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The Global Vigilance and Surveillance Database for Medical Products of Human Origin

TRANSPLANTATION, TRANSFUSION AND ASSISTED REPRODUCTION



# The NOTIFY Guide On Vigilance and Surveillance

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



Centro Nazionale Trapianti  
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on Vigilance and Surveillance for  
Human Cells, Tissues and Organs



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## 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 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 Organization (WHO) 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 enhances traceability and transparency around the world;
- 3) The maximal sharing of vigilance and surveillance information globally.

## 1.2 VIGILANCE AND SURVEILLANCE

**Vigilance:** An alertness to, or awareness of serious adverse events, serious adverse reactions, adverse occurrences related to donation and clinical application of blood, cells, tissues and organs involving an established process at a local, regional, national or international level for reporting and investigation.

**Surveillance:** The systematic on-going collection, collation and analysis of data for public health purposes and the timely dissemination of this.

Vigilance and surveillance (V&S) is a safeguard for donors, patients, health professionals and health authorities. The introduction of V&S systems facilitates the monitoring of adverse occurrences leading to preventive and corrective measures and an overall improvement in safety, as demonstrated by the impact of haemovigilance on transfusion services, donor care and patient 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 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.

The NOTIFY booklet provides 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](http://www.notifylibrary.org)). The success is the reflection of the work of all the professionals who have contributed to the NOTIFY Library.

Initially, the NOTIFY booklet was to be focused on cells, tissues and organs for transplantation, as well as gametes and embryos for ART. As the NOTIFY project is now expanding to cover all MPHO, blood and blood products have been included in the scope.

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. If you have comments or suggestions to improve this guide, please send them to: [notifylibrary@iss.it](mailto:notifylibrary@iss.it)

**Effective V&S** requires many players to collaborate together, each one fulfilling its particular role (Figure 1):

- 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;
- 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 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 MPHO 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.

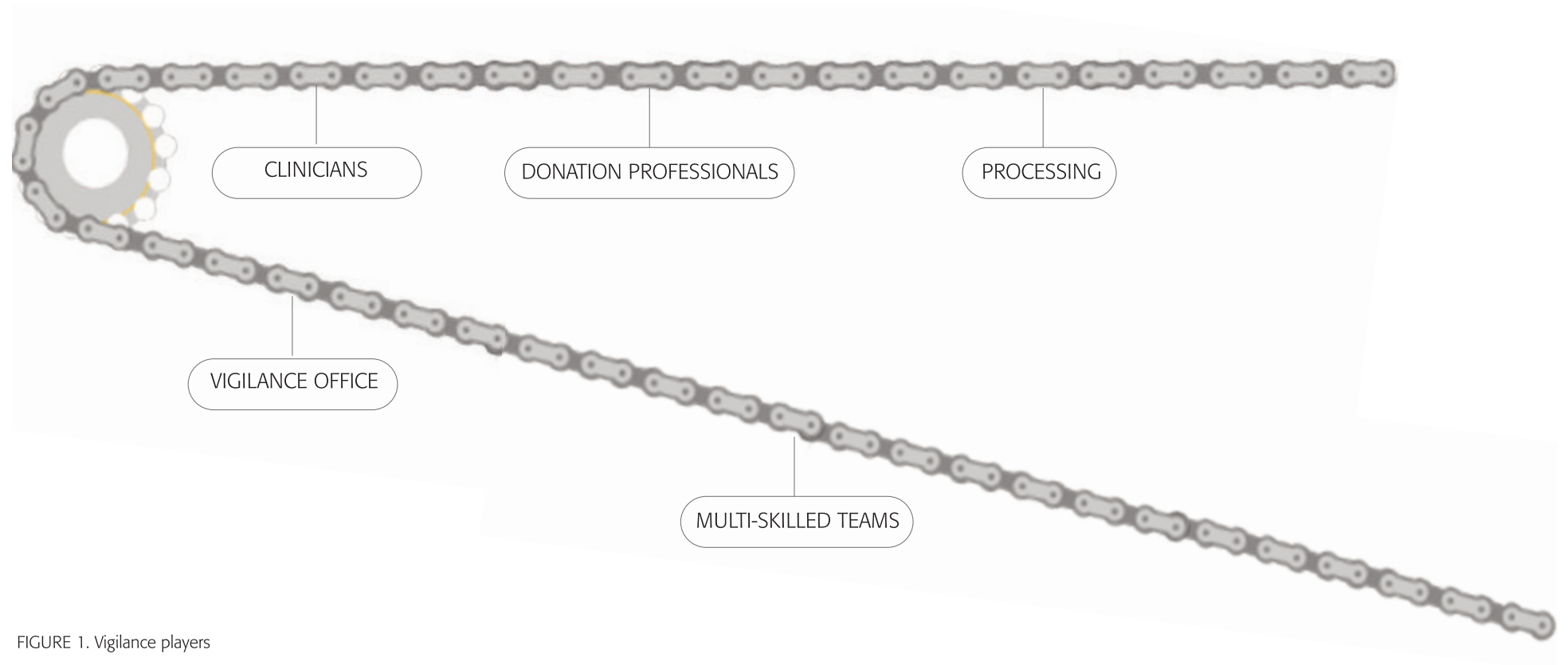


FIGURE 1. Vigilance players



### **HISTORY OF 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 or MPhO vigilance 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. It is both important and challenging to monitor and ensure appropriate access and availability of safe products both in the domestic and global arenas. This link focuses on the donor-related 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 urge Member States to develop vigilance and surveillance of adverse occurrences and the Resolution also calls on 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 serious adverse occurrences arising in the practice of blood transfusion, 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 where 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 RELY/depend ON HEALTH CARE STAFF**

Physicians and nurses in particular have the responsibility to identify adverse occurrences and to report them through the appropriate national channel. V&S is not a punitive system. It aims to improve and optimise safety, and therefore the increase 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 reduce costs. 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 occurrences. 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' (SOHO 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 occurrences. The initiative was called Project Notify. This link describes the project.

## **THE NOTIFY DATABASE - LEARNING FROM VIGILANCE**

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

## **RISKS ASSOCIATED WITH LIVING DONATION**

Living donors can provide blood and both allografts and autografts for transplantation of cells, tissues and organs. Such donations carry inherent risks that must be recognized for donor safety and for vigilance and surveillance to ensure a safe and ethical transfusion and transplantation chain. This link gives guidance for those active in promoting and organizing donation of MPHO.

## **INVESTIGATING HARM TO RECIPIENTS - INFECTIONS**

The recognition of infections transmitted through an auto or allograft or a blood component is crucial for diagnosis and treatment of the transplanted or transfused patient, both for better health outcomes of the recipient and 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 as well as clinicians who investigate suspected infectious transmissions.

## **INVESTIGATING HARM TO RECIPIENTS - NON INFECTIOUS BLOOD TRANSFUSION REACTIONS**

There are many different types of transfusion reactions, which can be subdivided in several ways, according to their occurrence, pathogenesis and/or their symptomatology. This link describes the various reactions related to blood components and categorized as either acute or delayed based on when symptoms occur after transfusion.

## **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 MPHO. Although the risk of malignancy transmission has been examined and reported since the first years of clinical transplantation, the frequency of donors with malignant tumours and the risk of transmission of malignant diseases from donors to recipients are unclear. This link provides guidance to professionals who need to investigate suspected transmissions.

## **INVESTIGATING HARM TO RECIPIENTS - GENETIC TRANSMISSIONS, HPC**

The establishment of haematopoietic progenitor 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 suspected 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 could potentially affect the recipient (offspring) with any genetic disease. This link is useful for those investigating suspected? genetic transmissions in the field of assisted reproduction.



## **CHARACTERISTICS, HANDLING AND CLINICAL ERRORS**

Each blood component, cell, tissue or organ allograft intended for transfusion, transplantation, implantation, infusion or transfer has specific quality attributes and characteristics determined by anatomy and usual function. Handling and processing activities that support the maintenance of desired efficacy or utility of the MPHO can affect clinical outcome. When a gap exists or a step or process fails, a risk of harm or actual harm can occur. 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, organs and blood components, during any step from procurement or collection, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue/blood establishment or the manufacturing facility receiving, processing or storing blood, tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying these 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 blood components, tissues/cells and 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 MPHO 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 with the methods of surveillance.

In practice a number of terms have been developed to describe V&S for specific types of products:

**Pharmacovigilance:** is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU. The WHO Programme for International Drug Monitoring came into effect in 1968, in response to the thalidomide disaster in the 1960s.

**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).

Haemovigilance systems have been implemented in many 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 collation 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 an 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 (3).

Since 1995, the Committee of the Ministers of European Council has endorsed the Recommendation No. R (95) 14 of the Committee of Ministers to member states on the protection of health of donors and recipients in the area of blood transfusion. Its Article 29 says “The patient's need for a transfusion should be assessed by pre-transfusion testing; post-transfusion tests are recommended in order to monitor and keep on record the effectiveness of the transfusion on the recipient. Haemovigilance systems should be implemented in order to detect possible adverse effects on the recipient”. Then the “Recommendation No. R (2002) 11 of the Committee of Ministers to member states on the hospital's and clinician's role in the optimal use of blood and blood products” suggests that a policy for clinical transfusion medicine should be developed at the country level. One of the key elements is the local application of existing guidelines for clinical use of blood and blood products, including implementing comprehensive quality procedures (covering pre-transfusion, transfusion and clinical surveillance), haemovigilance at all stages of blood transfusion. WHO has published an aide-memoire and a guidance document on the development of a national haemovigilance system.

Biovigilance: was incorporated into French law on 21 December 2003 with the publication of Decree n° 2003-1206. Its scope ranged from human organs, human tissues and cells to human cellular therapy preparations and ancillary products. It was then first incorporated into European legislation in the tissue and cell European Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 and in Directive 2010/53/EU of the European Parliament and of the council of 7 July 2010 for organs. In the United States, biovigilance has been extended to incorporate all MPOH including blood, tissues, cornea, cells, gametes and organs.

The **basic elements** of MPHO vigilance (haemovigilance and biovigilance) include:

- Identification and reporting of adverse occurrences involving harm to donors, recipients or children born following assisted reproduction with donated gametes or embryos
- Monitoring and reporting of adverse occurrences that imply a risk of harm
- Product quality assurance (including processing controls and error management)
- Emerging threat assessment using epidemiologic and laboratory data (e.g., TTI bioinformatics, repositories).

The WHO guideline on Adverse Events and Reactions 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 (4).

The guideline outlined the following **core concepts on MPHO vigilance**:

- 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. 2011 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 EU-funded SOHO V&S project (Vigilance and Surveillance of substances of Human Origin) 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 transfusion and 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 (5), (6). Regularly scandals involving the trafficking of human beings 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 (7). 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 immune-suppressed 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. An organization was discovered to be 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 in 2004**, 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 in 2006 (8).

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 in 2007** addressed perspectives on the ethics of human cell and tissue transplantation and arrived at a number of consensuses in 2007 (9). Consensus included (Table 1):

<b>Respect for persons</b>	<b>Non-maleficance</b>	<b>Justice</b>
<ul style="list-style-type: none"> <li>• Informed and voluntary consent for living Human Cells (HC)/Human Tissues (HT) removal</li> <li>• Explicit consent during lifetime or presumed consent for deceased HC/HT removal</li> <li>• Option to veto future uses of donated HC/HT for research and education (and/or cosmetic applications and/or international circulation)</li> <li>• Stewardship for donated HC/HT</li> <li>• Informed and voluntary consent for HC/HT <b>transplantation</b></li> </ul>	<ul style="list-style-type: none"> <li>• Minimal quality and safety standards for HC/HT procurement, processing and transplantation</li> <li>• Long-term follow-up of living donors and transplant recipients</li> </ul>	<ul style="list-style-type: none"> <li>• Fair criteria for donor identification and selection</li> <li>• Unpaid donation to reduce inequities in donation</li> <li>• Fair HC/HT distribution</li> <li>• General priority of local and/or national self-sufficiency to reduce global inequities in donation of and access to HC/HT</li> </ul>

Donors of blood, 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 transfusion and 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 MPH0.

With government support and oversight, the paradigm underwrites:

- Equity in donation from possible donors and equity in allocation
- Education about donation but also about prevention of conditions that create a need for MPHO
- 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.

In accordance with WHO ([http://www.who.int/bloodsafety/voluntary\\_donation/en/](http://www.who.int/bloodsafety/voluntary_donation/en/)) blood transfusion safety is based on voluntary, non-remunerated blood donors from low-risk populations. In the key global fact and figures in 2011 (Fact sheet number 279, in 62 countries, national blood supplies are based on 100% or almost 100% (more than 99.9%) voluntary unpaid blood donations. Forty countries collect less than 25% of their blood supplies from voluntary unpaid blood donors. The WHO goal is for all countries to obtain all blood supplies from voluntary unpaid donors by 2020 in accordance with World Health Assembly resolution 28.72, which was adopted in 1975.



### 5.1 THE DEVELOPMENT OF GLOBAL GOVERNANCE OF MPHOS

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. There are two main types of surveillance approaches, one utilising 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 (10; 11) 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.

**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.

**In 2009, the World Health Organization (WHO)** updated its Guiding Principles for the transplantation of organs, tissues and cells. 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 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.

**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, organisation 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 MPHOS, and to facilitate access by Member States to appropriate information including severe adverse occurrences. Recognizing the need for the surveillance of such occurrences, **the World Health Assembly (WHA)** (12) 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, tissues and organs, including data on severe adverse events and reactions'.

A substance of Human Origin 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:

1. The European Commission, which plays inter alia a coordinating and supportive role and maintains the rapid alert system for blood, tissues and cells;
2. The European Centre for Disease Control (ECDC), which monitors health threats;
3. National Competent Authorities that ensure that the requirements of the EU Directives are followed;
4. 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, Directive 2006/86/EC (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.

For blood components, Directive 2005/61/EC requires Member States to ensure that those facilities where transfusion occurs have procedures in place to retain the record of transfusions and to notify blood establishments without delay of any serious adverse reactions and events observed in recipients during or after transfusion which may be attributable to the quality or safety of blood and blood components. Member States shall also submit a complete report on serious adverse reactions and events to the Competent Authority on an annual basis.

## **5.2 A SAFEGUARD, A DAMAGE LIMITATION SYSTEM**

### *5.2.1 EARLY NOTIFICATION, TIMELY REACTION*

The human endeavour can be predicted to fail but harm from failure 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 Virus (XMRV), 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 MPHO. They may occur in the donation of the 'product' or 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. For example, aviation can be used as a model since it, like transplantation, is inherently dangerous. For example, one could use 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 organisations, 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 blood, 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.



### 6.1 GOVERNMENTS

In **France**, the field of biovigilance 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 biovigilance 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 legislation addressed specifically to ensuring the quality and safety of human tissues, cells and blood. The primary Directive for tissue and cells (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. Likewise the Directive 2002/98/EC Of The European Parliament And Of The Council Of 27 January 2003 sets the standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and the implementing Directives 2005/61/EC and 2005/62/EC set out respectively the requirements for traceability and notification of serious adverse reactions and events and Community standards and specifications relating to a quality system for blood establishments. The European Union has also legislation addressed specially for quality and safety of organ donation and transplantation in the Directive (2010/53/UE). **The major challenge lies in the implementation, maintenance and updating of the legislative requirements.**

Significant progress was made during the **EUSTITE 2006-2009** (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 subsequent EU co-funded project entitled Vigilance and Surveillance of Substances of Human Origin 2010-2013 (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 2009-2011** - the European Framework for the Evaluation of Organ Transplants – was a project co-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:

1. The European Commission, which plays inter alia a coordinating and supportive role and hosts rapid alert systems for blood, tissues and cells, the European Centre for Disease Control (ECDC), which monitors health threats.
2. National Competent Authorities that ensure that the requirements of the EU Directives are followed including annual reporting of their adverse reports to the EC.
3. Local blood banks and tissue and cell establishments that are in the forefront when there are adverse occurrences. Blood banks and Tissue Establishments must report adverse occurrences to the national competent authorities 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 (HHS). 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 in vitro diagnostic devices (IVD), 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 Human Cell & Tissue Products (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 blood, 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.

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 have, 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 (Table 2):

<b>SEAR - serious events and adverse effects registry</b>	<b>SPEAR – serious product events and adverse effects registry</b>
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 took into consideration being given a focus on V&S for tissue allograft types that pose the most risk. The document was disseminated to all stakeholders in order to optimize recognition, reporting and investigation.

In the field of blood, the ISBT working party on haemovigilance, in collaboration with the International Haemovigilance Network (IHN) (previously the European Haemovigilance Network), has pursued the development of definitions for non-infectious transfusion reactions and complications of blood donation since 2004. See chapter 14. Current definitions for blood donation complications (2014) and for non-infectious transfusion reactions (2011) are available on the websites of the IHN and ISBT. In addition, definitions (tools) are available for classifying severity of adverse reactions and their imputability, i.e. the likelihood with which they can be ascribed to the transfusion. These are aligned with the imputability levels and severity criteria, which are current in clinical trials as well as (international) guidelines and legislation, also in the domain of tissue, cell and organ vigilance. Some groups, including the European Commission, in drafting guidance for the mandatory reporting of serious adverse reactions and serious adverse events associated with transfusion of blood or blood components, refer to these definitions (13).



### 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

- Sao → Serious adverse occurrence reporting must be required.
- Rapid Alert → Rapid alert systems, with 24/7/365 availability, are essential to facilitate rapid action when a risk has been detected that might have wide implications (e.g. other recipients from the same donor or the same processing batch or a widely relevant risk detected) and should be developed
- Standardised reporting → Standardised 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 reporting
  - There should be feedback regarding the information collected and how it has been used to influence patient safety and changes to practice
- Cooperation → Cooperation among governments/competent authorities, 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 organisation, 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 → Cooperation among governments/competent authorities, 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 organisation, or formal system, a coordinating body, or a registry which is responsible for the collection of information as it occurs (for evaluation by specialists)
- Traceability → Traceability requirements must be put in place for 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, wherever possible.
- Inspections and training → Cooperation among governments/competent authorities, 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 organisation, or formal system, a coordinating body, or a registry which is responsible for the collection of information as it occurs (for evaluation by specialists)
- Compliance → 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.
- Global V&S → 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. The use of MPHO in therapy 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, with the expectation that the MPHO will perform or function in the recipient as it did in the donor. The focus, therefore, has been on validating processing and storage to demonstrate that they have not harmed the required national properties of the MPHO. Outcome data is often published but 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 vigilance as mentioned in section 3, should include: adverse occurrence monitoring (for recipients and donors), product quality assurance (including processing controls and error management), and emerging threat assessment using epidemiologic and laboratory data (bioinformatics, repositories).

There are two main types of surveillance approaches to these issues:

Adverse occurrence speed of reporting		Surveillance	
Hot	Cold	Active	Reactive
Rapid reporting, which must be done if other recipients may be at risk. Often with a preliminary report made before investigations have been completed	Reporting without specific time frame, generally when investigations are well under way or have been concluded	Feedback received on every MPHO. Actively searching for potential adverse reactions or events	Report submitted if an adverse reaction or an adverse event is noted Also referred to as passive surveillance or spontaneous reports

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 MPHO

A single donor may contribute numerous blood products and types of MPHO. Particularly after death, the altruistic act of 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 tissues crosses many medical specialties and can involve many recipients.

### 7.3.2 FOR MPHO

The different communities working with MPHO donation and supply function independently yet communication between them is often critical for effective vigilance. Any ineffective communication can result in an inability to track organs and tissues from a common donor and recognize adverse occurrences 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 relevant establishments can assist in avoiding such serious outcomes. Integration with haemovigilance systems is also important in closing gaps in communication.





### 8.1 QUALITY MANAGEMENT

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

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"(14). 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 vigilance systems, including the use of such systems for quality improvement, one must consider what types of occurrences 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 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 adverse occurrences 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 occurrences of interest may be more comprehensive. Capture of more common events may also allow benchmarking through comparison of 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 occurrences 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 transfusion, transplantation and assisted reproduction 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 (95). 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 MPH0 recipient (Notify Library's adverse occurrence type description in brackets) should be seen as triggers for a notification. It should be noted that the list is not exhaustive.

- Unexpected\* primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion) (Harm to a Recipient - Infection);
- 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 (Harm to a Recipient - Infection);
- Hypersensitivity reactions, including allergy, anaphylactic reactions or anaphylaxis (Harm to a Recipient - Immunological complications - Allergic Reaction);
- Malignant disease possibly transferred by the MPH0 (whatever the origin, donor or process) (Harm to a Recipient - Malignancy);
- Unexpectedly delayed or absent engraftment, graft failure (including mechanical failure) (Harm to a Recipient - Miscellaneous complications - Graft failure);
- Toxic effects from MPH0 or associated materials (Harm to a Recipient - Miscellaneous complications - Toxicity);
- Unexpected immunological reactions due to mismatch, e.g. ABO, HLA Rh, etc. (Harm to a Recipient - Immunological complications - Detrimental immunization)
- Aborted procedures involving unnecessary exposure to risk e.g. wrong MPH0 supplied, discovered after patient is anaesthetised and the surgical procedure has begun (Harm to a Recipient - Miscellaneous complications - Undue exposure to risk-intervention)
- Suspected transmission of genetic disease (Harm to a Foetus or Offspring - Genetic)
- Suspected transmission of other (non-infectious) illness (Harm to a Recipient - Non infectious, Non malignant transmissions)

\* In certain circumstances, clinicians may knowingly transplant an MPH0 from a seropositive donor (e.g. bone marrow transplantation from a CMV seropositive donor to a CMV seronegative recipient).

### 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 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 behavioural risks, such as injectable drug use) as well as physical examination by the team during collection/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 donation 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 blood, bone marrow, tissue, gametes or organs, the medico-social history is obtained from the donors 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 seroprevalence 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 (15; 16).

## 8.7 DEFINITIONS

A major contribution of the Notify project was the participation of a diverse group of professionals who come from different disciplines and who ordinarily do not communicate with one another. Transplant surgeons, orthopaedists, ophthalmologists, transfusion doctors and haematologists, infectious disease specialists, pathologists, nurses, embryologists and gynaecologists, eye bankers, blood and tissue bankers and regulators 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 and blood were considered appropriate and useful for international application, although they were mapped to less technical language to improve accessibility by the general public:

1. Directive 2004/23 defines a Severe Adverse Event (SAE)\* in the context of tissues or cells as 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. Similarly, Directive 2002/98/CE defines Severe Adverse Event (SAE) for blood components as any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity. In the Notify project these are referred to as cases of 'Risk of Harm'.
2. For tissues and cells in the EU a Severe Adverse Reaction (SAR) is 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 clinical application that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity. Similarly, Directive 2002/98/CE defines Severe Adverse Reactions (SAR) for blood components as an unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity. In the Notify project, these are referred to as cases of 'Harm to Donor', 'Harm to Recipient' or 'Harm to Fetus/Offspring'.

\* Note however that this use of the term Serious Adverse Event is different from that in the context of pharmacovigilance, where (serious) adverse event refers to harm to the patient, which might or might not have been caused by the drug concerned.

3. Imputability of harm should be assessed, i.e. the extent to which the harm detected is likely to have been caused by the MPhO donation or clinical application. The assessment should be based on available information and graded as: proven, probable, possible, and unlikely or excluded. The following Table 3 describes the possible outcomes of an imputability investigation. 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 if the evidence is conclusive beyond reasonable doubt for attributing the adverse occurrence to the quality/safety of tissues/cells/ blood components (for recipients) or to the donation process (for donors). For example if there is clear evidence of the same disease in the multi-organ 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 cause for the adverse occurrence. 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 that that an adverse occurrence was caused by the donation process or by the MPhO applied. 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 tests are negative).

Imputability should be graded as **possible** for all situations where a) data suggest a possible transmission but are insufficient to fulfil criteria for confirmed transmission (proven and/or probable) or b) a transmission cannot be formally excluded. In the case of infectious transmissions, 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 utilised. If some but not all recipients had an intervention but disease transmission was recognized in even one recipient, this category should not be used.

IMPUTABILITY GRADE	CRITERIA FOR INFECTIOUS AND MALIGNANT TRANSMISSIONS ADAPTED FROM DTAC (1)	ADAPTED FROM EUSTITE-SOHO V&S (2) AND PROPOSED STANDARD DEFINITIONS FOR SURVEILLANCE OF NON INFECTIOUS ADVERSE TRANSFUSION REACTIONS (3)	ADAPTED FROM EUSTITE - SOHO V&S IN ASSISTED REPRODUCTIVE TECHNOLOGIES (2)
Not Assessable	Insufficient data for Imputability assessment	Insufficient data for imputability assessment	Insufficient data for imputability assessment
Excluded	<p><b>Suspected transmission and fulfilment of at least one of the following conditions:</b></p> <ul style="list-style-type: none"> <li>- Clear evidence of an alternative cause;</li> <li>- The appropriate diagnostic tests performed have failed to document infection by the same pathogen in any recipient from the same donor;</li> <li>- Laboratory evidence that the recipient was infected with the same pathogen or had a tumour before the application of organs, tissues or cells.</li> </ul>	Conclusive evidence beyond reasonable doubt that the adverse occurrence can be attributed to causes other than the transfusion of blood components or transplantation of tissues/cells	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the ART process
Possible	<p><b>Suspected transmission and:</b></p> <ul style="list-style-type: none"> <li>- Laboratory evidence of the pathogen or tumour in a single recipient or</li> <li>- Data suggest a transmission but are insufficient to confirm it.</li> </ul>	The evidence is indeterminate for attributing the adverse occurrence either to the quality/safety of tissues/cells/blood components (for recipients), to the donation process (for donors), or to alternative causes	The evidence is in favour of attributing to the ART process
Likely/Probable	<p><b>The following two conditions are met:</b></p> <ul style="list-style-type: none"> <li>- Suspected transmission and</li> <li>- Laboratory evidence of the pathogen or the tumour in a recipient.</li> </ul> <p><b>And it meets at least one of the following conditions:</b></p> <ul style="list-style-type: none"> <li>- Suspected transmission and</li> <li>- Laboratory evidence of the pathogen or the tumour in a recipient.</li> <li>- Laboratory evidence of the same pathogen or tumour in other recipients;</li> <li>- Laboratory evidence of the same pathogen or tumour in the donor;</li> </ul> <p>If there is pre-transplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplantation.</p>	The evidence is indeterminate for attributing the adverse occurrence either to the quality/safety of tissues/cells/blood components (for recipients), to the donation process (for donors), or to alternative causes	The evidence is in favour of attributing to the ART process
Definite/Certain	<b>All the following conditions are met:</b>	The evidence is conclusive beyond	Conclusive evidence beyond

IMPUTABILITY GRADE	CRITERIA FOR INFECTIOUS AND MALIGNANT TRANSMISSIONS ADAPTED FROM DTAC (1)	ADAPTED FROM EUSTITE-SOHO V&S (2) AND PROPOSED STANDARD DEFINITIONS FOR SURVEILLANCE OF NON INFECTIOUS ADVERSE TRANSFUSION REACTIONS (3)	ADAPTED FROM EUSTITE - SOHO V&S IN ASSISTED REPRODUCTIVE TECHNOLOGIES (2)
Proven	<ul style="list-style-type: none"> <li>- Suspected transmission;</li> <li>- Laboratory evidence of the pathogen or the tumour in a recipient;</li> <li>- Laboratory evidence of the same pathogen or tumour in other recipients (if multiple recipients);</li> <li>- Laboratory evidence of the same pathogen or tumour in the donor;</li> <li>- If there is a pre-transplant laboratory evidence, it should be noted that the same recipient was negative for the pathogen before transplantation</li> </ul>	reasonable doubt for attributing the adverse occurrence to the quality/safety of tissues/cells/ blood components (for recipients) or to the donation process (for donors)	reasonable doubt for attributing to the ART process

**Table 3. Scale describing the possible outcomes of an imputability investigation in the case of harm to a recipient, a donor or a fetus/offspring.**

(1) Uniform 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

(2) SOHO 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>

(3) Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions, incorporating correction to TRALI definition (as adopted June 2013). ISBT Working Party on Haemovigilance [http://www.notifylibrary.org/sites/default/files/Proposed%20Definitions%20for%20surveillance%20of%20non%20infectious%20adverse%20transfusion%20reactions%202011-2013\\_0.pdf](http://www.notifylibrary.org/sites/default/files/Proposed%20Definitions%20for%20surveillance%20of%20non%20infectious%20adverse%20transfusion%20reactions%202011-2013_0.pdf)



The investigation of an unintended occurrence has resulted in a risk of harm essentially comprises a 'root cause analysis' (RCA) process. RCA is a structured approach to identify the factors that resulted in the nature, the magnitude, the location, and the timing of a harmful, or potentially harmful, occurrence. 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.
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 Table 4 and 5 below. 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).

**Table 4.** "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'
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 yearst
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 5.** "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 truts?	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.

## 9.2 CAUSE AND EFFECT ANALYSIS

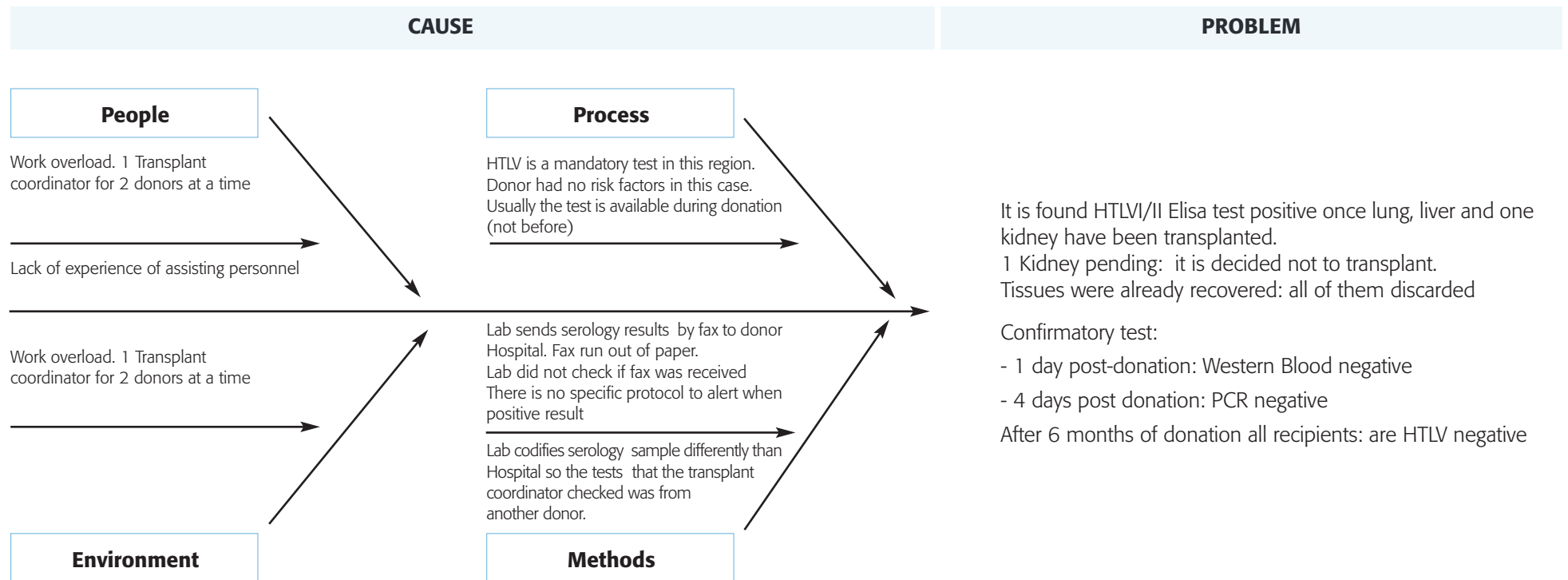
Also known as the Ishikawa Diagram or the Fishbone Diagram for Process Failure, this method encourages the investigation to follow a structured process of identifying contributing factors and risks. The technique uses a diagram-based approach for thinking through all of the possible causes of a problem.

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

The method permits to analyse the process and decide on further actions to test the different potential causes: (data analysis? survey? interview? Research?)

FIGURE 2. EXAMPLE OF A PROBLEM: HTLV/II TEST HAS A POSITIVE RESULT BUT IT WAS NOT ALERTED. THE TRANSPLANT COORDINATOR FINDS OUT ABOUT THE REACTIVE TEST ONCE LUNG, LIVER AND ONE KIDNEY HAVE BEEN TRANSPLANTED. EXAMPLE OF HOW TO USE ISHIKAWA DIAGRAM







Remarkable developments in the scientific, technical and medical fields have led to the increased therapeutic use of human organs, tissues and cells. The use of these substances of human origin (MPHO) in clinical applications 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 many MPHO, particularly for organs far outstrips the supply. While the demand for blood components is largely met in developed countries, many developing countries still lack an adequate supply for patients in need of transfusion. In relation to tissues and cells for transplantation and assisted reproduction, the shortages are not as acute and generally patient needs can be met in developed countries, with the possible exception of highly matched hematopoietic stem cells.

In spite of significant benefits derived from therapies using 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 adverse occurrences 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) 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' (SOHO 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.

### **10.1 NOTIFY PROJECT'S SCOPES**

The scope of the project started including 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 SOHO V&S project for an international meeting on vigilance reporting and investigation. The meeting explored the work already carried out online 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 (17)
- The SOHO 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](http://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 is 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 blood, 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.

Although the project started with the scope of organs, tissues and cells, it was broadened in 2013 to also include blood, incorporating the experience of vigilance of that field in the library.

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 transfusion, transplantation and assisted reproduction.

## **10.2 HAEMOVIGILANCE (HV), ARCHETYPE OF V&S FOR MPHO**

The scope of the project started including 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.

## **BLOOD HAS SHOWN THE WAY FOR THE DEVELOPMENT OF V&S FOR MPHO**

Blood products and blood transfusion lead MPHO by the time span of experience of more than a century of blood transfusion as well as the scope of activities. The WHO global database on blood safety estimated that 108 million units of blood were collected for transfusion in 2012.

## **BLOOD TRANSFUSION LINKS TWO CULTURES: A CULTURE OF PRODUCTION AND A CLINICAL CULTURE**

The industrial scale of blood donation and of processing for clinical application led to the implementation of quality systems progressively from the beginning of the 70's. Institutions with multiple establishments and quality management systems shared information on non-conformity, post marketing surveillance and other adverse occurrences.

## **BLOOD TRANSFUSION ILLUSTRATED RISKS FOR PATIENTS AND DONORS**

The human donor defines MPHO. The outcomes of blood donation for transfusion are crucial to the good functioning of the blood service. Clinical activities in blood transfusion involve recipients but also donors.

Donor safety is crucial to the credibility of the blood service. Risks must be minimal for donors, nevertheless rare complications do occur even with the most innocuous forms of donation. Blood donors are volunteers who must understand that their donation is respected and will be used for the best outcomes for the recipient. Therefore a thorough V&S system to optimize practices contributes to building up trust in the MPHO service as a community resource and motivation to donate.

## **BLOOD TRANSFUSION HAS SHOWN THE VALUE OF DISCOVERY OF ADVERSE OCCURRENCES THAT DO NOT LEAD TO HARM**

Events (or mistakes) that occur in the processes that accompany blood transfusion can sometimes be identified prior to the transfusion and patient harm. These can be used as valuable warnings and learning lessons for the transfusion service. An example of this type of event, sometimes called a “near miss” is an ABO mismatch that is spotted at the bedside when preparing the patient for transfusion.

## **OVER THE COURSE OF TIME, BLOOD TRANSFUSION HAS REVEALED THE VAST RANGE OF TYPES OF ADVERSE OCCURRENCES**

Transfusion transmitted infections are a good example of these types of events. Many of the types of adverse occurrences that occur in the process of collecting and transfusing blood and blood components are also observed with other MPO. Few are specific only to blood. Whether there is actual harm or risk of harm, the same root cause analysis and risk management should be undertaken.

## **BLOOD TRANSFUSION HAS PIONEERED INTERFACES WITH OTHER SURVEILLANCE SYSTEMS**

- Pharmacovigilance through plasma derived medicinal products and with drugs used by donors e.g.: transfusion transmitted infections (TTIs), Heparin.
- Device vigilance when faulty equipment or disposables are the cause of danger e.g.: blood bags, test kits, IT systems.
- Clinical governance and its risk management component: wrong unit, transfusion associated circulatory overload (TACO).

Blood provides the example for all MPO of the need to bring together information from various vigilance systems to generate a true comprehensive map of associated risks. The best possible information on risk is necessary for donors and recipients and their clinicians, as well as for all actors in the chain who must collaborate to ensure safety and prevention of future adverse events. This may be an industrial partner who will respond to blood transfusion establishments and clinical settings. Blood demonstrates that vigilance systems must have overlap and redundancy with good inter-organisational communication patterns for success.

In the last three decades good transfusion practices evolved into mandates that prescriptions, practices and outcomes are submitted to a systematic review. The assessment of outcomes developed as part of the transfusion procedure has evolved to being a required element of blood transfusion.

## **HV HAS DEMONSTRATED ITS EFFICACY BY IMPROVING BLOOD TRANSFUSION PRACTICES**

National data consolidation, review and analysis of adverse occurrences has led to recognition, quantification with denominator, prioritization and successful management of risks that were previously unknown or underestimated, including e.g. bacterial infections, transfusion-related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO).

## **THERE IS DIVERSITY IN NATIONAL HV SYSTEMS BUT THEY RETAIN COMMON OBJECTIVES OF PATIENT SAFETY AND QUALITY IMPROVEMENT**

National HV systems were established with different principles and structures in various countries. For instance reporting may be voluntary or mandatory, the responsible institution may be the regulatory authorities or it may be outsourced to a specific body or a relevant scientific and professional society. Likewise the scope of HV can be different from one country to another. It may be focused on any actual harm to patients transfused, only on transmission of infectious diseases, or on serious or lethal events. Adverse occurrence without harm to individuals (“near miss” or risk of harm) may not be required reporting in some HV systems. Conversely some HV systems require the reporting of any incident beyond deviations addressed by a quality management system.

However, all HV systems have contributed to developing an on-going dialogue between the stakeholders in transfusion safety quality and availability, namely operators, clinicians and appropriate health authorities where regulators and policy makers can be recognized. They share the responsibility of meeting patients’ needs and protecting donors as well as society, where anyone has the potential to need file-saving blood components. HV has evolved as a necessary tool to achieve this goal. Progressively with the recognition of the value of national HV systems, a global consensus took shape on what should be an ideal HV system. It is summarized by the WHO definition:

**Definition:** Haemovigilance is a set of surveillance procedures covering the entire transfusion chain, from the donation and processing of blood and its components, to their provision and transfusion to patients and their follow-up. Haemovigilance includes the monitoring, reporting, investigation and analysis of adverse events related to the donation, processing and transfusion of blood, as well as the development and implementation of recommendations to prevent their occurrence or recurrence.

HV system: a recognised factor of progress for transfusion services in low and middle income countries

In developing countries, rather than seeking to mimic the HV systems of developed countries, the priority is to correct deficiencies that are already apparent and obvious with whatever resources are available. The first step is often to correct fragmentation and foster an actual national service with an effective oversight where HV will show its value.

HV systems adapted to the local reality and introduced in a stepwise manner to yield reliable and accurate data are now recognized vectors of progress. The HV system delineates roles and responsibilities and enhances communication between stakeholders.

Blood transfusion an example of budding global dynamics for HV

Sharing of standardized information is key to HV. In the infancy of national HV systems professionals recognized the need for regional and global standards and communication. The ISBT has a specific working party and the IHN resulted from the global expansion of the EHN. Recent WHO consultations have projected global resources for HV that would provide a national system with reference information and experience.

HV has shown the way for the development of V&S services for other MPHOs. The responsibility for the donor as well as for the recipient common to MPHOs and the community of adverse occurrences led to develop the Notify Project where HV is a key source of inspiration and serves as a model. The description for what should be included in a HV system is available elsewhere (18).



A joint initiative co-sponsored by WHO, CNT and the SOHO 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) was launched to host, maintain and update the library of documented occurrences that has been developed here ([www.notifylibrary.org](http://www.notifylibrary.org)).

An international Steering Committee, under WHO and CNT, with regulatory and professional representatives from the fields of transfusion, transplantation and assisted reproduction, 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 was built to cover occurrences related to the clinical application of different MPHO: organs, blood, cells, tissues, reproductive tissues and derived medicinal products (Figure 3). Each of these generated multiple occurrences relating to the specific system and then could be divided by type (Figure 4).

FIGURE 3. NOTIFY LIBRARY - MPHO TYPE TAXONOMY (EXTRACT). THE COMPREHENSIVE TABLE IS AVAILABLE IN ANNEX 1.

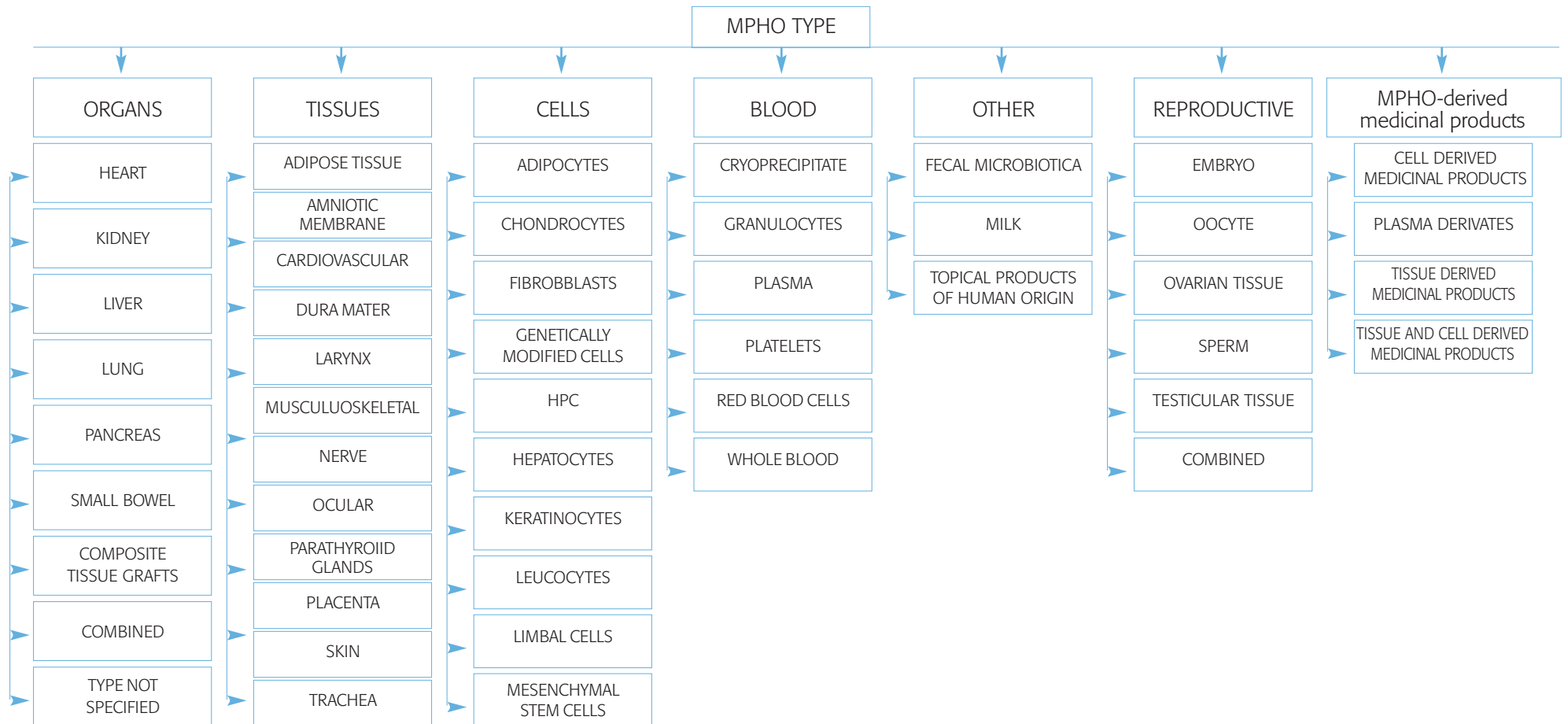
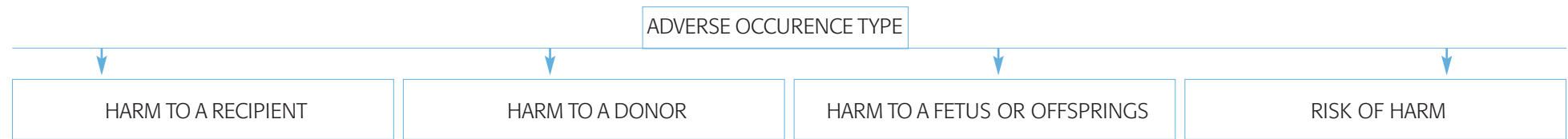


FIGURE 4. NOTIFY LIBRARY - ADVERSE OCCURRENCE TYPE TAXONOMY (EXTRACT). THE COMPREHENSIVE TABLE IS AVAILABLE IN ANNEX 2.



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

- Loss (highly matched or autologous material, suitable organs, large quantity of unmatched MPHO)
- Mix-up (gamete or embryo mix-ups, incorrect MPHO applied)
- Unsuitable MPHO released for clinical use
- Wrong blood in tube - product not transfused
- 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 professionals working on donor recruitment and selection 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, in the case of organ donation 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, dissimilarities between blood safety systems and what might be implemented in cell and organ transplantation (or Biovigilance systems) should be recognized. There is a difference in the overall volume of activity – blood donations occur in the millions in many countries while organ donations are in the thousands in only a very few countries and haematopoetic stem cell donations are even more rare. Secondly, there is the availability of donors - blood donors can be plentiful while organ donors are very scarce, and haematopoetic 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 would need to be aggregated in order to be able to detect even the reasonably frequent events (1:1,000 or 1:100,000)

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 (events) and denominator (numbers of procedures) 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 calculation.



### 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, Aphaeresis or HPC(A)). Not included in these numbers are an estimated 200,000 new-born infants whose umbilical cord blood (UCB) is collected and evaluated for potential storage in public cord blood banks and autologous HPC collections for medical therapies.

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 aphaeresis (19). As a result:

- Common reactions include headache, bone pain, splenomegaly and thrombocytopenia.
- Occasionally serious reactions such as arrhythmias, splenic rupture and vascular problems can occur.

The **collection** process itself involves **apheresis** of the mononuclear cell components, which can have its own complications (acute, immediate or chronic or delayed) including:

- Central line thrombosis, citrate toxicity, hypotension, infection, mild leucopenia and thrombocytopenia (unassociated with clinical complaints).
- More severe reactions have also been reported including pulmonary embolism, subdural hematoma, sepsis

**HPC(M) products** are almost always collected in surgical suites with donors having received general or regional (epidural or spinal) anaesthesia. Red cell transfusion with autologous is common (transfusion with allogeneic products is rare and classed an adverse event). 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 (acute or delayed) include

- Bone and back pain, anemia, fever, headache and hypotension.
- More severe reactions (including death which is very rare) have also very rarely been reported. These include stroke, air embolism, chest pain, endocarditis, fat embolism, iliac fracture and

**Allogeneic HPC(M)** 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 (20). 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-tumour 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 adverse reactions among TC donors. The most common procedure for TC donation is unstimulated leukapheresis that is similar to aphaeresis 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 harm can occur to donors and short-term mild side effects can be quite common. Cases of life threatening or fatal harm have been reported although they are rare. 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 than the general public.



### 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 and may not need to be reported. Life-threatening or fatal occurrences in the context of common donation-associated incidents should always be reported.
3. A mechanism for 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

Tissue transplantations from living donors may 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 associated 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. 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 mechanical fracture can occur.

Nerve injuries are usually associated with sensory symptoms such as pain, anaesthesia or paraesthesia. Motor sequelae 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

## 12.3 LIVING ORGAN DONOR REACTIONS

Transplantation using organs from living donors remains a significant source of transplantable organs. In the US, the number of live donated kidneys has been relatively static. In many parts of the world, live donation is the only reliable source of kidneys for potential recipients. 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. The value to the recipient of a live donor kidney is statistically longer graft function as compared to a deceased donor organ.

However, for living donation to progress successfully and possibly to 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 perioperative events in the donor and also with later complications that may be mis- or under diagnosed and, ultimately, be inadequately treated with health consequences to the donors (21).

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 suggested that if people are appropriately stratified, then there is a small increase in the risk for development of ESRD in the donor population (22).

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 under pressure to donate but don't always fully understand the risks involved, thus efforts should be made to develop standardized informed consents (23; 24).

### Recommendations:

1. Registries for living organs 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. Identification of (potential) donor co-morbidities, which would add excessive risk, should be undertaken.
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. The potential donor should be given sufficient information to make a good decision to minimize donor risk and maximize benefit for the intended recipient.
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 donor (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 healthcare in the new location should be provided)
8. Identification of adverse events should be thoroughly documented. If severe, they should be reported in timely fashion 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 analyse any problems that may have 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.

## 12.4 BLOOD DONORS

The majority of blood donors (BD) experience few side effects from donation; however, for a minority of donors, donation may lead to injury or long-term health problems. Adverse donor effects also have important negative consequences for the blood collection centre. Even mild reactions may decrease the likelihood of donor return, and severe reactions may lead to long-term disability and permanent donor deferral. Finally, reactions occurring during collection may lead to loss of the blood component due to incomplete collection resulting in an inadequate component volume.

BD vigilance is the systematic monitoring of adverse occurrences in BD care with a view to improving quality and safety for BD. Complications related to blood donation are adverse occurrences with a temporal relation to blood donation. These may be grouped into two categories: immediate or acute (reactions occurring at the time of donation) or delayed (occurring after donation); either may lead to long-term adverse effects. Acute complications may be related to the venipuncture itself, such as bruising or nerve injury, or may be systemic reactions such as dizziness, light-headedness, or fainting. For whole blood donation, long-term adverse effects consist in consequences associated with injury, as well as iron loss associated with donation, with reduced iron stores, iron deficient haematopoiesis, and eventually possible iron deficiency anaemia.

In order to be able to compare data between countries and Blood Transfusion Establishment (BTE), it is important to use standardized definitions. Great work has been achieved since 2008 by the IHN, in collaboration with the ISBT working party on Haemovigilance and the Donor Hemovigilance Committee of the AABB, to elaborate a standard list of definitions for the immediate complications during the donation or within 24 hours of the donation. The following are definitions as reported in the last revision (December 2014) (25).

## 12.5 IMMEDIATE (within 24 hours of the donation) BLOOD DONORS COMPLICATIONS

### 12.5.1 COMPLICATIONS WITH PREDOMINANTLY LOCAL SYMPTOMS

Are directly caused by the insertion of the needle. Some of these are characterized by the presence of blood outside vessels, whereas others are mainly characterized by pain;

- Complications mainly characterized by the presence of blood outside the vessels:

**Haematoma** (bruise): an accumulation of blood in the tissues outside the vessels. The symptoms are caused by blood flowing out of damaged vessels and accumulating in the soft tissues. For apheresis procedures, haematomas may also be caused by infiltration of the soft tissues by red cells during the return phase of the procedure. Large haematomas, particularly those in deeper layers of the forearm, may put pressure on surrounding tissues and nerves contributing to other complications such as nerve irritation and injury and more rarely compartment syndrome. Typical signs and symptoms include bruising, discolouration, swelling and local pain. Accumulation of blood in deeper tissues may result in more serious pain and pressure syndromes listed below.

**Arterial puncture:** a puncture of the brachial artery or of one of its branches by the needle used for bleeding the donor. Because of the rapid blood flow under high pressure, the risk of a large haematoma with resulting severe pain is increased. Signs and symptoms include a lighter/brighter red colour compared with venous blood, pulsation of the needle and tubing, and rapid filling of the blood bag. Arterial puncture may lead to more serious sequelae listed below (Arterio-venous fistula, pseudoaneurism, and compartment syndrome).

- Complications mainly characterized by pain:

**Nerve injury/irritation:** Nerve injury results from a direct hit to the nerve by the needle at insertion or withdrawal; nerve irritation usually results from pressure on a nerve due to a haematoma or inflammation of the soft tissues. Immediate radiating, often 'electrical' sharp shooting pain moving away from the venipuncture site are associated with direct nerve injury while, paraesthesias such as tingling, burning sensations in the hand, wrist or shoulder area distant from the venipuncture site are associated with nerve irritation by a hematoma or swelling. Symptoms may arise immediately when the needle is inserted or withdrawn, as in the case of direct nerve injury. With nerve irritation associated with a haematoma, pain may not be apparent at the time of donation and may start when the haematoma has reached a sufficient size to compress the nerve, sometimes days after the donation. Symptoms may be exacerbated with certain arm positions or motions. Rarely, weakness of the arm may develop.

- Localized infection/inflammation: **Inflammation** along the course of a vein may be associated with a clot within the vein and may progress to localised infection several days after phlebotomy. Infection is usually associated with introduction of surface bacteria into the deeper tissues with venipuncture: the superficial vein only (thrombophlebitis) or the surrounding subcutaneous tissue (cellulitis) may be affected. Signs and symptoms include warmth, tenderness, local pain, redness and swelling at the site of phlebotomy. The site and the vein may feel tender, firm, and warm to the touch. Fever may be present.

- Other major blood vessel injury (very rare):

**Deep venous thrombosis:** thrombosis of a deep vein in the donor's phlebotomy arm. Superficial venous thrombosis may progress into the deeper veins of the donor's arm. Deep venous thrombosis may also rarely occur without previous signs and symptoms of superficial thrombosis. Additional risk factors for deep vein thrombosis include the use of oral contraceptives and deficiencies in Protein C or S or antithrombin III. Signs and symptoms include swelling, redness and pain in the upper arm, with or without symptoms of preceding superficial inflammation and thrombosis.

**Arterio-venous fistula:** acquired connection between the vein and artery due to damage to the vessels, often related to arterial puncture. A channel forms between the lacerated vein and artery immediately post- venipuncture or as part of the healing process. Signs and symptoms include a pulsating mass with a palpable thrill and associated bruit. The affected area may be warm, though the distal part of the arm may be cool if significant shunting of blood is present. The distal veins may be dilated and may pulsate

**Compartment syndrome:** increased intracompartment pressure leading to muscle, nerve and soft tissue necrosis. Blood may accumulate in the frontal deep areas of the forearm, putting pressure on and constricting small blood vessels; the resulting loss of blood flow into the extremity results in muscle and nerve tissue necrosis. It may be related to arterial puncture with high pressure flow of large volumes of blood into the tissues. Signs and symptoms include cold, pale painful arm, swelling, paresthesias and partial paralysis.

**Brachial artery pseudoaneurysm:** a collection of blood outside an artery, contained by adventitia or the surrounding tissues alone. After a traumatic arterial puncture, blood may leak out of the artery and accumulate in the surrounding space. It is recognized by a pulsating mass in the arm usually accompanied by pain and paraesthesias; pseudoaneurysms may be preceded by a large hematoma following arterial puncture.

### 12.5.2 COMPLICATIONS CHARACTERIZED BY GENERALIZED SYMPTOMS

**Vasovagal reaction:** a generalised sensation of discomfort and weakness with anxiety, dizziness and nausea, which may progress to loss of consciousness (faint). Vasovagal reactions are the most common acute complications related to blood donation. Both physiologic and psychological factors may be important. The reaction is generated by the autonomic nervous system and further stimulated by psychological factors. Signs and symptoms include discomfort, weakness, anxiety, light-headedness/dizziness, nausea, chills, sweating, vomiting, pallor, hyperventilation, rapid or a slow pulse, and hypotension. Loss of consciousness (LOC) may occur and can be accompanied by loss of bladder or bowel control or convulsive movements. Reactions may occur at any time during the donation process including before phlebotomy (rare), during phlebotomy or immediately after phlebotomy, when the donor stands up, or after the donor has left the collection site. Most reactions occur within 12 hours of phlebotomy. Reactions accompanied by LOC carry a risk of injury, particularly if they occur once the donor has left the collection site (delayed vasovagal reactions) (26-30). Risk factors associated with vasovagal reaction have been thoroughly studied and include: female gender, young age, low weight, first-time donor status, and a small estimated blood volume.

- Vasovagal reaction without Loss of Consciousness (LOC): the donor does not faint;
- Vasovagal reaction with LOC: the donor faints for a period of time;

### 12.5.3 COMPLICATIONS RELATED TO APHERESIS

- **Citrate reaction:** a neuromuscular hyperactivity related to reduced ionized calcium levels. Infusion of citrate anticoagulant during apheresis binds calcium causing a fall in ionised calcium levels, leading to neuromuscular hyperactivity. Operator error with mix up of saline and citrate bags may occur with some apheresis equipment leading to rapid citrate infusion. Signs and symptoms include numbness or tingling of lips or fingers, feelings of vibrations, metallic taste, chills, shivering, light-headedness, feeling of tightness, muscle twitching, rapid or slow pulse and/or shortness of breath. Symptoms may progress to carpopedal spasms and vomiting; if untreated, symptoms may progress to generalised muscle contractions (tetany) and severe cardiac arrhythmias, including cardiac arrest.
- **Haemolysis:** Donor red cells may be damaged during apheresis procedures, releasing haemoglobin. Equipment malfunctioning valves, kinks or obstruction of tubing, incorrect installation of equipment, or other equipment failures affecting the extracorporeal circuit, most commonly cause this. In addition, incompatible replacement fluids, such as dextrose D5W, may be used in error. The presence of hemoglobin in the circulation is recognized by pink or red plasma, blood in lines or a dark appearing filter. The donor may notice pink or red urine after collection.
- **Air embolism:** Air bubble introduced into the donor's circulation. Air may enter into the lines due to incomplete priming of lines, as a result of a machine malfunction or defective collection kits or through incorrect manipulation by staff. Air in the donor's pulmonary circulation may occlude the pulmonary arteries in the lung and cause cardiopulmonary symptoms. Air may pass to the arterial circulation through an atrial septal defect, and reduce blood flow to the brain. This very rare event may be recognized by a bubbling sound or feeling at the venipuncture site accompanied by cough, dyspnea, apprehension, sweating, chest pain, confusion, tachycardia, hypotension, nausea and vomiting.

### 12.5.4 ALLERGIC REACTIONS

- **Local allergy:** presents as red or irritated skin at the venipuncture site. Reactions are typically caused by allergens or irritants in solutions used for disinfection of the arm (such as iodine or chlorhexidine) or used in manufacture of the collection set. Irritation may also result from application of the adhesive bandage (bandage adhesive dermatitis). An allergic reaction to latex used in the manufacture of supplies such as gloves may also occur. Local allergies cause itching and redness at the venipuncture site, the bandage site, or the entire skin disinfection area. In a true allergic reaction, there may be a raised rash or hives in these areas that may expand to cover a larger area of the arm. The reaction may occur soon after donation or in the hours to days post-donation.
- **Generalized allergic reaction (anaphylactic reaction):** anaphylactic type reactions are very rare, usually start soon after the procedure is begun and may progress rapidly to cardiac arrest. These extremely rare reactions are usually attributed to donor sensitivity to ethylene oxide gas used to sterilize some collection kits. Principal symptoms and signs are apprehension, anxiousness, flushing, swelling of eyes, lips or tongue, cyanosis, cough, wheezing, dyspnea, chest tightness, cramps, nausea, vomiting, diarrhea, tachycardia, hypotension, and altered mentation.

### 12.5.5 OTHER SERIOUS COMPLICATIONS RELATED TO BLOOD DONATION: MAJOR CARDIOVASCULAR EVENT

BD complications should be graded for severity and imputability that are also defined by IHN and ISBT. Certain complications of donation are by their nature mild or severe.

- Local reactions - Most local reactions (allergic, hematoma, arm pain syndromes) would not be considered severe, though nerve injury may rarely result in long term disability. Severe consequences are classified as separate reaction types: deep venous thrombosis, arteriovenous fistula, and compartment syndrome.

- Systemic reactions - Vasovagal reactions are characterised as those with or without LOC; they may be further sub-characterised by LOC with or without additional symptoms (convulsions, loss of bowel or bladder control and/or duration of  $\geq 60$  seconds), and LOC with or without injury.
- Complications that are by their nature severe include generalised allergic (anaphylactic) reactions, and all major cardiovascular events.

Numerous international studies on BD complications have been published. Unfortunately, definitions of the complications are not comparable and mild and delayed complications are likely to be underreported. Surveys from the USA, Japan and Europe reported incidence rates from 0.8 to 3.5%. Several studies reported reduced return following donor reactions (31-34). Although the bulk of donor haemovigilance literature addresses immediate adverse events, little data exists describing long-term morbidity of such complications. Among long-term complications of blood donation, studies have focused primarily on iron balance.

#### *12.5.6 LONG-TERM BLOOD DONOR COMPLICATIONS*

- The most recognised and studied long term complication is iron deficiency, more frequently associated with whole blood donation(35). The collection of 450 or 500 mL of whole blood, plus an additional 30 to 50 mL for blood tests, results in 480 to 550 mL of blood loss per whole-blood donation. These losses equate to a 60- to 88-g loss of haemoglobin (Hb) per whole-blood donation in women (based on a Hb range of 12.5 to 16.0 g per dL), and 204 to 299 mg of iron loss (based on 3.4 mg of iron per gram of Hb). Donation frequency accounts for the greatest impact on iron deficiency(36). In addition, collection of double red cell units by apheresis may increase the risk. Prevention of iron depletion could be achieved by increasing the inter-donation interval, switching to plasma or platelets apheresis instead of whole blood donation, or replacing iron lost through donation.
- Protein depletion may result from frequent plasma donation(37)
- Osteoporosis from calcium depletion may be a possible chronic effect of frequent citrate anticoagulation(38; 39). Some investigators showed altered bone metabolism, proven by changes in alkaline phosphatase, osteocalcin, intact parathyroid hormone (PTH) and 1,2 dihydroxyvitamin D levels. Protein and calcium depletion have only recently received attention and are not (yet) included in lists for reporting and surveillance.





The risk of transmission of infection through transplantation is well recognized (40) and cannot be completely eliminated, but processes and systems must be in place to ensure that overall risks are kept as low as reasonably possible, whilst still facilitating maximum clinical benefit from transplantation. Balance of risk-benefit is unique to each specific situation and is ultimately a responsibility of the transplanting team to consider them, with due involvement of and consent from the recipient. The transmission of infections to recipients of solid organs, tissues, and corneal grafts is well documented. The risk of infection also exists in association with blood transfusion, but is generally considerably smaller through the screening procedures, deferrals and testing.

A wide spectrum of viruses, bacteria, fungi and parasites have been associated with donor-derived infection, with transmissibility depending on several factors, including the type of graft, processing of the graft, and interdependent donor and recipient factors.

The recognition and full evaluation of potential allograft-associated infections is fundamental in the planning of prevention of disease transmission as well as mitigation of complications in recipients, when transmission occurs. Steps involved and interplaying factors include:

- Recognition on the part of clinicians that allograft-derived infection may occur in recipients and that, as such, requires careful microbiological evaluation.
- Clarity on mechanisms available for mandatory and timely reporting of suspected transmission events to the appropriate procurement organizations, tissue and blood establishments and other competent or public health authorities.
- Promotion of a “culture of safety and quality” that focuses on the prevention of transmission of inadvertent disease and improvement in outcomes in recipients rather than punitive approaches.
- Coordination of exchange of information between public health authorities, competent authorities, clinical centers, patients, tissue and organ procurement groups and blood establishments.
- Development of standard protocols for the investigation of transmission events to expedite management of other recipients possibly impacted by the exposure to a common source of infection.
- Agreement on the optimal panel of clinical microbiological assays for use in screening eye, organ, blood and tissue donors based on the SOHO procured, post-procurement processing, and the expected use of the MPH. 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. This must be informed by local epidemiology and risk assessment.
- Collection of epidemiologic data to inform trends, patterns and future guidance and policy.

### **13.1 INFECTION TRANSMISSION THROUGH ORGAN, TISSUE AND CELL TRANSPLANTATION**

Each year, over 70,000 organs are transplanted worldwide. Unexpected transmission of donor-derived infection is estimated to occur in less than 1% of solid organ transplant recipients, but few data exist that bear directly on the degree of risk of transmission of donor-derived infection through transplantation (41,42). The rate of infection transmission is influenced by a number of factors, including graft type, processing (for many types of tissue allografts), infectious organism and its pathogenicity, donor and recipient characteristics. Immunosuppressed transplant recipients (solid organs, hematopoietic stem cells) have enhanced susceptibility to infections of all types and may act as sentinels for transmissible disease. In addition, signs and symptoms of infection may be modified when compared to typical presentation in the immunocompetent host; this will be influenced by various factors, including the different mechanisms of pathogenesis and host response, and may vary from asymptomatic infection to accelerated, disseminated disease. Diagnosis may be hampered, either due to the lack of immediate, easily recognizable signs and symptoms or failure to suspect the potential origin of infection. 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 *Mycobacterium tuberculosis*, *Candida* and *Aspergillus* species, herpes simplex virus (HSV), human herpes virus 8 (HHV-8), lymphocytic choriomeningitis virus (LCMV), rabies virus, *Trypanosoma cruzi*, human immunodeficiency virus (HIV) and hepatitis C virus (HCV).

Detection of these unusual and infrequent transmission events is largely dependent upon the threshold of suspicion of the physicians caring for the transplant recipients; recognition of epidemiologic risk is an influential determinant and once a possible graft-related infection is considered, correct diagnosis will depend on availability of specific pathology specimens, access to appropriate microbiologic and histopathologic advice and testing which might include molecular-based techniques, amongst other things. Prompt reporting of suspicion is vital, enabling centralized and coordinated investigation, with assistance from the appropriate public health or other competent authorities, when and as appropriate.

Infections have also been reported more uncommonly due to tissue transplantation. This lower frequency is likely a reflection of chemical or radiation processing (disinfection) of some tissue grafts including ocular tissue transplants, degree of graft vascularization as well as the normal inflammatory and immune function of the hosts. 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 donor-derived infectious agents, including *Candida albicans* and other fungi, *Elizabethkingia meningoseptica*, *Clostridium* species, rabies virus, HCV, and group A *Streptococcus*.

Adverse reactions associated with ocular tissue transplantation 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.

Haematopoietic stem cells (HPCs) have also been associated uncommonly with transmissions of a wide range of viral (HIV, Parvovirus B19, CMV, EBV, HBV), bacterial (*Treponema pallidum*, *Brucella* species, *Bacillus* species), fungal and parasitic infections (*Plasmodium* species, *Toxoplasma gondii*). Transmission of some pathogens, such as bacteria and fungi usually occurs through contamination of the graft rather than being of donor origin.

TABLE 6. BASIC STRATEGIES TO MINIMISE THE RISK OF INFECTION TRANSMISSION THROUGH TRANSPLANTATION OF CELLS, TISSUES AND ORGANS

## **GUIDELINES AND STANDARDISATION FOR DONOR CHARACTERISATION (EVALUATION, COLLECTION OF INFORMATION AND HISTORY, TESTING AND SELECTION)**

DETAILED MEDICAL HISTORY	LIFE STYLE HABITS
PHYSICAL EXAMINATION	INCLUDE BODY MAP
LABORATORY TESTS AND SUBSIDIARY INVESTIGATIONS	ROUTINE MANDATORY SCREENING (AS PER LOCAL/NATIONAL POLICY) TESTS MUST BE PERFORMED ACCORDING TO LOCAL REQUIREMENT WITH CONSIDERATION OF THE LABORATORY PERFORMING THE ASSAYS, SPECIAL TESTING BASED ON THE EPIDEMIOLOGIC HISTORY OF THE DONOR, AND LABORATORY QUALITY CONTROL MEASURES, ANY FURTHER INVESTIGATIONS APPROPRIATE TO THE CASE, BASED ON CLINICAL PRESENTATION, EPIDEMIOLOGICAL HISTORY AND RISKS IDENTIFIED.

RECOMMENDED **AUTOPSY** WHEN CAUSE OF DEATH UNCERTAIN, INFECTIOUS CAUSE SUSPECTED AND AETIOLOGY NOT ASCERTAINED INTRA VITAM



### Recommendations:

Response to Possible Allograft-associated Transmission Event

1. The clinician must appropriately consider transmission of infection in association with allograft implantation. Specialist opinion should be sought at an early stage.
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 may 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 measurement, microbiological cultures and fixed tissue specimens as appropriate to the site of infection and clinical context
4. Donor autopsies should be encouraged when appropriate, 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 within 24 hours of recognition of potential disease transmission should be made mandatory
6. Notification of the appropriate organizations or public health authorities must be made to ensure appropriate investigation of transmission event.

## 13.2 TRANSFUSION TRANSMITTED INFECTIONS (TTIs)

Many advances in safety of blood transfusion relate to prevention of transfusion-transmitted infections (TTI). The development, standardization and implementation of an expanding array of immunoassays employed worldwide in routine screening of blood donated by voluntary blood donors, with exclusion of infected blood and their donors continue to reduce the risk of transmitting HBV, HCV, HIV-1/2, HTLV-I/II and *Treponema pallidum* infections. Nucleic acid tests (NAT) using enzymatic amplification of viral gene sequences have augmented the risk reduction in "window period" infections that are undetectable by the serological tests. The continuing risk of bacterial contamination, especially in platelet concentrates optimally stored at room temperature, has led to methods such as bacterial screening of platelets or pathogen reduction technologies to be adopted by some blood organizations. Besides the current effort devoted to microbial risk reduction, pathogen reduction technologies promise the theoretical reduction of the residual risk of known and emerging infectious agents. The effectiveness of the foregoing measures, international harmonization of practices and procedures, and continued hemovigilance portend best practice in transfusion medicine.

### 13.2.1 TRANSFUSION TRANSMITTED VIRUSES

Assessment of risk of infection through blood transfusion requires correlation of donor risks, epidemiological data (local incidence and prevalence of infection) and screening assay performance. Blood programs in industrialized countries maintain blood safety surveillance programs for transmissible infections and all blood services should aim to have this in place, as local data is essential to inform assessment.

Inadvertent recent or long past exposure to infectious agents or non-compliance with selection criteria by donors are still reasons behind infections identified in new or returning blood donors. Given the sensitivity of screening algorithms used, risk of missing infections is highest when the infection has happened in the very recent past and the donor is asymptomatic, undergoing very early stages of infection. Generic deferral due to recent acute viral-like illness and relevant travel broadly takes care of many potentially transmissible infections, whereas national donor selection guidelines will contain required acceptance criteria that must be adhered to.

### 13.2.2 TRANSFUSION TRANSMITTED BACTERIA

Bacterial contamination of blood and its cellular components remains the most common infectious cause of transfusion associated morbidity and mortality. Septic transfusion reactions are the second most common cause of transfusion-associated death in Western countries after blood type incompatibility reaction. Bacterial infections can be a result of environmental contamination during collection and processing, donor or recipient skin colonization or donor bacteremia. As a result, the most predominant bacteria isolated are usually commensals of the skin or gastrointestinal tract flora.

Measures to reduce the risk of bacterial contamination focus on different steps in the transfusion chain:

**Donor eligibility:** To reduce asymptomatic donor bacteremia, subjects with recent dental treatments, minor surgery or increased body temperature at presentation should be excluded from donation;

**Optimal product processing, handling and storage:** Continuous training and supervision of the responsible personnel for donation and product processing are key elements for high quality standards and product safety. Also, consistent storage temperatures (4°C for red blood cells and 22–24°C for platelets) need to be maintained to ensure product integrity;

**Skin preparation:** Improved donor arm disinfection has been shown to be crucial in reducing the numbers of remaining bacteria on the phlebotomy puncture site (44, 45, 46), even if there is uncertainty about the most effective regimen for reducing the microbial load (the number of microscopic bacterial organisms) on the donor arm;

**Removal of the initial whole blood collection (diversion):** It has been shown that removal of the first 30–40 ml of whole blood from the collection bag might reduce the contamination risk from skin bacteria. In fact, improved donor arm disinfection in association with blood diversion has been reported to reduce the risk of bacterial contamination by up to 77% (47, 48, 49).

**Bacterial detection methods:** Different methods have been investigated for detecting bacteria in platelet components including an automated bacterial culture method, direct bacterial staining, bacterial endotoxin and ribosomal assays, nucleic acids testing for bacterial DNA, and measures of O<sub>2</sub> consumption or CO<sub>2</sub> production (50,51,52,53). However, none of these detection methods seems to identify all bacterial contaminations and additional bacterial screening tests as well as better timing of bacterial testing (i.e. closer to the time of transfusion) might be needed to further improve the likelihood of correctly identifying bacterially contaminated blood products;

**Pathogen reduction methods:** The goal of pathogen inactivation is to reduce the risk of known and unknown pathogens susceptible to the treatment applied, without compromising therapeutic efficacy of the blood product or introducing secondary risks. It offers a log reduction and not necessarily elimination of infectivity of susceptible agents and requires monitoring for break-through infections.

### 13.2.3 TRANSFUSION TRANSMITTED PARASITES

Several parasites can be transmitted via blood transfusion, such as Plasmodium species, Trypanosoma cruzi and Babesia microti. The risk in non-endemic areas is introduced from either travellers to, or immigrants from, high endemic areas. Either testing the blood supply or applying appropriate donor deferral addresses the risk broadly and effectively. This last strategy may not always be optimal because many healthy donors may be deferred unnecessarily, leading to donation loss, and lengthy deferrals may discourage donors to return. Optimisation of donor deferral criteria, to better reflect local donor population epidemiology, scientific knowledge and access to testing can address some of these issues.

### 13.2.4 EMERGING INFECTIONS DISEASE (EID)

In more recent years, some emerging infectious diseases (EID) have been identified as potential threats to blood safety and required rapid responses, with particular mention to some arboviruses. Due to sustained globalisation and climate change, continued vigilance and horizon scanning for newly emerging or re-emerging infectious pathogens have become essential tools as regards to the microbiological safety of the blood supply. The classical attributes of a transfusion transmission threat include:

- An asymptomatic period of infection during which the agent is present in the blood
- The agent is transmissible by the intravenous route
- It causes symptomatic disease in some or all recipients
- It is resistant to blood processing and storage conditions.

Table 1 from Perkins et al (43) compares the features of established and EID of concern for blood safety. The new paradigm includes a wide array of agents that do not fit the classical model; instead, potential blood-borne infectious agents initially presenting in any region of the world can overcome the barriers of geographical restriction through rapid population movements.

In 2009 the Transfusion Transmitted Diseases Committee of the AABB) put together a list of agents that are known or have the potential to be transfusion-transmitted (55). Each agent was assigned a priority risk level under three different categories:

- Scientific/epidemiologic evidence regarding blood safety
- Public perception and/or regulatory concern regarding blood safety
- Public concern regarding the disease agent

The initial list includes **68 agents**, among them human variant Creutzfeldt-Jakob disease, dengue viruses, Babesia, Chikungunya virus, St Louis encephalitis virus, Leishmania, Trypanosoma cruzi, Chronic wasting disease, HHV8, human parvovirus B19, influenza A virus, subtype H5N1, simian foamy virus, Borrelia burgdorferi, hepatitis A virus (HAV), hepatitis E virus (HEV), Anaplasma phagocytophilum. Since then, the number has grown to 77 agents (56). It must be remembered that although most infectious agents have world-wide relevance, the assessment and classification was made with focus towards the USA and Canada.

### **Recommendations:**

**A) Surveillance and vigilance:** To safeguard the microbiological safety of blood supplies, blood systems must ensure:

1. Continued collection of donor and recipient data, including outcomes, to inform safety policy
2. Recognition of a transfusion-transmission threat, methods for quantitative risk assessments and the appropriate management of such threats
3. As regards specifically EID, methods to monitor agent (re)emergence and assessment of risk based on local parameters, including donor and recipient population characteristics
4. Mechanisms must exist to allow surveillance, threat assessments, triggers for action, and as needed, intervention development, implementation and assessment of efficacy

### **B) Response from transfusing facilities and blood establishments to possible TTI**

1. The clinician responsible for the recipient must appropriately consider transmission of infection in association with transfusion. Specialist opinion should be sought at an early stage.
2. There must be a formal reporting mechanism to the responsible blood organization with standardized minimum data set of information
3. Evidence of infection that triggered reporting must be carefully verified and appropriate samples from recipient(s) must be retained for investigation
4. Archive donation storage must be in place
5. Advice/oversight by a specialist in transfusion microbiology, with access to required tests. Determination of imputability may require specialist tests, which may include molecular-based techniques performed in referral centres
6. Production of report following each reported potential TTI with outcome and conclusion, which must include duty of care to the donor, when donor infection is confirmed. Appropriate feedback is important.



There are many different types of transfusion reactions, which can be subdivided in several ways, according to their occurrence, pathogenesis and/or their symptomatology. A common subdivision based on the time to the occurrence is between acute (< 24 h after) and delayed (> 24 h after transfusion) reactions. According to their pathogenesis, adverse reactions can be divided in infectious and non-infectious adverse reactions. Non-infectious acute reactions include: allergic reactions including anaphylactic reactions (AR), febrile non-haemolytic transfusion reactions (FNHTR), acute haemolytic transfusion reactions (AHTR), transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), hypotensive reactions and transfusion-associated hyperkalemia (TAH). Non-infectious delayed transfusion reactions include delayed haemolytic transfusion reactions (DHTR), delayed serologic transfusion reactions (DSTR), post-transfusion purpura (PTP), transfusion-associated graft versus host disease (TAGVHD), transfusion-associated necrotising enterocolitis (TANE) and Iron Overload. These can be caused by any of the blood components being transfused such as red cells, platelets or plasma. Some can also be caused by fractionated plasma components such as intravenous immunoglobulin (IVIg) or cryoprecipitate. The prevalence of these reactions has been estimated (57).

### 14.1 ACUTE REACTIONS

- **Allergic transfusion reactions (ATR)** occur during or within four hours of completion of transfusion with a blood component and are most frequently associated with platelet transfusions. Symptoms are caused by mediators such as histamine, released on activation of mast cells and basophils. Although reports gave incidents rates for ATR with platelets (PLTs) and red blood cells (RBCs) of 3.7% and 0.15%, respectively, a review of the literature showed that the incidence rate varied by more than 100-fold, probably because of differences in pre-medication use, patient characteristics, product manufacturing, storage time, reporting rates, reaction definitions and monitoring practices (58). Prevention of recurrence can include recognition of susceptibility and action to improve quality and safety of blood components. Improvement of blood components mainly consists in use of plasma-reduced or washed RBCs and Platelet Concentrates (PC) in patients with recurrent and severe allergic reactions.
- **Acute Febrile non-haemolytic transfusion reactions (FNHTR)** are common, occurring in about 1% of transfusion episodes (1–3% per unit transfused)(59), Evidence supports two mechanisms of FNHTR: anti-leukocyte antibodies and a storage lesion of released cytokines(60). Pre-storage leucocyte reduction can prevent FNHTR(61). The use of platelet additive solutions (PAS) can decrease the rate of reactions from 0.5% to 0.17%(62) in one study but has not been validated.
- **Acute haemolytic transfusion reactions (AHTR)**. An AHTR has its onset within 24 hours of a transfusion. Clinical or laboratory features of hemolysis are present. Common signs of AHTR are: fever, chills/rigors, Facial flushing, Chest pain, Abdominal pain, Back/flank pain, Nausea/vomiting, Diarrhea, Hypotension, Pallor, Jaundice, Oligo/anuria, Diffuse bleeding, Dark urine. Common laboratory features are: Hemoglobinemia, Hemoglobinuria, Decreased serum haptoglobin, Unconjugated hyperbilirubinemia, increased LDH and AST level, and decreased hemoglobin levels. Not all clinical or laboratory features are present in cases of AHTR. AHTR can be either immune or non-immune. Immune-mediated haemolysis can be acute or delayed. Non-immune haemolytic transfusion reactions occur when red blood cells are haemolysed by factors other than antibodies, such as co-administration of red blood cells with an incompatible crystalloid solution, incorrect storage of blood, or use of malfunctioning or non-validated administration systems. Mechanical valves, blood warmers, infusion catheters, and infusion pumps can cause non-immune haemolysis. Acute, immune-mediated haemolytic transfusion reactions are those that occur during or immediately after incompatible RBCs are transfused into a patient who already possesses the corresponding antibody. ABO-incompatible RBC transfusion is the prototypical example of an acute haemolytic transfusion reaction. Such a reaction could occur, for example, after transfusion of Group A RBCs into a Group O recipient who has antibodies to A. Transfusing as little as 30 mL of incompatible blood can be fatal, and there is a direct relationship between increasing volumes of incompatible blood transfused and mortality (63;64). An acute intravascular haemolytic transfusion reaction is a medical emergency and can be fatal.
- **Transfusion-related acute lung injury (TRALI)** incidence is estimated to be between 0.002% and 1.12% of blood transfusion. Diversity in clinical symptoms, absence of specific disease markers and diagnostic tests, and the absence of a clear definition could all have contributed to this large variation in estimations of the incidence of TRALI. Transfusion-related acute lung injury is characterized by the development of non-cardiogenic pulmonary oedema after transfusion.

Although understanding of the pathogenesis has increased greatly in the past few decades, it remains incompletely understood. A two-hit hypothesis has recently been proposed. The first step is the patient's underlying disease or condition (e.g. sepsis, surgery...) and includes priming of neutrophils as well as sequestration of the neutrophils in the lungs. The second step is the transfusion of a blood component containing either anti-HLA or HNA titres antibodies or neutral lipids and lysophosphatidylcholine, that activate neutrophils (65). Preventive measures are mainly based on exclusion of donors, who have high incidence of HLA or HNA, and pooling of plasma. Two groups of high risk donors have been identified: multiparous donors (the likelihood of HLA alloimmunization in donors increases with the number of pregnancies) and donors exposed to blood transfusion. Measures including the use of plasma only from male donors have resulted in a reduced incidence of TRALI (54; 66). Options for reduction of TRALI risk for platelets that have been adopted by many blood systems include suspension of platelet pools in 'male plasma', screening female apheresis donors for leucocyte antibodies, and the use of platelet additive solutions. (67).

- **Transfusion-associated circulatory overload (TACO)** is an under-recognized reaction, affecting about 1-8% of patients who are transfused (68-70). It's caused by an excessive quantity of transfused blood components or an excessive rate of transfusion (excessive being relative to each patient). The initial stages of TACO may be difficult to distinguish from haemolytic transfusion reaction, FNHTR, allergic reaction, or TRALI. Risk factors include being in the neonatal or elderly population, renal failure (especially if on dialysis), pre-existing fluid overload, cardiac dysfunction, administration of large volumes of blood products, and rapid administration rate. Prevention is based on assessment of patient risk and judicious transfusion practice.
- **Hypotensive transfusion reaction (HTR)** A less recognized, but severe acute transfusion reaction is observed during or immediately following a blood product infusion. For adults, the definition includes a drop in systolic blood pressure of  $\geq 30$  mm Hg to  $\leq 80$  mm Hg. For paediatric patients (1 year to less than 18 years old) an HTR is considered a greater than 25% drop in systolic BP from baseline. In neonates or small infants (less than 1 year or any age and less than 12 kg body weight) an HTR is a greater than 25% drop in the baseline value using whichever measurement is being recorded (e.g. mean BP). Two-thirds of cases involve surgical or critically ill patients with an overall incidence of 1 in 10,000 units transfused(71). The pathogenesis of this syndrome appears to be related to the activation of the contact pathway (prekallikrein converting to kallikrein) induced in plasma by the negatively charged surface of some leukoreduction filters. Kallikrein activation stimulates the conversion of high-molecular-weight kininogen to bradykinin. The syndrome is often more severe in patients concurrently treated with angiotensin-converting enzyme inhibitors, which doubles the half-life of the bradykinin degradation product des-Arg9- BK(72).
- **Transfusion Associated Hyperkalemia (TAH)** is defined as any abnormally high potassium level ( $> 5$  mml/l, or  $\diamond 1.5$  mml/l net increase) within one hour of transfusion. After blood transfusion, the rise in a patient's serum potassium level is usually transient due to the redistribution of the potassium load. While it is difficult to prove conclusively that RBC transfusions lead to cardiac arrest, available evidence suggests that transfusion-associated hyperkalemic cardiac arrest is a real phenomenon<sup>32</sup>, particularly in paediatric patients. Measures to reduce the risk of this complication in young children include anticipating and replacing blood loss before significant hemodynamic compromise occurs, using large-bore peripheral intravenous catheters rather than central venous access, checking and correcting electrolyte abnormalities and using fresher RBCs for massive transfusion(73).

#### 14.2 DELAYED REACTIONS

- **Delayed Haemolytic Transfusion Reaction (DHTR)** A DHTR usually manifests between 24 hours and 28 days after a transfusion and clinical or laboratory features of haemolysis are present. Signs and symptoms are similar to AHTR but are usually less severe. They may sometimes manifest as an inadequate rise of post-transfusion haemoglobin level or unexplained fall in haemoglobin after a transfusion. Blood group serology usually shows abnormal results. The incidence of DHTRs is one per 2500 transfusions, but rises to 11% in patients with sickle-cell disease (74). Patients at risk for delayed haemolytic or delayed serological transfusion reactions (DSTR) include those with a history of red blood cell antibodies (through pregnancy or transfusion exposure) in which the antibody titre subsequently decreases to levels undetectable by routine antibody detection testing. There is a DSTR when, after a transfusion, there is demonstration of clinically significant antibodies against red blood cells which were previously absent (as far as is known) and when there are no clinical or laboratory features of haemolysis (synonymous with alloimmunisation). With standard laboratory techniques, 25% of red blood cell alloantibodies become undetectable over a median follow-up of 10 months after initial development, thus putting patients at risk for delayed transfusion reactions. DHTR is usually due to an anamnestic immune response when the recipient is unknowingly transfused with a red blood cell unit that expresses the cognate antigen. Re-exposure to the foreign antigen causes a rise in red blood cell antibody titres 24 h to 28 days after transfusion, accompanied by either a fall in hemoglobin or failure of increment, rise in indirect bilirubin, or a positive direct antiglobulin (Coombs') test. Hyperhemolytic transfusion reactions can occur in multiply transfused patients such as those with sickle cell disease of thalassemia, often due to pre-existing antibodies although the pathophysiologic basis is not completely understood.



- **Delayed serologic transfusion reaction (DSTR).** is an under-recognized reaction, affecting about 1–8% of patients who are transfused (68-70). It's caused by an excessive quantity of transfused blood components or an excessive rate of transfusion (excessive being relative to each patient). The initial stages of TACO may be difficult to distinguish from haemolytic transfusion reaction, FNHTR, allergic reaction, or TRALI. Risk factors include being in the neonatal or elderly population, renal failure (especially if on dialysis), pre-existing fluid overload, cardiac dysfunction, administration of large volumes of blood products, and rapid administration rate. Prevention is based on assessment of patient risk and judicious transfusion practice.

Post Transfusion Purpura (PTP) Occurs roughly 1 in 100,000 transfusions, is a rare, self-limited thrombocytopenia occurring 5 to 10 days after transfusion in patients lacking a specific platelet antigen, usually HPA-1a, phenotypic frequency up to 2% depending on patient ethnic origin, (GPIIIa, CD61)(75), who have previously been alloimmunised by pregnancy, Indeed, approximately 85% of cases occur in women. However, other HPA antigens might be implicated. In elderly patients, platelet transfusions, multiple transfusions, and the presence of comorbidities are risk factors (76). Prevention of recurrence of PTP is uncertain but can include use of washed red blood cell units, or use of platelet and red blood cell units from HPA compatible donors.

Transfusion Associated Graft Versus Host Disease (TA-GVHD) is an extremely rare adverse event caused by transfusion of cellular components containing viable donor lymphocytes that recognize their new host as foreign and engraft in the recipient. It is a clinical syndrome characterized by symptoms of fever, rash, liver dysfunction, diarrhea, pancytopenia and findings of characteristic histological appearances on biopsy occurring 1-6 weeks following transfusion with no other apparent cause. The diagnosis of TA-GVHD is further supported by the presence of chimerism. At risk are severely immunodeficient patients such as recipients of haemopoietic stem cell transplantation (past and current) or patients with congenital immunodeficiency affecting T cells or Hodgkin's lymphoma; those in need of neonatal exchange transfusions; and patients taking high-dose chemotherapy or radiotherapy, purine- analogue drugs, or anti-thymocyte globulin for aplastic anaemia (77,78). Fetuses who need intrauterine transfusions are also at risk. Immunocompetent patients are at risk when receiving cellular components from blood relatives or if being transfused in a donor population with little HLA diversity. TA-GVHD can be prevented by irradiating cellular blood components with gamma-rays or x-rays, or by treating blood products with pathogen reduction technology to disrupt the residual lymphocytes' ability to proliferate (78).

Cumulative iron overload Patients receiving regular RBC transfusions unavoidably and invariably develop iron overload and, thereby, are at risk for iron toxicity (79). Excess iron accumulation in tissues results in a number of adverse clinical outcomes, with an associated increase in morbidity and mortality that correlates with the degree of iron toxicity. The main sequelae of excess iron deposition depend on the organ that is damaged: liver fibrosis/cirrhosis and hepatocellular carcinoma, in the heart congestive cardiomyopathy, endocrine dysfunction: pancreas (diabetes mellitus), anterior pituitary (growth hormone deficiency with short stature), testes/ovaries (hypogonadism with delayed puberty and infertility), thyroid (hypothyroidism), parathyroids (hypoparathyroidism), and adrenals (adrenal insufficiency). Because symptoms may not appear until substantial organ damage has occurred, it is important for clinicians to maintain a high degree of awareness of iron overload. Screening and monitoring tests include indirect measurements of iron, such as laboratory and imaging studies.



### 15.1 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, the use of organs from donors with known malignancy or with a high risk of malignancy has largely been avoided by current screening practices.

There have been no reports of the transmission of malignancies through transfusion of blood components. Historical estimates of cancer frequency in potential or actual donors range from less than 1% to almost 3%. However the actual frequency of donors with malignant tumors is not known with precision since it is often only through failures and unusual circumstances that transmissions have been reported. Limited information on such risks leads to a standardized approach for consideration of individual situations, based on a number of principles, as follows:

- **Strength of Diagnosis:** A diagnosis of cancer or history of cancer in the donor may be definite (known histologic type and stage), incomplete (definite cancer of indeterminate type) or probable/possible (diagnosis reported by a third party or uncertainty regarding cancer in history).
  
- **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 of a histologic type and/or stage that has a reasonable likelihood to metastasise in the normal population should be a contra-indication to donation.
  - b) Exceptions are made in some cases to permit donation from donors based on: a) a history of malignancy with low likelihood of recurrence: b) cancers that do not metastasise in normal population e.g. basal cell carcinoma of skin, small well differentiated thyroid cancer, c) some central nervous system (CNS) malignancies that almost never extend beyond the blood-brain barrier (BBB) and in which iatrogenic compromise of the BBB has not occurred, and d) some tumors such as small, solitary well-differentiated renal cell carcinomas that can be resected prior to transplant.
  
- **Tumour therapy** performed / current follow-up: Consideration for donation can be made in cases of specific cancers where the diagnostic evidence is explicit, but documented curative treatment and disease-free intervals are such that the risk of metastasis in the normal population is minimal or absent. Specific cancers that may behave differently in immunosuppressed populations are excluded even if they meet this criterion e.g. melanoma, Kaposi's sarcoma. Other tumours with known possibility of recurrence after extended disease-free periods, e.g., breast or colorectal cancer, also do not fit into this category.
  
- A literature review was performed in NOTIFY to summarise current knowledge on risks of malignancy transmission through the transfer of MPHO and was 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 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 and single center series) 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 7.



TABLE 7. LIST OF MALIGNANCIES FOR WHICH AT LEAST ONE REPORT ON TRANSMISSION THROUGH THE TRANSFER OF MPHO HAS BEEN IDENTIFIED

<b>CORNEA</b>	<b>ORGANS</b>	<b>HEMATOPOIETIC STEM CELLS</b>
PAPILLARY ADENOCARCINOMA	LYMPHOPROLIFERATIVE DISORDERS	NON-HODGKIN LYMPHOMA
GLIOMA	BREAST CANCER	LEUKEMIAS
	CNS NEOPLASIAS	ACUTE MYELOID
	CHORIOCARCINOMA	ACUTE LYMPHOCYTIC
	COLO-RECTAL CARCINOMA	CHRONIC MYELOID
	HAEMATOLOGIC MALIGNANCIES	CHRONIC LYMPHOCYTIC
	LIVER CANCER	
	LUNG CANCER	
	MELANOMA	
	OVARIAN CANCER	
	PANCREATIC CARCINOMA	
	PROSTATE CARCINOMA	
	RENAL CELL CARCINOMA	
	SARCOMA	
	BLADDER CANCER – UROTHELIAL CARCINOMA	
	NEUROENDOCRINE TUMOR/CARCINOMA	
	PHEOCHROMOCYTOMA, PARAGANGLIOMA	

## 15.2 PROVIDING GUIDANCE ON EARLY DETECTION AND PREVENTION OF TRANSMISSION

### 15.2.1 DECEASED DONORS

Strategies to minimise the risk of malignancy transmission related to donor evaluation through the transfer of MPHO are summarised in Table 8. It is recognised that the emergent situation of transplantation may compromise the ability to obtain complete information.

TABLE 8. STRATEGIES TO MINIMISE THE RISK OF MALIGNANCY TRANSMISSION THROUGH MPHO. \*ISOL: INTRACRANIAL SPACE OCCUPYING LESIONS

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#### 1. DETAILED MEDICAL HISTORY:

- 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 TUMOUR RECURRENCE AT ANY TIME
- LIFE STYLE HABITS RELATED TO NEOPLASTIC DISEASES (I.E. SMOKING BEHAVIOUR, ALCOHOL)
- MENSTRUAL IRREGULARITIES AFTER PREGNANCIES AND/OR MISCARRIAGES IN WOMEN
- FAMILY HISTORY OF CANCER

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#### 2. PHYSICAL EXAMINATION:

- EXAMINATION OF SKIN FOR SURGICAL SCARS (E.G., SUSPICION FOR MELANOMA EXCISION, UNDERLYING COLON CANCER RESECTION)

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#### 3. LABORATORY TESTS:

- STANDARD
- TUMOUR MARKERS, I.E. BHCG, PSA, IN SELECTED CASES (USE OF PSA AS A GENERAL SCREEN IS GENERALLY DISCOURAGED)

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#### 4. IMAGE TESTS:

- CHEST X-RAY
- ABDOMINAL ULTRASOUND
- CT OR OTHER IN SELECTED CASES

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#### 5. RECOVERY:

- INSPECTION OF ALL INTRA-THORACIC AND INTRA-ABDOMINAL ORGANS, REGARDLESS OF THEIR ELIGIBILITY FOR TRANSPLANTATION, INCLUDING BOWEL AND GENITAL ORGANS.

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#### 6. HISTOPATHOLOGICAL EXAMINATION:

- HISTOPATHOLOGICAL EXAMINATION OF ANY MASS OR LYMPHADENOPATHY IDENTIFIED DURING EVALUATION OR RECOVERY-INCLUDING ISOL\*

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#### 8. GUIDELINES:

- DONOR EVALUATION, TESTING AND SELECTION, SOPS
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### 15.2.2 LIVING DONORS

As for the deceased donor, potential living donors should be carefully evaluated to identify a previous history of malignancy or active neoplasia, based on a thorough medical history, physical examination and imaging 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 among countries. Hence, screening for prevalent malignant diseases in the population should be based on national cancer screening protocols.

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 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

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

### 15.3.1 TRACING, ALERTING AND NOTIFICATION

Traceability is defined as the ability to locate MPHOS at any stage of the chain from donation to transplantation or disposal. Tracing should include all MPHOS transferred from the donor involved in the case under study, which implies that linkage between the different tracing systems should be ensured. Usually, a team is not able to trace all recipients of MPHOS 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 imputability 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.

### 15.3.2 GRAFT REMOVAL AND CESSATION OF IMMUNOSUPPRESSION

Graft removal in the case of non-life-sustaining organs (i.e., kidney) is a potential therapeutic consideration that should take the informed wishes of the recipient into consideration. Treatment of donor transmitted malignancy may also harness the alloimmune response without prior transplantectomy 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, as documented by scattered reports in the literature. It must be emphasized that, although rejection of the graft is near certain, rejection of the tumour is by no means guaranteed with this method. This approach is generally not suitable for organs such as the heart, lung and liver, which must thus be treated by minimisation of immunosuppression and conventional therapy for the malignancy. Although re-transplantation has been attempted for non-renal allografts in some reports, the avoidance of tumour transmission has not always succeeded. It should be noted that mTOR inhibitors have some antineoplastic properties and switching the type of immunosuppression could be considered as one part of therapeutic management. However, oncologic consultation is encouraged.

### 15.3.3 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. These specialized techniques are generally not available in most centers.

### 15.3.4 GRAFT REMOVAL AND CESSATION OF IMMUNOSUPPRESSION

Overall mortality in transplant recipients with transmitted cancer is approximately 50% in published series. The variety of tumour types and the immunosuppressed condition of the transplant recipient require that any attempt at therapy balance specific tumour killing against the possibilities of opportunistic infection and/or loss of life-sustaining allograft. Oncologic consultation, preferably with an oncologist experienced in the care of this patient population, is encouraged to formulate a comprehensive treatment plan that takes all of these considerations into account.

## **15.4 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 imputability in the context of malignancy transmission is definite (certain), likely (probable), possible, unlikely or excluded. Although it is recognized that each case has its own peculiarities, the development of an objective and universal scale to help assess imputability is needed. However, the lack of a comprehensive scale does not preclude the description of the steps that should be followed in the case of a suspected malignancy transmission in order to assess imputability.

### *15.4.1 SUSPECTED TRANSMISSION MALIGNANCY*

Clinical manifestations of transmitted malignancies may be variable depending on the type of tumour. 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 (but not all) transmitted tumours appear within the first 14 months after transplantation. Therefore, it is unlikely that an aggressive tumour diagnosed in a recipient 5 years after transplantation is donor-transmitted. Other things to consider might be sex-or age-discordant tumours, metastatic disease with no known primary site, or CNS tumour appearing outside of the CNS (80). A previous description of similar transmissions may help support the suspicion and correct assessment of a case involves the analysis of the literature to understand whether the same tumour type has been transmitted before and the clinical presentation and course consequent to transmission. Registry reports and case reports provide information regarding the type of transmission and the methodology followed for the assessment of imputability.

### *15.4.2 TUMOUR HISTOLOGY IN DONOR AND RECIPIENTS*

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

### *15.4.3 KARIOTYPE OF DONOR AND RECIPIENT*

Several reports on transmitted malignancies have relied partially or totally on the investigation of karyotype mismatch between the tumour with respect to recipient tissues for assessing imputability. This strategy is generally limited to those cases where a gender mismatch exists between the donor and the recipient. The interphase Fluorescence In Situ Hybridization (FISH) for sex chromosomes has been used in these situations. As such, there would be no problem even with a neoplastic karyotype, since the sex chromosomes are still identifiable, so they would not lose these particular chromosomes (X and Y). Such studies are possible on routinely processed, formalin fixed paraffin-embedded tissue samples.

### *15.4.4 GENETIC TESTING OF SAMPLE FROM CANCER*

Other strategies rely on genetic testing of the cancer compared to that of donor and recipient tissue (e.g. HLA typing). Different gene sequences and polymorphisms have been studied in the process of assessing imputability. Tumour origin can be identified by microsatellite analysis using Polymerase Chain Reaction (PCR). Paternity test by genomic allelotyping investigation is another reliable technique to verify imputability. This test permits the analysis of multiple highly polymorphic loci for effective discrimination of donor/recipient tumour origin. Many molecular tests can be performed on routinely processed paraffin-embedded tissue samples, and appropriate laboratory consultation is useful in assisting the clinician to take advantage of the local resources available to assess imputability.



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 (81). In addition, a variety of autoimmune diseases have been transmitted including: Hyperthyroidism and autoimmune thyroiditis and thyrotoxicosis, alopecia areata, type 1 diabetes, atopy, autoimmune thrombocytopenia, myasthenia gravis, vitiligo, asthma and anti-Ciq antibodies of systemic lupus erythematosus (SLE). 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(82). 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 defect<sup>1</sup>. 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.

### Recommendations:

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:

- 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 other families. Consideration could be given to the development of a carefully worded standard leaflet explaining these issues that could be provided to all couples.
- 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. 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.
- 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.

### 17.1 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.

### Recommendations:

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 adverse occurrence with harm to a fetus/offspring so that the cause can be investigated and the learning points shared. Informing the clinic could protect other





### 18.1 ORGANS, TISSUES AND CELLS

Each MPH0 intended for transfusion, transplantation, implantation 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 MPH0, but there are also general processes to which each MPH0 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;
- Documentation and maintenance of records for all the above.

Some clinical 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 in 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 '**properties**' is described as it can be applied to blood components, organs, tissues, hematopoietic progenitor/stem cells, corneas, human breast milk and gametes and embryos used for transplantation or application, and how those properties can affect the outcome. 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 exposed to a 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. Another example is the purchase of human breast milk on the internet where collection and distribution are not controlled and unacceptable microbial contamination and dilution with cow's milk have been reported (83;84).

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 or donor testing, 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 as the cause of an adverse occurrence involving harm to a recipient, 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 progenitor/stem cells (HPCs), 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 HPC 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 of 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 in the case of an allograft.

Adverse occurrences where no patient has been harmed but where a risk of harm was identified, should be reported in certain circumstances. For tissues and cells, 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, the EU considers that 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 the 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 fulfil the criteria above and it is of central importance that selection of incidents expected 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 can also occur that result from errors/inadequate procedures at the level of the clinical user as opposed to reactions due to product-related causes. Three types of serious reactions include: acute haemolytic reaction, Graft versus Host Disease (GvHD), and circulatory overload associated with the transfusion of haematopoietic progenitor/stem cells (HPCs). All three are known from haemovigilance, as acute haemolytic reaction, transfusion associated GvHD (TAGvHD) and transfusion associated circulatory overload (TACO) respectively.

## **18.2 BLOOD**

Transfusion errors and deviations from standard operating procedures or hospital policies can happen at any point along the transfusion chain (vein to vein) but particularly in the following instances, which are considered the weakest links in the chain

### *18.2.1 DECISION TO TRANSFUSE*

The use of evidence based clinical guidelines minimises the adverse effects of transfusion (85). Clinical guidelines are systematically developed documents to assist physician and patient decisions about appropriate health care for specific clinical circumstances. Use of the term “evidence-based” in the context of clinical guidelines implies that the recommendations have been created using an unbiased and transparent process of systematically reviewing, appraising, and using the best clinical research findings.

Inappropriate, unnecessary and non-evidence-based decisions to transfuse may result in more harm than benefit to a patient. Although traditionally not looked upon as a “classical” transfusion error, this inappropriate usage of blood may actually be the largest source of preventable error that would benefit from further systematic scrutiny. A patient succumbing to TRALI from an unnecessary transfusion of a unit of fresh-frozen plasma (FFP) should be considered a possible preventable transfusion error. In deciding to transfuse, failure to provide the transfusion laboratory with details regarding the patient’s transfusion history or special blood requirements can result in serious morbidity and even mortality. These important details include a previously detected alloantibody, requirements for washed units, leucoreduced or irradiated blood components. Conversely, hospital transfusion laboratories should also have a system for recording special needs for patients including significant alloantibodies and the need for irradiation.

Piccin et al, has recently reported a review of TACO cases reported to the National Haemovigilance Office in Ireland(86). Between 2007 and 2010, a total of 99 TACO reactions were reported and in 19 (19%) of these reports, human error caused or contributed to the reaction. In seven of these cases, more than one human error was reported. These human errors are summarized as follows:

- 17 cases of failure to follow hospital policies regarding transfusion monitoring of vital signs and of fluid balance;
- Errors of communication and coordination of health care are common underlying causes of error. For example, components prescribed and transfused by two different doctors resulting in a patient receiving 6 RBC units instead of 3, failure to administer diuretics before transfusion, and failure to cancel prescription for RBCs that were subsequently transfused.
- Knowledge deficits on the part of clinical staff where there was a failure to assess the patient before transfusion or to recognize earlier symptoms of pending overload.

All of these human errors involved clinical staff and occurred in clinical areas. Four reports (21%) also identified system failures, such as organization culture issues that prevented junior clinical staff from questioning the requirement for transfusion and thus leading to an unnecessary RBC transfusion; another case where the patient developed a TACO and management priorities resulting in limited clinical supervision of inexperienced junior doctors.

### 18.3 SAMPLE ERRORS

The next critical stage of the transfusion process is blood sampling for pre-transfusion testing. Two general types of errors are usually reported in most HV system: mislabeled samples, where the label has errors, and miscollected samples, where the blood in the tube is not that of the patient whose name is on the label. Miscollected samples are also called wrong blood in tube (WBIT). A miscollected sample represents a greater risk. The rate of detected WBITs underestimates the true rate of miscollected samples because a miscollected sample may, by chance, match the blood group results on record for the patient named on the tube. A WBIT sample in an otherwise properly labeled tube represents a serious error, because the sample will be used by the laboratory for pretransfusion testing. WBIT samples where no previous blood group result for the patient is on record are a particular concern if the blood in the sample is not compatible with the true blood group of the individual named on the tube because blood products correctly crossmatched and correctly tagged using this sample will be incompatible with the recipient's blood. Evidence supports the concept that mislabeling of blood samples is associated with actual WBIT events. Indeed, Lumadue and colleagues(87) have shown that a WBIT sample is 40-fold more likely to be found in a specimen that is also mislabelled.

The frequency of samples in which the blood group differed from that obtained previously (wrong blood in tube) was assessed in an international study of nearly 700 000 samples in 10 countries done by ISBT working party (afterwards by Biomedical Excellence for Safer Transfusion group). The median rate of wrong blood in tube, similar across nearly all of the participating countries, was approximately 1:2000. Comparable rates were found in a national study in England (89). Practices resulting in 'wrong blood in tube' include labelling of sample tubes away from the bedside, failure to check patient identity and the use of preprinted labels, which are proscribed by the British Committee for Standards in Haematology Guidelines on Administration of Blood and Blood Components. Banning of preprinted labels results in a higher rate of samples rejected due to minor discrepancies, but a reduction in the incidence of 'wrong blood in tube'(88).

Poor techniques in blood sampling for diagnostic investigations may also give rise to inappropriate transfusion, sometimes with clinically significant consequences.

The UK Serious Hazards of Transfusion (SHOT) reported cases wherein blood was taken from a "drip arm," resulting in an erroneous haemoglobin values and an inappropriate decision to transfuse contributed to the deaths of two patients (66).

To reduce the risk of sampling errors, all staff undertaking phlebotomy must receive training and competence assessment. Hospital policies should state that blood samples must be taken from a free flowing venipuncture site, the tube filled to capacity and adequately mixed. The phlebotomist must complete the tube label before leaving the patient, checking that the identification details are correct verbally with the patient and against the identification wristband or equivalent.

### 18.4 LABORATORY ERRORS

Analysis of all cases reported to SHOT in 2014 shows that 2346/3017 (77.8%) were caused by error. Of these 334/1179 (28.3%) full cases originated in the laboratory, which is equivalent to what Linden et al. reported (90). In the 2014 SHOT report, laboratory errors include:

- Sample receipt and registration: Failure to take into account available historic information accounts for 60/94 (63.8%), demographic data entry errors for 25/94 (26.6%) and information missed by laboratory staff that was provided on the request form for 9/94 (9.6%)
- Testing: most errors that occurred in testing were due to procedural errors: Incomplete testing, Transcription errors, Misinterpretation of results. Among laboratory errors there were 9 ABO/D grouping errors all involved manual intervention (5 interpretation errors and 4 transcription errors). Despite recommendations for fully automated grouping some laboratories continue to perform manual ABO/D grouping for example in emergencies or out-of-hours, and in very small laboratories where large automation is not feasible
- Component selection: in 2014 SHOT report the following component selection errors are reported: selecting the wrong component (FFP when cryoprecipitate was requested), Late /omitted insufficient dose of anti-D Ig to women, Units that are not of correct specification (not irradiated or the correct phenotype), selection of expired units. These component selection errors could have been prevented if laboratory staff maintained their understanding, knowledge and skills within the transfusion laboratory
- Component labelling, availability, handling and storage: Many cases in this category are due to labelling errors (n=50), where labels were transposed when more than 1 unit was issued to the same patient. In 44 cases expired units were not discarded but reissued to patients or cold chain errors occurred that resulted in units which had been out of controlled temperature being transfused to patients, 3 further labelling errors where the labels for 2 units that were intended for different patients were transposed

It appeared that a high number of laboratory errors took place outside of "core hours" and at night, when staff is fewer in number, may be relatively inexperienced and working under pressure. Unless the transfusion laboratory is appropriately staffed throughout the 24-h period, requests for transfusion at night should be restricted to urgent and emergency cases.

## **18.5 BLOOD ISSUE AND ADMINISTRATION ERRORS**

The stage of great risk in the transfusion chain is the collection of the component from the blood bank or satellite refrigerator and its administration to the patient. Errors at these stages constituted 40% of "wrong blood" events reported to SHOT in 2003 and resulted in 12 ABO incompatible transfusions. Anecdotal case reports provide insights into the system failures. Inaccurate verbal instructions and the common pitfall of similar patient names can contribute to blood issue and administration errors. Of cases reported to SHOT in 2003, 10/45 patients for whom the wrong blood was collected from the blood bank and subsequently administered at the bedside were undergoing urgent or massive transfusions in critical care environments, such as operating theatres, recovery suites, emergency departments, intensive care units or delivery suites. Adverse events reported to SHOT are analysed to identify individual contributory errors. Consistently, the most common error in successive reports (27% in 2003) is a failure to carry out an adequate pretransfusion 'bedside' check. In the majority (87%) of adverse events in which the bedside check failed, a previous error might have been detected at this stage but was not, while in the remainder, the first and only error resulting in blood being given to the wrong patient was made at this final and most critical stage in the process. Contributory factors are checking of blood against a compatibility form away from the bedside, distraction of nursing staff during the checking process, patient identification wristbands missing, defaced or hidden under theatre drapes. The British Committee for Standards in Haematology (BCSH) guidelines on the administration of blood (which are the standards on which hospitals base their protocols for blood administration), state that it is essential that any patient having a blood transfusion must have an identification wristband in place. The National Comparative Audit of Blood Transfusion carried out in England and Wales under the auspices of the Royal College of Physicians and the National Blood Service in 2003 found that, 90% of 5014 patients were wearing wristbands during transfusion, which is encouraging. Of the 10% who were not, 52 (10% of these) were also unconscious. This is of concern, as clearly these patients would not be able to confirm their identity before blood was administered. This group of 52 constituted 1% of all patients audited and 14% of all unconscious patients. These unconscious patients were therefore at an increased risk of receiving a potentially fatal ABO incompatible blood transfusion. Should the wrong blood have been given, 12 of the 52 patients were in a side room or bay alone and would not be readily observed. In some hospitals more than 30% of patients had no wristband. Patients without wristbands most commonly belonged to paediatrics/Special Care Baby Units, oncology, ITU and haematology specialities.

Qualitative Evaluation for Safer Transfusion (QUEST) (91) aimed was to understand the pretransfusion checking process from the perspective of those who administer the blood products and to identify any common concerns with the process and suggestions to improve its safety. Twelve focus groups and seven individual interviews were conducted over a period of 22 months (May 2008 to March 2010), involving a total of 72 individuals. The participants included health care professionals from a wide variety of clinical areas. Five major areas of interest emerged from the analysis: the pretransfusion checking process, policy, training, opportunity for error, and monitoring. The pre-transfusion checking process varied between centres: four of the six sites used manual checking, one site used an automated bar-coding system, and another site used a combination of manual checking and a mechanical locking system on the blood bag. Each of the six sites had a formal hospital policy for the pretransfusion checking process. Regarding training: nursing staff, but not physicians, receive formal training in the pretransfusion checking process through one or more of the following: training at the corporate level, e-learning, and on-the-job training. Various situations were described in which the opportunity of human error could be increased, including having multiple people involved in the process and being distracted. In a busy clinical setting, multiple units of blood products may be delivered for several patients at the same time. In a busy environment, nurses may not get to spend a lot of time with any given patient and this can lead to creative ways of identifying the patient. Monitoring of transfusions generally occurred at the ward level and consisted of checking the paperwork related to the transfusions that had been administered. In summary, a number of areas for improvement were identified.





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 adverse outcomes becomes exceedingly important.

'Traceability' means the ability to locate and identify the organ, tissue/cell or blood unit 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 blood or 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 transplanting the organ, transfusing the blood component or 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 MPHO.

As previously described, the donor scandal in New York State involved tissues from over 1,000 donors, which was 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(92). 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 communities function independently and communication between them is 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 (93). 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 by adding to existing regulations. The International 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 labelling 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. This system has since been expanded to cover all MPHO.

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. The ISBT 128 system 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 (94).





MPHO (MEDICAL PRODUCTS OF HUMAN ORIGIN) TAXONOMY								
LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	
<b>MPHO</b>	<b>Organs</b>	Liver		<b>MPHO</b>	<b>Cells</b>	HPC (hematopoietic progenitor cell)	Marrow	
		Heart					Apheresis	
		Kidney					Cord blood	
		Lung					Type not specified	
		Pancreas				Leukocytes		
		Small bowel				Chondrocytes		
		Combined	Heart lung				Hepatocytes	
			Kidney pancreas				Pancreatic Islets	
			Liver Kidney				Limbal cells	
			Multivisceral				Fibroblasts	
		Composite tissue grafts	Hand				Adipocytes	
			Face				T-lymphocytes	
		Type not specified				Keratinocytes		
	<b>Tissues</b>	Musculoskeletal	Bone			<b>Blood</b>	Whole blood	
			Cartilage					Red blood cells
			Osteochondral					Platelets
			Tendon and ligament					Plasma
			Meniscus					Cryoprecipitate
		Cardiovascular	Blood vessels			Granulocytes		
			Conduit			Type not specified		
			Heart valves			<b>Reproductive</b>	Embryo	
			Pericardium				Oocyte	
		Ocular	Conjunctiva				Ovarian tissue	
			Cornea				Testicular tissue	
			Limbal tissue			Sperm		
		Sclera			Combined			
		Amniotic membrane			<b>Other</b>	Milk		
		Other fetal membranes				Fecal microbiota		
		Dura mater			<b>MPHO Derived Medicinal Products</b>	Topical products of human origin		
		Larynx				Plasma derivatives		
		Nerve				Cell derived medicinal products		
		Parathyroid glands				Tissue derived medicinal products		
Placenta			Tissue and cell derived medicinal products					
Skin								
Adipose tissue								
Trachea								
Umbilical cord tissue								



ADVERSE OCCURRENCE TAXONOMY							
LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4
<b>HARM TO A RECIPIENT</b>	<b>Infection</b>	Viral	Adenovirus	<b>HARM TO A RECIPIENT</b>	<b>Infection</b>	Bacterial	Ehrlichia
			Arenavirus				Elizabethkingia
			BK virus (BKV)				Enterobacter
			Colorado tick fever virus				Enterococcus
			Cytomegalovirus (CMV)				Escherichia
			Dengue virus (DENV)				Hafnia
			Enterovirus				Klebsiella
			Epstein-Barr Virus (EBV)				Legionella
			Hepatitis A Virus (HAV)				Listeria
			Hepatitis B Virus (HBV)				Morganella
			Hepatitis C Virus (HCV)				Mycobacterium
			Hepatitis E virus (HEV)				Mycoplasma
			Human Herpes Virus 6 (HHV-6)				Oerskovia
			Human Herpes Virus 8 (HHV-8)				Orientia
			Human immunodeficiency virus (HIV)				Prevotella
			Human papillomavirus (HPV)				Propionibacterium
			Herpes simplex virus (HSV)				Proteus
			Human T-lymphotropic Virus (HTLV)				Providencia
			Influenza virus				Pseudomonas
			Lymphocytic choriomeningitis virus (LCMV)				Psychrobacter
			Parvovirus B19				Richettsia
			Rabies virus				Salmonella
			Ross River virus				Serratia
			Tick-borne encephalitis virus				Staphylococcus
		West Nile virus (WNV)	Stenotrophomonas				
		Bacterial	Acinetobacter			Streptococcus	
			Alcaligenes			Treponema	
			Anaplasma			Veillonella	
			Bacillus			Yersinia	
			Bacteroides			Acremonium	
			Bartonella			Apophysomyces	
			Brucella			Arthrographis	
Cardiobacterium	Aspergillus						
Chlamydia	Candida						
Citrobacter	Coccidioides						
Clostridium	Cryptococcus						
		Histoplasma					

**ANNEX 2. Notify Library - Adverse occurrence type taxonomy GO BACK**

ADVERSE OCCURRENCE TAXONOMY								
LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	
<b>HARM TO A RECIPIENT</b>	<b>Infection</b>	Fungal	Paecilomyces	<b>Malignancy</b>	<b>Malignancy</b>	Blood and lymphoid	Lymphoma, B-cell, other or not further specified	
			Rhodotorula				Lymphoma, NK cell	
			Scedosporium				Lymphoma, T cell	
		Prion	CJD				Lymphoma, type not specified	
			vCJD				MGUS (monoclonal gammopathy of unknown significance)	
		Parasitic	Acanthamoeba				Multiple myeloma/plasmacytoma leukemia	
			Babesia				Myelodysplastic syndrome	
			Balamuthia				Plasmacytoma, extra medullary	
			Clonorchis				Polycythemia vera	
			Echinococcus				Bone and cartilage	Bone cancer, other or type not specified
			Halicephalobus					Chondrosarcoma
			Leishmania				Osteosarcoma	
			Plasmodium				Breast	Ductal adenocarcinoma
			Schistosoma					Lobular adenocarcinoma
			Strongyloides					Breast cancer, other or type not specified
			Toxoplasma				Cardiovascular	Atrial myxoma
	Trypanosoma	Cardiac, other or type not specified						
	Wuchereria	Central nervous system	Astrocytoma (WHO grade 1)					
	Type not specified		Astrocytoma (WHO grade 2)					
	Carcinoma of unknown primary site		Astrocytoma (WHO grade 3)					
			Adrenal	Astrocytoma/glioblastoma multiforme (WHO grade 4)				
	Adrenal		Adrenal cancer, other or type not specified	Astrocytomas and glioblastomas not further specified (WHO grade 1-4)				
			Adrenal cortical carcinoma	CNS lymphoma				
			Pheochromocytoma	CNS tumor, other or type not specified				
			Blood and lymphoid	Essential thrombocythemia (thrombocytosis)		Ependymoma (WHO grade 2-3)		
				Histiocytic neoplasm, not further specified		Medulloblastoma (WHO grade 4)		
				Hodgkin lymphoma		Gastrointestinal	Anal adenocarcinoma	
				Leukemia, lymphocytic, acute lymphoblastic			Anal squamous cell carcinoma	
				Leukemia, lymphocytic, chronic			Anus cancer, other or type not specified	
				Leukemia, lymphocytic, not further specified			Appendix adenocarcinoma NOS	
				Leukemia, myeloid, not further specified			Appendix mucinous adenocarcinoma	
				Leukemia, myeloid, promyelocytic			Appendix cancer, other or type not specified	
Leukemia, type not specified				Esophageal adenocarcinoma				
Lymphoma, B cell, follicular		Esophageal squamous cell carcinoma						
Lymphoma, B-cell, Burkitt		Esophageal cancer, other or type not specified						
Lymphoma, B-cell, diffuse large type								
Lymphoma, B-cell, mantle zone								
Lymphoma, B-cell, marginal zone								

**ANNEX 2. Notify Library - Adverse occurrence type taxonomy GO BACK**

ADVERSE OCCURRENCE TAXONOMY							
LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4
<b>HARM TO A RECIPIENT</b>	<b>Malignancy</b>	Gastrointestinal	Gastric adenocarcinoma	<b>HARM TO A RECIPIENT</b>	<b>Malignancy</b>	Liver, gallbladder and bile ducts	Cholangiocarcinoma
			Gastric cancer, other or type not specified				Hepatocellular adenoma
			Gastrointestinal carcinoid/neuroendocrine tumor				Hepatocellular carcinoma
			Gastrointestinal stromal tumor (GIST)				Liver, angiosarcoma
			Large bowel adenocarcinoma				Liver, hemangioendothelioma
			Large bowel cancer, other or type not specified				Liver cancer, other or type not specified
			Small bowel adenocarcinoma				Bile duct cancer (extrahepatic)
			Small bowel gastrointestinal stromal tumor (GIST)				Gallbladder cancer
			Small bowel cancer, other or type not specified				Lung cancer, adenocarcinoma
			Germ cell, sex cord and related tumors				Choriocarcinoma
		Embryonal cell carcinoma				Lung cancer, neuroendocrine and large cell cancer	
		Granulosa cell tumor				Lung cancer, small cell	
		Leydig cell tumor				Lung cancer, squamous cell (bronchogenic)	
		Mixed germ cell tumor				Lung cancer, other or type not specified	
		Seminoma/dysgerminoma				Tracheal cancer	
		Sertoli-Leydig cell tumor				Neuroendocrine carcinoma	
		Teratoma				Neuroendocrine tumor	
		Yolk sac tumor				Small cell carcinoma	
		Germ cell tumor, other or type not specified				Ovaries and fallopian tubes	Endometrioid ovarian carcinoma
		Sex cord tumor, other or type not specified	Mucinous ovarian carcinoma				
		Head and neck	Nasopharyngeal carcinoma				Serous ovarian carcinoma
			Ocular melanoma			Brenner tumor/transitional cell carcinoma	
			Salivary gland carcinoma			Ovaries and fallopian tubes, other or type not specified	
			Squamous cell carcinoma, larynx and hypopharynx			Pancreas	Acinic/acinar cell carcinoma
			Squamous cell carcinoma, tongue and oral cavity				Islet cell tumor
			Head and neck cancer, other or type not specified				Pancreatic (ductal) adenocarcinoma
		Kidney and urinary tract	Angiomyolipoma			Parathyroid	Pancreatic intraepithelial neoplasia (PanIN)
			Renal cell carcinoma				Pancreas cancer, other or type not specified
			Renal oncocyoma				Parathyroid carcinoma
			Renal cancer, other or type not specified			Pleura and peritoneum	Parathyroid cancer, other or type not specified
			Urothelial (transitional) cell carcinoma				Mesothelioma
			Bladder adenocarcinoma			Prostate	Pleura and peritoneum, other or type not specified
			Urinary tract neoplasm, other or type not specified				Prostate adenocarcinoma/carcinoma
							Skin
			Basal cell carcinoma				
			Melanoma				
							Merkel cell carcinoma

**ANNEX 2. Notify Library - Adverse occurrence type taxonomy GO BACK**

ADVERSE OCCURRENCE TAXONOMY							
LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4
<b>HARM TO A RECIPIENT</b>	<b>Malignancy</b>	Skin	Squamous cell carcinoma	<b>HARM TO A RECIPIENT</b>	<b>Immunological complications</b>	Delayed Serologic Reaction	
			Skin cancer, other or type not specified			Detrimental immunization (MPHO other than blood)	ABO immunisation
		Soft tissue/sarcoma	Angiomyolipoma			Rh immunisation	
			Angiosarcoma			HLA immunisation	
			Chondrosarcoma			Other detrimental immunization	
			Epithelioid hemangioendothelioma			Graft versus Host Disease	
			Ewing's sarcoma			Post Transfusion Purpura (PTP)	
			Fibromatosis/desmoid tumor			Rejection	
			Fibrosarcoma			TRALI	
			Kaposi's sarcoma			Acute Hemolytic Reaction non-immune	
			Leiomyosarcoma		Cardiovascular complications		
			Liposarcoma		Catheter related complications		
			Nerve sheath tumor NOS		Delayed engraftment		
			Neurilemmoma/schwannoma		Delayed Hemolytic Reaction non-immune		
			Neurofibroma		Febrile Reaction		
			Osteosarcoma		Graft failure		
			Paraganglioma		Hemosiderosis		
			Rhabdomyosarcoma		Hypertensive Reaction		
			Solitary fibrous tumor		Hypotensive Reaction		
			Sarcoma, other or type not specified		Inappropriate clinical application	Insufficient MPHO use	
		Thyroid	Follicular carcinoma		Ecessive MPHO use		
			Medullary carcinoma		Neurological complications		
			Papillary carcinoma		Pulmonary complications		
			Thyroid cancer, other or type not specified		Surgical site complications		
		Uterus, cervix and vagina	Endometrial carcinoma		TACO		
			Endometrial stromal sarcoma		TAD		
			Cervical adenocarcinoma		Toxicity	Citrate	
			Cervical squamous cell carcinoma			Potassium (hyperkalemia)	
	Cervical cancer, other or type not specified		DMSO				
	Cervical cancer, other or type not specified		Ethlene oxide				
	Uterine cancer, other or type not specified						
	<b>Non infectious, Non malignant transmissions</b>	Alloimmune					
Autoimmune							
Genetic							
Hypersensitivity/allergy							
<b>Immunological complications</b>	Acute Hemolytic Reaction						
	Allergic Reaction						
	Delayed Hemolytic Reaction						

**ANNEX 2. Notify Library - Adverse occurrence type taxonomy GO BACK**

ADVERSE OCCURRENCE TAXONOMY							
LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4
<b>HARM TO A RECIPIENT</b>		Undue exposure to risk/intervention		<b>HARM TO A FETUS OR OFFSPRING</b>	<b>Genetic</b>		
		Other					
<b>HARM TO A DONOR</b>	<b>Allergic reaction</b>	Local		<b>RISK OF HARM</b>	<b>Loss</b>	Loss of highly matched or autologous MPHO	
		Systemic /anaphylactic				Loss of suitable organ(s)	
	<b>Drug related reactions</b>	GCSF-related				Loss of large quantity of unmatched MPHO	
		Ovarian Hyperstimulation Syndrome			<b>Mix-up</b>	Gamete mix-up	
	<b>Drug related reactions</b>	Air embolism				Embryo mix-up	
		Fat embolism			Incorrect MPHO applied - no harm		
	<b>Excessive collection/removal</b>				<b>Unsuitable MPHO released for clinical use-no harm</b>		
	<b>Infection</b>				<b>Other</b>		
	<b>Malignancy</b>						
	<b>Miscellaneous complications</b>	Anesthetic agents					
		Cardiovascular					
		Catheterization/Intubation					
		Gastrointestinal					
		Immunological					
		Insertion of needle					
		Metabolic					
		Neurological					
		Psychological					
		Pulmonary					
Surgical site							
<b>Procurement outside legal framework</b>							
<b>Toxicity</b>							
<b>Undue exposure to risk/intervention</b>							
<b>Vasovagal Reactions</b>							
<b>Other</b>							





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