



NOTIFYLIBRARY

The Global Vigilance and Surveillance Database for Medical Products of Human Origin
TRANSPLANTATION, TRANSFUSION AND ASSISTED REPRODUCTION



The NOTIFY Booklet

Vigilance and Surveillance (V&S) of Medical Products of Human Origin (MPHO)

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1. Introduction	3	11. The NOTIFY Database - Learning from Vigilance	25
1.1 Medical products of human origin	3	11.1 The NOTIFY database as a reference for unusual donor suitability questions	25
1.2 Vigilance and surveillance	3	11.2 The Risk/Benefit Calculation:	
1.3 The vigilance and surveillance chain for medical products of human origin, a NOTIFY guide	4	Numbers, numerators, denominators and transparency	25
2. The V&S Chain for MPHOs	5	12. Risks Associated with Living Donation	27
3. History of Vigilance and Surveillance (V&S)	7	12.1 Haematopoietic Progenitor Cell Donation	27
4. Medical Products of Human Origin (MPHO) - Donation and Ethics	8	12.2 Autograft Tissue Donors	28
4.1 Ethical breaches, fraudulent, illegal practices	8	12.3 Living Organ Donor Reactions	28
4.2 The Voluntary Donor and Donor Families	8	13. Investigating Harm to Recipients - Infections	30
5. Towards a global governance of MPHO	10	13.1 The Graft Recipient and the Presentation of Allograft-Associated Infections	30
5.1 The development of global governance of MPHO	10	14. Investigating Harm to Recipients - Malignancy	32
5.2 A safeguard, a damage limitation system	11	14.1 Donor malignancies known to be transmitted or known not to be transmitted by cancer, organ and cell type	32
5.2.1 Early notification, timely reaction	11	14.2 Providing guidance on early detection and prevention of transmission	33
5.2.2 A necessity for the public, a responsibility for authorities	11	14.2.1 Deceased Donors	33
6. The V&S system is primarily a responsibility for health authorities	12	14.2.2 Living Donors	33
6.1 Governments	12	14.3 Providing guidance on intermediate steps to take for index recipient and other potentially affected recipients	34
6.2 Professional Associations	14	14.3.1 Tracing, alerting and notification	34
7. Organization for a comprehensive Vigilance & Surveillance System	15	14.3.2 Graft removal and cessation of immunosuppression	34
7.1 Key Factors for an Effective National Vigilance and Surveillance Scheme	15	14.3.3 Immunotherapy	34
7.2 Clinical Follow-up and Clinical practice surveillance	15	14.3.4 Conventional treatment strategies based upon cancer type if organ, tissue or cell cannot be removed	34
7.3 Integration	16	14.4 Providing guidance on steps to investigate and confirm the imputability of malignancy transmission	34
7.3.1 For the various risks associated with a given product	16	14.4.1 Suspected malignancy transmission	34
7.3.2 For MPHO	16	14.4.2 Tumour histology in donor and recipients	35
8. Vigilance & Surveillance – Recognition relies on health care staff	17	14.4.3 Karyotype of donor and recipient	35
8.1 Quality Management	17	14.4.4 Genetic testing of sample from cancer, e.g. HLA testing	35
8.2 Detection and Notification of Harm to Recipients	17	15. Investigating Harm to Recipients – Genetic Transmissions – HPSC	36
8.3 Triggers for a notification of suspected harm to a recipient	17	16. Investigating Harm to Offspring - Genetic Transmissions - Gametes and Embryos	37
8.4 Infection threat watch	18	16.1 Pre-implantation Genetic Diagnosis	38
8.5 Transmissible disease screening for donor suitability	18	17. Characteristics, handling and clinical errors	39
8.6 Product Centered	18	18. Traceability, an absolute pre-requisite for MPHO safety	42
8.7 Definitions	19	19. References	43
9. Investigating occurrences that could cause harm – Learning from Errors	21		
9.1 Five Whys	21		
9.2 Cause and Effect Analysis	21		
10. Project NOTIFY	23		



1.1 MEDICAL PRODUCTS OF HUMAN ORIGIN

Advances in science and healthcare technology have led to the development of replacement medicine with more human body components being collected for the preparation of medical products of human origin (MPHO). These encompass a wide range of medical products, from cells and tissues to blood and organs, from such anatomical components to secretion and excretion, all originating from the human body. Donated by a human with the goal to benefit others, these MPHO have indeed saved and improved human life through their clinical application. From donation to the follow-up care of the recipient, however, MPHOs have a shared exposure to risks –breaches of ethical, legal and safety standards for example or the risk of disease transmission with a potential undesirable outcome.

The World Health Organisation (WHO) has launched an Organization-wide initiative on MPHOs in 2013. This builds on the ongoing work by the WHO to optimize the services involving MPHOs, from blood transfusion to cell, tissue and organ transplantation, as well as assisted reproductive technologies (ART). The objective is to recognize the human origin as an over-arching characteristic of MPHOs and identify any ethical, legal and safety standards required by the different types of MPHO. The approach highlights the common requirements for donation, preparation and human application of MPHO, while acknowledging the specificities associated with each individual type.

The initiatives for MPHO identified three global governance approaches that are necessary:

- 1) The consensus on and implementation of a set of principles common to all MPHO to guiding practices;
- 2) The universal use of ISBT128, the global Information Standard for Blood and Transplant which enhanced traceability and transparency around the world;
- 3) The maximal sharing of vigilance and surveillance information globally.

1.2 VIGILANCE AND SURVEILLANCE

Vigilance and surveillance (V&S) is important for optimising MPHO, from donation to clinical application and follow-up care of patients; it includes alertness to the risks and systematic management of undesirable outcomes in donors and recipients. V&S is a safeguard for donors, patients, health professionals and health authorities. The introduction of V&S systems can facilitate the monitoring of adverse occurrences outcomes lead to preventive and corrective measures and an overall improvement in safety, as demonstrated by the impact of haemovigilance on transfusion services, donor care and donor safety.

1.3 THE VIGILANCE AND SURVEILLANCE CHAIN FOR MEDICAL PRODUCTS OF HUMAN ORIGIN, A NOTIFY GUIDE

This guidance aims to provide a didactic overview of V&S for MPHO targeting clinicians and health authorities. In order to facilitate its use, the booklet has been divided in chapters, each addressing an aspect of V&S for MPHOs. It demonstrates the necessity, and the potential, of V&S to improve practices and therefore the paramount importance of V&S for MPHO. The NOTIFY booklet provide examples which demonstrate the improvement of the care of both the recipients and donors, from the recognition and diagnosis of adverse reactions to the appropriate investigations and treatment after having drawn upon the references in the NOTIFY Library (www.notifylibrary.org). The success is the reflection of the work of the all the professionals who have contributed to the NOTIFY Library. Many of their recommendations for good practice have been published in a report of a NOTIFY consultation in Bologna in 2011 and in a series of guidance documents developed within the European Union (EU)-funded SOHO V&S Project (Vigilance and Surveillance of Substances of Human Origin) which collaborated in the organization of that consultation.

Initially, the NOTIFY booklet was to be focused on cells, tissue and organs for transplantation, as well as gametes and embryos for assisted reproduction (ART). As the NOTIFY project is now expanding to cover all MPHO, blood and blood products, the scope of the booklet will be expanded to include these in the future. This is a work in progress; it

should not be seen as a finished outcome, but as an evolving document where users can both learn from the guidance or contribute to improvement. The mechanism that characterizes the NOTIFY project, editorial workgroups of volunteer experts and support from national authorities, as well as scientific and professional societies, applies to the development of the booklet. Proposals for improvement will be assessed and edited by the NOTIFY team, with the help of a panel of experts, and will eventually be integrated to the booklet.

The structure of this document was designed for accessibility via the Internet where sections (links) can be consulted independently and adapted to the needs of the user. Effective V&S requires many players to collaborate together, each one fulfilling their particular role: clinicians detecting and reporting adverse outcomes in recipients; donation professionals detecting and reporting adverse outcomes in donors; technical personnel detecting and reporting errors and mistakes in processing, storage and delivery; multi-skilled teams investigating causes and defining corrective and preventive actions and responsible individuals or organizations publishing vigilance information to help others to learn from the cases and to prevent recurrence elsewhere. This document addresses each step in the vigilance chain as a link –to the links can be added to one another and constitute a chain. Like a chain, thanks to the effort of all stakeholders, V&S for MPHOs has the power to be the driver of excellence from donation to clinical application. To access the any section in this document, click on the link in the list below.



HISTORY VIGILANCE AND SURVEILLANCE (V&S)

Vigilance and surveillance is a collective term to describe the systematic, ongoing collection, collation and analysis of adverse outcome data for public health purposes and their timely dissemination for assessment and response as necessary. Biovigilance is the term used for the monitoring of adverse outcomes associated with MPHO. This link provides general background information.

MEDICAL PRODUCTS OF HUMAN ORIGIN (MPHO) DONATION AND ETHICS

Advances in science and healthcare technology have led to more biologic products being collected to sustain and improve the quality of human life. Challenges exist to monitor and ensure appropriate access and availability of safe products both in the domestic and global arenas. This link focuses on the donor-facing aspects of vigilance and the need to protect and care for donors.

TOWARDS A GLOBAL GOVERNANCE OF MPHO

In 2004, the World Health Assembly adopted Resolution WHA57.18 on Cell, Tissue and Organ Transplantation. In close collaboration with relevant scientific and professional societies and national health authorities, the World Health Organization (WHO) updated its Guiding Principles for cell, tissue and organ transplantation. WHO and all stakeholders engaged in activities to improve and harmonize access to safe, effective and ethical transplantation at national and regional level. Guiding Principle 10 and World Health Assembly Resolution WHA63.22 urges Member States to develop vigilance and surveillance of adverse outcomes and the Resolution also asks WHO to facilitate Member States' access to this information. This link describes the global initiatives to improve vigilance of MPHO.

THE V&S SYSTEM IS PRIMARILY A RESPONSIBILITY FOR HEALTH AUTHORITIES

National health authorities require timely reporting of severe occurrences arising in the practice of cell tissue and organ transplantation and assisted reproduction, whether they led to harm or could have led to harm. Cases where there has been harm to a donor, harm to a recipient or harm to a child born following in vitro-fertilisation, or a risk of serious harm has been detected, must be identified and reported. Several systems for the collection of data and their exploitation have been developed in various countries, whether run by the authorities or outsourced to scientific and professional societies. This link highlights the role of health authorities and professional societies in putting systematic vigilance systems in place.

ORGANIZATION FOR A COMPREHENSIVE VIGILANCE & SURVEILLANCE SYSTEM

A comprehensive V&S system has a number of key elements that must be taken into consideration, described in this link.

VIGILANCE & SURVEILLANCE FIRST RELIES ON HEALTH CARE STAFF

Physician and nurses in particular have the responsibility to identify occurrences adverse occurrences and to report them through the appropriate national channel. V&S is not a punitive system. It aims to improve and maximize safety, and therefore the trust of the public, MPHO donation and transplantation service. Attention to quality management in health care can bring a more rigorous and systematic approach to addressing documented deficiencies and cost savings. This link addresses health professionals highlighting their critical role in vigilance.

INVESTIGATING OCCURRENCES THAT COULD CAUSE HARM

The investigation of occurrences that imply risk essentially comprises a 'root cause analysis' process (RCA). RCA is 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. This link gives information for those who need to investigate such occurrences.

PROJECT NOTIFY

WHO, the Italian National Transplant Centre (CNT) and the EU-funded Project 'Vigilance and Surveillance of Substances of Human Origin' (MPHO V&S) joined forces to organize a major global initiative aimed at raising the profile of vigilance and surveillance (V&S) of substances of human origin and maximizing the didactic value of adverse outcomes. The initiative was called Project Notify). This link describes the project.

LEARNING FROM VIGILANCE – THE NOTIFY DATABASE

A new open access, searchable website (a Vigilance Knowledge Base) has been established to host, maintain and update the library of documented occurrences adverse occurrences that has been developed. This link describes the tool that is invaluable to clinical users. (www.notifylibrary.org)

RISKS ASSOCIATED WITH LIVING DONATION

Living donors can provide both allografts and autografts for transplantation of cells, tissues and organs. Such donations carry inherent risks that must be recognized both for patient safety and recognition for purposes of vigilance and surveillance. This link gives guidance for those active in promoting and organizing donation of MPOH.

INVESTIGATING HARM TO RECIPIENTS - INFECTIONS

The recognition of infections transmitted through an allograft is crucial for diagnosis and treatment of the transplanted or transfused patient, both for better health outcomes of the recipient and also to prevent further disease transmission to those who have been transplanted with organs and tissues or transfused with blood products derived from the same donor. This link provides guidance for transfusion and transplantation professionals who investigate suspected infectious transmissions together with the clinician treating the patient.

INVESTIGATING HARM TO RECIPIENTS - MALIGNANCY

The prompt identification of transmission risks and a high index of suspicion of transmitted diseases are essential and constitute the critical steps in international vigilance and surveillance applied to MPOH. Although the risk of malignancy transmission has been examined and reported since the first years of clinical transplantation, the frequency of donors with malignant tumors and the risk of transmission of malignant diseases from donors to recipients are clear. This link provides guidance to professionals who need to investigate suspected transmissions.

INVESTIGATING OCCURRENCES HARM TO RECIPIENTS - GENETIC TRANSMISSIONS, HPSC

The establishment of haematopoietic stem cell (HPC) donor registries and public cord blood banks worldwide has increased the availability of grafts from unrelated donors for patients requiring stem cell transplantation. Theoretically, all congenital diseases originating from bone marrow-derived cells are transmissible. This link is useful for those investigating genetic transmissions by HPC.

INVESTIGATING HARM TO OFFSPRING - GENETIC TRANSMISSIONS, GAMETES AND EMBRYOS

Although these events are not numerous, they show the need to consider the potential of genetic disease transmission using donor gametes. Gametes are the only cells that carry such genetic material, which could potentially affect the recipient (offspring) with any genetic disease. This link is useful for those investigating genetic transmissions in the field of assisted reproduction.

CHARACTERISTICS, HANDLING AND CLINICAL ERRORS

Each cell, tissue or organ allograft intended for transplantation, implantation, infusion or transfer has specific quality attributes and characteristics determined by anatomy and usual function. Handling activities that support the maintenance of desired efficacy or utility of the MPOH can affect clinical outcome. When a gap exists or a step or process fails, a risk of harm or actual harm can occur in which case a root cause analysis should be performed. This link provides guidance on the investigation of process errors.

TRACEABILITY - THE ABSOLUTE PRE-REQUISITE

Traceability/ denotes 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, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing 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 but also confirmation that transfusion/transplantation (or final disposal) actually took place. This link highlights the need for those involved in donation and clinical application of MPOH to ensure reliable traceability.

REFERENCES



Vigilance is derived from the Latin “vigilare”, to stay awake or to care for and is the process of paying close and continuous attention. Surveillance is defined as the systematic ongoing collection, collation and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary [1]. Vigilance and surveillance (V&S) are used in association to underline that the attitude of vigilance needs to be associated to the methods of surveillance. In practice a number of terms have been developed to describe V&S for specific types of products. Like pharmacovigilance describes V&S for medicinal products, “haemovigilance” was coined to be used for blood products. Haemovigilance is a set of surveillance procedures covering the entire transfusion chain (from the donation of blood and its components to the follow-up of recipients of transfusions), intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent the occurrence or recurrence of such incidents [2]. “Biovigilance” was incorporated into French law on 21 December 2003 with the publication of Decree no.°2003-1206. Its scope ranged from human organs, human tissues and cells to human cellular therapy preparations and ancillary products. In the United States, biovigilance has been extended to incorporate all MPO including blood, tissues, cornea, cells, gametes and organs.

Haemovigilance systems have been implemented in most developed countries to monitor the adverse occurrences associated with the transfusion of blood and blood products. In the early stages of haemovigilance, the concept was little more than coordination of existing data. Over the years, analysis and process improvement have led to enhanced patient safety. Haemovigilance systems arose as a response to the threat of emerging infections, such as HIV, to the safety of the blood supply. The recognition of the AIDS epidemic, which resulted in the deaths of thousands of recipients of blood and plasma products, led to public debates, commissions of inquiry, and legal prosecution stemming from management of the nascent HIV risk of the 1980’s. The epidemic also provided additional stimulus to assess the safety of transfusion services through ongoing risk assessment measures. Haemovigilance was developed first in Japan and then in France in 1993, which featured mandatory reporting. The UK developed the first voluntary system in 1996. Since this time, countries around the world have established Haemovigilance systems and have formed the International Haemovigilance Network to share common definitions and data.

The basic elements of bio-vigilance include: adverse reaction (AR) identification and reporting, adverse event (AE) monitoring and reporting (for recipients and donors), product quality assurance (including processing controls and error management), and emerging threat assessment using epidemiologic and laboratory data (e.g., TTI bioinformatics, repositories). The WHO guideline on AE reporting emphasizes that the effectiveness of the systems should be measured, not only by data reporting and analysis, but also by the use of such systems to improve patient safety. WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation, Guiding Principle 10, states “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 optimized on an ongoing basis”. This requires implementation of quality systems including traceability and vigilance, with adverse events and reactions reported both nationally and for exported human products. [3] The guideline outlined the following core concepts:

- The fundamental role of patient safety reporting systems is to enhance patient safety by learning from failures of the healthcare system.
- Reporting must be safe. Individuals who report incidents must not be punished or suffer other ill-effects from reporting
- Reporting is only of value if it leads to a constructive response. At a minimum, this entails feedback of findings from data analysis. Ideally, it also includes recommendations for changes in procedures and systems of healthcare.
- Meaningful analysis, learning, and dissemination of lessons learned require expertise and other human and financial resources. The agency that receives reports must be capable of disseminating information, making recommendations for changes, and informing the development of solutions.



Advances in science and healthcare technology have led to more biologic products being collected to sustain and improve the quality of human life. Challenges exist to monitor and ensure appropriate access and availability of safe products both in the domestic and global arenas. Efforts to increase the availability of these products may also increase the opportunities for transmission of infectious pathogens, including prions, viruses, bacteria, and parasites. The implications are amplified when there are multiple recipients from the same donor. The demand for organs, cells, corneas and tissues has grown immensely over the last two decades and, as a result, demand often exceeds supply, particularly for organs. More than 100 million red cell concentrates or whole blood units are transfused annually, more than 100,000 patients receive an organ transplant worldwide every year and this is estimated to only cover less than 10 % of the needs. Millions of patients receive tissues and cells of human origin. With medical and scientific advances, more complex procedures are being developed, incorporating MPHO that include composite materials and cells, whole hands and faces and genetically manipulated cells. Advances in stem cell biology have also amplified the demand for transplantation resulting in growing unrelated donor registries and cord blood banks throughout the world. The ability to match donors and recipients has also led to augment the sharing of these materials across national boundaries. It is now estimated that half of the unrelated stem cell and cord blood transplantation now cross national borders between donor and recipient. Current practices in transplantation raise several questions that need to be addressed jointly by clinicians, scientists, health regulators and ethicists as well as representatives of civil society, in particular donors and recipients.

4.1 ETHICAL BREACHES, FRAUDULENT, ILLEGAL PRACTICES

The increasing commercialization of MPHO in some countries has multiplied profit-making opportunities and increased the risk of clinically unsafe and unethical practices, particularly in tissue procurement. Recent scandals in the United States and other countries involving non-consented procurement underline the urgent need for a common global technical and ethical framework. Although a number of regulations on transplantation have been adopted in the past several years or are currently under discussion, national regulation and oversight of transplantation is limited or inefficient in many countries. Progress has been made through the MPHO V&S project with the development of guidance on the detection and investigation of illegal and fraudulent activities in the fields of tissues and cells. Procedures for enforcement actions by regulators have been recommended.

4.2 THE VOLUNTARY DONOR AND DONOR FAMILIES

The underlying basis for all of transplantation is the voluntary donation with consent of the donor or donor's family. Without the generosity of this altruistic effort, transplantation would not have been able to provide the medical care that has been developed over the last century. In the context of organ shortage, the importance of protecting donors and potential donors, particularly in vulnerable groups, has been highlighted in a number of international reports on the subject of trafficking of organs, tissues and cells [4], [5] Regularly scandals involving the trafficking of human being for the procurement of organs or the sale and purchase of organs and tissues from the deceased are shocking the public and challenging its trust in donation and transplantation services. National boundaries are no obstacle to unscrupulous individuals motivated by profit and seeking to take advantage of vulnerable poor populations in low and middle income countries [6]. Medical products of human origin circulate across national boundaries for good and bad reasons. In addition to importation of organs and tissues, patients are traveling between countries to receive transplants (i.e., transplant tourism) and thus the risk of importing new diseases in the immunosuppressed recipients is amplified. During 2005, a report from the state of New York in the U.S. identified a serious problem with donor recovery being undertaken outside of all standards and regulations. It was discovered that an organization was recovering donors from funeral homes without the permission of families, without adequate medical screening, and was, in many cases, falsifying records. Tissue was sold to a number of processing centers and distributed both nationally and internationally.

Noting the global increase in allogeneic transplantation of cells, tissues and organs, the World Health Assembly Resolution WHA57.18, urged member states:

1. To implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and traceability;

2. To cooperate in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including development of minimum criteria for suitability of donors of tissues and cells;
3. To consider setting up ethics commissions to ensure the ethics of cell, tissue and organ transplantation;
4. To extend the use of living kidney donations when possible, in addition to donations from deceased donors;
5. 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 [7].

The WHO Guiding Principles on Transplantation, adopted by WHA Resolution 63.22 in 2010 reiterated the need for all stakeholders to ensure that donors are not exploited or human substances commercialized.

An international consultation in Zurich addressed perspectives on the ethics of human cell and tissue transplantation and arrived at a number of consensuses [8]. Consensus included:

1. *Respect for persons*
 - Informed and voluntary consent for living Human Cells (HC)/Human Tissues (HT) removal
 - Explicit consent during lifetime or presumed consent for deceased HC/HT removal
 - Option to veto future uses of donated HC/HT for research and education (and/or cosmetic applications and/or international circulation)
 - Stewardship for donated HCs/HTs
 - Informed and voluntary consent for HC/HT transplantation
2. *Non-maleficence*
 - Minimal quality and safety standards for HC/HT procurement, processing and transplantation
 - Long-term follow-up of living donors and transplant recipients
3. *Justice*
 - Fair criteria for donor identification and selection
 - Unpaid donation to reduce inequities in donation
 - Fair HC/HT distribution
 - General priority of local and/or national self-sufficiency to reduce global inequities in donation of and access to HCs/HTs

Donors of organs, tissues and cells should not be exploited and the health risks associated with donation should be thoroughly explained and minimized. The following sections summarize these risks for the donation of different types of human substance.

To put an end to trafficking and exploitation of donors and recipient the best solution is to meet the needs of all patients in need and reach self-sufficiency by building efficient services for the donation and clinical application of medical products of human origin. Self-sufficiency can be defined as meeting the needs of patients from a given population with an adequate provision of transplantation services and supply of organs from that population. The self-sufficiency paradigm, as defined for organ during the Third WHO Global Consultation on Organ Donation and Transplantation (Madrid, 23–25 March 2010) applies to any MPH. With government support and oversight, the paradigm underwrites: (i) equity in donation from possible donors and equity in allocation; (ii) education about donation but also about prevention of conditions that create a need for MPHs; and (iii) transparency and professionalism. For example, striving towards self-sufficiency requires comprehensive management of chronic kidney disease, from prevention to renal replacement. Likewise, the national organ donation and transplantation service must provide the opportunity to donate organs after death in as many circumstances as possible.



5.1 THE DEVELOPMENT OF GLOBAL GOVERNANCE OF MPH O

In March 2010, the 3rd WHO Global Consultation on Organ Donation and Transplantation was held in Madrid. Its objective was to discuss the concept of national self-sufficiency in organ donation and transplantation and to outline strategies to achieve this goal. It was recognised that although there is a gap in the availability of organs for transplantation the needs of patients can better be met through greater awareness and involvement of the community resulting in an increase in donations.

The tragedies in the early 1960s, related to thalidomide and the undermining of public confidence in pharmaceuticals led to the implementation of pharmacovigilance. Vigilance is not only a state of mind but also a method of surveillance. 'Surveillance' itself is the systematic on-going collection, collation and analysis of data for public health purposes and the timely dissemination of this information for assessment and public health response as necessary [1]. There are two main types of surveillance approaches, one utilizing data analysis to uncover trends in aggregating data to reveal new concerns or the efficacy of interventions; and the other approach utilizing a "sentinel network" to detect singular events promptly that may have public health impact. An example of the latter approach would be the recognition of the outbreak of West Nile Virus, a new infectious disease that has never been previously recognized, in the United States.

In 2004, the World Health Assembly adopted Resolution WHA57.18 on Cell, Tissue and Organ Transplantation. It placed responsibility on Member States to enforce measures for monitoring the procurement, processing and transplantation of SOHO as well as ensuring their accountability and traceability. Two Aide-Memoires have been published addressing key safety measures for tissues and cells [9],[10]. The implementation of vigilance and surveillance can facilitate the application of these measures. To be effective, the participation of national health authorities, scientific and professional societies, and health care professionals are required.

In 2009, the World Health Organization (WHO) updated its Guiding Principles for the transplantation of organs, tissues and cells [3]. It noted inter alia that maintaining and optimizing their level of quality, safety and, efficacy requires the implementation of quality systems including traceability and vigilance. In May 2010, following consideration of these Principles, the World Health Assembly adopted Resolution WHA63.22 on Human Organ and Tissue Transplantation. It urges Member States inter alia 'to strengthen national and multinational authorities and/or capacities to provide oversight, organization and coordination of donation and transplantation activities, with special attention to maximizing donation from deceased persons and to protecting the health and welfare of living donors with appropriate health-care services and long-term follow up'. These entreaties reflect the conclusions of the Madrid Consultation. The Resolution also requested WHO to continue collecting and analysing global data related to the transplantation of MPH O s, and to facilitate access by Member States to appropriate information including severe adverse occurrences.

The International Health Regulations (IHR) (2005) is a global, legally binding framework against the international spread of disease, including public health emergencies and other public health risks. It sets out inter alia Member States' rights and obligations with respect to national and international surveillance and notification to WHO of key outbreaks and other public health events. It also presents WHO's functioning mandate including its responsibility to collect information about events through its surveillance activities and to assess their potential to cause the international spread of disease. The IHR were implemented in June 2007.

Recognizing the need for the surveillance of such occurrences, the World Health Assembly (WHA)[11] in May 2010, called on the World Health Organization (WHO) to facilitate inter alia Member States' access to 'appropriate information on the donation, processing and transplantation of human cells, tissues and organs, including data on severe adverse events and reactions'.

Human substances legislation in the European Union (EU) covers the quality and safety of blood, tissues, cells and organs. Specific requirements are in place for their collection, testing, processing and distribution. Vigilance in the EU links four levels: the European Commission, which plays inter alia a coordinating and supportive role and maintains the rapid alert system for tissues and cells; the European Centre for Disease Control (ECDC), which monitors health threats; national Competent Authorities that ensure that the re-

quirements of the EU Directives are followed; and local tissue and cell establishments that are in the forefront when adverse occurrences are detected. Directive 2006/86/EC (Article 7) requires Member States to provide the Commission with an annual report about serious adverse events and reactions notified to the Competent Authority. In the case of assisted reproduction, Article 6 identifies any type of gamete or embryo misidentification or mix-up as a serious adverse event that must be reported. A summary report is prepared by the Commission and returned to all CAs, which are then required to make it available to tissue establishments. The 2011 report covers data related to serious adverse incidents that occurred and/or were validated in 2009 (from 1st January to 31st of December).

5.2 A SAFEGUARD, A DAMAGE LIMITATION SYSTEM

5.2.1 Early notification, timely reaction

The human endeavour can be predicted to fail but can be mitigated by managing associated risks. The term 'horizon event' has entered the risk management vocabulary implying that the threat is new and 'below the horizon'. The risk could be new such as another vCJD, something misjudged as a threat, such as xenotropic murine leukemia virus-related (X MRV), or something not previously recognised, such as West Nile Virus. In all cases, however, these could have been predicted.

Risks are inherent in the use of MPH. They may occur in the donation of the 'product', within the manufacturing process, due to external factors or through human error. With basic epidemiological data, however, hazards can be identified early. Recording of information such as the source of an infection, the agent/disease, the risk level as well as a description of the problem can prove to be effective in detecting a potential crisis. An example involved the appearance of unexpected infections in a number of patients who had received bone marrow transplantations. The contamination was ultimately linked to a liquid nitrogen tank where all harvests had been stored.

In assessing an early warning reaction, an analysis of risk/benefit has to be the guiding principle. The risks to be prevented and the down sides of 'preventive action' need to be identified. Risk Management is a day-to-day function. Aviation can be used as a model since it, like transplantation, is inherently dangerous. Specifically, something like the table of aviation accidents/incidents in Australia, which included details of the aircraft, damage etc., reported over a two month period in 2010. With respect to transplantation risk management, aviation provided the following learning points:

- Global community ownership is possible
- A NO BLAME culture for reporting can work
- Self-reporting of 'I learned from that' also works
- Don't hide mistakes no matter how uncomfortable
- Everything human is fallible
- Rapid dissemination is essential
- Get the information to where it matters in real time
- Differentiate between doing the right thing from the correct thing
- Don't let the perfect be the enemy of the good

5.2.2 A necessity for the public, a responsibility for authorities

Human health risks are naturally of primary concern to those who may be affected. Responsibility for initial detection, investigation and reporting lies with clinicians. Procurement organizations, tissue and cell processors play an essential role in quarantine, investigation and recall of potentially implicated allografts. Adverse reactions that have been confirmed ultimately become the responsibility of competent authorities when they rise to the level of governmental attention. Global distribution of tissues and cells requires communications among national competent authorities to ensure effective risk mitigation.



Legislative, regulatory and reporting requirements vary from country to country. In addition, a variety of professional associations have established registries and reporting systems to capture adverse occurrences. Responsibility for initial detection, investigation and reporting lies with clinicians. Both procurement organizations and tissue and cell processors play an essential role in quarantine, investigation and recall of potentially implicated allografts.

6.1 GOVERNMENTS

In France, the field of bio-vigilance was incorporated into the law on 21 December 2003 with the publication of Decree no.°2003-1206. Its scope ranged from human organs, human tissues and cells to human cellular therapy preparations and ancillary products. The aim of bio-vigilance is to supervise and assess the risk due to the occurrence of adverse events attributable to products and activities in the field, and from adverse reactions to the living donor or recipient. It is based on the notification of adverse events and adverse reactions linked or possibly linked to human organs, tissues, cells and ancillary products and activities.

The European Union has three pieces of legislation addressed specifically to ensuring the quality and safety of human tissues and cells. The primary Directive (2004/23/EC) establishes standards from donation to distribution. The two implementing Directives set out specific technical requirements for donations, procurement and testing (2006/17/EC) and others for traceability, the notification of serious adverse occurrences as well as processing, preservation, storage and distribution (2006/86/EC). The publication of the legislation, however, is only the beginning of a process to ensure a common European standard and approach. The major challenge lies in the implementation, maintenance and updating of the legislative requirements.

Significant progress toward this end was made during the EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments) project, which was co-financed by the European Commission. EUSTITE addressed issues in support of the requirements for tissue and cell establishments to have systems in place for the monitoring and reporting of serious adverse occurrences. It established criteria for reporting adverse incidents to competent authorities and developed not only a severity grading system but also one for imputability for cases where donors or recipients have been harmed, with guidance on which level to report. Guidance documents were prepared on how to use these tools and on the management of adverse occurrences that have cross border implications.

A EU sponsored project entitled Vigilance and Surveillance of Substances of Human Origin (SOHO V&S) developed more detailed vigilance guidance. One of the main objectives of the project was to increase awareness among clinicians of the importance of vigilance and surveillance of tissues and cells. The V&S Guidance for Clinicians developed in the project aims at promoting vigilance and surveillance and helping to define the roles and responsibilities of clinical users in the traceability, recognition, reporting, and investigation of adverse occurrences in hospitals, as well as the management of recalls.

EFRETOS – the European Framework for the Evaluation of Organ Transplants – was a project funded by the European Union (EU) aimed at promoting the development of a pan-European registry of registries on the follow-up of patients who have undergone organ transplantation. It included recommendations on the implementation of a vigilance system as an integral part of the monitoring of such patients.

Vigilance in the EU links three levels: the European Commission, which plays inter alia a coordinating and supportive role and maintains the rapid alert system for tissues and cells, the European Centre for Disease Control (ECDC), which monitors health threats; national Competent Authorities that ensure that the requirements of the EU Directives are followed including annual reporting of their adverse reports to the EC; and local tissue and cell establishments that are in the forefront when there are adverse occurrences. Tissue Establishments must report adverse occurrences to the regulator in each Member State and each Member State must send an annual summary of reports received to the European Commission. With respect to the collection and reporting of adverse occurrences in relation to activity data, problems do exist with several countries only able to

provide partial activity information, thus making it difficult to allow estimation of frequency at the EU level. Consequently, incomplete data and different interpretations and reporting practices among Member States obviate any safe conclusions regarding frequency at this moment. With the further development of common data collection and reporting at the national level, a more consistent estimation of frequency is expected in the coming years.

In the United States, The Food and Drug Administration (FDA) is one of a number of agencies involved in biovigilance within the Department of Health and Human Services. The Center for Biologics Evaluation and Research (CBER) is the center within FDA with responsibility for regulating biological products for human use including vaccines, blood and its components and derivatives, cell and gene therapies, tissues, related devices including certain IVDs, xenotransplantation products and allergenic products.

As part of its activities, CBER reviews adverse reactions. An adverse reaction is defined as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that it caused the response. For the '361' HCT/Ps (HCT/P's Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the US Public Health Service Act), manufacturers must investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution and report it to the FDA if it was fatal, life-threatening, caused permanent impairment/damage or required medical or surgical intervention. Although reporting is voluntary for clinicians, they are encouraged to submit reports directly to the manufacturer and to the FDA. With regard to voluntary reporting, underreporting is likely, and manufacturers may remain unaware of safety issues if clinicians fail to report cases. Organ oversight and biovigilance in the United States was legislated in 1984 with the signing by the President of the National Organ Transplant Act (NOTA). It set out the framework for matching organs with individuals included in the waiting list as well as the equitable distribution of organs nationwide among transplant patients, and established standards for preventing the acquisition of organs that are infected with the etiologic agent for acquired immune deficiency syndrome (AIDS). The United Network for Organ Sharing (UNOS) / Organ Procurement and Transplantation Network (OPTN) are operated under contract with the Health Resources and Services Administration (HRSA), a division of the Department of Health and Human Services along with the FDA. Within UNOS a Disease Transmission Advisory Committee (DTAC) evaluates reports of potential disease transmission.

Furthermore the activities of the CDC, another division of HHS, include collaboration on investigations of possible disease transmission as the result of reports from diverse sources, such as State and local health departments, transplant clinicians, infectious disease specialists, pathologists, as well as patients and their families. CDC is neither a regulator nor an oversight authority, and investigates events through the assistance of local and state authorities. CDC works collaboratively with U.S. Public Health Service (PHS) agencies that have regulatory oversight over organs, tissues, and cells, including the FDA and HRSA.

For the future of biovigilance in the U.S., there are many gaps to fill, which will require coordination among blood/organ/tissue communities through public-private partnerships, both nationally and globally.

In Brazil, the Organs, Tissues and Cells Office (GTOR) of the National Health Surveillance Agency (ANVISA) is responsible for vigilance and surveillance of substances of human origin. Under the ANVISA Act, it became mandatory in 2010 for industries to report adverse events involving drugs and medical devices. The NOTIVISA information system was upgraded the following year. It is anticipated that organs, tissues and cells will be included in VIGIPÓS in 2012 and in NOTIVISA in 2013.

In Singapore, reportable events include:

- Patient death or serious disability associated with haemolytic reaction due to administration of ABO/HLA-incompatible blood or blood products;
- Transmission of diseases following blood transfusion, organ transplant or transplant of tissues;
- Incidents associated with assisted human reproductive procedure which has, or may have, resulted in:
 - Death, life-threatening condition, incapacitating condition, prolonged hospitalisation;
 - Transmission of communicable disease;
 - Loss or damage to embryos;
 - Gamete or embryo misidentification or mix-up.

WHO plays a coordinating role in the promotion of vigilance and surveillance systems globally, sharing the experiences of those countries with existing programs with those who

are at earlier stages in the development of such systems. Guiding Principle 10 can be summarised firstly as calling for reporting and analysis of short and long-term, donor and recipient outcomes, and secondly the development and implementation of quality systems, traceability, vigilance and adverse event reporting. In taking up GP10, however, recognition has to be given to the disparities in access and the systems – which are largely created by professionals through their societies and associations – that exist today to record and analyse the outcomes of donors and recipients on waiting lists and after transplantation.

6.2 PROFESSIONAL ASSOCIATIONS

Much of the work relating to identification of adverse occurrences has been carried out through professional associations. For example, the World Marrow Donor Association (WMDA) is an organization, which fosters international collaboration to facilitate the exchange of high quality haematopoietic stem cells for clinical transplantation worldwide and to promote the interests of donors. Its Clinical Working Group not only produces guidelines, recommendations and standards involving clinical aspects related to the donation of bone marrow and peripheral blood stem cells (PBSC) but also maintains the adverse events registry, S (P)EAR - the central reporting system for adverse events in unrelated donors. S(P)EAR is in fact comprised of two registries 1) SEAR - the serious events and adverse effects registry, and 2) SPEAR – the serious product events and adverse effects registry.

The SEAR registry compiles donor data related to: life-threatening disease, death, those who required in-patient hospitalization or considerable prolongation of existing hospitalization, and those who are facing persistent or significant disability / incapacity. It also compiles data on events related to an anaesthetic, cardiac complications, infective complications, mechanical injury, haemostasis and (late) malignancies / autoimmune complications.

The SPEAR registry compiles data covering impairment of the quality of the graft (clots), damage or loss of (part-of) the graft, infusion of the wrong product, serious transportation problems, serious unpredicted transmissible infection risk (e.g. hepatitis B), serious unpredicted non-infection transmissible risk (e.g. malignancy), and bacterial infection (only if the patient becomes unwell).

In the field of Cornea transplantation, the Eye Bank Association of America (EBAA) initiated an adverse reaction reporting system in 1990 and in 2004 the Online Adverse Reaction Reporting System (OARRS). With respect to eye bank adverse reaction reporting, the EBAA Medical Advisory Board requires that recipients be tracked and that they seek a 3 – 12 month follow-up. Reporting, which is part of the accreditation process, was redesigned in 2004 for online submission.

In the field of Tissue Banking, the American Association of Tissue Banks (AATB) has produced a Guidance Document that aims to educate end users/clinicians by providing them with direction on how to: define proper recognition of suspected allograft-caused adverse outcomes (reactions and graft failures); describe reporting responsibilities (communication); detail expectations of cooperation during investigation through closure; and promote the non-punitive concept. The document also gives tissue banks advice on how to: ensure compliance with their communication responsibilities; define their expectations for investigation protocols and timelines; develop outcome terms and definitions in coordination with EUSTITE; and list and describe international implications. Completion of the guidance document is anticipated in 2011 with consideration being given to a focus on V&S for tissue allograft types that pose the most risk. The document will be widely disseminated to all stakeholders in order to optimize recognition, reporting and investigation.



7.1 KEY FACTORS FOR AN EFFECTIVE NATIONAL VIGILANCE AND SURVEILLANCE SCHEME

In order for a national Vigilance and Surveillance (V&S) scheme to be effective, the following key elements should be in place.

- Serious adverse occurrence reporting must be required
- Rapid alert systems, with 24/7/365 availability, are essential and should be developed
- Standardized reporting by clinicians should be expected
 - Clinicians are the first to acquire information when a recipient has been harmed and are usually those who initiate reporting
 - Based on a consensus of subject matter experts, it is necessary to determine what is important and what is essential for reporting
 - Education for clinicians should be provided with clearly described and concise guidance for identification and reporting
 - There should be feedback regarding the information collected and how it has been used to influence patient safety and changes to practice
- Cooperation among governments / competent authority, professional associations and clinicians is essential
 - There is a need to identify the key contact for the reporting of adverse occurrences. This may be an organization, or formal system, a coordinating body, or a registry which is responsible for the collection of information as it occurs (for evaluation by specialists)
- MPhO V&S systems can be set up based on the extensive experience from the blood donation/transfusion V&S (haemovigilance) systems that already exist
- Traceability requirements must be in place by all stakeholders. Time-sensitive capabilities such as the use of quick and easy tracking systems should be promoted. These systems should make use of computerized databases and machine-readable labeled bar codes, which promote unique identification on the MPhO. The alternative is to rely on time-insensitive, laborious, manual searching of handwritten logs, donor records, distribution records, inventory records or individual recipient records
- Although there may be different oversight bodies for cells/tissues and organs within a Member State, their vigilance and surveillance systems should be linked directly to optimize response;
 - Inspections for licensing, accreditation, certification, etc., must include evaluation of the V&S system in place.
 - Provision of training and education for all stakeholders is necessary
- Traceability and reporting systems must include consideration of compliance to the expectations in the country receiving/using the MPhO as well as its country of origin. Neither system should be compromised.
- A global V&S data collection system for MPhO is desirable and can be coordinated by WHO.

7.2 CLINICAL FOLLOW-UP AND CLINICAL PRACTICE SURVEILLANCE

Medicinal products that enter the healthcare market place must go through a rigorous clinical trial followed by careful post-marketing surveillance to ensure that no adverse outcome ensues that was missed during a limited clinical trial. Transplantation has not been subjected to the rigors of this type of regulatory process but rather has taken a different pathway based on the medical model of trial and error. Moreover, responses to scientific publications documenting adverse outcomes can take a long time before changes in practice are implemented. By combining the capture of such incidents, a more rapid response can be developed and tested for efficacy.

The basic elements of biovigilance should include: adverse event monitoring (for recipients and donors), product quality assurance (including processing controls and error management), and emerging threat assessment using epidemiologic and laboratory data (e.g., bioinformatics, repositories). There are two main types of surveillance approaches to these issues: utilizing data analysis to uncover trends in aggregate data to reveal new concerns or the efficacy of interventions, and utilizing a "sentinel network" to quickly

detect singular events that may have public health impact. The former is so called “cold” or “passive” surveillance; while the latter is “hot” or “active” surveillance. In the US a great example of success in vigilance has been in the recognition of the magnitude of healthcare-associated infections (HAI). Although this system of vigilance has been in place within local medical institutions for many years, the impact on patient safety and healthcare cost has been only recently realized. Patient safety and cost recovery data are only currently becoming available but indicate that huge cost savings can be made if proper vigilance systems are used as part of a total quality system. Only by starting to look at various processes within the healthcare setting can one become aware of the health burden and the impact on health economics. One must also be aware of the cost of each proposed action to improve safety, which could also result in the loss of donors and the subsequent potential loss of life for recipients.

7.3 INTEGRATION

7.3.1 For the various risks associated with a given product

A single donor may contribute numerous types of tissue grafts. The altruistic act by a single donor or donor family may yield different musculoskeletal soft tissue and bone allografts as well as various organs such as kidneys, liver, lungs, heart, pancreas, bowel, and large vessels associated with an organ. Such tissue grafts are widely used by a variety of different surgical specialties. A recovery from a single donor may provide corneas for the ophthalmologist, vessels such as vein grafts and arterial conduits for the vascular surgeon, heart valves or vessels for the cardiovascular surgeon, tissue such as dura mater, bone, and nerve grafts for the neurosurgeon, soft tissue grafts for reconstructive bladder suspension by the urologist, skin soft tissue and bone for reconstructive procedures by the Plastic Surgeon. Therefore, the risk of a transmissible communicable disease from one single donor through organs and tissue crosses many medical specialties and can involve many recipients.

7.3.2 For MPHO

The organ, tissue and eye banking communities function independently yet communication between them is critical for effective vigilance. Any ineffective communication between these communities can result in an inability to track organs and tissues from a common donor and recognize adverse reactions in a timely fashion. Events, as previously described, in which lack of integration between transplant organizations sharing a common donor results in avoidable disease transmission to patients, can only be corrected by the introduction of a comprehensive and unified traceability system covering all biologics derived from a single donor. A reporting system that is integrated with all transplant establishments can assist in avoiding such serious outcomes. Integration with haemovigilance systems is also important in closing gaps in communication.



8.1 QUALITY MANAGEMENT

Attention to quality management in health care can bring a more rigorous and systematic approach to addressing documented deficiencies and cost savings. “Quality in public health is the degree to which policies, programs, services, and research for the population increase desired health outcomes and conditions in which the population can be healthy” [12]. By applying scientific standards and monitoring adverse occurrences, corrective actions can be put in place and monitored to determine effectiveness.

In examining frameworks for implementation of bio-vigilance systems, including the use of such systems for quality improvement, one must consider what types of events are captured. For instance, in order to capture rare events that are of significant singular importance for patient safety, a sentinel system should be

- 1) extremely sensitive, perhaps at the expense of specificity,
- 2) operated in real time in order to allow immediate registry of events, and
- 3) configured so that communication about the event allows critical response actions to take place.

An effective bio-vigilance program should be operationally capable of providing the core tools, infrastructure, and logistics necessary to support timely communication of critical information to the right people in order to make essential real-time interventions to avert clinical catastrophe and protect public health. Reporting must be safe. Individuals who report reactions or events must not be punished or suffer other ill effects from reporting. Otherwise, the fear of reprisal will limit the reporting and inadequate or false information may result in inappropriate or inadequate responses.

On the other hand, surveillance of more common events of interest may be more comprehensive. Capture of more common events also may allow benchmarking through comparison of event rates among facilities, which are most helpful if they are adjusted for factors that are not the focus of comparison. Such risk-adjusted rates allow valid comparisons and analysis, so that a quality program can be implemented and continuously evaluated, before, during, or after an intervention takes place.

Errors and accidents that result in adverse events are often blamed on personnel resulting in either retraining or dismissal. It has long been recognized that the majority of cases are due to a poor process rather than the fault of staff. When such events occur, the most efficient way of addressing them is through investigation and root cause analysis.

8.2 DETECTION AND NOTIFICATION OF HARM TO RECIPIENTS

It is clear that adverse outcomes following transplantation can be caused by diverse factors unrelated to the quality, safety or specific characteristics of the MPHO applied in the clinical setting. It is very important, however, that the treating physician should always consider the possibility that the MPHO might have been the source of a problem in a recipient.

The treating physician plays a pivotal role in detecting and then reporting adverse patient outcomes *that might* be associated with the MPHO, to the appropriate authority. These might be transmitted diseases and graft failures, or quality related issues that could imply errors in processing, storage, transport or handling. Without this information, organizations providing MPHO might continue to distribute infected or otherwise unsafe products for multiple patients.

There are many cases in the scientific literature where physicians did not report adverse outcomes such as patient infections, assuming that they were a complication of surgery when in fact they were transmitted by the MPHO and subsequent infections of other recipients could have been avoided.

8.3 TRIGGERS FOR A NOTIFICATION OF SUSPECTED HARM TO A RECIPIENT

Clinical symptoms or situations suggesting that any of the following reactions might have occurred in an MPHO recipient (abbreviated descriptions in brackets) should be seen as triggers for a notification. It should be noted that the list is not exhaustive.

- a) Unexpected* primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion) (**Infection - Donor**);
- b) Transmitted infection (viral, bacterial, parasitic, fungal, prion) possibly due to contamination or cross-contamination by an infectious agent on the procured tissues or associated materials from procurement to clinical application (**Infection – MPHO**);
- c) Hypersensitivity reactions, including allergy, anaphylactoid reactions or anaphylaxis (**Hypersensitivity**);
- d) Malignant disease possibly transferred by the MPH0 (whatever the origin, donor or process) (**Malignancy**);
- e) Unexpectedly delayed or absent engraftment, graft failure (including mechanical failure) (**Failure**);
- f) Toxic effects from MPH0 or associated materials (**Toxicity**);
- g) Unexpected immunological reactions due to MPH0 mismatch (**Mismatch**);
- h) Aborted procedures involving unnecessary exposure to risk e.g. wrong MPH0 supplied, discovered after patient is anaesthetised and the surgical procedure has begun (**Undue Risk**);
- i) Suspected transmission of genetic disease (**Genetic transmission**);
- j) Suspected transmission of other (non-infectious) illness (**Other Transmission**);

* In certain circumstances, clinicians may knowingly transplant an infective donation (e.g. a CMV positive bone marrow donation).

8.4 INFECTION THREAT WATCH

The rapidity with which infectious diseases can spread throughout the world can be exemplified by the transmission of severe acute respiratory syndrome (SARS) through the international travel of infected individuals observed in 2003. In 2007, about 105 cases of Chikungunya (CHIK) fever; a viral disease transmitted by *Aedes* mosquitoes and occurring mainly in Africa and Asia, were identified in the Emilia-Romagna region of Italy. In the United States, West Nile Virus (WNV) was first identified in birds in New York State but an organ transplant recipient became the first reported human infection and the virus spread rapidly throughout North America. The epidemic outbreak of WNV and its association with blood transfusion resulted in the establishment of a public-private partnership between AABB (formerly the American Association of Blood Banks) and several government agencies to collaborate on response to this emerging public health disease threat. This AABB Inter-organizational Task Force carried out weekly monitoring of transfusion related cases, prevalence of reactive WNV NAT results and discussions of public health policy including reporting of outcomes.

A significant number of organ transplant-transmitted infections have been investigated by U.S. Public Health Authorities over the period 1985-2009, including HIV, HCV and WNV. The clinician's role in identifying a problem was highlighted with the presentation of a specific case whereby two renal transplant patients from the same donor exhibited seizures and altered mental status within three weeks post-transplant. Investigations led to the finding that the young donor had Granulomatous amoebic encephalitis, which has only 150 described cases worldwide, and was the first transmission of a free-living amoeba via organ transplantation. The Centers for Disease Control and Prevention (CDC) has investigated dozens of transplant clusters of recipients with encephalitis-related illnesses (majority with fatal outcome) and likely many more left unidentified due to lack of recognition.

8.5 TRANSMISSIBLE DISEASE SCREENING FOR DONOR SUITABILITY

Potential transplant donors are screened for infectious risks on the basis of national standards and regulations. A first step in screening donors is a thorough medical and social history (including sexual history and other behavioral risks, such as injectable drug use) as well as physical examination by the surgical team during procurement to detect any unknown infections or malignancies. This initial evaluation, including travel, animal and environmental exposure history, may reveal risks for current or active infections that should be addressed prior to recovery of MPH0. Any such screening must be consistent with the requirements of the screening process as well as local and national policies and regulations.

8.6 PRODUCT CENTERED

Screening procedures vary based on the process of MPH0 donation. In the case of living donors such as stem cell, bone marrow, tissue, gametes or organs, the medico-social history is obtained from the donor themselves. In the case of deceased donors, the next of kin is interviewed concerning the medical/social history of the donor; which is less

sensitive and effective in eliciting a history that might exclude the donor. Studies of sero-prevalence comparing these donors with blood donors have demonstrated a significantly higher risk of this donor being in the window period for transmission of HIV and hepatitis viruses [13],[14].

8.7 DEFINITIONS

A major contribution of the Notify project was the participation of a diverse group of transplant professionals who come from different disciplines and who ordinarily do not communicate with one another. Transplant surgeons, orthopaedists, ophthalmologists, infectious disease specialists, pathologists, nurses, eye bankers, tissue bankers, regulators and scientists had the opportunity to interact and provide their own perspectives. From these discussions some common definitions that can be applied across all fields were agreed upon whilst others are under discussion.

The following definitions adopted in the European Directives for Tissues and Cells and for Organs were considered appropriate and useful for international application, although they were mapped to less technical language to improve accessibility by the general public:

1. Severe Adverse Event (SAE): any untoward occurrence, associated with the chain, from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity. In the Notify project these are referred to as cases of 'Risk of Harm'.

2. Severe Adverse Reaction (SAR): any unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity. In the Notify project these are referred to as cases of 'Harm to Donor', 'Harm to Recipient' or 'Harm to Fetus/Offspring'.

The EU definition for **imputability** of a potential adverse reaction should be assessed, based on available information, as either: proven, probable, possible, unlikely or excluded. A further category of 'intervened upon without documentation' has been used for organ transplantation situations where recipient treatment has been applied prophylactically in the context of a known risk. The stringent definition of **proven** or **definite** transmission should be used only if there is clear evidence of the same disease in the donor and at least one of the recipients. Absence of pre-transplant disease in the recipients should be documented. Variable involvement of different organs or tissues, different processing of organs and tissues, and recipient differences (i.e. pre-existing seroprotection or use of lymphocyte depleting induction in some but not all recipients) may contribute to variable disease transmission.

The stringent definition of **excluded** can be applied if there is clear evidence of an alternative, non-donor origin of disease. Often, this may occur if there was pre-existing infection in multiple recipients but infection could not be identified in the donor or if testing of the same infection failed to document a clonal or donor-phenotype in the identified infection.

The term **probable** should be applied if there is evidence strongly suggesting but not proving a reaction/event. Examples include if the same infection is documented in multiple recipients but not in the donor; or if there is epidemiologic evidence suggesting transmission (i.e. TB isolated from a recipient that types to a region where the donor lived, even if the donor studies are negative).

Possible transmission should be used for all situations where a) data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probable) or b) a transmission cannot be formally excluded. If only one recipient is available or other recipient(s) of the same donor cannot be appropriately tested, the maximum degree of indeterminate but probable transmission can be reached.

If all or some of the recipients received an intervention (i.e. antimicrobial therapy or organ removal) and no disease was recognized in any of the recipients, the term **intervened upon without documented transmission** (IWDT) was utilized.

If some but not all recipients had an intervention but disease transmission was recognized in even one recipient, this category should not be used. The following table describes the possible outcomes of an imputability investigation:

Table 1. Scale describing the possible outcomes of an imputability investigation

ADAPTED FROM EUSTITE-SOHO V&S ¹		CRITERIA FOR INFECTIOUS AND MALIGNANT TRANSMISSIONS ADAPTED FROM DTAC ²
Not Assessable	Insufficient data for imputability assessment	Insufficient data for imputability assessment
0 Excluded	<i>Conclusive</i> evidence beyond reasonable doubt for attributing an adverse reaction to <i>alternative causes</i>	Suspected transmission and fulfillment of <i>at least one</i> of the following conditions: <ul style="list-style-type: none"> • Clear evidence of an alternative cause; • The appropriate diagnostic tests performed have failed to document infection by the same pathogen in any recipient from the same donor; Laboratory evidence that the recipient was infected with the same pathogen or had a tumor before the application of organs, tissues or cells.
1 Possible	The evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells, to the donation process, or to alternative causes	Suspected transmission and <ul style="list-style-type: none"> • Laboratory evidence of the pathogen or tumor in a single recipient or Suspected transmission and <ul style="list-style-type: none"> • Laboratory evidence of the pathogen or tumor in a single recipient or • Data suggest a transmission but are insufficient to confirm it. Suspected transmission and
2 Probable	The evidence is <i>clearly in favor</i> of attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)	<i>The following two conditions</i> are met: <ul style="list-style-type: none"> • Suspected transmission and • Laboratory evidence of the pathogen or the tumor in a recipient And it meets <i>at least one</i> of the following conditions: <ul style="list-style-type: none"> • Laboratory evidence of the same pathogen or tumor in other recipients; • Laboratory evidence of the same pathogen or tumor in the donor; If there is pre-transplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplantation.
3 Definite; Certain	The evidence is <i>conclusive</i> beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)	<i>All the following conditions</i> are met: <ul style="list-style-type: none"> • Suspected transmission; • Laboratory evidence of the pathogen or the tumor in a recipient; • Laboratory evidence of the same pathogen or tumor in other recipients (if multiple recipients); • Laboratory evidence of the same pathogen or tumor in the donor; • If there is a pre-transplant laboratory evidence, it should be noted that the same recipient was negative for the pathogen before transplantation

¹SOHO V&S Guidance for Competent Authorities: Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells
<http://www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Communication%20and%20Investigation%20Guidance.pdf>

²Uniform Definitions for Donor-Derived Infectious Disease Transmissions in Solid Organ Transplantation Christian Garzoni and Michael G. Ison Transplantation • Volume 92, Number 12, December 27, 2011



The investigation of an unintended occurrence has resulted in a risk of harm essentially comprises a 'root cause analysis' process (RCA). RCA is 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. RCAs should be conducted in a structured and objective way, to reveal all the influencing and causal factors that have led to an adverse event. The aim is to learn how to prevent similar incidents happening again. The approach should shift the focus from individuals to the system. There will usually be a coordinator and a team that carries out the investigation. Normally, the following steps should be included in the process:

1. **Gathering Data** - to include full details of what happened, as well as relevant policies and procedures.
2. **Mapping the Information** - possibly in timelines, flowcharts or a chronological narrative of the chain of events allowing the identification of any information gaps and showing contributing factors.
3. **Identification of the problem(s) that contributed to the occurrence** - this could require a review meeting with relevant personnel involved.
4. **Analysis of the contributing factors** with prioritization.
5. **Identification and agreement on the root causes** - the fundamental contributory factors which, if resolved, will eradicate or have the most significant effect on reducing likelihood of recurrence
6. **Reporting.**

The implementation of corrective and preventive actions should be managed and monitored within the Quality Management System, including an action plan and audit, with any relevant findings being fed back into the original investigation report

It is easy to conclude that mistakes are caused by 'human error' but this error often has an underlying cause that must be identified and addressed if repetition of the error is to be avoided. The underlying causes might be understaffing, unduly long working hours, procedures that are not clear to staff, inadequate training or, indeed, true human error. It is recommended that a structured approach be adopted to arrive at the 'root' cause. Relevant personnel should be trained in effective methods for conducting RCAs.

9.1 FIVE WHYS

One well established quick and simple method is to ask a series of 'why' questions, continuing until a satisfactory explanation for what has occurred is reached. See examples in the Annex to this chapter. As a problem becomes more complex, this tool may not be sufficient to allow identification of the root cause and a more sophisticated technique may be needed, such as the Ishikawa (or cause and effect method).

9.2 CAUSE AND EFFECT ANALYSIS

Also known as the Ishikawa Diagram or the Fishbone Diagram for Process Failure, this method encourages the investigation to follow a structured process of identifying contributing factors and risks. The technique uses a diagram-based approach for thinking through all of the possible causes of a problem.

It can be summarized in the following steps and on the corresponding diagram below:

1. Identification of the problem - what has occurred to imply risk (what has gone wrong?)?
2. Identification of the factors that could contribute to causing the problem (systems? equipment? personnel? external factors? etc.)
3. Identify possible causes for each factor
4. Analyse the diagram and decide on further actions to test the different potential causes (data analysis? survey? interview? research?)

Table 2. 'Five whys' Examples why was the wrong virology report recorded?

QUESTION	ANSWER
Why was the wrong virology report recorded?	It was a human error – the technician saw the reactive result but ticked the 'non-reactive' box on the results form
Why did the technician make a mistake like this?	He was not used to manually recording results and was carrying out a number of tests simultaneously
Why was he manually recording results if he was not used to doing that?	The automated testing system is used during the normal busy day but not at night when the number of tests required is too low to justify the cost
Why was he not used to the night time procedure?	It was his first time working alone at night and he had not used the manual procedure for a number of years
Why was he carrying out a procedure for which his competence had not been checked?	The person who normally worked at nights was ill
Root Cause	The technician was carrying out a task for which he had not been adequately trained and supervised.

Table 3. 'Five Whys' Examples Why was the bone packaging torn when it was received in the operating theatre?

QUESTION	ANSWER
Why was the bone packaging torn when it was received in the operating theatre?	The cortical bone strut inside was sharp and tore the material
Why was material used for packaging that was susceptible to tearing by sharp bone?	It had always been used by the tissue bank for all their previous products
Why had this problem not been seen when the packaging was validated?	The validation was carried out only for ground bone products which did not have sharp points
Why was the packaging material not validated for this new product?	The validation already in place for ground bone was considered adequate
Why was this new risk not identified as a reason for validation of the packaging for cortical struts?	No risk assessment was carried out when this new product was introduced
Root Cause	Lack of a risk assessment when a product change was being introduced.



Remarkable developments in the scientific, technical and medical fields have led to the increased therapeutic use of human organs, tissues and cells. Transplantation of these substances of human origin (MPHO) has not only saved lives but also improved the quality of life of individuals. These achievements have resulted, however, in a situation whereby the demand for organs for transplantation far outstrips the supply. In relation to tissues and cells for transplantation and assisted reproduction, the shortages are not as acute and generally patient needs can be met, with the possible exception of highly matched hematopoietic stem cells.

In spite of significant benefits derived from the transplantation of MPHO there is an inherent risk of disease transmission and /or a negative outcome. There are numerous reports in the literature concerning infectious disease, malignancy and other serious reactions that have occurred associated with donor to recipient transmissions for all MPHO. The introduction of vigilance and surveillance systems can facilitate the monitoring of severe adverse occurrences and lead to improved measures for dealing with them as has been demonstrated with blood component transfusion and haemovigilance systems.

Recognizing the need for the surveillance of such occurrences, the World Health Assembly (WHA)[11] in May 2010, called on the World Health Organization (WHO) to facilitate inter alia Member States' access to 'appropriate information on the donation, processing and transplantation of human cells, tissues and organs, including data on severe adverse events and reactions'.

In accordance with these resolutions, WHO, the Italian National Transplant Centre (CNT) and the EU-funded Project 'Vigilance and Surveillance of Substances of Human Origin' (MPHO V&S) joined forces to organize a major global initiative aimed at raising the profile of vigilance and surveillance (V&S) of substances of human origin. The initiative was called Project Notify.

The scope of the project included organs, tissues and cells for transplantation and for assisted reproduction. Ten working groups collaborated in the effort. The work was conducted on a WIKI site where over 100 participants (regulators, clinicians, professional society representatives, scientific experts) collaborated to gather documented cases of occurrences across the scope of the substances under consideration, using published articles and vigilance system reports as their sources. Over 1,900 published references were inserted on the site. The cases were used as the basis for developing draft guidance on the detection and confirmation of occurrences, with an emphasis on the key role of the treating physician.

The Notify project culminated in a meeting of 116 invited experts from 36 countries that took place in Bologna from February 7th to 9th 2011. The participants represented regulatory and non-regulatory government agencies, professional societies and scientific and clinical specialties from all WHO regions. The meeting was made possible with funds raised by CNT together with those allocated within the MPHO V&S project for an international meeting on vigilance reporting and investigation. The meeting explored the work already carried out on-line and agreed on priorities for the future development of global V&S for organs, tissues and cells.

From the meeting, the Bologna Initiative for Global Vigilance and Surveillance (**BIG V&S**) was established resulting in these outcomes:

- A detailed report of the meeting has been published [15].
- The MPHO V&S project has proposed instruments and guidance for tissue and cell V&S in the EU based on the outcomes of the Bologna Initiative.
- A new dedicated site has been established by CNT, as part of a sustained collaboration with WHO, for the promotion of V&S (www.notifylibrary.org). The 'wiki'-style site will support the global dissemination of information and references regarding adverse events and reactions that have been documented for organs, tissues and cells. It is publicly accessible and is populated initially with all of the documented incidents already collected in the Notify Google site.

These cases, and new cases as they arise, will be posted on the site using key words and a minimum data set which will enable searching by, for instance, type of human-substance, type of infectious disease transmission agent, type of logistical error etc. The tool will be a source of information for clinicians, potential donors and patients who wish to better understand the risks associated with particular types of donation or human application; for professionals who need information when deciding on the suitability of a potential donor and for regulators who need information on previous experiences of specific types of reported events and reactions.

- An international Steering Committee, under WHO and CNT, with regulatory and professional representatives from the fields of organs, tissues and cells, has been established to oversee the work of the new website and to take forward the other outputs of the Bologna Initiative including the development of correspondence tables for terminology and agreement on common definitions, where possible.

WHO has published this document for clinicians as a reference to the guidance on detection and investigation of adverse occurrences that were developed by project Notify. The booklet will be provided to WHO Member States to promote V&S in transplantation.



A joint initiative co-sponsored by WHO, CNT and the MPho V&S Project culminated in a Global Consultation on Vigilance of Organs, Tissues and Cells (for transplantation and for assisted reproduction) in Bologna, February 7-9 2011. A new open access, searchable website (a Vigilance Knowledge Base) has been established to host, maintain and update the library of documented occurrences that has been developed here (www.notifylibrary.org).

An international Steering Committee, under WHO and CNT, with regulatory and professional representatives from the fields of organs, tissues and cells, has been established to oversee the work of the new website and database and to take forward the other outputs of the Bologna Initiative including the development of correspondence tables for terminology and agreement on common definitions, where possible. The database is organized:

By MPho type

The database was built to cover occurrences related to different allograft materials: solid organs, cornea and eye tissue, tissues other than ocular and stem cells of various origins. Each of these generated multiple occurrences relating to the specific system and then could be divided by type.

By Occurrence type

The various types of harm to recipients or donors were then classified by type such as: donor transmitted infections, including viruses, bacteria, fungi, parasites, prions, etc.; malignancies of all kinds; living donor reactions relative to organ donation, stem cell or bone marrow donation; and autologous tissue donations (excluding stem cells).

Occurrences implying a risk of harm were also classified depending on defined criteria:

- Loss of highly matched or autologous material
- Gamete or embryo mix-up
- Loss of suitable organ(s)
- Loss of large quantity of unmatched tissues or cells
- Unsuitable MPho released for clinical use
- Other

11.1 THE NOTIFY DATABASE AS A REFERENCE FOR UNUSUAL DONOR SUITABILITY QUESTIONS

As the database has grown along with the participation with health care professionals, it has become more and more apparent that the information available to transplant coordinators and practitioners would be a valuable resource for addressing donor suitability issues. Although the well-known risks of donor derived infections and malignancies can be addressed through well-designed questionnaires used to interview either living donors or families and next of kin of deceased donors, each donation event can present with unique challenges to those who must make quick decisions, often in the middle of the night when access to experts is limited. In addition, the rare occurrences, which have been captured in the database, can provide insight to the eligibility of the donor. In the short time that the system has been in development, it has already been utilized in that regard.

11.2 THE RISK/BENEFIT CALCULATION: NUMBERS, NUMERATORS, DENOMINATORS AND TRANSPARENCY

Although haemovigilance systems have been in place for nearly two decades with notable success in reducing risk, the most important issue that needs to be understood is the dissimilarities between blood safety systems and what might be implemented in cell and organ transplantation. The first relates to the volume of activity – blood donations are

in the millions in many countries while organ donations are in the thousands in only a very few countries and haematopoietic stem cell donations are even fewer. The second deals with the scarcity of donors – blood donors can be replaced while organ donors are very scarce and haematopoietic stem cell donors are usually unique for each recipient.

Moreover, mortality rates on organ transplant waiting lists are substantial as are unavoidable mortality rates from transplantation. Risks from the transmission of disease are very small under standard procedures but there is the need for a critical understanding of the risk of causing more deaths than one might save through implementing specific safety strategies. It is also important to realise that the frequencies of transplants, even in the most active countries (such as the USA), are such that the data from across the world will need to be put together to be able to detect even the reasonably frequent events (1:1,000 or 1:100,000). The clinician plays an important role in this context by deciding whether or not organs are suitable for transplantation.

Ultimately, the public must be engaged in understanding the risks and benefits of transplantation as they have been in blood donation. Transparency is key in gaining public trust and involvement in the entire cycle of transplantation from donation to patient outcome. In order to better understand relative risks both numerator and denominator data are necessary to calculate the various occurrences that can occur with MPHO. Adequate data collection systems have not been universally implemented and are needed for such calculations.



12.1 HAEMATOPOIETIC PROGENITOR CELL DONATION

Living donors provide an estimated 25-30,000 HPC products annually for use in related- and unrelated-donor allogeneic hematopoietic cell transplantation (HCT). These are donations of bone marrow (HPC, Marrow or HPC(M)) and peripheral blood stem cells (HPC, Apheresis or HPC(A)). Not included in these numbers are an estimated 200,000 newborn infants whose umbilical cord blood (HPC, Cord Blood) is collected and evaluated for potential storage in public cord blood banks and autologous HPC collections for medical therapies. Adverse reactions (AR) and serious adverse reactions (SAR) are not known to occur among cord blood donors, so they have been excluded from this report. Also excluded, are autologous HPC donations, even though such donations represent a much larger number of transplants. Nevertheless, reactions can be similar but patients are involved rather than healthy donors. In addition, regulatory issues are very different due to this practice.

Today, HPC(M) donations from children and adults are much less frequent than HPC(A) donations, which comprise about 80% of the total. Preparation for HPC(A) donation almost always involves mobilization of HPC from the bone marrow space into the peripheral blood stream through administration of a mobilization agent. Most often the mobilizing agents are filgrastim or lenograstim administered subcutaneously, once or twice daily for 4 to 5 days prior to apheresis [16]. As a result, occasionally serious reactions such as arrhythmias, splenic rupture and vasculitis can occur. Common reactions include headache, bone pain, splenomegaly and thrombocytopenia. The collection process itself involves apheresis of the mononuclear cell components, which can have its own complications including central line thrombosis, citrate toxicity, hypotension, infection, leucopenia and thrombocytopenia. More severe reactions have also been reported including pulmonary embolism, subdural hematoma, sepsis and leukemia. In addition, reactions can be acute and immediate or chronic or delayed.

HPC(M) products are almost always collected in surgical suites with donors having received general or regional (epidural or spinal) anesthesia. Red cell transfusion with autologous or allogeneic products is common. In some countries the standard of care for HPC(M) donors is hospitalization for 1 or 2 days, but in many others "day surgery" without overnight hospitalization is the usual practice. Common reactions include bone and back pain, anemia, fever, headache and hypotension. More severe reactions including death have also been reported. These include stroke, air embolism, chest pain, endocarditis, fat embolism, iliac fracture and myeloproliferative diseases. Similarly, reactions can be acute or delayed.

Allogeneic HPC donations by children are common in the related donor setting. The use of children as HPC donors has been the subject of ethical discussions and occasional controversies [17]. The wisdom and safety of HPC(A) donation by children has been debated, but it appears these donations are safe.

Therapeutic cells (TC) are cells collected from a donor that are not intended for HCT, per se. These include cells such as unfractionated mononuclear cells, T lymphocytes, antigen-presenting cells, mesenchymal cells, et cetera. TC are employed, for example, for immunomodulation, immune reconstitution, tissue repair, anti-viral treatment and anti-tumor therapy. Most often allogeneic TC donors are also HPC donors providing additional products for their recipients, but donations of TC that are not coupled to HPC donation appear to be increasing.

There are few data on AR among TC donors. The most common procedure for TC donation is unstimulated leukapheresis that is similar to apheresis procedures for platelet or red cell donation. Considerable information exists on the risks of these unstimulated apheresis procedures.

HPC donation is most often a safe procedure but Serious Adverse Reactions (SARs) do occur and can be quite common, life threatening or fatal. SARs have been reported although they are rare and can be readily managed with symptomatic interventions. In long-term follow-up, new-onset cancers and autoimmune disorders are encountered, but there is currently no evidence that these occur at higher-than-expected rates.

Recommendations:

1. Recommendations for reporting are largely based upon conclusions from the global donor follow-up conference held in Bern, Switzerland, in 2009.
2. Adverse occurrences at any time between initiation of the donation procedure and 30 days after completion of the collection should be reported. Reporting of hospitalization-related occurrences that result from common donation-associated incidents, e.g., nausea, vomiting, pain, headache, may be excessive because the distinction between adverse occurrences and hospital-related incidents in these cases is highly dependent upon geographical differences, practice standards, and regulatory requirements. Life-threatening or fatal occurrences in the context of common donation-associated incidents should always be reported.
3. Long-term follow-up of HPC donors is recommended on an annual or biannual basis for at least 10 years. At a minimum, donors should be contacted at 1, 5 and 10 years following completion of donation. The assessment should include survival, and if not surviving, a cause of death; new onset of hematologic or non-hematologic malignancy and new onset of autoimmune disease. Diagnoses should be specified by ICD codes.

12.2 AUTOGRAFT TISSUE DONORS

More often, tissue transplantations from living donors concern autologous grafts. Autologous grafts have the advantage of providing active living cells and tissue matrix on the recipient site. They are easily integrated with few local reactions but are necessarily limited in volume and associate with morbidity at the donor site.

With bone autograft donations, the most frequent complications other than those from the anaesthesia, involve the donor site:

- Hematoma;
- Wound infection;
- Persistent pain and nerve injury;
- Bone fracture, e.g. iliac crest
- Fatigue fracture, e.g. tibial;
- Scar.

Nerve injuries are usually related to sensory symptoms such as pain, anaesthesia or paraesthesia. Motor sequella are rare and usually due to a surgical error. Sensory problems are immediate, and often resolve spontaneously within 3 to 6 months. Some are permanent. After extraction of the autologous bone graft, a bone defect will remain at the donor site. Depending of the size, location and configuration of the defect, a fracture or a fatigue fracture could develop.

12.3 LIVING ORGAN DONOR REACTIONS

Transplantation using organs from living donors has resulted in a significant increase in the overall number of solid organ transplant procedures worldwide. In this context, it is notable that living donation accounts for more than 50% of the kidney transplants undertaken in the US in the last decade and that living kidney donation is rapidly increasing to similar levels in other countries. In contrast, living donation has only marginally impacted on the overall number of transplants undertaken for other solid organs such as liver, pancreas, lung and intestine. Still, even if the number of the latter procedures represents less than 1% of the overall number of transplants made possible with the use of living donors, they are an invaluable source of organs for patients in terminal organ failure.

However, for living donation to progress successfully and possibly further expand, all the steps must be in place to ensure that these procedures take place in the context of the existing regulatory frameworks and that all the fundamental ethical principles are applied. Furthermore, efforts must be made to minimize the risk of undesirable events in the donor and to maximize the benefit to recipients.

Indeed, undesirable events have been reported following live organ donation. These vary widely among organs in terms of type, time of onset, severity and incidence that is estimated to be up to 28% in the case of liver transplantation. The risk of major complications is reasonably low. Still, living donation has been associated with fatal peri-operative events in the donor but also with later complications that may be mis- or under diagnosed and, ultimately, be inadequately treated with health consequences to the donors.

Several studies have now reported that living donor nephrectomy is associated with the risk of increased blood pressure, proteinuria and possibly end stage renal disease. Furthermore, although survival of living kidney donors is similar to that of the general population, it has been hypothesized that this may be due to the optimal [or even superior] donor conditions at the time of their donation.

Taken together, these observations unquestionably demonstrate that living organ donation is inextricably associated with some degree of risk to the donor health. In this light, the development of a set of recommendations to identify and correct any health issue in living organ donors is encouraged. This is essential in order to enable the safe expansion of living donation programs worldwide. Furthermore, recent studies suggest that living donors feel pressure to donate but don't always fully understand the risks involved, thus efforts should be made to develop standardized informed consents [18].

Recommendations:

1. Living organs donor Registries should be developed in each country with ongoing transplantation programs, which entail the use of living donors. Registries should be organ-specific and should report details on the donor characteristics, type of procedures and outcomes. Registries should be kept updated.
2. A centralized supra-national organ-specific database should be considered.
3. A task force of international experts in live organ donation should be constituted [one for each organ]. These experts should convene annually to review the data collected in the registries. This task force should preferably be operating under the guidance/"umbrella" of the WHO.
4. Long-term clinical follow up of any live organ donor should be mandatory and implemented according to standards/principles internationally agreed upon that clearly indicate timing and type of investigations to be conducted after live organ donation
5. Consideration should be given to developing a standardized informed consent for each organ type in order to provide donors the best information on risks.
6. The donor follow up should be conducted throughout the donor lifespan and should continue with the same meticulousness irrespective of the outcome of the transplant itself. A strategy should be identified to ensure that no patient is lost during follow up.
7. Donor follow up should be provided free of charge and without "logistic burden" (i.e.: if the donor moves to another area or country, access to free healthcare in the new location should be provided)
8. Identification of adverse events should be thoroughly documented. If severe, they should be timely reported to national health authorities, the [organ-] specific task force of international experts, and to those responsible for updating registries. If deemed necessary, the task force of international experts may decide to convene to specifically analyze the problem arisen.
9. In conjunction with the WHO, the task force of international experts may release reports or documents to be distributed to National Health Authorities to possibly recommend measures that may have to be put in place as a consequence of the reported adverse event.



The transmission of infections or malignancies to recipients of solid organs, tissues, and eye grafts is well documented [19-21]. A wide spectrum of viruses, bacteria, and parasites have been associated with allograft-associated infection, with transmissibility depending on the type of graft, processing of the graft, and the immunocompetence of the recipient and many malignancies have been transmitted by organ transplantation.

The recognition of allograft-associated infections has importance in terms of the health of the recipient as well as the health of other recipients of tissues derived from the same donor. This observation increases the importance of prevention of disease transmission as well as the recognition and full microbiological evaluation of transmission events when they occur. In addition, transmission events require:

- Recognition on the part of clinicians employing tissue allografts in clinical practice that infection may occur in recipients and that, as such, require careful microbiological evaluation.
- Mandatory and timely reporting of transmission events to procurement organizations, tissue and eye establishments and public health authorities. Clinicians require education on reportable events including specified clinical syndromes and the mechanisms available for these reports. In general, allograft recipients with evidence of unexplained infection early after graft placement, with recovery or recognition of common or unusual organisms, or with uncommon clinical syndromes (e.g., encephalitis) merit reporting. Confirmation of transmission events is needed to assure the adequacy of epidemiologic data.
- A “culture of safety” should be promoted that will focus on the prevention of disease and improvement in clinical practice rather than punitive approaches to reporting of possible transmission events.
- Coordination of information between public health authorities, competent authorities, clinical centers, patients, and between tissue and organ procurement groups must be facilitated. Standard paradigms must be developed for the investigation of transmission events to expedite treatment for other recipients possibly impacted by affected tissues.
- Agreement must be reached regarding the optimal panel of clinical microbiological assays for use in screening eye, organ and tissue donors based on the tissues procured, post-procurement processing, and the expected use of such tissues. Flexibility must exist in the specific testing paradigms to allow for shifts in microbiologic epidemiology and variations in endemic infections. Decisions must be made regarding the types of assays to be performed and the sensitivity and specificity of each assay.

13.1 GRAFT RECIPIENT AND THE PRESENTATION OF ALLOGRAFT-ASSOCIATED INFECTIONS

The efficiency of disease transmission is likely due to a number of factors, including graft type, processing (for many types of tissue allografts), and recipient immunocompetence, which is the greatest issue in immunosuppressed transplant recipients (solid organs, hematopoietic stem cells) who have enhanced susceptibility to infections of all types. As a result, these individuals act as sentinels for transmissible disease. In immunosuppressed hosts, symptoms of infection are often decreased and the classic signs of infection (leukocytosis, erythema) are replaced by non-specific signs (altered mental status, elevation of blood liver function tests, wound dehiscence, unexplained hypotension). In immunosuppressed hosts, the transmission of blood or organ-derived infection due to West Nile Virus, for example, more often manifests as neurological disease with poor clinical outcomes than in normal hosts. Multiple clusters of infection associated with organ transplantation (multiple recipients from the same donor) have included tuberculosis, *Candida* and *Aspergillus* (and other fungal) species, herpes simplex virus (HSV) and human herpes virus 8, lymphocytic choriomeningitis virus (LCMV), rabies virus, Chagas disease, HIV and hepatitis C virus. Detection of these unusual transmission events is dependent upon the suspicion of the clinicians caring for the transplant recipients, availability of pathology specimens, access to advanced microbiologic testing including nucleic acid amplification technologies (NAT), recognition of epidemiologic risks, and assistance with investigation of the outbreaks by public health authorities.

Infections have also been reported more uncommonly due to tissue and eye tissue transplantation. This lower frequency is likely a reflection of chemical or radiation processing (disinfection) of some tissue grafts as well as the normal inflammatory and immune function of the hosts, and possibly improved healing and vascular supply in many recipients

of such grafts. The risk of transmission varies, depending on the graft type and the extent of processing for the graft; some grafts are heavily processed (e.g., bone chips), while some grafts are minimally processed (e.g., cardiovascular tissue). Tissue transplants have been associated with transmission of *Candida albicans* and other fungi, *Chryseobacterium meningosepticum*, now *Elizabethkingia meningoseptica*, *Clostridium* species, HCV, Epstein-Barr Virus (EBV), and group A *Streptococcus*. These infections may present with local signs of graft failure, purulence, unexplained erythema, persistent pain, or systemic infection.

Adverse reactions associated with eye tissues have been associated with primary graft failures (PGF), bacterial and fungal endophthalmitis and keratitis, corneal dystrophy/degeneration, and scleral graft rejection. Often, although infection is suspected, microbiological cultures may not be obtained routinely and/or a specific pathogen is not identified. A significant reduction in adverse events resulted from use of 5% ophthalmic povidone-iodine solution by eye banks prior to recovery of eyes or corneas.

Despite screening and processing, hematopoietic stem cells (HPCs) have also been associated uncommonly with transmissions of a wide range of viral, bacterial, fungal, and parasitic infections.

Recommendations

Response to Possible Allograft–associated Transmission Event

1. The clinician must be suspicious that transmission of infection may occur in association with allograft implantation.
2. In the setting of unexpected graft dysfunction, local signs (e.g., erythema, edema, pain) of infection or inflammation, fluid collections or bleeding, recipient samples must be obtained for diagnostic analysis. These include analysis of both fresh and fixed tissue. Concerning microbiologic methods, Gram stain and culture, bacterial and fungal cultures, and, if appropriate, mycobacterial smears and cultures. Special assays may be indicated based on the nature of the graft or reaction. Complete blood counts with differential counts should also be obtained.
3. Systemic signs of infection or inflammation (fever, leukocytosis, hypotension, confusion, pneumonia, meningismus) merit blood cultures, and sputum or cerebral spinal fluid cell counts, glucose and protein, microbiological cultures and fixed tissue specimens as appropriate to the site of infection.
4. Donor screening assays must be performed according to local requirements with consideration of the certification of the laboratory performing the assays, special testing based on the epidemiologic history of the donor, and laboratory quality control measures. Donor autopsies should be encouraged, and autopsy specimens and other fixed tissue from biopsy should be accessed if there is a transmission investigation.
5. Notification of the organ, eye or tissue bank (as appropriate) of the possibility or demonstration of infection in the allograft donor must be achieved within 24 hours of recognition of potential disease transmission.
6. Notification of the appropriate public health authorities must be made to ensure appropriate investigation of transmission event.



14.1 DONOR MALIGNANCIES KNOWN TO BE TRANSMITTED OR KNOWN NOT TO BE TRANSMITTED BY CANCER, ORGAN AND CELL TYPE

Although the risk of malignancy transmission has been understood and reported since the first years of clinical transplantation, donors with known malignancy or with a high risk of malignancy have thus been screened and avoided. The frequency of donors with malignant tumors are thus not known with precision since it is only through failures and unusual circumstances that transmissions have been reported. The limited information on such risks leads to the standard approach to consideration of individual / undocumented situations, based on a number of principles, as follows:

Diagnosis: A diagnosis of cancer in the donor, which may be definite (known histology), or probable (diagnosis reported by a third party).

Biological behaviour of the tumour: The characteristics of the expected biological behaviour and prognosis of the specific cancer in the normal population.

a) A cancer that has the potential to metastasise in the normal population should be a contra-indication to donation.

b) Exceptions are made specifically to permit donation from donors with a history of malignancy: skin cancers that do not metastasise in normal population e.g. basal cell carcinoma; and some central nervous system (CNS) malignancies that are known to be contained in the specific individual donor within the blood brain barrier through absence of intervention.

Tumour therapy performed / current follow-up: Consideration is made of specific cancers where the diagnostic evidence is explicit, but curative treatment and disease-free intervals are definitely observed such that the risk of metastasis in the normal population is minimal. Specific cancers that may behave differently in the immunosuppressed populations are excluded even if they meet this criterion e.g. melanoma, Kaposi’s sarcoma. A literature review performed in NOTIFY sought to review the current knowledge on risks of malignancy transmission through the transfer of MPHO and intended to determine if the principles outlined above do or do not provide a continuing basis for assessing the transmission risk for malignant disease. This information was mainly derived from dedicated follow-up registries, particularly in the field of organ transplantation e.g. the Australian and New Zealand Dialysis and Transplant Registry, the Centro Nazionale di Trapianti Tumour Registry, the Danish Tumour Registry, the Israel Penn International Transplant Tumor Registry, the Organización Nacional de Trasplantes Tumour Registry, and the United Network for Organ Sharing Registry. The review of the published information (mainly case reports) also intended to serve for outlining the clinical manifestations of transmitted malignancies and providing guidance on how to determine the likelihood of malignancy transmission. As a result of the aforementioned literature review, a list of reported MPHO transmitted malignancies is provided in Table 4.

Table 4. List of malignancies for which at least one report on transmission through the transfer of MPHO has been identified.

Cornea	Organs	Hematopoietic Stem Cells
Papillary Adenocarcinoma	Lymphoproliferative disorders	Lymphoproliferative disorders
Glioma	Breast cancer	Non-Hodgkin Lymphoma
	CNS neoplasias	Leukemias
	Choriocarcinoma	Acute Myeloid
	Colo-rectal carcinoma	Acute Lymphocytic
	Haematologic malignancies	Chronic Myeloid
	Liver Cancer	Chronic Lymphocytic
	Lung Cancer	
	Melanoma	
	Ovarian Cancer	
	Pancreatic Carcinoma	
	Prostate Carcinoma	
	Renal Cell Carcinoma	
	Sarcoma	
	Bladder Cancer – urothelial carcinoma	

14.2 PROVIDING GUIDANCE ON EARLY DETECTION AND PREVENTION OF TRANSMISSION

14.2.1 Deceased donors.

Strategies to minimize the risk of malignancy transmission related to donor evaluation through the transfer of MPHO are summarized in Table 5.

Table 5. Strategies to minimize the risk of malignancy transmission through MPHO.

Detailed medical history:	<ul style="list-style-type: none">• History of malignancy: date of first diagnosis, detailed histological report including stage, grade, type and date of surgery, chemotherapy and/or radiotherapy, regular follow-up visits conducted, latest follow-up visit and results, complete remission and tumor recurrence at any time• Life style habits related to neoplastic diseases (i.e. smoking behavior)• Menstrual irregularities after pregnancies and/or miscarriages in women
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Physical examination

Laboratory tests:	<ul style="list-style-type: none">• Standard• Tumour markers, i.e. βHCG, PSA, in selected cases
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Image tests:	<ul style="list-style-type: none">• Chest X-ray• Abdominal ultrasound• CT or other in selected cases
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Inspection of all intra-thoracic and intra-abdominal organs, regardless of their eligibility for transplantation, including bowel and genital organs

Histopathological examination of any mass or lymphadenopathy identified during evaluation or recovery-including ISOL*

Recommended autopsy when possible

Guidelines for donor evaluation, testing and selection

*ISOL: intracranial space occupying lesions

14.2.2 Living Donors

As for the deceased donor, potential live donors should be carefully evaluated to identify a previous history of malignancy or an active neoplasia, based on a thorough medical history, a physical examination and image tests. It should be noted that the risk of clinical and subclinical malignancy increases markedly with age and that the risk of different cancers differs between countries. Hence, screening for prevalent malignant diseases in the population should be based on national cancer screening protocols.

The follow-up of the living donor to detect and treat any complication related to donation and appearing in the short, mid or long term is a recognized international standard. On the other hand, during the follow-up of the living donor, potentially transmissible diseases, including malignancies, might arise, which were not detected during the donor evaluation preceding the transplantation. Cases of malignancies appearing in living donors shortly after donation have been described in the literature. This situation should lead to alerting the relevant teams. Needless to say, the procurement / transplant team should take care / responsibility of the live donors in terms of treatment and follow-up care.

14.3 PROVIDING GUIDANCE ON IMMEDIATE STEPS TO TAKE FOR INDEX RECIPIENT AND OTHER POTENTIALLY AFFECTED RECIPIENTS

14.3.1 Tracing, alerting and notification

Traceability is defined as the ability to locate MPHO at any stage of the chain from donation to transplantation or disposal. Tracing should include all MPHO transferred from the donor involved in the case under study, which implies that link between the different tracing systems should be ensured. Usually, a team is not able to trace all recipients of MPHO from one donor on its own. The allocating body should hence participate in tracing and in alerting the other teams, as foreseen in the corresponding jurisdiction.

Clinicians diagnosing a malignancy after transplantation that might be donor-transmitted should alert the teams in charge of other potentially affected recipients. Even if attributability has not yet been determined, the suspicion of a transmitted malignancy should activate the alert, since preventive and therapeutic measures might be needed for other recipients. Moreover, the collective investigation started by each team is required in the assessment of the case, understood as a whole, including determination of transmission of disease from the donor to one or more recipients.

Once alerted, notification of the case to the relevant authority should follow.

14.3.2 Graft removal and cessation of immunosuppression

Treatment of donor transmitted malignancy may harness the alloimmune response if the graft is not life sustaining. Cessation of immunosuppression and precipitation of graft rejection may lead to rapid rejection of the tumour as well as the graft, with reported cases of cure of metastatic melanoma when it was donor derived. This approach is not available for organs such as the heart, lung and liver, which must thus be treated by minimisation of immunosuppression and conventional therapy for the malignancy.

In the case of tumours inadvertently transmitted through organs other than kidney, the strategy is less well defined with regards to graft removal and management of immunosuppression. Although re-transplantation has been attempted in some reports, the avoidance of tumour transmission has not always succeeded.

14.3.3 Immunotherapy

Cases of transmitted malignancies have been treated by stimulating rejection of both the allograft and the tumor, through the use of Interferon, tumor vaccines, pooled allogeneic cell vaccination, and adoptive immunotherapy using lymphokine-activated killer cells.

14.3.4 Conventional treatment strategies based upon cancer type if organ, tissue or cell cannot be removed

14.4 PROVIDING GUIDANCE ON STEPS TO INVESTIGATE AND CONFIRM THE IMPUTABILITY OF MALIGNANCY TRANSMISSION

Except for the scale developed by the Disease Transmission Advisory Committee in the United States, no common and objective criteria are being applied to consider whether attributability in the context of malignancy transmission is definite (certain), likely (probable), possible, unlikely or excluded. Although allowing for the specific peculiarities every case has, developing an objective and universal scale to help assess attributability is needed. However, this does not preclude the description of the steps that should be followed in case of a suspected malignancy transmission occurs, in order to assess attributability.

14.4.1 Suspected transmission malignancy

Clinical manifestations of transmitted malignancies may be variable depending on the type of tumour considered. In the context of solid organ transplantation, the identification of a malignancy in the transplanted organ, with or without extra graft involvement, should raise the suspicion of a transmitted malignancy. However, some reports have described a different clinical picture where the transmitted malignant tumour does not involve the allograft itself.

Temporal sequence should be reasonable according to the tumour type under study. Most transmitted tumours appear within the first 14 months after transplantation. Therefore, it is unlikely that an aggressive tumour diagnosed in the recipient 5 years after transplantation is donor-transmitted.

A previous description of the transmission may help support the suspicion. A correct assessment of a case involves the analysis of the literature in order to understand whether the same tumour type has been transmitted before. Registry reports and case reports provide information regarding the type of transmission and the methodology followed for the assessment of attributability.

14.4.2 Tumour histology in donor and recipients

When neoplasia is detected in the donor before or immediately after transplantation, histological examination and immunohistochemistry can help to identify the pathology for comparison with any subsequent tumors developing in the recipient or recipients. For example, identification of a lung carcinoma in the donor needs detailed investigation of the tumor (histology, grade and immunohistochemical profile) and either graft removal or careful follow up of the recipients. If a tumor develops in one or more of the recipients of organs from this donor, the morphological comparison of the tumor in the donor and the tumor arising in the recipients can confirm the donor origin of the tumor.

14.4.3 Karyotype of donor and recipient

Several reports on transmitted malignancies have relied totally or partially on the investigation of a karyotype mismatch between the tumour cells with respect to that of the recipient for assessing attributability. This strategy is obviously limited to those cases where a gender mismatch exists between the donor and the recipient. Careful attention should be paid to the interpretation of results and accurate molecular diagnosis might be necessary as tumour cells might lose their karyotype and express a different one. The interphase Fluorescence In Situ Hybridization (FISH) for sex chromosomes has been used in these situations.

14.4.4 Genetic testing of sample from cancer, e.g. HLA testing

Other strategies applied rely on genetic testing of the cancer compared to that of donor and recipient tissue. Different gene sequences and polymorphisms have been studied in the process of assessing attributability. The origin of the tumor can be identified by microsatellite analysis by Polymerase Chain Reaction (PCR) using different markers. Paternity test by genomic allelotyping investigation is another reliable technique to verify attributability. This test permits the analysis of 16 highly polymorphic loci (with the AmpF/STR identifier PCR amplification kit) for effective discrimination of donor/recipient tumor origin.



Until relatively recently, bone marrow grafts from sibling donors were the only stem cell source available to patients in need of a transplant. The establishment of haematopoietic stem cell donor registries and public cord blood banks worldwide has increased the availability of grafts from unrelated donors for patients requiring stem cell transplantation.

The safety of the volunteer donor is an extremely important issue for the Donor Centres and a series of laboratory tests along with medical assessment are now mandatory. Donors are considered eligible for the donation when all medical data conclude that they are healthy. This assessment has a dual purpose. That is, not only to avoid placing the life of the donor at risk by aggravating asymptomatic health problems, but also to protect the recipient from the transmission of viruses and any other potentially transmissible disease. Although volunteer donors are not screened for genetic diseases, it is assumed that donors with genetic diseases are deferred as this can be deduced from the medical history or from findings of the laboratory tests undertaken.

Transmission of genetic diseases by cord blood units has a significantly higher risk than stem cells from peripheral or bone marrow donation since the disease might not be easily recognised at birth or even for some time later. Although public cord blood banks request that information on the health status of the newborn/donor be provided by the family even sometime after the donation and prior to the listing of the unit, it is possible that some genetic diseases will be missed as they might not manifest until much later in life.

Theoretically, all congenital diseases originating from bone marrow-derived cells are transmissible. Very few cases of genetic disease transmission through haematopoietic cells have been reported. Cyclic neutropenia and Gaucher's disease were transmitted via sibling HPC transplantation (Krance et al. 1982). In addition, a variety of autoimmune disease have been transmitted including: Hyperthyroidism and autoimmune thyroiditis and thyrotoxicosis, alopecia areata, type 1 diabetes, atrophy, autoimmune thrombocytopaenia, myasthenia gravis, vitiligo, asthma and anti-Ciq antibodies of SLE [15].

According to the EU Directives for tissues and cells, genetic disease transmission by tissues and cells is considered an adverse reaction and, as such, should be reported to the Competent Authority and investigated to confirm the transmission.

Recommendations

1. Donors originating from areas with a high frequency of certain genetic diseases should, if the risk is identified during the medical examination, be screened for the disease, and if found to be positive, should be deferred.
2. The medical history questionnaire for cord blood donation should cover maternal and family history and the expectant parents' ethnic background. If responses generate medical concern then the application/collection should be rejected/cancelled.
3. Cord blood units that are or were collected from families that are potential carriers of genetic diseases should be screened prior to listing and use and if found positive to be discarded. Mechanisms to inform the family should be in place.
4. Cord blood banks that have stored cord blood units that are not found to carry a genetic disease but show the trait of a genetic disease e.g. trait of beta thalassaemia, should provide this information to the transplant centre requesting the release of the unit.
5. The cord blood from babies that were conceived through the use of donor gametes should not be collected and stored unless the medical history of the sperm donor is available. If an oocyte donor is involved, blood samples from the oocyte donor can be collected.



Conditions such as Severe Congenital Neutropenia (SCN) 1, Hypertrophic Cardiomyopathy 2, 3, Autosomal Dominant Cerebellar Ataxia (ADCA), Opitz Syndrome, Neurofibromatosis type 1 (NF 1), Autosomal recessive Polycystic Kidney Disease (ARPKD), Congenital adrenal hyperplasia (CAH), and Phenylketonuria (PKU) have been reported in offspring originating from gamete donation [22]. Although these events are not numerous, they show the need to consider the potential of genetic disease transmission using donor gametes. Gametes are the only cells that carry such genetic material, which could potentially affect the recipient (offspring) with any genetic disease. Information should be shared with women/couples requesting this service/treatment, as any donor could be a potential carrier of a genetic disease.

One could argue that the number of children born with a genetic disease that are conceived through Assisted Reproduction Technology (ART) and gamete donation is probably larger than reported since couples are reluctant to reveal or share information regarding the method of conception and the use of a donor gametes. Also, the fact that a large percentage of couples resorting to cross border care opt for the use of donated gametes.

According to the European Directives on Tissues and Cells the donor's medical history must be assessed and genetic testing be applied if required. Screening could be targeted and certainly applied in situations where any serious autosomal or recessive genetic disease has prevalence more than 1:5000 (a carrier frequency of 3%) e.g. Beta Thalassaemia in the Mediterranean population, Cystic fibrosis in Caucasians and Familial Mediterranean Fever in the Middle East.

The following questions arise:

- i) Should the transmission of a genetic illness from a gamete donor be considered as a Serious Adverse Reaction?
- ii) Should there be systems for the reporting of such transmissions to regulators?

Given that in most of the cases reported and documented in the NOTIFY database, it would have been very difficult, or impossible, to have identified the risk in advance of the initial donation, it might be argued that these tragic occurrences will inevitably happen on rare occasions. It is very important to note, however, that in many of the cases reported, where the sperm donor was the source of the genetic defect, the sperm bank continued to supply sperm from that donor, without knowing about, or without taking account of, a genetic transmission that had occurred. The result was multiple children affected by the same genetic defect. For example, in a case of SCN transmitted by a sperm donor, 5 children were born with the defect¹. Another donor transmitted Hypertrophic Cardiomyopathy to 9 children. In the early years of ART, a single donor, whose sperm was used to create 42 children, was shown to carry the gene for Opitz Syndrome, with a 50:50 chance of inheritance. The first affected child was conceived just before the Human Fertilisation and Embryology Authority (HFEA) was created in 1991 in the UK; the regulator restricted to 10 the number of offspring from one donor.

It is these cases of multiple affected offspring that highlight the value of vigilance reporting of genetic transmissions by ART. In some cases the condition is diagnosed immediately after birth or early in the life of the child. In these cases, if a serious adverse reaction report was made, it could prevent further use of the sperm and the birth of further children with the same condition. In some cases, the condition manifests itself only years after puberty so an SAR report will be too late to prevent further use of the sperm. For example, sperm from a donor with ADCA was used for the conception of 18 children in 13 women. Half of the children would have inherited the gene but it would not have been detected in the offspring until after puberty. In this case, the donor himself was the first to manifest the condition and an immediate serious adverse event report might have prevented further use of the sperm.

One of the challenges of notification, either by the families of affected children or by donors, is the secrecy that often surrounds gamete donation and the use of ART to conceive. Genetic conditions are diagnosed in children in specialist units and may never be communicated to the sperm bank or to the clinic where an oocyte donation was performed. This is complicated by the degree to which couples travel to other countries for ART, usually due to restrictive laws in their own country. There are no international registries of gamete donors.

Recommendation(s)

1. The birth of a child with a genetic illness following donation of gametes or embryos should be reported as a suspected serious adverse occurrence. It should be investigated as such so that further gametes, or embryos created from that donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality. It is important to check whether the condition could have arisen from a genetic abnormality in the non-donor partner e.g. possible oocyte origin if the offspring were conceived using donor sperm.
2. The diagnosis of a genetic condition in an adult who has previously donated gametes or embryos should be reported as an adverse occurrence implying risk of harm so that stored gametes, or stored embryos created from that donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
3. Sperm banks should have access to clinical genetic expertise for advice in developing donor screening policies and in investigating suspected genetic transmissions to offspring.

To facilitate the effectiveness of vigilance reporting in these circumstances, the following is recommended:

4. Couples having ART treatment with donated gametes or embryos should be strongly advised to inform any doctors subsequently treating the resulting child(ren) of the donor origin. They should understand that, in the unlikely event that a child will manifest an inherited condition, informing the clinic could protect further families. Consideration could be given to the development of a carefully worded standard leaflet explaining these issues that could be provided to all couples. In the analogous situation of allogeneic cord blood banking, some banks provide the donor mother with a leaflet asking her to contact the bank in the unlikely event that the donor child manifests a genetic or other illness, so that the transmission of the illness by transplantation of the cord blood can be prevented.
5. Gamete and embryo donors should be strongly advised to inform the clinic where they donated, in the event that they are subsequently diagnosed with any genetic condition. In this case also, a standard information leaflet for donors might be considered.
6. Specialist genetic centres should always consider whether a child manifesting a genetic condition might have been conceived with donor gametes or embryos. This issue should be raised immediately and openly with the parents in the interests of other potential offspring and when parents acknowledge the involvement of a donor, they should be strongly urged to contact the ART Centre. The issue should be included in the appropriate professional standards and guidance for specialist genetic centres.

Consideration should be given to the establishment of international registries of gamete and embryo donors so that contact can be more easily maintained for the purposes of vigilance and, in the case of oocyte donors, donor follow-up.

16.1 PRE-IMPLANTATION GENETIC DIAGNOSIS

Some couples with a high risk of transmitting an inherited condition, cystic fibrosis, Beta-thalassemia, sickle cell disease and many others, opt for ART with the objective of preventing the transmission of the disorder. In these cases, Pre-implantation Genetic Diagnosis (PGD) is used to select embryos for implantation that do not carry the condition. An error in the process of PGD might lead to the birth of a child with the particular condition. However, the test has an expected error rate so it could be argued that this type of outcome should not be considered as an issue for vigilance reporting.

Monitoring cases of PGD error, which result in the birth of children with the condition that the treatment aimed to avoid, would allow trends to be followed and facilitate regulatory action where PGD error is more frequent than normal.

Recommendation(s)

Where an error in PGD results in the birth of a child with the condition that should have been avoided, this should be considered as a reportable SAR so that the cause can be investigated and the learning points shared.



Each MPHO intended for transplantation, implantation, infusion or transfer has specific quality attributes and characteristics determined by anatomy and usual function. Handling activities that support the maintenance of desired efficacy or utility of the organ, tissue or cells can affect clinical outcome. When a gap exists or a step or process fails, a serious risk of harm or actual harm can occur.

The overall activity or process from donation to clinical use involves multiple steps in handling and is carefully developed to maintain certain characteristics of the allograft so it serves a specific clinical need. Handling varies among many different subtypes within general types of MPHO, but there are also general processes to which each MPHO is exposed that can affect outcome. This section addresses those adverse occurrences relating to the physical properties (characteristics) of organs, tissues and cells and to changes in the properties due to events surrounding procurement, storage and processing or other aspects that may alter viability or other physical or chemical properties desired. To maintain desired allograft characteristics, clinical utility, and availability for use, controls should be in place for steps involving:

- Consent/authorization;
- Donor screening, testing (including controls regarding the blood sample) and test kits;
- Recovery, procurement or collection;
- Preservation/processing (this can include qualification of materials, reagents, equipment and facilities as well as maintenance, where applicable, and validation of processes that incorporate process controls and/or verification of steps);
- Storage, transport and distribution;
- Selection for use and allocation (where applicable);
- Preparation for use (or other final disposition);
- Qualified personnel with sufficient training who are deemed competent; and
- Documentation and maintenance of records for all the above.

Some allograft outcomes and risks are anticipated (expected) while some may be unanticipated (unexpected). Additionally, steps taken to report or notify are critical when an unexpected outcome occurs. There is value to collection, analysis, and sharing this type of information because there may not only be national or regional implications, but also concerns on an international scale.

The process surrounding the handling of an allograft so it performs as expected involves careful development and execution of protocols. The well being of living donors is also included in protocol development and evaluation.

The concept of 'tissue properties' is described as it can be applied to organs, tissues, hematopoietic progenitor cells, corneas and gametes and embryos used for transplantation or application, and how those properties can affect the post-grafting course. There are examples when failures occurred and the allograft could not be used; the potential affect this has on the intended patient must be assessed. Adverse occurrences where patients were posed to be at risk, or harmed, by some intrinsic property of the product related to its recovery, processing, evaluation, storage, transport, and distribution are addressed according to the "Vigilance and Surveillance of Tissues and Cells in the European Union - Final Recommendations of the European Union Standards and Training for the Inspection of Tissue Establishments (EUSTITE) project", June 7, 2010. As an example, ocular tissues are examined in some detail and the same principles of how product properties can influence outcomes extend to other types of traditional non-ocular tissues.

Traditional (conventional) tissues transplanted include skin, bone with or without cartilage, musculoskeletal soft tissues, and cardiac and vascular tissue types. While these tissues can be gifts provided by deceased donors, living donors also provide them. Steps in allograft donor screening, tissue recovery and handling throughout production can be

discovered to be the root cause of an adverse occurrence. Tissue allografts made available for transplantation that come from one donor can number a few to over 100, and these can be used to alleviate pain and/or restore function in as many recipients. Tissue risk reduction measures include: obtaining valid consent/authorization for donation; qualification of donors through standardized donor screening and testing; applying controls to recovery/procurement procedures; use of tissue treatment (processing) steps that reduce, eliminate, or inactivate contaminants; selecting equipment and materials that are qualified for their intended use; properly validating tissue culture methods and other procedural steps; establishing controls for tissue storage environments that are conducive to the tissue preservation method selected; establishing tissue tracking measures to be able to (quickly) trace each tissue allograft from the donation event through final use or other disposition; and, evidence of all steps taken are maintained via detailed recordkeeping. In the event that, after a thorough investigation, a tissue allograft is implicated to be the cause of a serious adverse reaction, all of these risk mitigation measures may need to be reviewed.

Adverse occurrences can be linked to dysfunctions identified in tissue establishment operations that resulted in a significant loss of product, reducing availability for use. In the case of reactions in recipients of ocular tissue most cases are limited to graft failure, which can be influenced by the tissue itself, its handling, surgical technique or the recipient. The recent evolution of corneal transplantation has increased the involvement and responsibility of eye banks in the preparation of suitable tissues for keratoplasty, but this also means an increase in handling. Sound validation of methods and procedures, good communication between tissue and cell establishments and clinical users of their allografts, and a reliable reporting system are essential in order to identify trends and opportunities for process improvement.

In the case of haemopoietic stem cells (HSC), donations may be from the patient or family members, or from unrelated donors (e.g., bone marrow registry donors, cord blood bank). Autologous cells, usually peripheral blood stem cells (PBSC), are collected, cryopreserved, and stored for subsequent use, whereas related or unrelated donations are collected and transplanted quickly. The same applies for all three types of HSC donation if in the form of bone marrow. Cord blood donation can be from unrelated or family HSC donations and banked for an extended period of time prior to use. Autologous cord blood banking can be a commercial activity but autologous units from low risk families are rarely used. Any HSC donation requires an expectation for a high level of cell viability. There are specific critical aspects relating to the quality of banked HSCs including initial cell dose (potency), cryopreservation methodology and preservation agents, potential for contamination, rate and mode of freezing and thawing as well as maintaining a controlled, deep frozen state throughout storage and during transportation that ends at time of use. The recipient must receive conditioning therapy prior to transplant, and immunosuppression afterwards.

Adverse occurrences, where no patient has been harmed, should be reported in certain circumstances. It was recommended by the EUSTITE project that deviations from Standard Operating Procedures in tissue or cell processing facilities, or other adverse incidents, which have implications for the quality and safety of tissues and cells should result in reporting to the regulator when one or more of the following criteria apply:

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

Reporting of such occurrences allows the identification of corrective actions that can be shared widely to prevent recurrence in other facilities.

Organ transplantation differs in some regards from tissue and cell transplantation, with two major aspects being: 1) the time constraints in procurement and transplantation including the lack of processing and banking, and 2) the typically life-saving nature of organ transplantation. These two aspects have an influence on the strategy taken in organ transplantation by involved stakeholders: some risks that can be excluded in tissue and cell transplantation through extensive testing have to be accepted as "calculated risks" in

organ transplantation. This idea is reflected in the EU directive 2010/53/EU of the European Parliament on standards of quality and safety of human organs intended for transplantation: "The risk-benefit ratio is a fundamental aspect of organ transplantation. Owing to the shortage of organs and the inherent life-threatening nature of diseases leading to the need for organs for transplantation the overall benefits of organ transplantation are high and more risks are accepted than with blood or most tissues and cell-based treatments. The clinician plays an important role in this context by deciding whether or not organs are suitable for transplantation."

Nevertheless there is "a need for common quality and safety standards for the procurement, transport and use of organs at Union level." This is of special importance in light of the fact that organs are exchanged daily between Member States. According to Article 11 of the Directive a reporting system shall be in place for "serious adverse events that may influence the quality and safety of organs and that may be attributed to the testing, characterization, procurement, preservation and transport of organs as well as any serious adverse reactions observed during or after transplantation which may be connected to those activities." Similar events and concerns apply to other regions (e.g., Canada, the United States, Australia) where allocation of organs can occur across provincial, state or territorial borders.

There are quite a number of incidents that might fulfill the criteria above and it is of central importance that selection of incidents to be reported is organized in such a way that it can be readily managed by stakeholders (organ procurement organizations, organ exchange organizations, transplant centers). In the context of organ shortage, events that result in loss of organs have a direct impact on patients waiting for an organ transplant; such events should be centrally collated to maximize the opportunities for process improvement.

Serious reactions resulting from errors/inadequate procedures at the level of the clinical user as opposed to reactions due to product-related causes can also occur. Three types of serious reactions include: acute hemolytic reaction, Graft versus Host Disease (GvHD) and circulatory overload associated with the transfusion of hematopoietic progenitor/stem cells (HPCs). All three are known from haemovigilance, respectively as acute hemolytic reaction, transfusion associated GvHD (TAGvHD) and transfusion associated circulatory overload (TACO). The extensive experience with these reactions is available in haemovigilance literature.



In addition to transmitted infections, transmitted malignancies have been reported primarily through organ transplantation but have also been transmitted by stem cells and cornea. Beyond disease transmission, other concerns include adverse allergic reactions, reaction to toxins, or decrease in expected function. These non-infectious events may be due to deficiencies in the product, or a mismatch between the product and recipient immunologic profile, but consequences may be as severe as for infectious disease transmission events. In all of these adverse incidents, the ability to trace potential outcomes becomes exceedingly important.

Traceability means 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, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing 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.

As previously described, the donor scandal in New York State resulted in tissue from over 1,000 donors being recovered during a three-year period of time. Nearly 50,000 tissues were produced of which 15,000 could be recalled prior to transplantation. Over 25,000 tissues were distributed to unsuspecting patients without appropriate testing or medical review [23]. Because records from these donors had been forged, over 2,000 of these tissues were untraceable including 800 that had been distributed outside of the United States. The real concern however, is that even apart from these unusual scandals, there is not a uniform system for tracking many of these tissues, nor to detect adverse events from their use. In fact, most of the reported infectious transmissions from tissue transplants have included the inability to identify some of the recipients.

In addition, the organ, tissue and eye banking community's function independently and communications between them are often lacking. This lack of communication can result in an inability to track organs and tissues from a common donor. For example, a report in 2005 described a number of hepatitis C virus (HCV) transmissions to several organ and tissue recipients from a single donor. This case generated much publicity because there were 91 grafts produced from the donor (7 organs, 2 corneas and 82 other tissues), 44 transplants and 40 recipients in 16 states and 2 other countries over a period of 22 months. Three organ recipients were infected and 32 of the tissue recipients could be identified and tested of which 5 were HCV positive and infected. One recipient could not be identified. All of the tissue recipient infections would have been prevented if recognition of infection in the organ recipients had resulted in notification of the tissue bank before tissue was processed or released. More than 6 months elapsed between recognition of the organ recipient infections, donor linkage, and the time that tissue was processed [24]. Events of this nature can only be avoided by the introduction of a comprehensive and unified traceability system covering all biologics derived from a single donor.

The increased recognition of issues related to traceability has resulted in various professional Associations strengthening their standards and Governments taking actions in adding to existing regulations. The International Society of Blood Transfusion (ISBT) charged its Working Party on Automation and Data Processing [subsequently renamed the Working Party on Information Technology (WPIT)] with creating a standardized means of labeling blood products so that identifiers were globally unique and bar codes (as well as other means of electronic information transfer) would have the same meaning internationally. The new coding system was named ISBT 128. The '128' in ISBT 128 comes from the barcode symbology which was selected at the time the standard was developed - this symbology is called Code 128, so the ISBT coding system using Code 128 bar codes became known as ISBT 128.

Although the transfer of blood across national boundaries is not a common occurrence, the situation for cells and tissues is very different. For this reason the case for globally unique identification is at least as strong as that for blood transfusion. A globally unique identification system is required, and this should extend across all biologic materials – blood, cells, tissues and organs. International Cell Therapy Associations, as well as International Eye Banking Associations, have agreed to the adoption of standard terminology and the ISBT 128 system and implementation is underway. The tissue banking and organ transplant communities are also in the process of determining how this system might be accepted and implemented [25].



1. WHO, *International Health Regulations*, W.H. Organization, Editor. 2005.
2. Faber, J.C., *Work of the European Haemovigilance Network (EHN)*. *Transfusion clinique et biologique : journal de la Societe francaise de transfusion sanguine*, 2004. 11(1): p. 2-10.
3. Secretariat, W.H.O., *Human organ and tissue transplantation*. Report by the Secretariat. 2010.
4. UN. Report on the Vienna Forum to Fight Human Trafficking. in *The Vienna Forum to Fight Human Trafficking*. 2008. Vienna, Austria: United Nations.
5. Caplan, A., Dominguez-Gil, B, Matexanz, R. and Prior, C., *Trafficking in organs, tissues and cells and trafficking in human beings and the replies to the questionnaire for Member States on organ and tissue trafficking (2009)*, C.o.E.a.U. Nations, Editor. 2009, Directorate General of Human Rights and Legal Affairs Council of Europe: Strasbourg, Cedex. p. 1- 98.
6. Chaney, A., *Body Brokers*. 2006, New York, New York: Random House.
7. WHO, *Human and Organ and Tissue Transplantation*. *Transplantation*, 2006. 79: p. 635-637.
8. Schulz-Baldes, A., N. Biller-Andorno, and A.M. Capron, *International perspectives on the ethics and regulation of human cell and tissue transplantation*. *Bulletin of the World Health Organization*, 2007. 85(12): p. 941-8.
9. WHO, *Aide-Memoire - Access to Safe and Effective Cells and Tissues for Transplantation*. 2006, World Health Organization: Geneva, Switzerland. p. 2.
10. WHO, *Aide-Mémoire on Key Safety Requirements For Essential Minimally Processed Human Cells and Tissues For Transplantation*. 2002, World Health Organization: Geneva, Switzerland. p. 19.
11. World Health Assembly, *Sixty-Third World Health Assembly. WHA63.22. Agenda item 11.21 Human organ and tissue transplantation*. 21 May 2010.
12. Honore, P.A., et al., *Creating a framework for getting quality into the public health system*. *Health affairs*, 2011. 30(4): p. 737-45.
13. Zou, S., et al., *Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States*. *N Engl J Med*, 2004. 351(8): p. 751-9.
14. Ellingson, K., et al., *Estimated Risk of Human Immunodeficiency Virus and Hepatitis C Virus Infection among Potential Organ Donors from 17 Organ Procurement Organizations in the United States*. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2011. 11(6): p. 1201-1208.
15. *Notify. Exploring Vigilance Notification for Organs, Tissues and Cells*. in *Organs, Tissues & Cells*. 2011. Bologna, Italy: Editrice Compositori. <http://www.notifylibrary.org>
16. Anderlini, P., et al., *Allogeneic blood progenitor cell collection in normal donors after mobilization with filgrastim: the M.D. Anderson Cancer Center experience*. *Transfusion*, 1999. 39(6): p. 555-60.
17. Diekema, D.S., et al., *Policy Statement-Children as Hematopoietic Stem Cell Donors*. *Pediatrics*, 2010. 125(2): p. 392-404.
18. Valapour, M., J.P. Kahn, R.F. Bailey and A.J. Matas, *Assessing elements of informed consent among living donors*. *Clinical Transplantation*, 2011. 25(2): p. 185-190.
19. Fishman, J.A., *Infection in Solid-Organ Transplant Recipients*. *New England Journal of Medicine*, 2007. 357(25): p. 2601-2614.
20. Eastlund, T. and D.M. Strong, *Infectious disease transmission through tissue transplantation, in Advances in Tissue Banking*, G.O. Phillips, Editor. 2004, World Scientific: Singapore. p. 51 - 131.
21. Gandhi, M.J. and D.M. Strong, *Donor derived malignancy following transplantation: a review*. *Cell Tissue Bank*, 2007. 8(4): p. 267-86.
22. SOHO V&S. *Guidance on Vigilance & Surveillance in Assisted Reproductive Technologies in the European Union*. 2011. <http://www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Guidance%20on%20V%26S%20in%20ART%20in%20the%20European%20Union.pdf>
23. Warren, J., *BTS stolen body parts scandal generating gruesome headlines, fears of infection; NY grand jury meeting*. *Transplant News*, 2006. 16(1).
24. Tugwell, B.D., et al., *Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor*. *Ann Intern Med*, 2005. 143(9): p. 648-54.
25. Strong, D.M. and N. Shinozaki, *Coding and traceability for cells, tissues and organs for transplantation*. *Cell Tissue Bank*, 2010.

