials have not been released for use until their quality has been judged to be satisfactory.

Quality improvement Describes the planned and performed actions to develop a system to review and improve the quality of a product or process.

Quality management Designs the co-ordinated activities to direct and control an organisation with regard to quality.

Quality system The organisational structure, defined responsibilities, procedures, processes and resources for implementing quality management, including all activities that contribute to quality (directly or indirectly).

Quarantine The initial status of retrieved tissues or cells whilst awaiting a decision on their acceptance or rejection, or tissues or cells isolated physically or by other effective means from

other donated material for other reasons until their suitability for use is established.

Recall Removal from use of specific, distributed tissues and cells suspected or known to be potentially harmful.

Rapid alert An urgent communication to relevant individuals/organisations to ensure the protection of donors or recipients when an unexpected risk has been identified.

Recipient Person to whom human tissues, cells or embryos are applied.

Registry A repository of data collected on cell, tissue and organ donors and/or transplant recipients for the purpose of outcome assessment, quality assurance, healthcare organisation, research and surveillance.

Retrieval or recovery See procurement.

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.

Return Sending back tissues or cells that may or may not present a quality or safety defect to the tissue establishment that supplied them for clinical application.

Root cause analysis A structured approach to identifying the factors that resulted in the nature, the magnitude, the location and the timing of a harmful or potentially harmful outcome.

Secondary packaging Any material employed in the packaging of tissues and cells, excluding

any outer packaging used for transportation or shipment not intended to be in direct contact with the graft.

Serious adverse event Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patient or which might result in, or prolong, hospitalisation or morbidity.

Serious adverse reaction An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Skin The thin layer of tissue forming the natural outer covering of the human body. Skin is composed of two primary layers: the epidermis and the dermis, both layers are separated by a thin sheet of fibres called the basement membrane. Keratinocytes are the major cells, constituting 95% of the epidermis. The dermis provides tensile strength and elasticity to the skin through an extracellular matrix composed of collagen fibrils, microfibrils, and elastic fibres, embedded in proteoglycans.

Standard operating procedure Written instructions describing the steps in a specific process, including the materials and methods to be used and the expected result.

Sterilisation Any process that eliminates (removes) or kills all forms of microbial life, including transmissible agents (such as fungi, bacteria, viruses, spores, etc.) present on a surface, contained in a fluid, in medication or in a compound such as biological culture media. Sterilisation can be achieved by applying the proper combinations or conditions of heat, chemicals, irradiation, high pressure and filtration.

Sterile Free from biological contaminants.

Storage Maintenance of a product under appropriate controlled conditions until distribution.

Storage temperature The temperature at which tissues and cells must be stored to maintain their required properties.

Surveillance The systematic collection, collation and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health responses, as necessary.

Tendon A tough band of fibrous connective tissue that usually connects muscle to bone and is capable of withstanding tension.

Third countries Term used within the EU to refer to countries that are not members of the EU.

Third party Any organisation that provides a service to a procurement organisation or a tissue establishment on the basis of a contact or written agreement.

Tissue An aggregate of cells joined together by, for example, connective structures and performing a particular function.

Tissue bank See Tissue establishment.

Tissue establishment A facility or a unit of a hospital or another body where the activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells.

Toxicity The degree to which a substance can damage a living or non-living organism.

Traceability The ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal. This implies the ability to identify the donor and the tissue establishment or the processing facility that receives processes or stores the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s). Traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells.

Transmissible disease Comprises all clinically-evident illnesses (i.e. characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of micro-organisms in an individual recipient originating from the tissues or cells applied.

Transplantation/ Implantation/Grafting The transfer (engraftment) of human cells, tissues or organs from a donor to a recipient with the aim of restoring function(s) in the body.

Transport The means used to transfer or convey tissues and cells from one place to another.

Unique identification code (donor number) A code that unambiguously identifies a particular donor or donation.

Validation Establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its pre-determined specifications and quality attributes. A process is validated to evaluate the performance of a system with regard to its effectiveness, based on intended use.

Vigilance An alertness or awareness of serious adverse events, serious adverse reactions or complications related to donation and clinical application of cells, tissues and organs, involving an established process at a local, regional, national or international level for reporting.

Withdrawal A process instigated by a tissue establishment to recall tissues or cells that have been distributed.

Appendix 4. Sample patient assessment form and rationale document

Patient Assessment Form

Directions for completion

- 1 This six-page form must be completed in **black or dark blue ink** by the **SN-OD/NP/ANP/Tissue Transplant Co-ordinator** and signed where required.
- 2 The original copy should be retained by the **SN-OD/NP/ANP/Tissue Co-ordinator** for the donor file.
- 3 A copy should be made for the patient's medical records.
- 4 In the event of organ and tissue donation, a legible photocopy should be sent to the relevant **Tissue Establishment/CTS Eye Bank**, where required.

NOTE: The term patient is used throughout the form to refer to the potential donor.

ODT Donor number

PATIENT ASSESSMENT

(Information obtained from relative/significant other)

Patient's name

Please print

Donor hospital

Hospital/CHI number

Cause of death:

Patient date of birth

(dd/mm/yyyy)

In order to proceed with organ and tissue donation it is necessary for us to ask you some questions - which should be answered to the best of your knowledge - about your relative's medical and behavioural history. All information will be treated with the strictest confidence.

For paediatric patients under the age of 18 months or those who have been breast-fed in the past twelve months the mother is required to answer these questions with regard to both her own and her child's health.

For children: has your child been breast-fed in the last twelve months?

Yes ☐No ☐Not applicable ☐

NOTE: For all donors under the age of 18 months and any baby or child who has been breastfed in the last 12 months, a blood sample is required from the mother of the donor

For ALL female patients aged between 13 and 53 years of age

Is there a possibility that your relative could be pregnant?

Yes ☐No ☐Unknown ☐

GENERAL HEALTH INFORMATION

1 Has your relative visited his/her general practitioner in the last two years? Was he/she currently seeing or waiting to see their general practitioner or any other healthcare professional?

Yes ☐No ☐Unknown ☐

If YES, give details

2 Did your relative have diabetes?

Yes ☐No ☐Unknown ☐

If yes, were they on insulin?

Yes ☐No ☐Unknown ☐

Is there a family history of diabetes?

Yes ☐No ☐Unknown ☐

If yes, is it insulin dependent diabetes?

Yes ☐No ☐Unknown ☐

3 Did your relative take regular medication?

Yes ☐No ☐Unknown ☐

If YES, give details

4 Did your relative ever undergo any investigations for cancer or have they ever been diagnosed with cancer?

Yes ☐No ☐Unknown ☐

If YES, give details

5 Did your relative recently suffer from any significant weight loss?

Yes ☐No ☐Unknown ☐

If YES, give details

6 Did your relative have any signs of recent infection, eg colds, flu, fever, night sweats, swollen glands, diarrhoea, vomiting or skin rash?

Yes ☐No ☐Unknown ☐

If YES, please specify

7 Did your relative come into contact with any infectious disease recently or have any immunisations within the last eight weeks?

Yes ☐No ☐Unknown ☐

If YES, give details

8 Did your relative ever have hepatitis, jaundice or liver disease?

Yes ☐No ☐Unknown ☐

If YES, give age and any diagnosis

Patient Assessment Form		ODT Donor number
GENERAL HEALTH INFORMATION continued		
9 Did your relative have a history of ocular disease or previous eye surgery or corrective laser treatment? If YES, give details	Yes ☐ No ☐ Unknown ☐	
10 Did your relative ever suffer from any bone, joint, skin or heart disease, eg rheumatic fever? If YES, give details	Yes ☐ No ☐ Unknown ☐	
11 Did your relative ever have any operations or illnesses including an organ or tissue transplant? <i>If no go to question 13.</i> If YES, give details	Yes ☐ No ☐ Unknown ☐	
12 Did your relative ever have neurosurgical operations for tumour or cyst of the spine/brain or implantation of dura mater, before August 1992? If YES, please specify	Yes ☐ No ☐ Unknown ☐	
13 Did your relative receive a blood, or blood product/component transfusion (such as Fresh Frozen Plasma (FFP), Platelet, Cryoprecipitate or Immunoglobulins) at any time (particularly since 1980)? If YES, give details	Yes ☐ No ☐ Unknown ☐	
14 Was your relative ever told never to donate blood? If YES, give details of where, when and the reason	Yes ☐ No ☐ Unknown ☐	
15 Did your relative suffer from any chronic or autoimmune illness or disease of unknown cause, eg inflammatory bowel disease, multiple sclerosis, sarcoidosis? If YES, give details	Yes ☐ No ☐ Unknown ☐	
16 Did your relative suffer from any type of brain disease such as Parkinson's disease, Alzheimer's disease, recent memory loss, confusion or unsteady gait? If YES, give details	Yes ☐ No ☐ Unknown ☐	
17 Did your relative have a family history of prion disease or do you know if they were ever told that they were at risk of CJD, vCJD, GSS or FFI? If YES, give details	Yes ☐ No ☐ Unknown ☐	
18 Did your relative ever receive human pituitary extracts, eg growth hormones, fertility treatment or test injections for hormone imbalance? If YES, give details	Yes ☐ No ☐ Unknown ☐	
19 Did your relative ever have any other serious infection such as tuberculosis, malaria, West Nile virus, SARS, typhoid fever, toxoplasmosis, rabies, encephalitis, Lyme disease or brucellosis? If YES, give details, and any treatment received	Yes ☐ No ☐ Unknown ☐	
20 Did your relative have any acupuncture, tattooing, body piercing, botox, injections or cosmetic treatments that involves piercing the skin in the last six months? If YES, give details	Yes ☐ No ☐ Unknown ☐	

Patient Assessment Form

ODT Donor number

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GENERAL HEALTH INFORMATION continued

- 21 In the last twelve months has your relative been in close contact with a bat anywhere in the world or been bitten by an animal whilst abroad? Yes ☐ No ☐ Unknown ☐
If YES, give details of animal and place of treatment

- 22 Did your relative ever have a sexually transmitted infection e.g. syphilis, gonorrhoea, genital herpes, genital warts? Yes ☐ No ☐ Unknown ☐
If YES, give details of diseases, dates and treatment

TRAVEL RISK ASSESSMENT

- 23 Did your relative ever travel outside the UK?
(If NO or UNKNOWN, proceed to 26b then continue with Behavioural Risk Assessment. If YES, continue with questions below) Yes ☐ No ☐ Unknown ☐

- 24 Has your relative travelled outside the UK in the last 12 months? Yes ☐ No ☐ Unknown ☐
If yes, give details of date of visit/return and destination.

- 25 Ever had a fever or received treatment for an illness whilst abroad or within six months of leaving an area where there is malaria or West Nile Virus? Yes ☐ No ☐ Unknown ☐
If YES, give date of fever/illness and places visited

- 26 (a) Ever live or work in rural Central or South America for a continuous period of four weeks or more? Yes ☐ No ☐ Unknown ☐
If YES, specify place and date of last visit, and details of living conditions

- 26 (b) Was your relative or their mother born in Central or South America? Yes ☐ No ☐ Unknown ☐

- (c) Was your relative ever given a blood transfusion in that country? Yes ☐ No ☐ Unknown ☐

- 27 (a) Ever spend a continuous period of six months or longer in an area where there is malaria at any time during his/her life? Yes ☐ No ☐ Unknown ☐

- (b) If YES, have they travelled to a malaria area since then? Yes ☐ No ☐ Unknown ☐

If YES, give details of where

BEHAVIOURAL RISK ASSESSMENT

- 28 Did your relative:
(a) consume alcohol? Yes ☐ No ☐ Unknown ☐
If YES, approximately how many units per week

- (b) smoke tobacco or any other substance? Yes ☐ No ☐ Unknown ☐
If YES, give details

- 29 Is it possible that any of the following apply to your relative?

- (a) is, or may be infected with HTLV, HIV or hepatitis B or C? Yes ☐ No ☐ Unknown ☐

- (b) has ever injected or been injected with non-prescriptive drugs, including body building drugs, even if it was a long time ago or only once? Yes ☐ No ☐ Unknown ☐

- (c) has ever been given payment for sex with money or drugs? Yes ☐ No ☐ Unknown ☐

- (d) (for male patients only) ever had sex with another man with or without a condom? Yes ☐ No ☐ Unknown ☐

Patient Assessment Form

ODT Donor number

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GENERAL HEALTH INFORMATION continued

- 21 In the last twelve months has your relative been in close contact with a bat anywhere in the world or been bitten by an animal whilst abroad? Yes ☐ No ☐ Unknown ☐
If YES, give details of animal and place of treatment
- 22 Did your relative ever have a sexually transmitted infection e.g. syphilis, gonorrhoea, genital herpes, genital warts? Yes ☐ No ☐ Unknown ☐
If YES, give details of diseases, dates and treatment

TRAVEL RISK ASSESSMENT

- 23 Did your relative ever travel outside the UK?
(If NO or UNKNOWN, proceed to 26b then continue with Behavioural Risk Assessment. If YES, continue with questions below) Yes ☐ No ☐ Unknown ☐
- 24 Has your relative travelled outside the UK in the last 12 months? Yes ☐ No ☐ Unknown ☐
If yes, give details of date of visit/return and destination.
- 25 Ever had a fever or received treatment for an illness whilst abroad or within six months of leaving an area where there is malaria or West Nile Virus? Yes ☐ No ☐ Unknown ☐
If YES, give date of fever/illness and places visited
- 26 (a) Ever live or work in rural Central or South America for a continuous period of four weeks or more? Yes ☐ No ☐ Unknown ☐
If YES, specify place and date of last visit, and details of living conditions
- 26 (b) Was your relative or their mother born in Central or South America? Yes ☐ No ☐ Unknown ☐
- (c) Was your relative ever given a blood transfusion in that country? Yes ☐ No ☐ Unknown ☐
- 27 (a) Ever spend a continuous period of six months or longer in an area where there is malaria at any time during his/her life? Yes ☐ No ☐ Unknown ☐
- (b) If YES, have they travelled to a malaria area since then? Yes ☐ No ☐ Unknown ☐
If YES, give details of where

BEHAVIOURAL RISK ASSESSMENT

- 28 Did your relative:
(a) consume alcohol? Yes ☐ No ☐ Unknown ☐
If YES, approximately how many units per week
- (b) smoke tobacco or any other substance? Yes ☐ No ☐ Unknown ☐
If YES, give details
- 29 Is it possible that any of the following apply to your relative?
- (a) is, or may be infected with HTLV, HIV or hepatitis B or C? Yes ☐ No ☐ Unknown ☐
- (b) has ever injected or been injected with non-prescriptive drugs, including body building drugs, even if it was a long time ago or only once? Yes ☐ No ☐ Unknown ☐
- (c) has ever been given payment for sex with money or drugs? Yes ☐ No ☐ Unknown ☐
- (d) (for male patients only) ever had sex with another man with or without a condom? Yes ☐ No ☐ Unknown ☐



Blood and Transplant

Patient Assessment Form

ODT Donor number

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BEHAVIOURAL RISK ASSESSMENT continued

(e) (for female patients only) had sex in the last 12 months with a man who has had sex with another man with or without a condom?

Yes ☐ No ☐ Unknown ☐

(f) been in prison or a juvenile detention centre for more than three consecutive days within the last 12 months?

Yes ☐ No ☐ Unknown ☐

NB: This excludes those who have been in a police cell for <96 hours.

(g) had sex in the last 12 months with:

(i) anyone who is HIV or HTLV positive?

Yes ☐ No ☐ Unknown ☐

(ii) anyone who has hepatitis B or C?

Yes ☐ No ☐ Unknown ☐

(iii) anyone who had a sexually transmitted disease?

Yes ☐ No ☐ Unknown ☐

(iv) anyone who has ever been given payment for sex with money or drugs?

Yes ☐ No ☐ Unknown ☐

(v) anyone who has ever injected drugs?

Yes ☐ No ☐ Unknown ☐

(vi) anyone who may ever have had sex in any part of the world where AIDS/HIV is very common (this includes most countries in Africa)?

Yes ☐ No ☐ Unknown ☐

Having answered all the previous questions is there anyone else who you think may provide more information?

Yes ☐ No ☐

If YES, please specify

Question number	Relevant additional information

Question number	Relevant additional information

Information discussed with

Name	Please print	Relationship	Please print
Signature of healthcare professional obtaining information			
Designation of healthcare professional obtaining information			
Date of interview	/ / 20		
	Time of interview		

Patient Assessment Form

ODT Donor number

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CALCULATION FOR PLASMA DILUTION: WHEN NO PRE-TRANSFUSION BLOOD SAMPLE IS AVAILABLE

Record ALL fluid administered in the 48 hours prior to death

[illegible]

Patient Assessment Form

ODT Donor number

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CALCULATION FOR PLASMA DILUTION continued

CRYSTALLOID INFUSED:

INTERVAL PRIOR TO SAMPLING	VOLUME INFUSED (ml)	% RETAINED	VOLUME RETAINED (ml)
> 24 HOURS		0	NONE
2-24 HOURS		25	
1-2 HOURS		50	
<1 HOUR		75	
TOTAL CRYSTALLOID RETAINED:			

BLOOD/COLLOID INFUSED:

INTERVAL PRIOR TO SAMPLING	VOLUME INFUSED (ml)	% RETAINED	VOLUME RETAINED (ml)
24-48 HOURS		100 (Blood) 50 (Colloid)	
0-24 HOURS		100	
TOTAL BLOOD/COLLOID RETAINED:			

ESTIMATED TOTAL BLOOD VOLUME:

70ml per kilogram of body weight
50 ml per kilogram of body weight in ICU

% HAEMODILUTION

(CRYSTALLOID RETAINED + BLOOD/COLLOID RETAINED) X 100
BLOOD VOLUME:

ACCEPT (<50%)/REJECT (>50%)

Signature of health care
professional obtaining information

--

Please print name

--

Date of interview

				2	0		
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Time of interview

	:		
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Comments

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Appendix 4 - Cont.

Rationale document for patient assessment form PA1 (vo3)

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 Specialist Nurse – Organ Donation (ODT), Nurse Practitioner/ Assistant Nurse Practitioner (Tissue Services) and Tissue Transplant Co-ordinator (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 re organ donation	Action to take re tissue donation
FOR PAEDIATRIC DONATION: has your child been breast-fed in the last 12 months?	There is a risk of vertical transmission of some 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 fallback 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 fallback position if required. - Babies greater than 18 months not breastfed should only require infant sampling.
For ALL female patients aged between 13 and 53 years of age Is there a possibility that your relative could be pregnant?	If there is a possibility that the patient could be pregnant then a pregnancy test should be performed, to determine whether the foetus is viable. 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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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. 1.2. Note: It is important to obtain accurate information on past medical history. Therefore it is a requirement that the GP is contacted to complete the NHSBT GP questionnaire (FRM1602).	Donation acceptable. 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. Not an absolute contraindication except for pancreas; inform recipient centres. Not an absolute contraindication; inform recipient centres.	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. For tissue only donation this is usually done post-donation. Donation acceptable except for pancreatic tissue. 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.
2. Have diabetes? If yes, were they on insulin?	2.1. Due to the effect diabetes can have on a number of organs particularly the kidneys additional tests/information relating to function may be necessary.		
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.		

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
	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; isotretinoin (roaccutane), acitretinate (neotigason), etretinate (tigason) used to treat acne and dandruff (avodart) and finasteride (proscar) used to treat prostatic hyperplasia all have specified deferral periods. See current version of TDSG-DD.
4. Ever undergo any investigations for cancer or ever been diagnosed with cancer?	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 may be masked.	Not an absolute contraindication; inform recipient centres.	Must not donate if immunosuppressed.
	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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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. 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. Not an absolute contraindication; inform recipient centres	See current version of TDSG-DD. 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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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. 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. 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.
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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
	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 <i>dura mater</i> 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 <i>dura mater</i> , before August 1992?	12.1. This is to ascertain if the donor may have been given a <i>dura mater</i> graft as part of a neurosurgical procedure. This material is known to have transmitted CJD in around 200 cases. Brain surgery often required <i>dura mater</i> repair. Neurosurgeons may use different materials for this but before 1992; <i>dura mater</i> from cadaveric donors was used in brain and spinal surgery. Spinal fusion and burr holes did not usually involve using <i>dura mater</i> .	Not an absolute contraindication; inform recipient centres.	If yes, tissue donation can only be accepted if it can be shown that <i>dura mater</i> was not used.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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. 13.2. If there has been significant blood loss and replacement of fluids with blood components and/or colloids within the 48-hour 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-period before sampling is required to enable the haemodilution calculation to be performed. 13.3. The reason for the blood transfusion should be obtained as this may itself be a contraindication to donation.	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-hour 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-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

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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. 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.	Contraindication if person told never to give blood owing to CJD risk.
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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
	15.2. Inflammatory bowel disease can also increase the risk of bacteria entering the blood stream. 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. Not an absolute contraindication; inform recipient centres.	Crohn's disease and ulcerative colitis are exclusions for tissue donation except for corneal donation. Acceptance criteria are specific for each condition, see TDSG-DD. Single organ autoimmune disease such as thyroid disease or vitiligo is acceptable. Rheumatoid arthritis is excluded for non-ocular tissue if the donor has needed to immunosuppress in the last 12 months. Systemic lupus erythematosus and polyarteritis nodosa are contraindications.
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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
17. Have a family history of CJD, vCJD, Gerstmann-Straussler-Schriener 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.
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 be noted (Question 25).	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.	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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
	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.	Malaria Contraindication to donation if there is a known active infection and no curative chemo-therapy 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.	
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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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 is yes, it is important to obtain as much information as possible. Untreated STD's 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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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:			
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. Travelled 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 to 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 had 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.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
26a. Ever live or work in rural Central or South America for a continuous period of 4 weeks or more?	26a1. Individuals who have ever lived in Central or South America are at risk of <i>Trypanosoma cruzi</i> 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 <i>T. cruzi</i> is not a deferral criterion. For other tissues a <i>T. cruzi</i> antibody test is required. Refer to the TDSG-DD and GDRI.
26b. Was the deceased or their mother born in Central or South America?	26b1. <i>T. cruzi</i> 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 <i>T. cruzi</i> is not a deferral criterion. For other tissues a <i>T. cruzi</i> antibody test is required. Refer to the TDSG-DD and GDRI.
26c. Given a blood transfusion in that country?	26c1. As <i>T. cruzi</i> is endemic in this area and individuals remain asymptomatic for years after infection many blood donors are infected by this organism. <i>T. cruzi</i> 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 <i>T. cruzi</i> is not a deferral criterion. For other tissues a <i>T. cruzi</i> antibody test is required. Refer to the TDSG-DD and GDRI.

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
27a. Ever stay for 6 months or longer in an area where there is malaria, at any time in his/her life?	27a1. 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?	27b1. An individual who is classified as "resident" is managed differently from a non-resident for <u>each</u> 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. 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 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 re organ donation	Action to take re tissue donation
BEHAVIOURAL RISK ASSESSMENT				
To the best of your knowledge did your relative:				
28a. Consume alcohol?	28a1. 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. 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.		
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 did your relative:				
29a Is or may be infected with HTLV, HIV or hepatitis B or C?	29a1. 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.	

Question	Reason for asking the question	Action to take re organ donation	Action to take re tissue donation
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?	29b1. 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?	29c1. 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?	29d1. 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?	29e1. 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 hours.	29f1. 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 re organ donation	Action to take re 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)? Having answered all the previous questions is there anyone else who you think may provide more information?	29g1. 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.

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. Sample tissue donor physical assessment form from the AATB



Sample Tissue Donor Physical Assessment Form

Identification

Name stated on Consent (Authorization) : _____

Age: _____ days months years Recovery Agency ID#: _____

Sex/gender: Male Female Race: _____ ID#: _____

Weight: _____ lbs. kgs Weight is: estimated/team, reported (source: _____), ☐ actual

Height: _____ ft. in. cm. Height is: estimated/team, reported (source: _____), ☐ actual

Manner identified by: hospital ID band, toe tag, other (describe) _____

Identification Band/Tag

ID re-created as closely as possible,

or circle N/A (if not present).



Personnel confirming donor identification: _____ Date/time: _____

Evidence of Donation/Autopsy

Eye donation: whole eyes, corneas only, N/A; Organ donation: Yes No UNOS#: _____

Autopsy: tissue recovery is pre, or post autopsy (full, limited); no autopsy planned; or, plan unknown

Recovery Team Assessment:

Is there evidence of:

Jaundice _____	Yes _____	No _____
Genital lesions _____	Yes _____	No _____
Enlarged lymph nodes _____	Yes _____	No _____
Tattoo/piercing _____	Yes _____	No _____
White spots in the mouth _____	Yes _____	No _____ Unable to visualize _____
Non-medical injection sites _____	Yes _____	No _____
Enlarged liver (hepatomegaly) _____	Yes _____	No _____
Insertion trauma/perianal lesions _____	Yes _____	No _____
Rash/scab/skin lesion (non-genital) _____	Yes _____	No _____
Blue/purple (gray/black) spots/lesions _____	Yes _____	No _____
Trauma/infection to potential retrieval sites _____	Yes _____	No _____
Abnormal ocular finding (e.g., icterus, scarring) _____	Yes _____	No _____ Unable to visualize _____

Notes/Explain if "unable to visualize", or if any answers are "Yes": _____

General Appearance

Cleanliness: Good Poor; Describe if "poor" _____

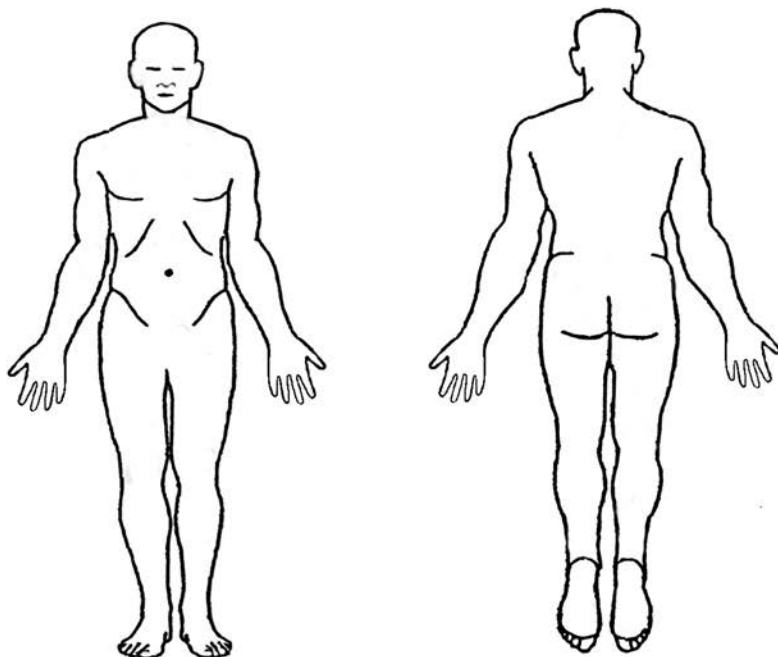
Personnel performing physical assessment: _____ Date/time: _____

Name of Person Completing Form (Print)	Signature	Initials	Date
--	-----------	----------	------

AATB Sample Tissue Donor Physical Assessment Form

Recovery Agency ID#: _____

Recovery Team Assessment: (continued)



Key to schematics:

- | | | |
|--------------------------|--|-----------------------------------|
| (A) Abrasion | (J) Team blood draw site | (T) Tattoo – requires description |
| (B) Bruise/Contusion | (L) Laceration/Wound | (U) Urethral catheter |
| (C) Cast/Ortho device | (M) ID band/tag | (V) Skin lesion |
| (D) Dressing/Bandage | (N) Needle entry site | (W) Scab |
| (E) ET tube/NG tube | (O) Organ recovery incision | () _____ |
| (F) Fracture/Dislocation | (P) Body Piercing – requires description | () _____ |
| (H) Hematoma | (R) Rash | () _____ |
| (I) IV/Arterial line | (S) Scar (surgical/trauma) | () _____ |

Summary

A review of available medical records & physical assessment findings were completed & found to be
acceptable/not acceptable prior to recovery. _____

(Circle one)

(Responsible person)

(Date/time)

Appendix 6. Sample haemodilution algorithm

DONOR ID # _____

Date and Time of Specimen Collection _____

Donor's weight in kg _____

A = Total volume of blood transfused in the 48 hours before death or sample collection, whichever comes first

B = Total volume of colloid infused in the 48 hours before death or sample collection, whichever comes first

C = Total volume of crystalloid infused in the 1 hour before death or sample collection, whichever comes first

BV = donor's blood volume

Calculated blood volume = donor's weight (kg) / 0.015 OR
donor's weight (kg) x 70 mL/kg

PV = donor's plasma volume

Calculated plasma volume = donor's weight (kg) / 0.025 OR
donor's weight (kg) x 40 mL/kg

Calculate **both**:

1. Is $B + C > PV$?
2. Is $A + B + C > BV$?

[Enter a zero if a category (A, B, or C) was not transfused/infused.]

Determination of Sample Acceptability for Infectious Disease Tests:

If the answers to **both** 1 and 2 are NO, the post-transfusion/infusion sample is acceptable.

If the answer to **either** 1 or 2 is YES, the post-transfusion/infusion sample is not acceptable; use a pre-transfusion/infusion sample or reject the donor

Note: An alternative example of a haemodilution algorithm is included in Appendix 4.

Reference: www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf.

Appendix 7. Example of a process validation

Tissue transportation

(Reproduced *with permission* from Winters M & Lomas R. *The Principles of Process Validation and Equipment Qualification*. In: Tissue and Cells Processing: An Essential Guide. Eds: Fehily D, Brubaker S, Kearney J and Wolfinbarger L . 2012 Wiley-Blackwell Publishing)

The example of a process validation outlined below describes a process that will be common to most, if not all, tissue establishments, i.e. the need to transport tissues from one place to another (for example, from the site of procurement to the processing facility or from the bank to the end user). Control of the conditions of transportation is critical to ensuring tissue quality. The example provided here refers specifically to the transportation of skin allografts from the procurement site to a tissue establishment at refrigerated temperatures. However, the principles are the same for all types of transportation.

The first stage is to define the process in detail. This was achieved by addressing the following questions:

- What type of tissue and what maximum volume will be transported?
- How is the tissue contained? What is the nature, volume and temperature of any transport solution to be used? What type of packaging is used?
- What refrigerant is used and what is its specification and volume?
- What are the specifications of the transport container, i.e. dimensions, insulation, etc.?

- What are the most extreme transportation conditions allowable in terms of transport time and ambient temperature?
- Once the process had been defined, the acceptance criteria needed to be defined. In the case of our example, they were:
- That the temperature of the skin allograft must remain within a range of 0 to 10 °C for the duration of the transit.
- That the integrity of the tissue packaging must be maintained during transit.
- That the integrity of the transport container must be maintained during transit.
- That the pH of the transportation fluid must be within the range 7.0 to 7.5 at the end of the transportation.

For some tissues, it may be advisable to go further and validate the quality of the tissue following transit; for example, an assessment of its viability or histological structure.

It was determined that the maximum amount of skin that would be transported would be 6,000 cm², immersed in a minimum volume of 300 mL transport fluid. The specifications of the packaging, transport container and refrigerant were also documented. The most extreme acceptable transportation conditions were defined as an ambient temperature of 40 °C (for example, a hot summer day in a vehicle) for a maximum of 12 hours, with the minimum volume of refrigerant and transport solution, and the maximum volume of tissue.

A protocol was written and a model prepared using skin obtained from donors unsuitable for clinical donation, based on the defined transport solution, refrigerant, packaging and container specifications. A calibrated data-logging thermometer was used to record the temperature on the external surface of the tissue packaging and the container was placed into a shaking incubator set at an ambient temperature of 40 °C. A shaking incubator was used to model the agitation of the container during vehicular transit (the model should approximate as closely as practically possible real-life conditions).

The study was repeated in triplicate, and acceptable results were obtained each time. As all of the results were well within the pre-defined acceptance criteria, the process was accepted based on the results of the three replicates.

Note, however, that it may be necessary to find a compromise between an “ideal” validation and operational practicalities that cannot be avoided. For example, it may not be possible or ethical to obtain and sacrifice large amounts of tissue for validation studies. In these cases, an acceptable compromise should be reached using risk assessment principles; for example, the use of animal tissue as a substitute.

The application of sufficiently robust process validations, for example by challenging a transport process with extremes of time and temperature, obviates the need for routine temperature monitoring of the process. Thus, if the physical conditions identified by the validation study are complied with (e.g. the correct container, containing at least the minimum amount refrigerant, in transit for less than the maximum modeled time), then it can be reliably concluded that the process itself has been performed correctly. Therefore, to demonstrate compliance with the validated process, all operatives need to do is confirm that they have complied with the relevant standard operating procedures.

Appendix 8. Adverse Reaction or Event

The Impact Assessment tool assists practitioners and regulators in planning their response to a given adverse reaction or event, 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 likelihood of occurrence/recurrence of the SARE

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to happen again
3	Possible	May occur occasionally
4	Likely	Expected to happen again, but not persistently
5	Probable	Expected to happen again on many occasions

Step 2: Assessing impact/consequences of the SARE should it recur

Impact level		On individual(s)		On system		On tissue/cell supply
0	Insignificant	Nil	OR	No affect	OR	Insignificant
1	Minor	Non-serious	OR	Minor damage	OR	Some ap- plications postponed
2	Moderate	Serious	OR	Damage for short period	OR	Many cancella- tions or post- ponements

Impact level		On individual(s)		On system		On tissue/cell supply
3	Major	Life-threatening	OR	Major damage to system – significant delay to repair	OR	Significant cancellations – importation required
4	Catastrophic/extreme	Death	OR	System destroyed – need to rebuild	OR	All allogeneic applications cancelled

Step 3: Applying the impact matrix

Likelihood of recurrence ➡	1 Rare	2 Unlikely	3 Possible	4 Likely	5 Certain/ almost certain
Impact of recurrence ⬇					
0 Insignificant	0	0	0	0	0
1 Minor	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Major	3	6	9	12	15
4 Catastrophic/ extreme	4	8	12	16	20

Step 4

The response of a tissue or cell bank or a health authority to a specific SARE should be proportionate to the potential impact as assessed by the matrix described.

White: The tissue or cell bank to manage the corrective and preventive actions and the Health Authority to file the report and keep a “watching brief”.

Pale shading: Requires interaction between the tissue or cell bank and the Health Authority which may request an inspection that focuses on the SARE and corrective and preventive actions to be followed up, including evidence of effective recall, where necessary. Written communication to professionals working in the field might be appropriate.

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.

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:

- reducing 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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Human tissues and cells are being used in an increasing variety of new ways, and advances in transplantation therapy have unquestionable benefits. Human cells and tissues for transplantation can save lives or restore essential functions, but using human tissues and cells also raises questions of safety and quality. Only tissues and cells recovered, processed and stored following strict quality and safety standards are likely to function satisfactorily, and careful evaluation of donors is essential to minimise the risk of transmission of infections or malignancies. Furthermore, since human tissues and cells can currently only be derived from the body of a person, strong ethical principles need to be associated with their donation and use.

The Council of Europe approaches tissue and cell transplantation in compliance with the principles of non-commercialisation and voluntary donation of materials of human origin. This 1st Edition of the *Guide to the quality and safety of tissues and cells for human application* contains sound information and guidance for all professionals involved in donation, banking, transplantation and other clinical applications of these medical products of exceptional nature.

For matters dealing with the use of organs and blood or blood products, see the Council of Europe *Guide to the quality and safety of organs for transplantation* and *Guide to the preparation, use and quality assurance of blood components*, respectively.

The EDQM is a Directorate of the Council of Europe, an international organisation founded in 1949 that covers almost the entire continent of Europe. The Council of Europe aims to develop common democratic and legal principles based on the European Convention on Human Rights and other reference texts on the protection of individuals.

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ISBN 978-92-871-7639-4



9 789287 176394

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EDQM Guide to the quality and safety of tissues and cells for human application 1st Edition