Centro Nazionale Trapianti

World Health Organization

SohoV&S Public Health

NOTIFY

Exploring Vigilance Notification for Organs, Tissues and Cells

A Global Consultation
Organised by CNT with the co-sponsorship of WHO and the participation of the EU-funded SOHO V&S Project

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Part A
Bologna Consultation Report

NOTIFY
Exploring Vigilance Notification for Organs, Tissues and Cells
Bologna, February 7-9, 2011

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Preamble

Remarkable developments in the scientific, technical and medical fields have led to the increased therapeutic use of human organs, tissues and cells. Transplantation of these substances of human origin (SOHO) has not only improved the quality of life of thousands of individuals but also prolonged their lifespan. These achievements have resulted, however, in a situation whereby the demand for organs for transplantation far outstrips the supply. In relation to tissues and cells for transplantation and assisted reproduction, the shortages are not so acute and generally patient needs can be met but, in this context, expectations and requirements for safety and quality are necessarily demanding.

In spite of significant benefits derived from the clinical application of SOHO, there is an inherent risk of disease transmission or other negative outcome. The introduction of vigilance and surveillance systems can facilitate the management of severe adverse reactions and events and lead to improved measures for limiting the impact and preventing recurrence.

Recognizing the need for the surveillance of such reactions and events, the World Health Assembly (WHA)[1] 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 the context of this global mandate, 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 organise a global initiative aimed at raising the profile of vigilance and surveillance (V&S) of substances of human origin; the initiative was called Project NOTIFY.

The scope of the project included organs, tissues and cells for transplantation and for assisted reproduction. International experts were invited to lead 10 working groups with specific defined tasks and Dr D. Michael Strong was tasked by WHO with co-ordinating the work of these 'virtual' teams. The work was conducted on a Google site, created for this purpose, where over 100 participants (regulators, clinicians, professional society representatives, scientific experts) collaborated to gather documented cases of reactions and events across the scope of the substances under consideration, using published articles and vigilance system reports as their sources. Over 1,500 published references were inserted on the site. The cases were used as the basis for developing guidance on the detection and confirmation of reactions and events, with an emphasis on the key role of the treating physician.

The NOTIFY project culminated in a meeting of 113 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 specialities 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 on-line and agreed on priorities for the future development of global V&S for organs, tissues and cells.

This document presents the results of the NOTIFY Bologna Initiative. It is structured in two parts – the presentations made during the plenary sessions and the reports of the working groups. During and since the meeting, a series of didactic papers were developed from the data collected prior to Bologna. These address infections, malignancy, handling, characteristics and clinical errors, donor reactions and genetic transmission; they are published in association with this report. The report and didactic papers together are intended to provide policy makers, as well as health care providers, with information about what work has already been done with respect to vigilance and surveillance and what further work in the view of the participants is needed.

1 Sixty-Third World Health Assembly. WHA63.22. Agenda item 11.21. Human organ and tissue transplantation. 21 May 2010.

1 Opening session and background

1.1 Introduction

The Notify meeting participants were welcomed by Dr Alessandro Nanni Costa who expressed his enthusiasm at what he referred to as a great event bringing together experts in the areas of tissues and cells, organs and assisted reproduction from around the globe. He then proceeded to introduce Dr Lorenza Ridolfi, Coordinator of the Regional Transplant Centre of the Emilia Romagna Region in Italy. Dr Ridolfi extended a warm Italian welcome to participants on behalf of Dr Sergio Venturi, Chief Executive of Sant'Orsola (Bologna University Hospital) and Dr Carlo Lusenti, Policy Director of the Health Authority of the Emilia Romagna Region. She wished everyone a successful event and declared the meeting open.
Brief introductory comments were then made by the Chairs of the Scientific Committee. Dr Deirdre Fehily recalled that in preparation for the meeting, discussion documents had been prepared and put on a NOTIFY website accessible by username and password. These documents would serve as the basis for discussion during the Working Groups. She expressed her thanks to Drs Mike Ison and Mike Strong for their technical support and to the rapporteurs who would aim to capture the key discussion points and conclusions during the meeting.
Dr Mike Strong remarked that this was a very special occasion to have at the same meeting specialists in organ, cell and tissue transplantation and from the area of assisted reproduction. He acknowledged the considerable diversity of experience and expertise among participants and he encouraged all to participate actively. He recalled that the objective of the NOTIFY project is to build on current endeavours to improve vigilance and surveillance of adverse incidents associated with the transplantation of human cells, tissues or organs.
Dr Luc Noel expressed his gratitude to the meeting participants for their interest and support for the NOTIFY initiative. He reminded the meeting of the importance given to vigilance and surveillance of human cells, tissues and organs by the WHA and of the necessary trust of the public for successful donation programmes particularly needed for organ transplantation where demand is increasing and supply scarce. He thanked Deirdre Fehily and Mike Strong for their preparatory work.

1.2 CTO Vigilance at CNT

Alessandro Nanni Costa

The process from donation to transplantation of an organ, tissue or cell is dynamic and requires the comprehensive management of both donor and recipient. In spite of all precautionary measures taken, however, there is still an element of risk. In Italy, the National Centre for Transplantation (CNT) has included five levels of risk for organ donors in its guidelines:

1. Unacceptable risk;
2. Increased but acceptable risk;
3. Calculated risk;
4. Not assessable risk and/or potentially high risk for infectious disease transmission;
5. Standard risk.

The potentially high risk of transmitting an infectious disease arises when a donor has been involved in an unsafe behaviour, such as intravenous drug use or sexual intercourse (homo or hetero) with HIV positive persons, within two weeks prior to the donation, thus making microbiological detection of an agent difficult. Organs from these donors may be transplanted to patients whose lives are threatened or who have elected to have the procedure and have signed a consent form.
The complexity of the transplant field has given rise in Italy to a service – available 24 hours per day, seven days a week – whereby a second opinion on organ suitability and suggested therapy for either the donor or the recipient can be sought. It is supported by specialists in infectious disease, pathology, immunology and two national coordinators. In the event an infected organ has been transplanted, the centre involved is asked to provide regular follow-up data to the National Centre for Transplantation. Statistics have shown that since the introduction of the guidelines and the 24/7 service, the frequency of neoplasia identification before transplantation has increased, while after transplantation it has decreased.
With the outbreak of the West Nile Virus, there was a calculated risk of transmission by transplantation so specific measures were introduced to reduce it. In addition, recommendations were distributed on how to deal with cases of H1N1 influenza. In spite of guidelines and procedures, however, adverse incidents do occur, as evidenced by the transplantation of HIV positive organs to three individuals due to a clerical error. This case led to the introduction of an infectious disease safety programme. A National Safety Audit Commission comprised of experts from the Ministry of Health, the National Transplant Centre, regional transplant centres and laboratories was established. Two questionnaires covering aspects of processes and procedures were prepared and sent to the regional transplant centres, and to laboratories involved in the transplantation process, for completion. The information received in the questionnaires was supplemented by on-site visits.
The primary objective of the programme is to enhance transplant safety. With information gleaned from the questionnaires and site visits, national guidelines and procedures can be developed that can ensure quality and facilitate a homogeneous approach to infectious disease safety.
The prevention and management of adverse events in the process of organ procurement and transplantation is another area of concern in Italy.

Since February 2007, information on all the non-compliances, events and reactions has been compiled and the need to systematize it recognized. To this end, a national reporting form, along with one for providing a detailed event/reaction description, was adopted in May 2010. Development of these materials has drawn from the experience with EUSTITE including its severity and imputability scales, and its matrix for assessing impact. The latter provides guidance on appropriate responses to take after an adverse reaction and/or event has been detected. Depending on the score assigned to the serious adverse reaction or event (SARE) during the assessment, the action to be taken may involve:

- actions at the local level – information alone to the regional centre;
- reporting to regional authorities that carry out inspections and analyses with medium term corrective actions;
- prompt communication to regional authorities and the Competent Authority (CA) with short term corrective actions;
- prompt communication to all involved facilities and the CA and the appointment of a task force; and
- preventive and corrective actions put in place with inspections by the CA.

In order to reduce subjectivity in the assessment of SARE, a group of experts is involved in the procedure. The gathering of vigilance data, and the application of evaluation tools, has become an integral part of managing transplantation risk at CNT.

1.3 CTO Vigilance and Surveillance in WHO

Luc Noel

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 be met through greater awareness and involvement of the community.

It was the tragedies in the early 1960s related to thalidomide and its undermining of public confidence in pharmaceuticals that led to the implementation of pharmacovigilance. The term 'vigilance', derived from the Latin 'vigilare' meaning to watch, to stay awake, but also to care, for a child for instance, implies a process of paying close and continuous attention. Vigilance is a state of mind, an attitude, an openness enhancing the ability to recognize risks. Vigilance is complemented by the methodical approach of "surveillance". 'Surveillance' is defined by the International Health Regulations as the systematic on-going collection, collation and analysis of data for public health purposes and the timely dissemination of this information for assessment and public health response as necessary.[1]

In 2004, the World Health Assembly adopted Resolution WHA57.18 on Cell, Tissue and Organ Transplantation. It placed responsibility on Member States to put in place measures for monitoring the procurement, processing and transplantation of these substances of human origin as well as ensuring their accountability and traceability at national level. Health authorities are identified as responsible.

Following Resolution WHA57.18, the WHO updated its Guiding Principles for the transplantation of organs, tissues and cells following a three year comprehensive consultation programme.[2] Guiding Principle 10 notes *inter alia* that maintaining and optimizing their level of quality, safety and, efficacy requires the implementation of quality systems including traceability and vigilance. In May 2010, following the endorsement of these Principles, the World Health Assembly adopted Resolution WHA63.22 on Human Organ and Tissue Transplantation. It urges Member States *inter alia* 'to strengthen national and multinational authorities and/or capacities to provide oversight, organization and coordination of donation and transplantation activities, with special attention to maximizing donation from deceased persons and to protecting the health and welfare of living donors with appropriate health-care services and long-term follow up'. The Resolution also urged Member States "to collaborate in collecting data including adverse events and reactions on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation". Resolution WHA63.22 also requests WHO "to continue collecting and analysing global data on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation of human cells, tissues and organs" and "to facilitate 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".

The importance given in the resolution to the reporting and dissemination of any severe adverse events and reactions, and therefore to vigilance and surveillance, acknowledges that it constitutes an essential component of donation and transplantation services.

Authorities are ultimately responsible for the provision of therapies based on donated parts of the human body. V&S comes as a complement to the necessary quality management systems at each level of the process from donor identification to long term follow-up. It supplements the ongoing improvement loops/ Deming wheels established by operators at all levels to optimize the system. V&S is a safeguard, ensuring authorities are informed of what is going wrong and could go wrong. As part of their oversight, health authorities have to be informed of failures and risks, as the responsibility for reacting and communicating will eventually fall to them. They are accountable to the Public. Of course, as indicated, the scope is wider than donor transmitted diseases.

Yet existing V&S systems emphasize different types of risks with different purposes. V&S can be focused on transmissible infections and aiming at identifying emerging agents. In other settings, the objective of V&S is to know the risk of disease transmission from the donor to recipient(s), in particular infections and neoplasias. V&S can also be seen as a post marketing surveillance of adverse events associated with the transplant or to its risks. In some countries, beyond the quality of the transplant, inappropriate procedures leading to missed transplant opportunities, unethical practices and illegal and fraudulent practices are also seen as part of vigilance and surveillance.

The current International Health Regulations (IHR)[3] is a global, legally-binding framework to combat 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

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1 International health regulations (2005), Part 1, Article 1 Definitions.

2 Human organ and tissue transplantation. Report by the Secretariat. World Health Organization. Sixty-third World Health Assembly. Provisional agenda item 11.21. A63/2425. March 2010. Annex. WHO Guiding Principles on human cell, tissue and organ transplantation.

3 International health regulations (2005) – 2nd ed. World Health Organization 2008.

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 entered into force in June 2007. Member States maintain or develop core public health capacities for domestic surveillance, assessment and response concerning public health risks and events. In this respect, the capacity to exert vigilance for health products of human origin is identified as desirable. The possibility of international dissemination of risks is inherent to the necessary cross boundaries circulation of persons and to some extent of transplants. Transplant tourism taking advantage of poor and vulnerable populations from less advanced countries, either "active" when the recipient travels to obtain a transplant, or when the donor or the organ travel, is notoriously associated to the transmission and circulation of infectious agents.

Maintaining vigilance over substances of human origin complements WHO's role of surveillance and management of public health events with international consequences.

Drawing upon the knowledge and experience of health care professionals and other stakeholders, the V&S Project NOTIFY aims to understand the what, why and how of vigilance and surveillance. It aims to document what can go wrong when cells, tissues and organs are transplanted, map risks according to current global evidence, recognise problems and propose investigative measures. It aims to progress towards a global vigilance and surveillance system linked to national and regional schemes and increase community involvement and collaboration between stakeholders. The work has just begun.

1.4 SOHO Vigilance in the EU

Olga Solomon

Human substances legislation in the European Union (EU) covers the quality and safety of blood, tissues and cells and organs. Specific requirements are in place for their collection, testing, processing and distribution. With respect to donations of tissues and cells (T&C), it is estimated that each donor provides on average less than five substances. Each substance is manipulated and transported individually creating a tree-like network with many 'branches'. In the EU, there are thousands of local establishments supplying tens of thousands of tissues and cells to care providers where transplantation or other clinical application takes place.

Five so-called 'pillars' support vigilance of substances of human origin (SoHO) – detection, informing, tracing, assessing and response. Through vigilance, problems associated with individual substances can be detected, assessed and managed. Traceability facilitates the location of related substances within the tree-like network from donor to recipient. Donor-related risks, such as infectious diseases, can affect the entire 'tree', while process-related risks, such as contamination, affect one or more 'branches'.

Vigilance in the EU links three levels – at European level there is the European Commission, which plays, among other roles, a coordinating and supportive role and maintains the rapid alert system for tissues and cells and the European Centre for Disease Control (ECDC), which monitors health threats; at national level, there are the Competent Authorities that ensure that the requirements of the EU Directives are followed; and at local level, the tissue and cell establishments that are in the forefront when there are occurrences of SARE.

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

In order to facilitate the reporting of SARE, a common approach document was prepared which helps to ensure that reported information is exploitable, optimises the collection exercise to avoid unnecessary burden at all stages, and ensures consistency between information reported from different Member States.

A SARE would be reported if it influenced the quality and safety of the T&C, could be attributed to procurement, testing, processing, storage and distribution, or was a reaction in a donor that could impact quality and safety. Although it is outside the legal requirements, it will be possible to report reactions in donors (e.g. Ovarian Hyper-stimulation Syndrome in oocyte donors, reactions to haematopoietic stem cell mobilising agents in peripheral blood cell donors) that do not have an impact on the quality and safety of tissues and cells.

A tissues and cells description list has been prepared and classified according to skeletal, haematopoietic, cardiovascular, reproductive, other tissues or cells, skin, and advanced therapy medicinal products. The statistics collected are:

- The total number of tissues and cells transported or delivered to a clinical unit, even on the same floor. One unit = single bag or container of cells, individual package or container
- Number of recipients affected: number of recipients who received tissues or cells that were associated with a reaction in a recipient. When implicated tissues or cells have been distributed to different Member States, CAs should communicate so as to ensure that the affected recipients and reactions that occurred are only included in one report.
- Total number of recipients of that type of tissue/cell: number of individual patients who had at least one unit of tissues or cells applied as a transplant or during assisted reproductive therapy during the considered year. If this information is not available, it should be noted in the comments space.
- Nature of SAR
- Number of SAR: each individual who has had an adverse reaction following the application of human tissues and cells should be counted as one – when the reaction is serious.

Assessment of severity is based on a scale that ranges from insignificant and non-serious to serious, life-threatening and death. The imputability level is rated as not assessable (NA), excluded/unlikely 0, possible 1, probable 2, and definite, certain 3.

A guidance document on reportable serious adverse events identifies an SAE as one which may have affected the quality and safety of tissues and cells due to a deviation in procurement, testing, transport, processing, storage, distribution, materials. A serious risk is listed as:

• inappropriate tissues /cells distributed for clinical use;
• implications in other patients/donors;
• irreplaceable loss of autologous or highly matched T&C; or
• loss of a significant quantity of unmatched tissues or cells.

With respect to the collection and reporting of SARE data, problems do exist with several countries only able to provide partial information. Consequently, incomplete data and different interpretations and reporting practices among Member States obviate any safe statistical conclusions at this moment. With the further development of the common approach document, a more consistent reporting is expected in the coming years.

1.5 Lessons learned from 7 years of experience: Biovigilance as part of SOHO vigilance

Sophie Lucas-Samuel

The field of biovigilance was incorporated into French law on 21 December 2003 with the publication of Decree no. 2003-1206. Its scope ranged from human organs, human tissues and cells to human cellular therapy preparations and ancillary products. Excluded from its coverage, however, were gametes and embryos, labile blood products, cell and gene therapy products regulated according to the European Union's marketing authorization system, other medical devices, human-derived medicinal products (blood-derived medicinal products), and *in vitro* diagnostic devices. Gametes and embryos are under the regulatory responsibility of the *Agence de la Biomédicine* (Biomedicines Agency).

The scope of French biovigilance extends from the procurement of the donation and the follow-up of living donors to the follow-up of patients after the graft administration. In between are activities related to testing, processing, shipment, preservation, importation, exportation and distribution.

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 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 definitions used in the French biovigilance context for the terms adverse event and adverse reaction are slightly modified (underlined) as compared with those given in the EU legislation. In France, an adverse event is a failure of an element at one step of the process (procurement, processing, testing, and storage) that can entail an adverse reaction for the living donor or for the patient/recipient. An adverse reaction is an expected (or not) and serious (or not) clinical and/or biological manifestation that happens to the living donor (including increased risk for living donor) or to the recipient (including loss of chance).

The French biovigilance network functions at both national and local levels. At the national level AFSSaPS (*Agence Française de Sécurité Sanitaire des Produits de Santé)* is the Competent Authority responsible for centralising information from local correspondents. At the local level, healthcare professionals in health establishments and in tissue and cell establishments, private healthcare professionals, and biovigilance correspondents (443 in 2009) comprise the network.

In 2009, there were 153 notifications to the biovigilance system. Of the 69 adverse reactions, 42% involved organs, 40.6% involved cells, and 17.4% tissues. Of the 84 adverse events, 57.5% involved organs, 30% cells, and 12.5% tissues. In 2009, there were 4,999 organs procured of which there were 4,580 grafts. There were 25,162 tissues procured leading to 34,000 grafts. 423 BM, 5,245 PBC, and 5839 OCB leading to 4,423 grafts. Accordingly, in 2009, there was around one adverse reaction for 493 grafts (0.2%) – less than the vigilance data for labile blood products (0.28%).

The biovigilance system is not without its difficulties and limitations. Within the broad spectrum of medical practice, clinical indications for the same type of product are heterogeneous. Many adverse reactions are not reported to AFSSaPS when they occur because they are considered as expected therapeutic risks. In addition, clinicians may report their adverse events to professional healthcare organisations (e.g. PROMISE for haematological cancer) instead of to the local correspondent and AFSSaPS. Maintaining the biovigilance system at the national level, therefore, is a huge task but feasible and cost-effective over the long term. Activities at the European level should be supported over the long term.

1.6 From EUSTITE to SOHO V&S with WHO

Deirdre Fehily

The European Union has put in place three pieces of legislation addressed specifically to ensuring the quality and safety of human tissues and cells. The primary Directive (2004/23/EC[4]) establishes the responsibilities of Member States (MS) for the regulation of tissues and cells from their donation to their distribution. The two implementing Directives set out specific technical requirements for donation, procurement and testing (2006/17/EC[5]) and others for traceability, the notification of serious adverse reactions and events as well as processing, preservation, storage and distribution (2006/86/EC[6]). The publication of the legislation, however, is only the beginning of a process to ensure a common European standard and approach. The major challenge is in the implementation, maintenance and updating of the legislative requirements.

Significant progress toward effective implementation was made during the EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments) project, which was co-financed by the European Commission. In parallel with developing inspection and authorization guidance, 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 reactions and events (SAREs) as set out in Directive 2004/23/EC (Article 4). It established criteria for reporting SAREs to Compe-

4 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. L102, 7.04.2004, p. 48.

5 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Official Journal of the European Union. L38, 9.2.2006, p. 40.

6 Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cell. Official Journal of the European Union. L294, 25.10.2006, p. 32.

tent Authorities, developed not only a severity grading system but also one for imputability for serious adverse reactions (SARs) with guidance on which level to report. It also drew up an impact grading system (risk matrix including wider system implications) for SAEs and SARs.

Guidance documents were prepared on how to use these tools and on the management of SAEs and SARs that have cross-border implications. Between July 2008 and June 2009, twenty countries participated in a pilot vigilance and surveillance project on the reporting of SAREs. Of the 306 SARE reported, 122 were linked to reproductive cells and 104 to HPC. It is unclear whether SARE are more common with these types of tissues and cells or whether there was more experience in vigilance in those fields and therefore more compliance with reporting requirements. Reported events that were classified as 'life-threatening' or involving death included haemorrhage post retrieval of oocytes and pulmonary haemorrhage in a sibling bone marrow allograft recipient leading to death of the patient. Graded as 'serious' was the appearance of *Enterococcus* and later *Staphylococcus* and *Streptococcus* cultured from a wound following femoral head grafting.

Serious Adverse Event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

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

Directive 2004/23/EC Article 2

EUROCET (European Registry for Organs, Tissues and Cells), a project initially funded by DG INFSO of the European Commission, established a registry on organ, tissue and cell donation and transplantation activity. Combing the data reported to EUROCET on tissue and cell transplantation activity with the vigilance cases collected in the EUSTITE pilot, some approximations can be made regarding the frequency of SARE for particular types of tissues or cells. For example, in 2008, 17,096 corneas were transplanted in 15 of the countries that participated in the pilot phase of the project; there were six serious adverse reactions associated with corneas in those countries in 2009. Of 150 SAEs, 70 could be attributed to human error, 35 to equipment failure and 29 to tissue and cell defects. Examples of SAE included: the identification by pathology of lymphoma in a donor after the cornea had been transplanted; the insemination of a woman with the wrong partner sperm due to a mix-up at the clinic; and reported false-negative syphilis results.

The aim of the SOHO V&S (Substances of Human Origin Vigilance and Surveillance) project, co-financed by the DG SANCO of the European Commission, is to support EU Member States in the establishment of effective vigilance and surveillance systems for tissues and cells used in transplantation and in assisted reproduction. It is coordinated by the CNT with a steering committee comprising nine organisations and it has 26 collaborating partners. The project aims to develop a number of activities highlighted by its predecessor EUSTITE, including the following:

- a report of a survey conducted to better understand the current level of development of V&S systems in the EU;
- a document adapting EUSTITE vigilance tools and terminology to assisted reproduction therapy (ART) and identifying what should be reported in that field;
- a new area on the Eurocet platform for the sharing of vigilance information;
- guidance on vigilance for living donors (non-ART);
- guidance on the investigation of cases involving illegal or fraudulent activity;
- a single guidance document for regulators on the investigation of all kinds of adverse incidents; and
- guidance for hospital level staff on their responsibilities for traceability, adverse reaction detection, investigation and reporting.

1.7 Traceability and Biovigilance in the USA

Timothy L. Pruett

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). Dr. Pruett, Past President of the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) noted that these organizations are operated under contract with the federal government.

The OPTN/UNOS comprises a Board of Directors, which approves policy, a Membership and Professional Standards Committee, which evaluates and enforces member compliance with policy, and a Disease Transmission Advisory Committee (DTAC), which evaluates reports of potential disease transmission. Both committees advise the Board.

In order to ensure traceability, every organ donor is assigned a UNOS identification number. Every organ is rank matched via a central match run with all appropriate recipients and the match run number is recorded. Every organ placement is assessed for allocation consistent with OPTN/UNOS policy. Every organ and recipient is linked and deviations from a match run must be reported and explained.

Over the 2005-9 period, 96,147 deceased donor kidneys were recovered, 83,562 were transplanted and 12,585 discarded (13.1%). Between 2006 and 2009, the kidney discard rate alone by donor status was:

- Standard criteria donor (SCD) 9.3%
  [not an ECD as defined below (less than 60 years with no significant medical morbidities) in a person declared dead through neurologic criteria (brain dead)].
- Extended criteria donor (ECD) 43.4%
  Either:
  1. >50 years and with two or more of the following: history of hypertension, elevated serum creatinine over 1.5 mg/dl or died from a stroke, or
  2. >60 years of a person declared dead through neurologic criteria. These kidneys have been shown on a population-based analysis to have less longevity than SCD kidneys in transplant recipients.

- Donation after cardiac/circulatory death (DCD) 16.9%
  These are all the kidneys that come from donors meeting the various Maastricht criteria (mostly three in the USA). However, they have circulatory death rather than neurologic death.
- DCD/ECD 46.2%
  Combination of the two above
- Overall 18.1%

DTAC was established to assess reports of potential transmission of infection or cancer from donors to recipients after transplantation. It reviews all reports from UNOS members and through peer review, makes a judgment with respect to likelihood of donor-origin of the disease transmissions.
At its face-to-face biannual meeting, DTAC attempts to assign a classification to each event that has completed the review cycle. Classifications are made to help the committee determine diagnoses where education and/or a policy change may be beneficial. The current classification categories for cases that have been reviewed are:

- Expected or unexpected
- Probability of donor-derived nature:
  - **Proven**: Disease in donor and at least one recipient;
  - **Probable**: Disease in one or more recipients with suggestive data about the donor;
  - **Possible**: Evidence to suggest but not prove transmission;
  - **Intervention without documented transmission** (IWDT): No transmission occurred because antimicrobials were used;
  - **Unlikely**: Limited evidence to suggest transmission could have occurred but no transmission documented.

In 2010, 157 reports were received with a complete assessment conducted on 131 (through October 2010) with 19 (15%) being classified as proven or probable transmission. These consisted of:

- 32 malignancies: 8 proven/probable;
- 20 blood borne viruses (HIV, HBV, HCV): 1 proven/probable;
- 12 viral (WNV, CMV, HSV): 1 proven/probable.
- 41 bacteria: 3 proven/probable;
- 16 fungus: 3 proven/probable;
- 9 other (parasites etc.): 3 proven/probable;
- 1 other: excluded from analysis.

DTAC's 2010 results comprised:

- From 8 Donors with proven/probable malignancy (seven deceased donors with malignancy and one live donor report – a renal cell carcinoma that was resected/removed from the donated kidney and the kidney graft was transplanted).
  - 23 organ recipients from identified donors;
  - 11 with graft transmitted disease (not the LD);
  - 8/11 deaths.
- From 12 Donors with proven/probable non-malignancy transmissions
  - 37 organ recipients from identified donors;
  - 16 with graft transmitted disease;
  - 6/16 deaths.

There were 152 reports of suspected disease transmissions in 2009. Twenty-four were proven and nine were probable with 13 recipient deaths related to donor-derived disease transmission. However, all potential risks for disease transmissions, whether ultimately confirmed or disproven, were reported to the member transplant centres caring for the recipients after DTAC was notified.
In 2009, there were over 100,000 people on America's national waiting list. The additions to the list number 54,866 with 21,854 removals due to deceased donor transplants, 6,609 due to living donor transplants, and 10,732 removals due to death or too sick to transplant. There were 13 deaths in 101 recipients with disease transmission from organs.
Screening thresholds are different for deceased tissue or organ donors. An informal survey conducted of four representative organ procurement organizations shows the percentage of organ donors that ultimately donate tissue:

- OneLegacy (Los Angeles): 55%
- Lifesource (Minn, SD, ND): 40%
- LifeNet Health (Virginia): 45%
- Transplant Resource Center of Maryland: 25%

The evaluation process for tissue donation and the resultant discard rate differs from organs in terms of time and testing performed. The amount of retrieved musculoskeletal tissue subsequently discarded is about 15-17%. The most common reason for tissue discard is positive serology (+40%) and autopsy findings (about 10-15%). However, the time to make a final decision and release tissue from quarantine is usually 30-60 days. If an autopsy report is needed, the time is increased to around 120 days. Certainly, the processes and thresholds used in tissue donation differ from those required for organ donation decisions.
With respect to tissue traceability, manufacturers are required by the FDA to maintain traceability from recovery to distribution (e.g. to the hospital). Hospitals are required by the Joint Commission to maintain traceability to the recipient, although compliance is far from complete. There is no discrimination regarding tissue types and/or processing methods (e.g. terminally sterilized vs. aseptically processed, etc.).
As for biovigilance in the USA, recognition of disease transmission through organs is not yet complete, as evidenced by increasing numbers of reports since 2005. However, the numbers appear to be plateauing. In the big picture of biovigilance (system assessments of biologic products transferred from one person to attain therapeutic benefit), the risk of death from lack of organ availability appears to be significantly greater than

that of disease transmission. It is incumbent that regulatory agencies consider the effects of proscribed screening practices for disease transmission risk assessment upon cumulative risk of death to potential organ recipients and not solely a unidimensional infectious/neoplasm risk. If organ availability is significantly diminished without proportional reduction in adverse disease transmission events, then the biovigilance efforts will result in more overall deaths due to its negative impact upon numbers of transplantable organs. Using the tissue donor guidelines is unlikely to garner significant benefit as the issues and the time processes for determining suitability are very different.

2 V&S: Communication for Action: an exploration of vigilance developments around the globe

Chair: David Eastlund

2.1 ART vigilance in France: overview of a new vigilance system

Hervé Creusvaux

ART vigilance in France is defined as the surveillance of adverse events associated with gametes, germinal tissues and embryos used for the purposes of assisted reproduction therapy (ART) or fertility preservation and of adverse reactions which may occur in the donors of gametes or in patients treated for infertility. The Biomedicine Agency (*Agence de la biomédicine*) (ABM) is the CA for the notification of adverse events and reactions (AER) associated with ART, which in France is mandatory.

Notification of SARE associated with ART is assessed during the processes of authorisation of ART activities, certification of hospitals, and inspection according to an established set of criteria.

The reporting of an SARE does not result in the launch of an inspection by the CA except if there is some form of legal action.

The French ART vigilance system was established first in February 2007. The requirements of the EU tissues and cells Directive were transposed into French law in 2008 through an additional decree. In 2008, ART activities represented 68,150 *in vitro* fertilisations (IVF), 53,365 intra-uterine inseminations (IUI) and 16,105 transfers of frozen embryos. There are now 274 ART establishments in the country of which 105 are performing ART clinical activities. Each establishment has identified a local vigilance correspondent.

Although it was set up independently of the organ, tissues and cells vigilance systems in France, there is close coordination with other vigilance systems, e.g. the medical devices vigilance system and the biovigilance system at AFSSaPS.

The notification of SARE comprises 2 steps: immediate notification (notification form part A) and follow-up actions and conclusions (notification form part B). Part B includes assessment of SARE typology, seriousness, and imputability. Notification of SARE is reported via an on-line system using the internet.

The ABM collaborates extensively with ART health professionals, not only through the reporting of SARE but through the feedback information provided to them. A spirit of mutual confidence has been established as there are no penalties involved when SARE are reported. There is a continued effort to improve the tools for reporting, analysing and investigating SARE. The ART vigilance system is oriented to learning from errors made. Its scope includes SARE related to ART practices (public health and patient safety).

Over the years 2007-2010, there were a total of 259 adverse events and 596 adverse reactions reported to the vigilance system with an increasing trend each year. With respect to typology, 54% of the SARE were linked to ovarian hyperstimulation syndrome (OHSS) with 19% to ART procedures. Of the 476 cases related to ovarian stimulation, 360 were OHSS resulting in patient hospitalisation. Of the 123 adverse events linked to the loss of gametes or embryos, 57 were due to equipment failure and 33 to human error.

Among various actions carried out by the ABM, the following may be pointed out.

- Investigation on the role of puncture needles in relation to hemoperitoneum. This has been done in collaboration with AFSSaPS and its medical devices vigilance system.
- Development of tools for self-assessment of practices in case of severe OHSS.
- When the mix-ups of gametes occurred, a 'Dear doctor letter' has been sent to all ART centres.
- Finally, after the death occurring in 2 young women with Turner's Syndrome who received ART treatment, specific recommendations to monitor pregnant women with this condition were published (*Cabanes, EJOG, 2010*[7]).

The next steps and challenges facing the ABM are to continue to develop a culture of reporting among ART health professionals (and others); sustain their mutual trust; improve feed-back to them; and develop coordination with other national vigilance systems and cooperation with other EU Member States.

2.2 V&S in Brazil: link with clinicians and achievements

Daniel R Coradi Freitas

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. In 2003, ANVISA established the 'Sentinel hospital' project in 100 hospitals spread throughout the country and by 2010 it comprised more than 200 hospitals. The project involved the notification of adverse events in drugs, medical devices and blood. An on-line informatic system named NOTIVISA was then established in 2006 to facilitate the reporting of adverse events (AE) and technical complaints (TC). It covered an extensive list of products including drugs and vaccines (also those involved in clinical research), diagnostic kits, medical devices, medical equipment**,** blood, cosmetics and pesticides. It did not, however, include organs, tissues and cells.

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7 Cabanes L., Chalas C., Christin-Maitre S., Donadille B., Felten M.L., Gaxotte V., Jondeau G., Lansac E., Lansac J., Letur H., N'Diaye T., Ohl J., Pariente-Khayat A., Roulot D., Thepot F., Zénaty D., *Turner syndrome and pregnancy: clinical practice. Recommendations for the management of patients with Turner syndrome before and during pregnancy*. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2010. **152**(1): 18-24.

In 2007, the Bio and Haemovigilance Office (UBHEM) was created. It then became mandatory, under an Act issued by ANVISA, for all eye, bone and muscle banks to report any adverse event involving their tissues to UBHEM. Unfortunately, the type of AE to be reported was not defined, there was very low acceptability and clinicians did not inform eye banks when problems occurred.
The year 2009 saw the Ministry of Health, under its Act nº 1660/2009, establish VIGIPÓS – the system for the vigilance, surveillance and investigation of AE and TC related to health services and health products (post market surveillance). Coordinated by ANVISA, VIGIPÓS includes all health products.
Under the ANVISA Act, it became mandatory in 2010 for industries to report adverse events involving drugs and medical devices. The NOTIVISA system was upgraded the following year. It is anticipated that organs, tissues and cells will be included in VIGIPÓS in 2012 and in NOTIVISA in 2013.
The challenges related to vigilance and surveillance that Brazil now faces include:
• Establishing a unique coding system for donor identification;
• Initiating the biovigilance of infectious disease in tissues (marrow, cornea and bone);
• Including the reporting of renal and cornea failures;
• Including cell-based products into the reporting system.

2.3 Haematopoietic stem cell donor reactions and events

Bronwen Shaw

As Chair of the Clinical Working Group (CWG) of the World Marrow Donor Association (WMDA), Dr Bronwen Shaw addressed the matter of adverse reactions and events associated with haematopoietic stem cell donors. The WMDA is an organization which fosters international collaboration to facilitate the exchange of high quality haematopoietic stem cells for clinical transplantation worldwide and to promote the interests of donors. Its Clinical Working Group not only produces guidelines, recommendations and standards involving clinical aspects related to the donation of bone marrow and peripheral blood stem cells (PBSC) but also maintains the adverse events registry, S(P)EAR – the central reporting system for adverse events in unrelated donors. S(P)EAR is in fact comprised of two registries:
1) SEAR – the serious events and adverse reactions registry, and
2) SPEAR – the serious product events and adverse reactions registry.
The SEAR registry compiles donor data related to: life-threatening disease, death, those who required in-patient hospitalization or considerable prolongation of existing hospitalization, and those who are facing persistent or significant disability/incapacity. It also compiles data on events related to an anaesthetic, cardiac complications, infective complications, mechanical injury, haemostasis and (late) malignancies/auto-immune 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).
Information included in S(P)EAR originates with the Chief Medical Officer (or other designated individual) of each registry who is responsible for reporting it to the office of the WMDA. This reporting is a requirement for WMDA accreditation. Once information is received, the WMDA office, which keeps a central registry, informs the chair of the CWG who presents a biannual report to the association. Each year, the WMDA formally requests each registry to confirm that all events have been reported, de-identifies them and puts them on its website – http://www.worldmarrow.org/. This site also provides information related to adverse events, links to manuals, reporting forms, and reports.
S(P)EAR has made considerable progress of late. It has developed an online reporting system, improved its reporting forms, introduced conformity in its definitions and developed an 'internal review board' which aims, inter alia, to expedite reporting both within and outside the WMDA.
In spite of its progress, S(P)EAR is currently trying to determine the best way to ensure that reported events in unrelated donors are communicated to the physicians looking after related donors, to identify the events that should be reported as the registry at this time is only for severe events and reactions, to determine how long after transplantation should data be collected, and whether this system should be extended to related donors, taking into account issues such as capacity and cost.

2.4 50 years of cornea vigilance by the Eye Banking Association of America

Marian Macsai

Dr Marian Macsai, Chair of the Eye Bank Association of America (EBAA) presented the history of the association. Founded in October 1961 with 25 member banks, it had by 1980 established its medical standards, by 1981 had introduced EBAA accreditation, by 1990 had initiated an adverse reaction reporting system and in 2004 the Online Adverse Reaction Reporting System (OARRS). Membership comprises 100% of the eye banks in the United States with additional international membership. The EBAA establishes Medical Standards for the procurement and distribution of ocular tissues, produces bi-annual updates, and provides certification and education for eye bank technicians. It has an international process for accreditation of eye banks and publishes a technical procedures manual.
The uses of ocular tissue are:
- Full Thickness
  - Penetrating keratoplasty
- Partial Thickness
  - Epithelial Keratoplasty
  - Endothelial Keratoplasty
  - Lamellar Keratoplasty
- Sclera Grafts
  - Hydroxyapatite
- Scientific Studies

Ocular tissue nomenclature is established by the ICCBBA Technical Advisory Group for the ISBT 128 coding standard. Draft Final Recommendations are put forward by the EBAA, EEBA (European Eye Bank Association), EBAI (Eye Bank Association of India), EBAANZ (Eye Bank Association Australia New Zealand), and the APABO (Pan American Association of Eye Banks) with the aim of achieving global standardization of eye tissue nomenclature**.**

In 2009, according to U.S. Eye Banking Statistics, there were 59,784 corneas provided: 42,606 were used in the USA with 17,178 exported. There were over 100,000 donors.

With respect to eye bank adverse reaction reporting, the EBAA Medical Advisory Board requires that recipients be tracked and that the providing banks seek a 3 – 12 month follow-up. Reporting, which is part of the accreditation process, was redesigned in 2004 for online submission.

Adverse reactions are defined as incidents that directly pose a health risk or impact safety for the recipient. All other adverse events in the transplantation processes are reported as part of QA/QI system within the bank, and require evaluation and documented corrective action (policy change or education) along with reporting to EBAA statistics. All tissue is tracked with 28,771 corneas having been reported as unsuitable for transplant.

In the context of an eye bank, an adverse reaction is any communicable or other disease reasonably likely or proven to be transmitted by transplantation of donor eye tissue including infection and biologic dysfunction. [G1.000 Medical Standards EBAA (updated definition 7/2007)]. It is important to remember that the recipient is not tested prior to transplantation.

In accordance with medical standards, any systemic infectious disease such as HIV, hepatitis, syphilis, or CJD that develops in a recipient, whether or not it is suspected to be due to donor tissue, must be reported to the EBAA (G1.000).

A '**Reasonably likely**' graft transmitted infection exhibits signs of inflammation or infection consistent with the infectious agent (pain, redness, loss of vision) from or near the operative site within one month of implantation. The likelihood is greater if there is**:**

a. A match between the pre-implant donor and recipient culture findings in a recipient with no known pre-operative, intra-operative, or identified risk factors for the disease;
b. Report of graft-associated infection in other recipients of ocular tissues from the same donor;
c. Evidence of failure to comply with SOP for aseptic technique prior to distribution of the tissue.

A '**Proven**' graft transmitted infection is one where there has been confirmation by appropriate laboratory testing (e.g. genotyping, PCR wet prep) that demonstrates scientific evidence linking the infectious agent in the recipient with the donor samples, OR when testing is not possible, there is presence of the same infection in both recipient and donor with no other identified risk in the recipient.

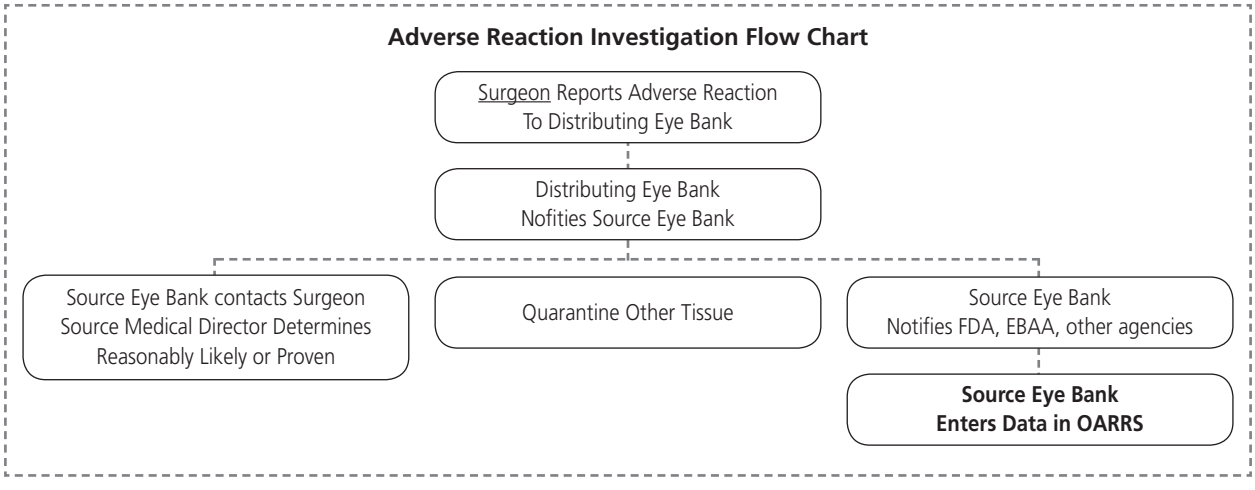
An example of '**Donor-associated primary graft failure**' or 'Biologic dysfunction' is corneal edema present from the time of keratoplasty that does not clear after 8 weeks and has no known operative or post-operative complications or recipient conditions that explain the biologic dysfunction**.**

In order to investigate an adverse reaction, it is necessary to make use of the following common definitions:

- Recovery establishment: an entity that procures tissue from a donor;
- Source establishment: an entity that releases tissue following donor eligibility determination;
- Processing establishment: an entity that performs post recovery tissue preparation;
- Storage establishment: an entity that retains tissue at any time prior to distribution to the end user;
- Distribution establishment: an entity that is reimbursed for providing tissue to the end user;
- End User: a hospital, surgeon, surgicenter, research center or any entity that uses tissue.

The steps in the process are:

- The surgeon reports the adverse reaction to the distributing eye bank;
- The distributing eye bank notifies the source eye bank (unless it is the same entity) which is responsible for coordinating the investigation;
- Other ocular tissue from the same donor is quarantined and the status of mate tissue investigated;
- The source eye bank notifies other agencies/stakeholders.



Reporting of the incident to the EBAA is not done by the surgeon. The Medical Director of the source eye bank contacts the surgeon to determine if there are possible pre-existing/pre-disposing conditions, intra-operative complications or possible sources of contamination that may have influenced the outcome. If pre-existing or pre-disposing conditions do exist, the case is reviewed with the source eye bank to determine if further investigation is warranted.

The EBAA Online Adverse Reaction Reporting System (OARRS) enables easy reporting of adverse reactions, surgery, microbiological results, tissue-mate status (the status of the other cornea from the same donor), tissue source, transportation and comments. The EBAA Medical Review Subcommittee reviewed data over the 1991-2010 dealing with primary graft failures, endophthalmitis, keratitis, cornea dystrophy/degeneration and sclera graft rejection.

In order to best manage adverse reactions, several steps should be followed:

- Obtain information- gather the facts;
- Evaluate the mate cornea;
- Recall or quarantine the tissue;
- Assess the system;
- Inform the surgeon;
- Advise the medical director;
- Evaluate the donor event relationship;
- Report to the EBAA;
- Implement changes if necessary;
- Get outside help if needed such as infection control, ID, microbiology, CDC, EBAA.

When information about an adverse reaction is received, the Medical Review Subcommittee reviews the reported adverse reaction, looking for trends or specific site related issues, requests an 'off cycle' inspection of an eye bank, and notifies industry or testing facilities, should trends warrant, requesting an investigation.

2.5 EFRETOS: EU organ project with V&S as part of recipient follow-up

Rosario Marazuela, Beatriz Domínguez-Gil, Axel Rahmel

EFRETOS – the European Framework for the Evaluation of Organ Transplants – is 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 has included recommendations on the implementation of a vigilance system as an integral part of the monitoring of such patients.

The project is being developed by a consortium of seven partners [*Eurotransplant*, project leader, *European Society of Organ Transplantation*, the *Agence de la Biomédecine* (France), *Centro Nazionale Trapianti* (Italy), *NHS Blood and Transplant* (United Kingdom), *Organización Nacional de Trasplantes* (Spain) and *Scandia Transplant*], with collaborating partners from the Czech Republic, Germany, Greece, Italy, the Netherlands, Poland, Portugal, Slovakia and Slovenia. The specific objectives of the project are: to prepare the specifications for a registry of registries on the follow-up of transplanted recipients: to promote common definitions of terms and methodology: to set up a quality assurance system for obtaining high quality data on transplantation outcomes: and to provide recommendations on setting down a safety management system, including a Vigilance System applied to human organs intended for transplantation. EFRETOS is addressing these objectives through different work packages (WPs). WP6, led by the *Organización Nacional de Trasplantes* (ONT), is responsible for looking into issues related to safety management with its content being reviewed during the Bologna meeting of the NOTIFY project.

It is noted that all health care interventions are aimed at an improvement in health **–** a benefit – but entail a probability of hazard – a risk. Thus there is a risk/benefit ratio. The possibility of disease transmission is inherent in any transfer of biologic material between individuals. This risk should be **known, quantified, and reduced** as much as possible, this being the objective of a Safety Management System. In the transplantation of organs and substances of human origin, the risk is often shared by teams physically located distant from each other.

Classification of donors

Organ donors can be classified according to the risk they pose for transmitting diseases. In the EU context, according to a classification provided by the *Centro Nazionale Trapianti* (CNT), an individual designated as a **standard risk** donor would not have shown evidence or particular identified risk of any transmissible disease during the evaluation process. There are four classifications, however, for non-standard risk donors (NSRD). One designated as at **unacceptable risk** would have been identified as not suitable for transplantation due to medical history or test results implying real risk of infection. The designation **increased but acceptable risk** would indicate a donor with risk for transmissible organisms or diseases that were identified during the evaluation process, but the use of the organ(s) would be justified due to the recipients specific health situation or the severity of his/her clinical condition. A **calculated risk** (criteria referring to protocols for elective transplants) would indicate a donor with transmissible diseases, but transplantation is allowed for a recipient with the same disease or with a protective serologic status, independently of the severity of his health conditions. **Not assessable risk** would identify a donor in whom the evaluation process does not allow an appropriate risk assessment for transmissible diseases.

NSRD have increasingly been used; therefore, EFRETOS proposes to include information on NSRD and the recipients of these transplants as part of the systematic data collection performed in dedicated follow-up registries (and hence, in the registry of registries to be built). As a result, the risk of donor to recipient disease transmission may be retrospectively estimated by analyzing such pooled data. The first part of EFRETOS WP 6 has in fact proposed a number of variables that can be incorporated into the records in order to generate such evidence on NSRD. They are defined on the basis of one of the following conditions: acute intoxication as the direct cause of death; past or present history of malignancy; positive serology – anti-HCV, HBsAg, Anti-HBc; risk factors for viral infectious disease/serology pitfalls; or emergent infectious diseases. Following a literature review, a survey among EFRETOS participants, and drawing upon expert opinion, recommendations were made for this dedicated data collection in a Registry of Registries, with such information classified as mandatory, mandatory in the future, or voluntary.

In the case of disease transmission, a risk may be identified **before the transplantation** and accepted by both the recipient and the physician when balanced with the risk of not performing the transplant, as mentioned above (NSRD situation). The risk of disease transplantation estimated before transplantation, however, may change after such a procedure has been performed, as new information on the donor or the organ becomes available or because clinical manifestations of disease transmission become apparent in the transplanted recipient(s).

Directive 2010/53/EU[8] sets out in Chapter II on the quality and safety of organs two Articles – one on traceability (Article 10) and one on reporting system and management concerning serious adverse events and reactions (Article 11). There are requirements for the systematic collection of information (through notification), the analysis of reported information and the management of reported and analysed information. This can best be organized in networks whose main objective is prevention.

A survey conducted in 2003 on the number of traceability and reporting systems in EU Member States, as well as Turkey and Norway, showed that 25 had a national registry containing data on the origin and destination of organs, 20 had a system of reporting adverse events/reactions, while there was no system that allowed tracing of cross-border cases in spite of the fact that there are about 4,000 organs exchanged between Member States (MS) each year. However, the result of a survey conducted by EFRETOS showed that only one MS – France – had a systematised approach to the vigilance of organ transplantation that is supported by national regulation.

EFRETOS, through the second part of WP 6, aims at providing minimum recommendations to Member States for the implementation of a standardized vigilance system (V-System) on human organs intended for transplantation as required by Directive 2010/53/EU. The objectives of an organ V-System are to prevent the transmission (occurrence) of a health problem to organ transplant recipient(s) linked to the donor or to the phases extending from donation to transplantation and to living organ donors linked to donation, testing, characterization or procurement.

The proposed design for a V-System, essentially based on a number of steps, namely reporting, assessment and management, has included recommendations on the elements of the system, as well as the necessary functions and flows required for its appropriate implementation. Reporting criteria proposed for EFRETOS are specified in detail as they can be of interest for the audience and the objectives of the Notify Project.

The drafted reporting criteria for a serious adverse event (AE) which are recommended are:

a) Deviation from operating procedures or other AE during the chain from donation to transplantation that results in the deterioration of the quality/safety of the organs, when at least one patient has been transplanted or subjected to anaesthesia for the purpose of transplantation (even if the organ has not been transplanted);
b) Infection or positive serological state discovered in an organ donor (deceased or living) when at least one organ has been transplanted;
c) Malignant tumour discovered in an organ donor (deceased or living) when at least one organ has been transplanted;
d) Discovery of any other potentially transmissible disease in an organ donor (deceased or living) when at least one organ has been transplanted;
e) Other.

The drafted reporting criteria for serious AR in transplanted recipients are:

a) Unexpected and serious immunological reactions;
b) Abandoned transplantation procedure due to a deviation in an operating procedure in the process or to other AE involving unnecessary exposure to risk;
c) Unexpected infection or serological conversion in an organ transplant recipient that might be donor-transmitted or derived from the donation process;
d) Malignant tumour in an organ transplant recipient that might be donor transmitted;
e) Other unexpected disease in an organ transplant recipient that might be donor-transmitted;
f) Other.

The reporting criteria for serious AR in living donors are:

a) Death of a living donor as a consequence of donation;
b) Serious, surgical and non-surgical, donation-related complications in a living donor;
c) Loss of a graft from a living donor before transplantation is performed;
d) Other.

The recommendations are proposed bearing in mind the specific characteristics of organ donation and transplantation, avoiding as much as possible overburdening the system and respecting the internal organisation of each MS. In order that the system objectives are met and the principles under which the system is designed are observed, a test of the proposed recommendations should be considered from each MS before its full implementation.

2.6 V&S for SOHO in Singapore

Yvonne Koh

Singapore is a small tropical country in South East Asia comprised of one main island and 63 surrounding islets. With a multicultural [Chinese (77%); Malays (14%); Indians (8%); others (1%)] population of 4.8 million, it has four official languages – English, Malay, Mandarin and Tamil. The infant mortality rate is 2.1 per 1000 live births and the average life expectancy rate is 80.6. Cancer, heart disease, and pneumonia are the leading causes of death.

A Working Group to deal with cells, tissues and related therapeutic products was formed in 2006. It is comprised of representatives from the Ministry of Health (Health Performance Group, Health Regulation Group including the Regulatory Compliance Division and legal department) and branches of the Health Sciences Authority (Clinical Trials, Pharmaceuticals and Biologics, Generics and Biosimilars, Medical Devices, Vigilance, Audits, Compliance and legal department).

Human cell- and tissue-based therapeutic products (CTT) are those containing or consisting of autologous or allogeneic human cells or tissues that are used for or administered to, or intended to be used for or administered to, human beings for the diagnosis, treatment or prevention

8 Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation. Official Journal of the European Union. L207, 6.08.2010, p. 14).

of human diseases or conditions. Human conditions include any revision or change in the appearance, colour, texture, structure, or position of bodily features of a person, which most would consider otherwise to be within the broad range of 'normal' for that individual.

Excluded from the CTT classification are human tissues for transplantation regulated under the Human Organ Transplant Act (HOTA) i.e. liver, heart, cornea and kidney, and whole blood and blood components intended for transfusion, which are not considered to be high-risk CTT products. Blood components include red cells, white cells, platelets, plasma, cryoprecipitate, or granulocytes collected by either manual whole-blood collection or automated aphaeresis techniques. Tissues or cells for assisted reproductive procedures are also excluded from the CTT classification.

Regulations have been proposed that would have the Ministry of Health (MOH) regulate the clinical use of CTT products and the Health Sciences Authority (HAS) regulate the quality, safety and efficacy of high risk CTT products as required under the Medicines Act for other biological medicinal products. All registered practitioners will have to get a CTT specialized service license from the MOH before administering such products to their patients under the Private Hospitals and Medical Clinics Act (PHMCA). High-risk CTT products will be regulated first with low-risk CTT products regulated at a later phase. MOH CTT license for tissues and cells will include requirements for informed consent; donation, procurement and testing; and personnel, facilities, documentation and quality assurance.

Products will be classified by the HSA as either 'high-risk' or 'minimally manipulated' cells and tissues (MMCTs). A high risk CTT product is one that has been subjected to substantial manipulation, is intended for non-homologous use, or is combined with a drug, biologic or device. Additional controls will be required for high risk products including a GMP certificate, mandatory serious adverse reaction reporting, and a mandatory patient registry.

With respect to vigilance, the existing systems for detecting safety issues continue to be applicable to CTT products. Pre-market licensing conditions will be required including a risk management plan, product sales data, educational materials to physicians, and specific post-marketing follow-up of patients for products that may have potential for long term complications. All fatal and life-threatening adverse reactions will have to be reported within seven days and other serious AEs within 15 days.

Enhanced vigilance requirements will include mandatory adverse drug reaction reporting, both serious and non-serious; the establishment of an online patient registry into which physicians have to register their patients using high risk HCTs. This registry will be maintained by HSA and the data entered will form the basis for capturing patient exposure.

The rationale for these enhanced vigilance requirements is to identify early complications related to HCTs, such as infectious disease, complications linked to surgical procedures, as well as adverse reactions reported by market authorisation holders and healthcare providers. This form of vigilance will hopefully help in the identification of late complications such as malignant diseases, immunogenic reactions, and emerging diseases with long incubation periods, so that these potential signals will not be missed.

The objective of the patient registry is to collect information on those who are being prescribed high-risk HCT products, the brand name and batch number of the product being prescribed for each patient, and the adverse reactions that are bring reported. The reported information will serve as a patient exposure database for the purpose of:

a) Determining incidence of adverse reactions to high risk HCTs;
b) Vigilance and surveillance;
c) Future epidemiological studies and collaboration with existing registries e.g. National Registry of Diseases Office, National Death Registry, National Birth Defect Registry and the Communicable disease Centre to track long-term patient outcomes.

The information captured in the registry will include specific data on the patient, products and treating physician. It will also collect all serious adverse reactions reported for high risk HCTs that are mandated for use under the MOH directive for doctors and pharmaceutical companies. The Registry will have an online ADR reporting form for doctors and pharmaceutical companies to complete.

Singapore's haemovigilance programme started in 2002 as a joint initiative between the Blood Services Group and the public and private hospitals. It aims to gather and analyse reports of all adverse and untoward events occurring during transfusion of blood and components; gather and analyse 'near miss' events during the transfusion process; use the information acquired to determine the morbidity of transfusion; provide guidance on corrective measures to prevent the recurrence of some accidents, and to improve transfusion safety; and to improve public confidence by demonstrating to public, patients and professionals the safety of the existing transfusion system.

Recent Directives have been issued to healthcare institutions by the Ministry of Health for the review of serious reportable events include the establishment of a quality assurance committee to review serious reportable events; corrective action to address areas and issues identified, and reporting to the MOH within two working days of identification of an event. 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;
- Incident associated with assisted human reproductive procedure which has, or may have, resulted in:
  - Death, life-threatening condition, incapacitating condition, prolonged hospitalisation;
  - Transmission of communicable disease;
  - Loss or damage to embryos;
  - Gamete or embryo misidentification or mix-up.

2.7 Croatia, the challenge of establishing a SOHO V&S system

Vanja Nikolac

Croatia is a small country (56,594 km^2) of about 4.5 million people (2010 estimate) with a population density of 81 per square kilometre. Assisted reproductive technology services are provided through establishments spread across the country; practically every gynaecological clinic provides these services as well as various private institutions. The legal framework under which these services are provided is the Act on Explantation and Transplantation of Parts of the Human Body for Therapeutic Purposes (OG 177/2004; OG 45/09). In addition, there are several ordinances among which are measures to ensure the safety and quality of parts of the human body for medical use, procedures for allogeneic haematopoietic stem cell collection, processing and transplantation, methods of co-operation for the exchange of organs or tissues for transplantation, and the reporting of serious adverse events and reactions (OG 67/09).

The Act on Medical Fertilization (OG 88/09; OG 137/09) includes ordinances covering donor assessment procedures, reproductive cell reception and storage procedures, spouse/extramarital spouse consent on reproductive cells donation, and consent for procuring, preservation and storage of spermatocytes and oocytes.

The Competent Authority is the Ministry of Health and Social Welfare. It is responsible for national biovigilance of organs, tissues and cells. *Inter alia*, it establishes and manages the SAR & SAE registry, assesses reports coming from tissue banks, procurement and transplantation establishments and defines necessary measures, and notifies tissue establishments about SAR and SAE based on information acquired from other sources. Within the Ministry, the Directorate for Medical Affairs oversees the Inspection Service with two departments: Department for Inspection and Monitoring of Blood, Tissues and Cells, and Department for Health Inspection, both of which are involved in aspects of the collection and use of blood, tissues and cells.

Establishing an effective and efficient biovigilance system requires educating not only staff of the Competent Authority, but tissue and ART establishments as well as end users and clinicians. An EU-funded workshop on tissues and cells for regulators was held in Croatia in December 2009. A project (IPA 2009) was funded by the EU in the context of Croatia's application for EU membership. The project on Strengthening the Institutional Capacity for Blood, Tissues and Cells (T&C) involved an assessment of the current situation regarding practices and relevant documentation linked to biovigilance in all tissues and cells establishments and the preparation of a comprehensive assessment report. It recommended designing guidelines and SOPs on biovigilance for T&C establishments. The SOPs should include communication protocols including one for rapid alert. The SOPs should be in accordance with the EU regulations and best practices and with Croatian legislation. There should also be guidelines for the design of a biovigilance (blood, tissues and cells, ART) system database.

There is now a strategic plan for tissue banking development. This includes a common model for tissue procurement, storage and distribution at the national level and the establishment of a common SAE & SAR vigilance and surveillance system.

2.8 AATB guidance on 'Identifying, reporting, and investigating tissue recipient adverse reactions'

Scott Brubaker

Significant advances in tissue processing and allograft development during the 1990's led to an increased use of tissue allograft. Hospital routine death-referral requirements resulted in a rise in the number of organ, ocular and tissue donations (as well as 'shared' donors) and a further growth in the use of tissue grafts.

Early in the new millennium, there was increased recognition of disease transmission via allograft transplantation. Cases of *Clostridium* (and other bacteria) contamination of tissue allografts as well as one death were reported. Testing and communication failures resulted in HIV and HCV transmissions. Consequently, the AATB identified gaps and began to develop guidance to overcome them.

Several events influenced the AATB. In the summer of 2005, the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and Health Resources and Services Administration (HRSA) convened a Workshop on 'Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention'. The workshop was initiated by CDC's Blood, Organ and Other Tissue (BOOT) Safety Working Group. The American Association of Tissue Banks (AATB) participated in the workshop and provided survey results regarding tissue bank experiences during 2003 and 2004 when handling reports of possible allograft-caused infections. Trends and gaps were identified.

From the autumn of 2005 through early 2009, the Transplantation Transmission Sentinel Network (TTSN) pilot project was underway. Its aim was to detect, communicate, track, and prevent the transmission of infections from organ, tissue and ocular donors to transplant recipients. In 2007, therefore, the AATB Task Force was formed within a framework of 'identifying, reporting and investigating adverse outcomes'. Its goals are to fill gaps identified by surveys and experiences, develop a best practice guidance document; harmonise with similar projects (where possible), and seek support from professional associations of tissue allograft end users and other clinicians as well as other stakeholders.

The AATB Guidance Document that has been drafted 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. In order to recognize the possibility of disease transmission to a recipient there should be both clinical and laboratory evidence to support the notion the allograft may have caused the bacterial/fungal or parasitic/viral infection. A 6-month period (post-op) has been selected for suspicion related to a 'bacterial/fungal' transmission since this is evidence-based from organ and tissue transplant infection investigations, and a year post-op was selected for suspected transmission involving a viral or parasitic disease. Reporting of common community-acquired diseases that occur post-op (flu, colds) is not desired.

Investigations leading to probable and proven infections show that:

- symptoms were recognized between 2-113 days post-op;
- patients were readmitted within 30 days of surgery; and
- unexpected organisms from the wound or site were cultured.

Recognition criteria are being developed for disease transmission when there is a malignancy or a human TSE involved. If there has been a graft failure reported, there is the possibility of hypersensitivity or a toxicity reaction (as per EUSTITE). The reason for a structural failure should consider a link to noncompliance by the recipient; the investigation should not solely be focused on the allograft.

Completion of the guidance document is anticipated in 2011 with consideration being given to a focus on V&S for tissue allograft types that pose the most risk. The document will be widely disseminated to all stakeholders in order to optimize recognition, reporting and investigations. In the short term, tissue V&S systems should harmonize their terminology in order to improve the ability to collect useful global information. International system designs should be based on mandatory participation with national systems from which the allograft was sourced.

3 Engaging all relevant stakeholders in V&S

Chair: Rosario Marazuela

The following presentations set out the experience of regulators and professionals and identify areas of collaboration for successful vigilance of cells, tissues and organs.

3.1 FDA and Biovigilance

Diane Maloney

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

According to its vision statement, CBER aims to use sound science and regulation to: protect and improve public and individual health in the USA and globally; facilitate the development, approval, and access to safe and effective products and promising new technologies; and strengthen CBER as a pre-eminent regulatory organization for biologics.

The regulatory framework for CBER products includes a premarket review for biological products (e.g. vaccines, gene therapy) which are then licensed /approved if FDA finds that they meet the statutory criteria. The process for ensuring their safety includes pre-licensure evaluation of clinical, nonclinical, product and manufacturing data, as well as inspection of the facility itself. There may be a pre-licensure review of the pharmacovigilance plan. There are also biennial inspections and post-marketing evaluations of adverse event reports and studies. CBER also regulates some products for which premarket review is not required. A number of tissue products such as skin and bone, are examples of such products and CBER regulates these products under the Public Health Service Act requirement for preventing communicable disease transmission.

FDA has two systems for post-market safety monitoring of approved medical products – a passive system and an active system, which includes the Sentinel Initiative. The former draws upon reports from external sources, such as healthcare professionals, patients, manufacturers and adverse event reporting systems, about suspected adverse reactions. The latter is a long-term effort to create a national electronic system for monitoring product safety. It is hoped that this will enable the FDA to actively gather information about product safety after approval with the assistance from collaborating institutions (e.g. academic medical centres, health care systems and health insurance companies). The goal is to access data from 25 million people by July 2010 and 100 million people by July 2012.

With respect to human cells, tissues, and cellular and tissue-based products (HCT/Ps) intended for implantation, transplantation, infusion, or transfer into a human recipient, there are two regulatory pathways based on risk – lower risk products are regulated solely under section 361 of the Public Health Service Act, which provides FDA authority to develop regulations to prevent the introduction, transmission, or spread of communicable disease. The second pathway calls for pre-market review and approval based upon a finding by FDA that the products are safe, pure, and potent before they can be marketed.

CBER is involved in many biovigilance activities. Examples of some of these activities include CBER's work with the Department of Health and Human Services, workshops, outreach, and international engagements. CBER participates in the Department of Health and Human Services' Advisory Committee on Blood Safety and Availability. This expert advisory committee advises the Department of Health and Human Services on issues related to transfusion and transplantation issues linked to blood, organs and tissues.

As part of its activities, CBER reviews adverse reactions. An adverse reaction is defined as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that it caused the response. For the '361' HCT/Ps, 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.

CBER has an interdisciplinary Tissue Safety Team (TST) that follows a coordinated approach for handling HCT/P adverse reaction reports. Each one that is received is reviewed, a follow-up investigation is conducted, the clinician and manufacturer are contacted for additional information as needed, and all cases are evaluated at TST meetings. Deviations related to distributed HCT/Ps are investigated and those related to core good tissue practices must be reported. Deviations are defined as: 1) an event that represents a deviation from the regulations, standards or specifications that relate to prevention of communicable disease transmission or 2) that is an unexpected or unforeseeable event that may relate to prevention of communicable disease transmission.

CBER representatives serve on the Public Health Service Biovigilance Task Force. One of this task force's objectives was to review current biovigilance efforts in the USA and recommend a national plan for biovigilance in the future. The Task Force issued a report identifying a number of gaps including the fact that there is limited information on the potential for HCT/Ps to transmit infectious disease, and the limited ability to ascertain whether reported infections in HCT/P recipients can be attributed to the tissue. Additional findings included the following: regulations concerning HCT/P adverse reaction reporting do not extend to the level of the healthcare facility or healthcare provider; current mechanisms for tracking HCT/P grafts to the level of the recipient are limited; adverse reaction reporting for HCT/Ps regulated solely under Section 361 of the PHS Act is limited to infectious diseases; and information about adverse reactions in other recipients of HCT/Ps from an implicated donor may not be readily available. Further information about CBER's activities in biovigilance is available at http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default

3.2 Italy's outreach to transplant clinicians, recipients, donors and the public

Alessandro Nanni Costa

In Italy, the organ transplantation system is a well-functioning network with strong links among all parties involved in the process from the donor to the recipient. The donor and the transplant centres are linked to a Regional Transplant Centre (RTC) and through this to the National Transplant Centre (CNT).

In the tissue field, tissue establishments (TEs) are situated within the network between the donor hospital and the application centre and they link them to the Regional Centres.
Since 2006, there has been a system in place for the management of serious adverse events and reactions (SARE) as required by the European Directive. TEs are required to provide instructions to transplant centres and to all units involved in any phase of the process about the need to notify SARE and how to proceed. Each TE should have a written rapid and verifiable procedure to allow the withdrawal from distribution of any product that could be linked to serious events/reactions. The responsible person at the TE guarantees that any occurrence of a serious adverse event and/or reaction is promptly communicated to its Regional Centre and the CNT. Investigations about SARE are carried out by the TE. However, if required or upon a request by the TE, there is collaboration with the RC and the CNT. Such collaboration may also be required in the event that corrective action needs to be implemented. Following evaluation of the investigation results, CNT decides whether additional measures are required.
Reports on notified SARE, in terms of types and amount, are presented yearly in a meeting with the Regional Centres. Reports are also given and discussed in meetings with the TE inspectors and in training courses for TE staff. Moreover, the results of the surveillance and vigilance system are shared with the broader transplantation network in Europe.
In the event that there is a warning or communication issued by the European Commission or other Competent Authority, CNT transmits this information to the RCs and the TEs. A similar scheme is in place for organs and cells.
There is an on-going effort in Italy to try and engage all professionals involved in the transplantation process to understand that the notification of SARE is not only necessary but that the sharing of information is of a great value in enabling not only single centres, organizations or TEs to learn from these SARE, but the whole network.

3.3 The significance of serious adverse events in tissue and cell vigilance

Christiane Niederlaender

The Human Tissue Authority (HTA) is one of two regulators of tissues and cells in the United Kingdom and is responsible for regulating all activities associated with tissue and cell transplantation. Assisted reproduction therapy (ART) is regulated by the Human Fertilisation and Embryology Authority (HFEA). Unlike many other Competent Authorities in the UK, the HTA is an independent body and regulates the use of human tissue also in other areas such as research and pathology. It has no formal connections with the regulation of medicines and medical devices but has good links with the body responsible for these. In spite of this, however, problems can arise because of the need to be aware of adverse events (e.g. device failures) that affect tissue establishments.
In addition to its role as a regulator, the HTA is also an inspectorate. Dr Niederlaender remarked that the management of serious adverse events and reactions and the reporting to a centralised body forms part of any functional vigilance and surveillance system in health care and is pivotal for ensuring that tissues and cells continue to be safe for human application. Serious adverse events and reaction management helps tissue establishments pick up any defect or potential defect in their products before patients come to harm, but also it ensures timely lessons are learnt when recipients or donors of tissues and cells have been adversely affected. HTA's adverse event and reaction submissions system for online reporting was formalised in 2007. In 2010, 98 SAE and 24 SAR were reported.
The HTA's criteria for reporting an adverse event are those developed in the EUSTITE project:
- 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 loss of a significant quantity of unmatched allogeneic tissues or cells.

It applies the EUSTITE impact assessment tool whereby the consequences of an adverse event in terms of its severity for an individual, the transplant or fertility system or the tissue/cell supply is assessed against the likelihood of recurrence to give an overall impact assessment.
The HTA requires notification related to all tissue and cells that it licenses. Where establishments procure for advanced therapy medicinal products (ATMPs) the HTA's remit extends to procurement and testing, and establishments must report events and reactions related to these activities. Liaison efforts are underway with the Medicines and Healthcare products Regulatory Agency (MHRA) to facilitate a coordinated way of responding.
Examples of the HTA's experience with managing serious adverse events and reactions at the HTA were presented focussing in particular on what was learnt about the importance of reporting adverse events. In one case, there were several reports of defects with the lids of storage jars indicating a production fault, which could not have been picked up at the level of individual establishments. With the risk of bacterial contamination present, a regulatory alert was issued and the batch of jars was recalled. It was not possible, however, to identify the used pots. From this experience, the need for improvement in the batch traceability system was identified.
In another case, incorrect data had been transferred into the donor registry system resulting in the situation where organs or tissues had been taken despite the fact that appropriate consent had not been indicated by the donor. This had potential serious consequences for the public willingness to donate. An investigation showed that the data in over 800,000 records were wrong and over 300,000 letters had to be sent to potential donors by the Department of Health.
A third SAE example related to the storage of autologous skull flaps for craniotomy patients. The bone was autoclaved prior to reimplantation. An increase in microbiological contamination was observed. Upon investigation it was found that > 30% of flaps were necrotic within one year. This practice was phased out as the hospitals performing it realized that they would have to be regulated as tissue establishments in order to continue.
Ms Niederlaender hoped that these SAE examples demonstrated to the participants the importance and benefits of reporting SAEs even where no patient has been harmed.

3.4 Vigilance notification and risk assessment: the principles

Susie ElSaadany

Transplantation, whether it is of cells, tissues or organs (CTO), has risks associated with it. They may be the transmission of an infectious or immune-mediated disease, an adverse immunological response, and even a graft failure. The management of these risks can be facilitated

through traceability systems, vigilance and surveillance programmes, standardised terminology and product identification, as well as systems for reporting and monitoring adverse events and reactions. Additionally, communication among organ procurement organizations, tissue banks, clinicians and public health agencies can be of great assistance.

In situations where information related to CTO transplantation is scarce, knowledge is limited, and uncertainties are high, even though theoretical risks may be low, expert consultation is recommended. The application of the Precautionary Principle can also mitigate infinitesimal or theoretical risks in the framework of public health. The use of structured Expert Elicitation (EE), a systematic process for formalizing and quantifying expert opinions for something that is uncertain, can prove beneficial and informative.

In Canada, structured EEs have been conducted on the use of N95 masks to prevent SARS infecting healthcare workers and on the spread of vCJD, and the Xenotropic Murine Leukemia Virus–related (XMRV) Virus. Another structured expert elicitation is planned to be held in May 2011 on the Chronic Wasting Disease (CWD).

The Structured EE approach in relation to the XMRV virus was presented. It involved selecting a group of problem domain experts who met to assess a set of 'calibration items' whose true values were known. Each expert expressed his or her views, assigned probabilities to what they believed, with their responses treated as statistical hypotheses and scored for statistical likelihood that they were correct. Experts answered 32 questions related to epidemiology, aetiology, serology and histology of XMRV. They ranked twelve possible routes of infections of XMRV using experts' educated opinions of preferences collected during the exercise. The possible routes of infection ranged from non-leucoreduced packed red blood cells as number one to albumin as number twelve. Overall, it was summarized that the experts viewed XMRV as a virus with low infectivity and the risk to blood safety by various exposures was low with wide uncertainty.

The presentation concluded with the message that Expert Elicitation with mathematical formalization can provide estimates with uncertainty ranges for future risk until research provides evidence based data. Moreover, EE procedures and Pairwise comparison exercises can help support improved decision making related to emerging disease risk, such as XMRV where uncertainty is high, where data may be missing, are sparse or are questionable.

3.5 Maintaining vigilance in the case of exported tissues (from 'anywhere')

Scott Brubaker

When addressing vigilance and the exportation of allografts from tissue establishments in the United States (US), it should be understood that the issues described here can be relevant to a tissue establishment located anywhere that distributes tissue across national borders. To prepare this information, an informal survey of a number of AATB-accredited tissue banks was performed. The executive office of the Eye Bank Association of America was also contacted to gather export and vigilance experience with their tissue types.

For ocular tissue, there are a limited number of grafts per donor (corneas and sclera) as well as a limited number of recipients. Historically, eye banks have enjoyed very good communication with end users/clinicians which has resulted in enhanced data collection, evaluation and process improvement. When evaluating the final disposition and outcome of ocular tissue, the fact that graft preservation methods vary leading to a shelf life that can be short (days) or long (years) has to be recognized. In spite of this, US eye banks routinely obtain information on the use and/or the recipient quickly, and after 3 to 12 months conduct a follow-up. The situation is not the same for exported ocular tissue. Patient information is rarely received and when it is, the form may be missing expected information so is not useful and, as a result, patient outcome is often unknown. Returned implant information may be provided using a non-Latin alphabet and symbols used are incompatible with computer databases. Moreover, certain foreign locations will not include hospital identification or other unique identifying number for the recipient. This may be related to local law, which essentially disrupts tracking from the tissue's origin to the recipient.

Experience regarding vigilance of other tissues has been facilitated by use of written agreements and contracts. It is important to make sure that the exporter's contract with a distributor is explicit in its requirements for traceability and the response/turnaround time in the event of a recall, report of serious adverse reaction or other complaint. The contract language must accommodate local laws and regulations (and the local tissue paradigm). For example, the situation differs in two European Union Member States: in one, the regional tissue banks share responsibility with distributors while, in the other, the regional tissue banks control distribution and may be the only point of contact.

With respect to written agreements or contracts, it is recommended that the exporter require the distributor to have a written agreement with the distributor's customers or end users. It should describe responsibilities for:

1. maintaining local registration or licensing as a professional or clinical office (or equivalent);
2. not re-selling products;
3. maintaining the use of processor/manufacturer identifiers so that tracking to the recipient, and date of use, is known;
4. maintaining recipient records for an appropriate (per regulation) period of time;
5. SAE-SAR reporting requirements to both the appropriate authority and to the processor/distributor (with timelines included); and
6. agreeing to cooperate promptly and fully as directed in the event of field corrections or recalls by the processor/manufacturer or appropriate regulatory authority.

One of the main barriers to be overcome is language. When a problem occurs, it is important to communicate details to the most knowledgeable party but language barriers can make this difficult. Allograft labelling is often only in English *(or the native language of the tissue supplier's country)* but there should be an accurate translation provided by the sponsor/Designated Individual/distributor. There should also be a package insert with instructions and preparation for use that can easily be followed by the user. Contact information and reporting instructions should also be provided but if not readable by the user, can lead to unexpected outcomes. Additionally, in countries where laws are not available in English *(or the native language of the tissue supplier*), the tissue supplier must rely on translation that may fail to capture original intent. This can be problematic and relate to non-compliance.

Barriers and challenges to effective vigilance may include difficulties working with the Designated Individual or sponsor. This person may be very protective of client information and disallow usual feedback. There may be reluctance to allow direct communication with the end user/clinician

in the event of an adverse reaction, recall, complaint, or inquiry regarding allograft processing, characteristics, or use. And the implant card return system may not be used (at all). These barriers go against the concepts of maintaining a Quality Management System.
There are several unknowns including the potential for multiple tissue distribution intermediaries to handle an allograft. There are storage issues related to distribution and re-distribution. The tracking capabilities need to be ensured particularly where there is the possibility of importation into one country and then redistribution to others. Although a contract can disallow this, it may not become known (unless discovered at audit) because the distributor/importer is protective of client information. For the exporter, traceability ends with the first stop in the chain of custody; the final disposition of grafts can remain unknown.
With this knowledge, it is important to:
- Develop carefully written contracts, to include a provision that the exporter perform periodic audits of the distributor and run 'test' recalls and perform tracking exercises;
- Understand local laws and ensure that importing distributors understand how to meet US (or the source tissue bank's national) requirements in the context of local ones;
- Recognize that delays can occur along communication avenues; and
- Except for language barriers, address similarities that may exist regarding experiences with domestic distribution

How can traceability and the safety of recipients be handled best in regard to cell/tissue distribution between countries? An analogy can be used. Although a fort or fortress appears to be in place to protect the homeland, a closer look shows it may also be a lighthouse that offers protection to others. Tissue recipients fit into this scenario because they expect safety measures are taken in their best interest. However, their protection is disrupted by actions that affect tracking abilities or communication avenues. Their safety, and the safety of future recipients, should be the focus when developing or enhancing local requirements regarding vigilance and surveillance activities. The expectations of the cell or tissue bank from which the allograft originated must not be ignored and should work in concert with regulation in the country where the allograft's final disposition, or the adverse reaction of the recipient, takes place. The needs of all stakeholders should be satisfied.

3.6 ART vigilance, the professional perspective

Luca Gianaroli

Since 1974, records show that there has been a continual decrease in fertility across Europe to the point that in 2004 it had fallen below the population replacement level. That year the total fertility rate was at a low of 1.5 while the actual replacement total fertility rate was 2.1. A chart issued by the Council of Europe showed that around 2003, the mean age of women at the birth of their first child was above 26 in many countries of the European Union.
Information derived from the registers of the European IVF Monitoring (EIM) programme and the Consortium of the European Society of Human Reproduction and Embryology (ESHRE) show that anonymous sperm donation is forbidden in 10 countries of Europe and 10 forbid sperm donation with identification of the donor. In two of all these countries (Italy and Turkey) sperm donation is illegal. Anonymous egg donation is forbidden in 10 countries and egg donation by identifiable donors is forbidden in 13.
Vigilance in assisted reproductive technology (ART) and in all other fields, aims to:
- Prevent serious adverse events (SAEs) and serious adverse reactions (SARs) and
- Provide operators with tools to help them deal with SAEs and SARs.

It has to be recognised that each phase of the ART process implies risk. SAE and SAR in ART, however, have a very low incidence rate and very few cases have been reported in the literature due to the strict vigilance carried out by ART operators to guarantee traceability, safety and quality. A flow chart setting out the process was presented from the admission of the donor to the program through the screening process for infections, to the actual donations, and ultimately to the embryo transfer or cryopreservation.
In relation to adverse reactions, an extensive list ranging from hypersensitivity to medical and surgical complications was presented. Adverse events may be linked to cryopreservation including:
- inappropriate freezing technique or equipment failure during processing or storage resulting in damage or loss of gametes and embryos;
- warming/premature thawing of gametes and embryos during a cryobank audit;
- loss or misreading of labels or failure to keep accurate records resulting in missing gametes and embryos, and
- damage to samples due to containment failure and contamination.

Adverse events unrelated to cryopreservation may also occur and include:
- inappropriate gametes/embryos distributed for clinical use, even if not used;
- delivery of semen infected with bacteria or from a donor with transmissible viral infection;
- birth of a newborn genetically unrelated to one or both parents due to a mix up;
- loss or damage of gametes and embryos due to contamination of embryo culture and semen.

All SAEs could have implications for other patients or donors because of shared practices, services, supplies or donors.
Following the birth of twins of mixed races in the Netherlands, good practice guidelines for *in vitro* fertilisation were revised. ESHRE implemented a series of initiatives in order to promote and ensure vigilance in ART. It established a Special Interest Group on the 'Safety and quality in ART' as well as a Task Force to address requirements of the EU tissues and cells Directives. It elaborated guidelines for ART professionals and organized educational activities for them. It has instituted collaboration with national and international competent authorities, European institutions and national governments and is supporting European Union projects (e.g. EUSTITE, SOHO V&S,). The EIM began monitoring ART data in Europe (including complications).
ESHRE is applying an efficient system of prevention and alert to reduce SAEs and SARs and to minimize their potential consequences in ART. The effective functioning of this system depends on the definition of specific regulations, the involvement of experts in the definition of regulations and synergy between individual units and competent authorities.

3.7 Enhancing clinician awareness of tissues and cells V&S in the EU

Izabela Uhrynowska-Tyszkiewicz

One of the major objectives of the EU project on Vigilance and Surveillance of Human Origin (SOHO V&S) is to increase awareness among clinicians of the importance of vigilance and surveillance of tissues and cells. A specific activity of the project, known as Work Package 9 – Promotion of V&S of Tissues and Cells at the Clinical User Level – aims to do this. Led by the National Centre for Tissue and Cell Banking [*Krajowe Centrum Bankowania Tkanek i Komórek*] (KCBTiK) in Poland in cooperation with four associated and 13 collaborating partners, the Work Package seeks to provide guidance for professionals working in hospitals and clinics on their roles and responsibilities in supporting traceability and vigilance of tissues and cells for transplantation and assisted reproduction. The guidance document will highlight the essential role of the clinical staff who apply the tissues and cells in making sure that traceability is ensured and that serious adverse reactions and events are promptly reported via the appropriate channels.

> 'traceability' means the ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells; Article 2. g[10]

Commission Directive 2006/86/EC[9] sets out the requirements for the traceability of tissues and cells as well as the notification of serious adverse reactions and events. Its Article 9 (paragraph 2) on Traceability requires tissue establishments and organisations responsible for human application to retain specific data, as set out in Annex VI, for at least 30 years, in an appropriate and readable storage medium. The minimum donor/recipient data set that has to be kept includes donor and donation identification, product and human application identification, date of distribution/disposal and identification of clinicians or end user/facility. It also requires organisations responsible for human application to keep data on identification of the supplier tissue establishment, the clinician or end user/facility, the type of tissues and cells, product identification, as well as identification of the recipient and date of application.

There is no obligation set out in the legislation, however, for the 'routine' flow of information between organisations responsible for human application and tissue establishments. There is no requirement for information to be maintained regarding: the final fate of distributed tissue grafts – whether transplanted or disposed, clinical indications, nor results of short and long-term follow-up including the clinical efficacy of the graft.

With respect to serious adverse events and reactions, Directive 2004/23/EC[10] sets out definitions for these terms. Article 11 on Notification requires Member States to have a system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells and which may be attributed to their procurement, testing, processing, storage and distribution, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells. Moreover, all persons or establishments using human tissues and cells regulated by the Directive must report any relevant information to establishments engaged in the donation, procurement, testing, processing, storage and distribution of human tissues and cells in order to facilitate traceability and ensure quality and safety control.

The V&S Guidance for Clinical Units that will be developed under Work Package 9 is aimed at promoting vigilance and surveillance and helping to define the roles and responsibilities of clinical users in the traceability, recognition, reporting, and investigation of SAREs in hospitals, as well as the management of recalls. It will include a summary of the EU legislation in the field and be loosely based on a similar booklet produced by the AATB, AABB and EBAA entitled **'**Hospital Tissue Management: A Practitioner's Handbook'. Towards this end, a first editorial meeting was held in Warsaw in January 2011 at which time the title, scope, and general structure of the guidance document were agreed. Consultations are to be held over the forthcoming months with tissue and cell-specific professional societies in order to address issues related to traceability, vigilance and those of a practical nature. For traceability, questions as to who should be responsible at the hospital or clinic and how and where should traceability records be kept will be addressed. With respect to vigilance issues, recognition of the clinical triggers, reporting responsibilities and causative investigations linked to adverse reactions will be discussed. For adverse events, the types that occur at the user site and how they should be managed will be considered. Practical issues, such as the handling of tissues and cells; proper storage, unpacking, and preparation prior to surgery; the management of unused tissues/cells; and responsibilities and procedures in the case of tissue/cell recall will be addressed.

Discussions will be held with the European Association of Tissue Banks (EATB) for tissue transplantation (excluding ocular tissues); with the European Eye Banking Association (EEBA) for ocular tissues (mainly cornea) transplantation; with the European Society for Bone Marrow transplantation (EBMT) and with the World Marrow Donor Association (WMDA) for haematopoietic stem/progenitor cells transplantation; as well as with the European Society for Assisted Reproduction (ESHRE) for assisted reproduction (including gametes, embryos).

Publication of the 'V&S Guidance for Clinical Units' document in printed and electronic form is scheduled for December 2012. It will be provided to all Competent Authorities for tissues and cells and individual CAs may translate it for national distribution to their hospitals directly or via tissue establishments.

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9 Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. L294, 25.10.2006, p. 32.

10 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. L102, 7.04.2004, p. 48.

4 Proactive Vigilance

Chair: Francis Delmonico

4.1 Implementing WHO Guiding Principle 10 in Transplantation

Jeremy Chapman

On 22 May 2010, the World Health Assembly (WHA) endorsed the WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation. The revised Guiding Principles (GPs) placed the responsibility for two new GP's on professionals and governments alike. The WHA's Resolution 63 R22 and GP 10 call upon those involved in dealing with these substances of human origin to collaborate in the development and implementation of quality, safety and efficacy systems globally. GP 11 calls for donation and transplantation activities, as well as their clinical results, to be transparent and open to scrutiny, while respecting confidentiality of donors and recipients.

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.

In Japan in 2005, 11,564 people were on kidney transplant waiting lists and more than 250,000 were on dialysis – with reliance on a small numbers of living donors. Almost invisible are the deceased donors that other countries avail of to provide life to so many. In Australia, the transplant waiting list is age-dependent with less than 5% of those aged 65 and above on it. Surprisingly, only small percentages among the young age groups are listed. Once on the list, however, the overall chance of being transplanted is 30-40%. Perhaps this statistic remains an inhibiting factor to listing more patients. It is clear that many dialysis patients are medically unsuitable for transplantation, but are such a large proportion of those under 50 years really unsuitable?

In Australia, the short and long-term outcomes of renal transplantation are recorded in a professionally run but fully comprehensive registry. The continuous improvement in outcomes has demonstrated the results of such an approach to measuring and analysing transplantation activity across the country. The detail on causes of graft loss and the timeframes of that graft loss have permitted actions to be taken that have improved clinical practice. There has been a 50% reduction in patient death from cardiovascular disease and infection, but a slowly rising tide of malignancy – attributable to the increased duration of follow up.

The analysis of outcomes has not been limited to the kidney transplant population but is in fact comprehensive across all forms of organ and tissue transplantation, with patient survival rates improving for liver, pancreas, lung and heart transplantation. It is also true of corneal and haematopoetic stem cell transplantation.

At the global level, the Collaborative Transplant Study (CTS) is a voluntary, professional and open registry that has been established in Heidelberg by Professor Gerhard Opelz. There are about 25,000 transplants reported each year to the CTS and accumulated numbers of liver (56,000), heart and lung (43,000) and kidney (320,000) transplants from many hundred centres across the world with the exception of the USA where the SRTR (Scientific Registry of Transplant Recipients) records another 25,000 transplants each year. Thus at least half of the 100,000 transplants performed each year (WHO Global Knowledge Database) are reported to outcome registries. CTS follow up is 80% (kidney) to 90% (heart) complete. It has a free standalone personal computer (PC) database available for any transplant unit in the world wishing to collect their own data, whether or not they want to report it to the central CTS database.

Patient and graft survival is also reported by CTS with the information available on their website (www.ctstransplant.org) which includes overview data and specific analyses of interest to transplant programmes. Although it is possible to analyse data by country, the identifying information remains confidential.

The World Bone Marrow Transplant (WBMT) has brought together around 70 organisations under one umbrella to bring cohesion and capacity to countries throughout the world. The European registry EBMT and the research affiliation between the International Bone Marrow Transplant Registry (IBMTR)/Autologous Blood and Marrow Transplant Registry (ABMTR)

WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation

World Health Assembly - 22 May 2010

1. Consent for deceased donor's donation
2. No conflict for death determination
3. Deceased but also consenting live donors
4. Protection of minors and incompetent persons
5. No sale or purchase
6. Promotion of donation no advertising nor brokering
7. Responsibility on origin of transplant
8. Justifiable professional fees
9. Allocation rules
10. Quality safety efficacy of procedures and transplants
11. Transparency and confidentiality

Guiding Principle 10

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

The level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, must be maintained and 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.

Global Activity Survey 2006: final data
Main indications

Indication	Allo	Auto	Total
Leukemias	15210 (89%)	1839	17049
Lymphoproliferative disorders	3502 (13%)	23990	27492
Solid tumors	153 (5%)	2772	2925
Non Malignant disorders	2396 (92%)	197	2593
Total	21516 (43%)	28901	50417

Worldwide Network for Blood and Marrow Transplantation

and National Marrow Donor Program (NMDP) [Center for International Blood and Marrow Transplant Research (CIBMTR)] together record and analyse around 80% of all haematopoetic stem cell transplants permitting analyses of substantial relevance to individuals facing the need for such transplants. With the affiliation between IBMTR/ABMTR and NMDP, the CIBMTR now has expanded its representation to more than 500 centres from 54 countries worldwide.

The outcomes of organ and bone marrow donors are not so well collected. This is partly because donors regard themselves – usually rightly – as fit normal individuals and not in need of medical follow up. As evidence of this fact, the first successful organ donor just died on 27/12/2010 – 56 years after his donation. Properly controlled data analyses is not yet available to identify whether or not donor outcome is as benign as many suggest from sub-optimal comparisons of donors with the general populations. The latter include individuals who would not have been accepted as living organ donors.

The WMDA has collected, collated and analysed data on the safety of unrelated bone marrow and peripheral stem cell donation – through its SEAR (donor safety) and SPEAR (product adverse event) registries. This required the world data to be collected to identify these rare events.

The most important issue that needs to be understood is the dissimilarities between blood safety systems and what might be implemented in cell and organ transplantation. The first relates to the volume of activity – blood donations are in the millions in many countries while organ donations are in the thousands in only a very few countries and haematopoetic stem cell donations are even fewer. The second deals with the scarcity of donors – blood donors can be replaced while organ donors are very scarce and 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 will need to be put together to be able to detect even the reasonably frequent events (1:10,000 or 1:100,000).

As a clinician with more than 20 years of experience in determining whether or not to accept individuals as organ donors, Dr Chapman believes that a resource is needed which helps in making better informed decisions on questions that occur rarely and for which there may be guidance available somewhere in the world, but which is not accessible urgently day and night.

He believes that each country needs to be able to balance the human cost of loss of donors from safety oriented decisions – what is the difference between the mortality on the waitlist and the mortality after transplantation?

In Australia, for organ donors the number needed to kill one person (NNTKOP) is about 2 (1 person dies in one year for each donation that is deferred.) In South Africa for organ donors the number is 0.33 (3 people die in one year for each donation that is deferred). What is needed is an immediately available and reliable resource at 2 a.m. to answer the hard questions. But even then most of the time there will be no answers.

Each proposed action designed to increase safety has a financial cost – the Cost of Avoiding One Death (CAOD) – which must be known and like other health interventions be costed against a standard – a death or perhaps a QALY.

Also needed are some metrics against which to make and defend decisions on donor safety. Two possible indexes, the NNTKOP and the COAD, are proposed for consideration.

In closing Dr Chapman said that we must appeal to different responsibilities – individual, organisational, national and international – to undertake a variety of different actions to reduce patient risks, to create globally accessible knowledge and to build upon what has been created over the last 40 or 50 years of continuous actions designed to improve outcomes.

4.2 Responding to emerging infectious risks: a national experience and international implications

Paolo Grossi

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. Overall, the epidemic in Italy can be said to be the result of the combined effect of the globalisation of vectors and humans, which occurred through a two-step process: i) the introduction and adaptation of the vector *Aedes albopictus* to a new environment (i.e., a temperate climate); and ii) the introduction of CHIKV in a previously infection-free country, with totally susceptible subjects, as the result of population movement (i.e., travelling human hosts, acting as a sort of Trojan Horse). CHIK causes severe joint swelling in the extremities, pain in the large joints, and in some cases a rash. A joint WHO/ECDC risk assessment evaluation found that the vector *Aedes albopictus* was present throughout Italy and in a few isolated areas in other areas of Europe.

This CHIK outbreak prompted the Italian National Center for blood (CNS) and CNT, in September 2007, to issue preventive measures for all blood, organ and tissue donors. This included excluding from blood and tissue donation all asymptomatic individuals who had spent even a few hours in the epidemic area during the prior four weeks, and all individuals with proven or suspected chikungunya infection up to six months prior to the donation. Tissues from asymptomatic living tissue donors, whether living or staying in the epidemic area, had to be quarantined for at least four weeks after the donor had left the area. If the donor remained asymptomatic, the tissue could be released.

Preventive measures were also issued for organ donations. All asymptomatic individuals living or staying even for few hours in the epidemic area during the three weeks prior to the donation, those with a documented infection for at least three weeks after abatement of the fever and all individuals with an on-going infection were excluded. Those individuals, who did not have an on-going infection, could be considered suitable for organ donation, in consultation with national experts, if the infection was excluded by molecular testing.

By the end of September, this first outbreak of autochthonously transmitted CHIK virus in Europe has been completely controlled. Of the 334 suspected or probable CHIK virus cases involved in the outbreak, samples were examined of 281 and 204 were laboratory-confirmed by PCR, haemagglutination-inhibition or both. Reasonably, the number of laboratory-confirmed cases most likely constitutes an underestimate of the

extent of the outbreak, since blood or serum samples were not available for all of the individuals who fulfilled the clinical and/or epidemiological criteria of the case-definition.

Moving to another emerging infection, for the first time in Italy, two patients with meningoencephalitis were diagnosed with West Nile virus (WNV) infection in September 2008. The patients live in the Bologna and Ferrara provinces of Emilia Romagna where WNV infections had previously been noted in horses, crows and magpies. Given that cases of donor-transmitted WNV had been reported in the United States, again measures were introduced to prevent its transmission by organ transplantation. All potential donors of organs, tissues and cells from the Bologna and Ferrara provinces in the Emilia-Romagna region had to be tested to exclude infection. Where there was evidence of infection, organs, tissues and cells will not to be used.

In the rest of Italy and in the other Emilia-Romagna provinces, the following rules were applied:

- Investigation of the history of potential **tissue donors** will include enquiries regarding a possible overnight stay in the provinces of Bologna and/or Ferrara during the previous 28 days. If a potential donor has visited one of these provinces, they will not be considered eligible for donation, unless laboratory test results for WNV are negative;
- For **organ donors**, a case by case evaluation is conducted in order to assess the infection risk, which is acknowledged to be very low, taking into account the nature and benefits of transplantation and the health status of the patient on the waiting list.
- Since the occurrence of WNV infection in humans in 2008 in Italy, an epidemiological survey of the Emilia-Romagna and a retrospective screening of Italian organ donors in 2009 which did show that there had been an unpredicted circulation of the virus.
- Based on these 2010 and 2011 data, the CNT has modified the rule indicating mandatory testing, within 72 hours from organ donation, of all organ and tissue donors living, or with an overnight stay during the previous 28 days, in the provinces with active transmission. In case of positive result the recipients have to be intensively monitored for possible WNV transmission and treated prophylactically with plasma from blood donors known to have a high titer of anti-WNV-specific antibodies.

Examples of the sensitivity and specificity of different NAT Assays for the detection of WNV in blood samples were presented. It was reported that 1:5 potential WNV-infected blood donors may be missed through MP-NAT testing because the virus level is below the detectable limit. It was recommended that new, approved assays be introduced with caution when changing epidemiologic patterns so indicate. The 'list' of pathogens for which organ donors should be screened could be influenced by some specific questions such as whether:

- the prevalence of the pathogen is sufficiently high in the general population for the screening test to be useful;
- there is evidence that the pathogen can be transmitted by organ transplantation;
- the transmission would result in significant morbidity and mortality;
- there is a reliable and logistically applicable test available for screening.

For the majority of recent transmission events, including lymphocytic choriomeningitis virus (LCMV), the other reported arenaviruses, and rabies, all of the above criteria are not fulfilled. Finally, the hospitalization in Italy of two individuals with a fever of unknown origin, test results showed that they had been infected with the Alkhurma virus (ALKV) has been mentioned. Both had been in southern Egypt where ALKV had not been previously reported. Although the probability of a susceptible vector in Europe is small, and the infection seems not to be transmissible from human to human, geographic distribution of the ALKV could be broader than previously thought and, since the potential transmission from donor to recipients is currently unknown, an accurate investigation of the travel history with further testing of all potential donors is highly recommended.

In conclusion, global temperature extremes are an example of a geoclimatic issue that is changing zoonotic disease distribution. Arthropod vectors, such as mosquitoes and ticks, are intimately tied to changes in ambient temperature and an active surveillance system able to detect any epidemiological change must be in place in order to prevent possible unexpected pathogens transmission.

4.3 The shape of risks to come: lessons from the past

Matthew J. Kuehnert

The activities of the US Centers for Disease Control and Prevention (CDC) 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 is only allowed to investigate events through the assistance of local and state authorities. CDC works collaboratively with U.S. Public Health Service (PHS) agencies that have regulatory oversight over organs, tissues, and cells, including the Food and Drug Administration and the Health Resources and Services Administration. A significant number of organ transplant-transmitted infections have been investigated by U.S. Public Health Authorities, with assistance from CDC, 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 ultimately to the finding that the young donor had Granulomatous amoebic encephalitis – which previously had been depicted by only 150 described cases worldwide, and was the first transmission of a free-living amoeba by organ transplantation. From this and other cases, the CDC determined that over the last decade, there were dozens of transplant recipients with encephalitis-related illnesses (majority fatal) that were recognized, and likely hundreds more unrecognized.

The transmission of antimicrobial-resistant *E. coli* to two kidney recipients led the CDC to recommend that procedures be revised for communicating important information from organ procurement organizations (OPO) to transplant centres. It also discouraged the use of fax and phone communication in favour of structured electronic communication with a 'paper trail'.

In another case, the transmission of HIV and HCV by organs transplanted from a donor who tested negative by serology, and upon investigation found subsequently positive by nucleic acid testing, led to questioning of the need to update the definition of elevated risk behaviours and associated screening. Such investigations have made it clear that current guidelines that define risk in organ donors, published in 1994, need to be updated. In 2011, the PHS 'Guideline for Preventing Transmission of HIV, HBV and HCV through Transplantation of Human Organs' will be

released for public comment. The process for developing this guideline, from the organizing of advisors, to literature searches, to the production of evidence, was presented.

In 2009, a known HCV+ vessel conduit was stored in a transplant centre and later inadvertently used in the transplantation of an HCV- living donor recipient. When additional potential cases came to light indicating an on-going problem, CDC recommended that the practice of storing vessels for transplant recipients from donors seropositive for hepatitis should stop.

The increasing use of tissue allografts presents not only technological advances but challenges in preventing tissue-transmitted infections. A 2002 AATB survey showed that tissues from 23,000 donors were distributed throughout the USA and to 39 other countries. In Canada, 100% of dental bone and at least 70% of other tissues implanted are imported. According to WHO, 'As this globalization of cells and tissue transplantation develops, the need for common product names and definitions and for unique product identification becomes essential'.

A CDC/FDA/HRSA Workshop in 2005 identified the need for unique donor ID linking organs and tissues, clear mechanisms for adverse event reporting, and a better communication network within and between the organ and tissue community. Systems do exist for adverse event reporting related to organs and tissues, but they are passive. They do not ensure the participation of the clinician. The FDA only regulates the tissue banks, but not what transpires after the tissues are distributed to the healthcare setting.

The Transplantation Transmission Sentinel Network (TTSN) was developed with the aim of detecting and preventing disease transmission through: improved communication among those in the organ and tissue community (e.g., tissue recovery organizations, OPOs, tissue preparers & distributors), healthcare facilities, and public health officials, concerning potential risks for transmission of infection. The pilot phase has been completed and a quality review for implementation nationally is on-going. As a consequence of comments on the TTSN through a public request for information, it has been determined that a new infrastructure will be needed to build a sentinel network for organs and tissues.

The National Healthcare Safety Network (NHSN) is a secure, internet-based surveillance system that integrates patient and healthcare personnel safety surveillance systems managed by the Division of Healthcare Quality Promotion (DHQP) at CDC. As it already has a biovigilance component, including surveillance of transfusion-related adverse events (i.e., incidents and reactions) through its Hemovigilance Module, the possibility of having organ and tissue surveillance added to the NHSN has been raised. Organ transplant safety, however, is the most challenging issue in biovigilance, with the balance between safety and availability to be taken into account. The risks may be lower for tissues, but lack of awareness concerning non-sterility and traceability for certain grafts are unresolved issues. Definitions for adverse events are needed globally, particularly for tissues where international coding is critical.

The U.S. Health and Human Services has defined 'biovigilance' as a comprehensive and integrated national patient safety program to collect, analyse, and report on the outcomes of collection and transfusion/transplantation of blood components and derivatives, cells, tissues, and organs.

For the future of biovigilance, there are many gaps to fill which will require coordination among blood/organ/tissue communities through public-private partnerships, both nationally and globally. Current collaborative CDC activities on Biovigilance includes the revision of guidelines to define the risk of transmitting HIV and hepatitis viruses, a study to define the yield of using HIV and HCV nucleic acid testing to screen organ donors, standardization/validation of donor history questionnaires, 'toolkits' to facilitate the investigation of transplant-associated adverse events by local health departments, and a CDC website to disseminate information relevant to transfusion and transplant issues. It will be critical to have common nomenclature and exchange of information on Biovigilance globally.

4.4 Early warning systems to support preventive action

Richard Tedder

In addressing the topic of an early warning system, Dr Tedder began by questioning what warning is all about, what is meant by it, and how it is tackled. He asserted that human endeavour can be predicted to fail but could be mitigated by managing associated risks. The term 'event horizon' 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, such as X murine retrovirus MRV, or something not recognised, such as West Nile Virus. In all cases, however, these could have been predicted.

Risks are inherent in the use of substances of human origin. They may occur in the donation of the 'product', within the manufacturing process, due to external factors or through human error. With basic epidemiological data, however, hazards can be identified early. Recording of information such as the source of an infection, the agent/disease, the risk level as well as description of the problem can prove to be effective in detecting a potential crisis. The example was presented of the human retrovirus XMRV, the information exchanges that raised the alert, the time frame over which they occurred and the resulting identification of the implications for the blood transfusion service. A second example involved the appearance of 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.

Dr Tedder suggested that in looking at an early warning system, 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. He used aviation as a model since it, like transplantation, is inherently dangerous. Specifically, he referred to a table of aviation accidents/incidents in Australia, which included details of the aircraft, damage etc., reported over a two month period in 2010. He said that with respect to transplantation risk management, aviation tell us

- 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
- Perhaps differentiate between doing the right thing from the correct thing

5 SOHO V&S by Products

Chair: D Michael Strong

Participants were divided in 5 breakout groups where the leaders of Working Groups 1-5 were asked to present the work already achieved on the Google site prior to the meeting,. Each WG had gathered information and references of documented SARE for a specific substance type. In total, over 1,400 references had been entered on the site by these 5 groups. In the breakout groups, this work was summarised and the participants were asked to review the known reactions for their substance type, identify the typical alerting signals, and detail how it was confirmed that the donation or transplant caused the reaction. Each breakout group then fed back the outcome of their discussions to the plenary meeting.

5.1 Working group 1 – Organs

Paolo Grossi (Presenter), Frank Delmonico (Facilitator),
Matthew Kuehnert (Rapporteur)

Four tables were presented that delineated the infections caused by viruses, bacteria, fungi and parasites that can occur in organs; the malignancies, as well as other reactions, were also presented including those to the living donor.

Adverse events and reactions can occur in the organ donation and transplantation process. An 'serious adverse event' means any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead: to the transmission of a communicable disease, to death or life- threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity.

Adverse events and reactions can be attributed to the following:

- **Error:** a failure in planning and carrying out a series of actions leading to the failed, non-casual, achievement of desired objective. Among which there is failure in the identification of the potential donor; and failed transplantation due to organizational, logistic or casual issues that prevent organ use in the identified recipient;
- **Medical error**: a missed intervention or inappropriate intervention, from which a clinically significant adverse event is derived;
- **Minor adverse event**: a sudden event connected with any phase of the donation and transplant process leading to an unintended and undesirable damage to the patient;
- **Sentinel event**: a particularly serious adverse event, potentially highlighting a malfunctioning of the system that cause a loss of trust in the system by citizens, independently from the provoked damage;
- **Near miss**: an error that has concrete potential to provoke a serious adverse reaction, that does not take place by hazard or preventive remedial action or does not have consequences for the patient, the system or the staff.

The Severity Tool proposed by the EUSTITE project for tissues and cells for adverse reactions was reviewed, with the reporting requirements increasing in importance with severity.

Non serious

Mild clinical/psychological consequences. No hospitalisation. No anticipated long term consequence/disability

Serious

Hospitalisation or prolongation of hospitalisation and/or persistent or significant disability
or incapacity or intervention to preclude permanent damage
or evidence of a serious transmitted infection
or birth of a child with a serious genetic disease following ART with donor gametes or embryos.

Life-threatening

Major intervention to prevent death or evidence of a life-threatening transmissible infection
or birth of a child with a life-threatening genetic disease following ART with donor gametes
or embryos**.**

Death Death

Definitions for Imputability of donor-origin diseases transmission

With respect to imputability of donor-origin disease transmission, it was considered critical to have standard definitions to attribute the likelihood that the transmission event was or was not of donor origin. Although the two extreme definitions (*proven* and *excluded*) are reasonably self-evident, available data often limits the ability to provide absolutely rule-in or rule-out donor origin for the disease transmission.

Several issues were identified as potentially limiting the ability to definitively categorize such disease transmission events, including:

1. Inadequate donor specimens: appropriate specimens to confirm or exclude the presence of the infectious disease in the donor prior to donation;
2. Inadequate recipient specimens: appropriate specimens to confirm or exclude the presence of the infectious disease in the recipient prior to implantation of the organ or tissue;
3. Incomplete testing of infectious disease: even when a pathogen is identified in both the recipient and the donor, available testing may not definitively determine if the two organisms are unique.

Potential donor-derived disease transmission events are categorized based on available information, as either:

- Proven
- Probable
- Possible
- Intervened upon without documented transmission
- Excluded

Although standardized definitions were developed, it is recognized that there is some degree of subjectivity in how these individual definitions may be applied.

The stringent definition of ***proven*** transmission should only be used if there is clear evidence of the same disease in the donor and at least one of the recipients. Absence of pre-transplant disease in the recipients should be documented. Variable involvement of different organs or tissues, different processing of organs and tissues, and recipient differences (i.e. pre-existing seroprotection or use of lymphocyte depleting induction in some but not all recipients) may contribute to variable disease transmission.
The stringent definition of ***excluded*** can be applied if there is clear evidence of an alternative, non-donor origin of disease. Often, this may occur if there was pre-existing infection in multiple recipients but infection could not be identified in the donor or if testing of the same infection failed to document a clonal or donor-phenotype in the identified infection.
The term ***probable*** disease transmission should be applied if there is evidence strongly suggesting but not proving a disease transmission. Examples include, if the same infection is documented in multiple recipients but not in the donor; or if there is epidemiologic evidence suggesting transmission (i.e. TB isolated from a recipient that types to a region where the donor lived, even if the donor studies are negative).
Possible transmission should be used for all situations where a) data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probable) or b) a transmission cannot be formally excluded. If only one recipient is available or other recipient(s) of the same donor cannot be appropriately tested, the maximum degree of *indeterminate but probable* transmission can be reached.
If all or some of the recipients received an intervention (i.e. antimicrobial therapy or organ removal) and no disease was recognized in any of the recipients, the term ***intervened upon without documented transmission*** (*IWDT*) was utilized.
If some but not all recipients had an intervention but disease transmission was recognized in even one recipient, this category should not be used but one of the alternative categorization systems should be utilized.

5.2 Working group 2 – Other tissues (non ocular)

Ted Eastlund (Presenter), Johann Kurz (Facilitator),
Maurice Hinsenkamp (Rapporteur)

5.2.1 Recipient Reactions

From the cases collected on the NOTIFY web site and from the literature, it clearly shows that disease transmission is a risk of allograft use and that the type of processing, or lack of processing and sterilization, of the tissues have a significant influence on the risk of contamination or other adverse effect on the recipients. For more than 20 years, no infectious disease transmission has been reported from processed, freeze dried allografts (except dura) using a validated process that ensures microbial and viral safety. The risk is greater for fresh, frozen or cryopreserved allografts (Table 1).

No specific postoperative reaction, clinical situation or event can establish allograft contamination as its cause making notification, without further diagnosis, useless and confusing. Septic or inflammatory symptoms appearing in wounds after multiple surgical procedures, which is often the case when bone graft is used (prosthetic replacement, traumatic bone loss …), alone do not establish that the complication was from a contaminated allograft. Conversely, once the type of complication is diagnosed, causation by the allograft can be considered and it will be easier to establish whether the allograft is related.

Table 1. Infectious disease transmission by tissue allografts.

Bacteria	Tuberculosis	Epstein-Barr Virus
Fresh Cornea	Frozen Bone	Fresh Nerve
Fresh Cartilage	Cryopreserved Heart valve	
Frozen Tendon		
Frozen Bone		
Frozen Pericardium		
Fresh Skin		
Cryopreserved Heart valve		

HIV-1	Hepatitis C	Hepatitis B
Frozen Bone	Frozen Bone	Fresh Cornea
Frozen Tendon	Frozen Tendon	Cryopreserved Heart valve
	Cryopreserved Veinn	

Rabies	CJD_	Yeast, Fungus
Organ-associated Artery	Freeze-dried dura	Fresh cornea
Refrigerated Corneas	Refrigerated cornea	Cryopreserved heart valve

Cytomegalovirus	Herpes simplex	HTLV-I
Fresh Skin	Fresh Cornea	Frozen Bone

Table 2. Time of onset of infections after tissue transplantation.

Infection	Latency periods based on published cases
HIV, Hepatitis B & C	3 to 4 weeks, up to 3 months
Bacterial infection	Usually a few days to weeks, up to 3 months
Fungal infection	2.5 weeks in one heart valve case, five months in another, up to one year
Classical CJD	18 months to 24.5 years (median 12.5 yr)
Disseminated Tuberculosis	2-8 months
Rabies	3 to 4 weeks, up to 3 months

After investigating whether the pathogen could have arisen from environmental contamination in the operating theatre, or was from patient origin, the infection should be reported to the tissue bank. Providing a precise diagnosis, the type of pathogen and exclusion of environmental and hospital causes will be very important so the tissue bank can focus on its own investigation. For example, if the suspected allograft contamination is viral with symptoms developing weeks or months after the surgery, the tissue bank focuses on donor eligibility and not on failures of tissue processing. (Table 2)
The tissue bank considers several elements when investigating a report of infection. The type of the allograft processing (fresh, frozen, cryopreserved, freeze dried), the origin and the nature of the graft (bone, tendon, skin, vascular), review of the donor evaluation, including blood tests, possible retest of stored donor blood samples and retained co-processed tissues and environmental monitoring results.
An investigation by the tissue bank will determine the cause of the contamination and whether their practices were followed, whether there could have been failures in tissue processing and donor selection and testing and whether corrective action can be applied. The tissue bank is responsible for reporting this to the government regulators/competent authority. Thus, the initial evaluation, investigation and reporting by the surgeon is important in improving future medical care.
It is common for a surgeon to provide follow-up of the patient after surgery. Generally there is a long-term follow-up by the surgeon annually (as is the standard for orthopedic implants e.g. hip arthroplasty). Sometimes due to distance or other factors, follow up care is provided by the general practitioners and other health care providers in charge of the patient. Those who provide post-operative follow-up should report to surgeons any significant disease that arose after surgery. They are an important part of a vigilance biosurveillance system. Otherwise, the connection between an infection and an allograft may be missed and a tissue bank not notified.

5.2.2 Donor Reactions

Allograft donors

Human tissues that are ordinarily discarded during surgical procedures can be donated to others without risk to the donor.
Donations of bone allografts such as femoral heads during hip arthroplasty have no additional risks to the donor that are not ordinarily included in the surgical procedure itself. The femoral head would otherwise be discarded.
Donations of cord blood and placenta amnion do not place the maternal donor at risk.
In the case of donating a sural nerve the donor undergoes risk and this is ordinarily a directed donation from a relative, not a donation for public use.

Autograft donors

More often, tissue transplantations from living donors concern autologous grafts. Autologous grafts have the advantage to provide active living cells and tissue matrix on the recipient site. They are easily integrated with few local reactions but are necessarily limited in volume and associate with a morbidity at the donor site.
With bone autograft donations, the most frequent complications other than those from the anaesthesia, involve the donor site:

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

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

5.3 Working group 3 – HPC

Dietger Niederwieser (Facilitator), Laura St Martin (Presenter),
Kathy Loper (Rapporteur)

Group members met to review the work achieved thus far. Dr. St. Martin presented a summary of the work products which primarily consisted of a spread-sheet based repository of reactions and events related to HPC product donors and recipients as well as bibliographical references. She reviewed the challenges as well, particularly regarding the issue of imputability and the necessity for applying some clinical judgment for

confirmation of those reactions which were either not described fully in the literature or for which there was no confirmatory diagnostic test.
Dr. Niederwieser then led the group discussion regarding the following questions:

- Which reactions should not be considered notifiable?
- How do we handle donor reactions?
- Which events or clinical situations would be notifiable (to assist with the development of educational materials for clinicians)?

After a robust and enthusiastic discussion, consensus was reached on the following points which are summarized below. Stem cell transplant (SCT) carries significant morbidity due to the recipient's clinical situation, disease status, preparative regimen by chemotherapy and radiation, and duration of immunocompromised condition until engraftment. Therefore, those reactions and situations which are expected to occur in the transplant setting should be excluded from the V&S system unless they are life threatening. Examples would include dimethylsulfoxide (DMSO) toxicity, constitutional symptoms, etc. It was felt that collecting these common and transient reactions would inundate the system with somewhat useless data and possibly obscure important and rarer reactions and events. Issues related to the biology of the disease and efficacy such as graft versus host disease (GVHD) should not be captured by the system. However, GVHD would be reported if it is due to an adverse event, such as a product mix-up.

Donors

For donors of HPC, bone marrow and HPC, apheresis products, the following reactions would be reported:

- Reactions related to donation that are life threatening or fatal
- Unexpected or serious reactions such as bleeding from the spleen
- Significantly debilitating reactions

It was the group consensus that long term follow up through adult registries was essential and donor follow up should be performed at a minimum of one, five and ten years. The follow up and reporting should include donor malignancies and autoimmune diseases for mobilized donors. Participants noted the reporting parameters must be carefully formulated to provide useful and comparable data. Regarding related donors, participants noted that the incidence of malignancy may be increased above the general population due to motivational factors that bias donor to donate HPC products, and due to familial/genetic predisposition. Routine and expected donor reactions such as headache and bone pain would not be reported.
For cord blood donors, the group did not reach full consensus and some questions remain. The primary view was that there were no reactions or events in the literature related to umbilical cord blood donation. However, some theoretical risk does exist for anemic neonates if the umbilical cord is clamped early. Participants opined that this would be an important trend to watch and might indicate the need for additional education and training, particularly in developing programs and countries. Some attendees shared personal anecdotes of this situation and the impact of additional training. It was also noted that a positive culture for any unusual or atypical bacteria should be noted. 'Unusual' might include those not previously known or reported in the literature. Since these products would likely not be stored and infused, consensus was not reached on this issue. Some felt it would serve to clutter the database and impede reporting compliance.

Recipients

The group decided that immediate reactions that occur within 24 hours of product infusion which are unexpected or life threatening should be reported. As previously mentioned, DMSO toxicity (hives, flushing, transient bradycardia, etc.) would not be reported. However, life threatening anaphylaxis would be reported. Adverse events associated with the infusion of the incorrect product and near misses such as wrong product thawed would be reported. Avoidable adverse events related to processing error during manufacturing and storage of the product would also be reported. Examples include but are not limited to clinically significant human errors and transportation errors, and equipment failure that result in damage or loss of product. Regarding microbial contamination, the system should capture those reactions and events which are probably or definitely related to disease transmission by the product. Untreated sepsis related to transmission by the product that is serious would be reported as SCT patients are routinely placed on antibiotics during the transplant procedure, and untreated sepsis is avoidable. Infectious diseases which have a high probability that the source was the product or donor would be reported.
For long term follow up, all donor-derived malignancies (i.e. malignancies that develop from donor cells, but no malignancy is present in the donor) would be reported if they are also unexpected. In this regard, EBV related PTLD would be excluded from reporting since it is so common. Donor-transmitted malignancy (i.e. malignancy present in donor at time of donation) would be reported as well as genetic conditions of donor origin. It was noted that references on donor malignancies recently added and addressed by Group 10 would be reviewed for relevance and included on the Group 3 worksheet.

Summary comments

It was reconfirmed that the system would not capture events related to biology of SCT; efficacy issues (non-engraftment, GVHD, known complications of transplant, DMSO reactions, etc.) and other situations which are typical of SCT.
Clinicians should specifically be encouraged to report anything in their clinical judgment that is unexpected and life threatening or fatal, or results in significant disability. Specific attention should be paid to how the data are analyzed at the national and international level to ensure optimal utility of the V&S system.

5.4 Working group 4 – Ocular

Naoshi Shinosaki (Facilitator), Marian Macsai (Presenter),
Paul Dubord (Rapporteur)

Following the presentation on the work that had been achieved to date, Working Group 4 addressed the assigned topics.
A **notifiable reaction** in a recipient for ocular tissue includes:

- Primary Graft Failure – a graft that does not clear at eight weeks with no known intra-operative or post-operative cause;
  The incidence of primary graft failure has been accepted as a good indicator of the quality of tissue being provided by a particular eye bank establishment (typically less than 0.5%).

Endothelial or lamellar procedures may have special consideration related to processing and surgeon experience (greater than 10 cases). Endothelial lamellar procedures where the corneal tissue is manipulated either by the surgeon while doing surgery deserves special consideration. These delicate surgical procedures are more complicated and require more tissue manipulation. They require a skill set with a very steep learning curve with tissue manipulation that may lead to poor tissue functioning. Typically, quality assurance procedures are better with eye bank pre-cut procedures versus surgeon cutting or processing. Less frequent operating surgeons generally have an increased complication rate due to the learning curve.

Assessment of this procedure as to Graft failure should be assessed by the Medical Director i.e. EBAA surgeon with <10 procedures with graft. Failures are usually attributed to the learning curve.

All endothelial and lamellar new emerging procedures may lead to increased demand for more tissue due to tissue discards.

- Infectious disease transmission. A local infection appears within 1 to 31 days after surgery. However, the 31 day limit is arbitrary. Examples of Systemic Infectious Disease Transmission include CJD, HIV, and hepatitis. Local infection may be limited to cornea (keratitis or endothalmitis). Specific recipient issues, however, impact on the incidence of this complication.
- Corneal degenerations and dystrophies
- Local ocular malignancies (anterior segment). Local ocular malignancies are more usually related to metastatic disease to anterior segment of the donor's eye (i.e. adenocarcinoma). These donors typically would be deferred by appropriate eye evaluation prior to tissue collection.

  There is no evidence of systemic malignancy related to transplantation (corneal).

  Tissue that has had previous refraction laser procedures are generally not appropriate for thickness keratoplasty due to unpredictable refractive outcomes but satisfactory for endothelial lamellar procedures.

The **product specific** clinical situations that should alert clinicians are:

- Local infectious disease within 1 to 31 days post surgery
- New onset systemic disease (HIV, CJD, hepatitis) without another cause
- Development of corneal degeneration or dystrophy
- Local ocular malignancy (anterior segment)
- Primary graft failure – if the corneal graft is not clear from post-operative day one to at least 8 weeks with no known intra operative or post-operative complications.

The **donor reactions** that should be reported are:

- Reactions in other tissues from the same donor (emerging infection disease).
- Does this apply only to living donors? Does it apply to cadaveric donors? Surgeons must be aware of potential issues related to the donor that might impact corneal transplant.

The **incidents in clinical practice** that may need to be considered for reporting are:

- Deviation in aseptic technique, processing, distribution
- Wrong recipient or tissue allocation error
- Tracking error
- Adverse events that occur only after the tissue is deemed transplantable by the eye bank or accepted by the surgeon or both
- Medical Director review should be required before reporting! It is to be noted that in most jurisdictions the surgeon makes the final evaluation of whether tissue is appropriate or not for transplantation.

5.5 Working group 5 – Gametes and Embryos

Luca Gianaroli (Facilitator), Mauro Costa (Presenter),
Anne Cathrine Bollerup (Rapporteur)

The key discussion points for Group 5 were: 1) What should be focused on going through the different adverse reactions and 2) should vigilance include all the aspects of the process from rare complication to the most common adverse reactions?

OHSS was presented as an example. If OHSS should be included, then there is the need to differentiate between severe (hospitalisation) and non-severe OHSS. Adverse reactions are reported in many ways and may have nothing to do with the quality and safety of the tissues or cells.

From the point of view of WHO, the donor focus within this program should be on severe donor reactions. Although it is important to keep all types of donor reactions in the database it is necessary to monitor the severe ones in order to meet global needs. From the global point of view there is no argument to exclude severe donor reactions.

With respect to a definition and reporting system, it was indicated that if an OHSS case is admitted to intensive care then it should be notified to the pharmacovigilance system. However, the effectiveness of the system will decrease if a wide spectrum of reactions is notified. For a severe syndrome such as OHSS, each country should be monitor in one way or another. The systems should be simple but enable professionals to communicate.

During discussion on a list of adverse reactions, the question raised was 'Should vigilance only take into consideration the product (as per the EU Tissues and Cells Directive) and not quality of practice?' If everything is to be included, then inclusion criteria have to be defined. Malta expressed its concerns and as a small country with little resources advocated for a minimum list.

Although there was a recommendation that the focus should be on severe donor reactions, there appeared to be a difference of opinion between Europe and the rest of the world. There was disagreement as to whether severe donor reaction should be included although oocyte donors might be an exception. A list of types of different reactions is needed.

In the case of the birth of a newborn with a genetic illness after donation (oocyte, sperm), it is necessary to have a system in place to be able to ensure that a donor with a known genetic illness is not used further. It could be of value to discuss limiting the number of offspring a donor could create in order to reduce the risk. With respect to oocyte donation, 200 million citizens go across borders for this treatment and don't inform their doctors of this. Monitoring of the real risk of donation is difficult as nearly half of all oocyte donations come from abroad to the country where

they donate. Should the same list of adverse reactions be used? Are reactions in the foetus included? There should be guidance for couples having treatment with donor oocyte and sperm. The question of new hazards arose. Should the system include complications of pregnancy (e.g. Turners syndrome) post ART? There is a high incidence of other situations, e.g. abortion, premature delivery which may not necessarily be related to ART. In fact, some countries do not declare that pregnancy is part of ART.

With respect to adverse events, they can be related to cryopreservation and not related to cryopreservation. There is the need to make a list of priorities and divide them into steps according to the procedure (as has been done in the document developed in WP 5 of the SOHO V&S project).

The conclusions/recommendations arrived at were that it would be extremely difficult to monitor every complication to the outcome of pregnancy particularly due to the non-disclosure of the origin of the pregnancy (e.g. small country or religion reasons), cross border health care and illegal procedures in some countries.

6 SOHO V&S by Reaction/Event type

Chair: D. Michael Strong

The participants again split in 5 breakout groups and the leaders of Working Groups 6 to 10 presented their work on the Google site and discussed it with the participants. They had taken the information collected by WGs 1 to 5 and had analysed it by reaction/event type to consider the implications for clinicians in identifying adverse reactions, to analyse any gaps across product categories and to highlight confirmation criteria.

6.1 Working group 6 – Infection

Jay A. Fishman (Facilitator), Michael G. Ison (Presenter),
Richard Tedder (Rapporteur)

The process in which Group 6 looked at the issue of 'infections' involved the issuance of a call for participation, the allocation of work, the extraction of infectious disease entries from the worksheets of Groups 1-5, and their division into the following pathogen-specific sub-workgroups: bacteria, fungi, parasites, viruses and other agents (Prions). A literature review followed.

Analysis of the data that was compiled included:

- An assessment of which tissue types were associated with transmissions
- A tabulation of the number of transmissions by category
  - Proven, Probable, Possible, Unlikely, Intervention without documented transmission (IWDT), Excluded, or Not Assessable
- Consideration of the modulating factors (i.e. pathogen inactivation, immune suppression)
- Time of onset relative to implantation
- Presentation of transmission (i.e. symptoms)
- Diagnostic Testing

A background document was then prepared that set out in its Introduction,

- Key clinical features
- Donor screening
- Donors at Increased Risk of Infection Transmission
- Presence of documented pre-procurement infections
- Assay window period
- Laboratory testing of donor logistics

The definitions that were used were drawn from discussions held with key stakeholders at an ESOT meeting held in Paris in 2009 as well as existing definitions. The need to differentiate between *expected* and *unexpected* transmissions was identified, as expected transmission have a known epidemiology and typically are accepted in tandem with risk mitigation techniques (i.e. prophylaxis or close monitoring for disease).

It is clear that the overall goal of vigilance and surveillance systems is to enhance patient care and safety. A couple of caveats were presented. First, the risks of infectious disease transmission associated with transplantation can never be reduced to zero. Second, it is assumed that there is a need for rapid, real-time communications surrounding transmission events ('alerts') between involved centers and organ-tissue-eye communities.

Specific objectives are to:

- Increase the recognition by clinicians, through education, that syndromes are different in different hosts (e.g. immunocompromised organ recipients) and that they differ by region/geography/country;
- Refine the evaluation of donors (screening) based on accumulated data in order to minimize risk and maximize donations. Consideration needs to be given to the impact of new pathogens (e.g. West Nile Virus) and the use of optimal microbiologic assays. New assays need to be developed and the collection of a donor's social and travel history needs to be improved through a donor specific questionnaire without free text.
- Improve interventions based on data (e.g. antimicrobials, resection)
- Improve the informed consent process (i.e. better communication about the potential risks and benefits) through the use of risk specific consent forms.

There is the need to define what needs to be reported. The focus should be on the unexpected and/or clinically serious events in allograft recipients. The data that should be collected include:

- Imputability: clusters, microbiologic data in the donor and recipient, histology in graft;
- Syndromes (e.g. pneumonia, sepsis, graft dysfunction, meningoencephalitis). A link to 'events' in other recipients, particularly organs and unusual illness, should be included;
- Microbiologic diagnoses: unusual, unexpected, un-reported;

• Handling of expected transmissions (e.g. CMV, HCV) requires careful consideration. Data should be collected if the normal outcome of the known infection is incompletely understood in all transplant populations or if it varies by region. It is also important to recognize the changing epidemiology of infection.

Gaps in what constitutes vigilance and surveillance exist. Gaps identified by the group include:

• Should an HIV-infected tissue be used in an HIV+ recipient? Is this considered to be biovigilance or is it clinical research?
• Which conditions suggest the need for a 'new' screening assay? Pandemic A/H1N1 virus outbreak? >10% seropositivity for *T. cruzi*?
• This could be justified if intervention is possible. Whether screening is part of vigilance elicited a divided opinion. The collection of knowledge is always informative but it should not be bound by legal implications/EC directives. Tests must be validated if a change is considered.
• The need for a communication system can be addressed by using the international networks via the internet; but standard international definitions need to be developed, to facilitate this communication.
• The role of public health authorities needs to be clarified.
• Screening assays for common infections (TB, bacterial and fungal (Candida, endemic) infections, resistant pathogens (e.g. VRE, ESBL gram negative bacteria, MRSA, azole-resistant yeasts) and parasites) need to be developed and tested in the individual donor populations.

When faced with a possible infection, clinicians should:

• Consider the possibility of a donor-derived graft infection; education needs to be developed to raise awareness.
• Determine which samples and assays are available – blood, urine, graft cultures; Serologic assays, NAT tests; the laboratories with theses samples needs to be alerted so that they do not inadvertently dispose of samples per usual protocols.
• Consider storing samples for later testing. This may depend on the donor and should be justified for scientific purposes as the storage costs can be prohibitive.
• Determine who should be notified – the source/provider, public health authorities, others – and when. There should be a unique identifier for the recipient, who may not always realise that they have had an allograft, and a unique ID for every tissue especially when there is cross-country border transfer.

Cases of novel infection transmissions should be published to educate the community.

Still to be addressed were:

• The risk of infected donor tissues to staff, this includes those in the mortuary
• The risk that infected health care personnel might contaminate donated tissues; the development of guidelines for this situation is very challenging.

Response to a possible allograft–associated transmission event

The clinician must be suspicious that transmission of infection may occur in association with an allograft implantation. The exact response to the infection may be modulated by the degree, if any, of immune suppression and pre-existing immunity in the recipient. Any clinical course that is not typically experienced by an individual recipient of transplanted substances of human origin should raise the suspicion of a possible donor-derived infection transmission. Additionally, unexpected graft dysfunction, local signs of infection or inflammation (e.g. erythema, edema, pain), fluid collection or bleeding may indicate an ongoing infection; in such instances, donor-origin of the infection should be considered.

In evaluating a potential allograft-associated transmission event, the team should carefully review all donor cultures and screening for infections; rarely infections may have been present but not recognized at the time of procurement of tissue. Additionally, local samples must be obtained for microbiological analysis. These include samples from infected site for Gram stain and bacterial culture, fungal stains and 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 and differential counts should also be obtained. Collection of blood, sputum, urine, cerebrospinal fluid, and other deep fluids and/or tissues should be collected. Additionally, because of endemicity of certain infections, special testing based on the epidemiologic history of the donor, and laboratory quality control measures.

Notification to the organ or tissue bank of the possibility or demonstration of infection in the allograft donor should occur as quickly as possible, not to exceed 24 hours following recognition of potential disease transmission. Reporting should occur quickly and not await results of confirmatory testing. Notification of the appropriate public health authorities must also be made to ensure appropriate investigation of transmission event.

During and since the meeting, the group developed a didactic paper on this topic which is published in the second part of this supplement.

6.2 Working group 7 – Malignancy

Jeremy Chapman (Facilitator), Rafael Matesanz (Presenter),
Antonietta Derrico Grigioni (Rapporteur)

Working Group 7 focused on the transmission of malignancies through substances of human origin. The aims of this group were:

1. To list donor malignancies known to be transmitted or known not to be transmitted by tissue, organ and cell type;
2. To provide guidance on early detection and prevention of transmission;
3. To provide guidance on immediate steps to be taken for an index recipient and other potentially affected recipients; and
4. To provide guidance on steps to investigate and confirm the attributability of disease transmission.

Information related to malignancy transmission that had been identified in the literature by WGs 1 to 5 was reflected in a worksheet used by the working group. It covered the:

• Type of malignancy;
• Cell, tissue or organ involved;
• Typical alerting signals (including time since diagnosis);
• Demonstration of attributability;
• Comments (exposure);
• References.

A table was presented that showed the malignancies reported to have been transmitted through solid organ transplantation. They are:
breast cancer, choriocarcinoma, CNS malignancies (usually with risk factors), colorectal carcinoma, germinal cell carcinoma, haematopoietic malignancies, Kaposi´s sarcoma, liver and lung cancer, melanoma, neuroendocrine tumours, ovarian cancer, pancreatic carcinoma, prostate carcinoma, renal cell carcinomas, sarcoma
The table also included the following malignancies reported not to have been transmitted through solid organs.
CNS malignancies (usually without risk factors), non-melanoma skin cancer, in-situ cancers, and curatively treated cancers
A second table presented malignancies reported to have been transmitted through tissues and cells. The malignancies are usually haematological with haematopoietic stem cells being the second product in frequency for transmission. The malignancies are:
PTLD, malignancy of donor origin, T-cell large granular lymphocyte leukaemia, ALL, AML, CML, T-cell lymphoma, B-cell lymphoma, myelodysplastic syndrome/acute myeloid leukaemia, Burkitt type ALL, B-cell ALL, immunoblastic sarcoma.
The immediate steps that may need to be taken for an index recipient and other potentially affected recipients include:
1. Tracing, alerting and notification of suspected cases and their potential transmission. It is necessary to:
- Trace all involved CTOs
- Alert all teams involved
  - Introduce measures for potentially affected recipients
  - Undertake an assessment of attributability (a collective investigation)

Note: The immediacy/urgency of the alert depends on whether all transplant procedures have occurred or not.
- Notify/report to the relevant authority (according to the regulation in place)
  - Systematic approach

1. Graft removal and cessation of immunosuppression
2. Immunotherapy
3. Conventional therapy upon cancer type

Investigation and confirmation of attributability of disease transmission
When there is any suspicion of transmission of a malignancy, steps should be taken to investigate it and to confirm its attributability.

1. Suspected transmission malignancy
- Clinical triggers/Alerting signals. It has been reported that 75% of these signals occur in the first 14 months following transplantation
- Time sequence
- Reported cases in literature

2. Trace donors and recipients
- Donor with same histological tumour. Role of histology.
  1. a detailed histological study of the primary tumour: histotype, grade, immunohistochemical profile
  2. characterization of the neoplasia of the recipients
- Other recipients with same histological tumours: Donor transmitted *vs*. Donor derived

3. Karyotype FISH

4. Genetic testing SSTR\HLA\other

There is the need to build a body of evidence on what is best to do in any particular case.
Terminology related to risks used in the context of transplantation is heterogeneous. The term 'donor-derived' may be used by some while 'donor-transmitted' may be used by others. The terminology used in the European Union and the United States for example differs with respect to terms related to malignancy transmission (i.e. certain, probable, possible, unlikely). There is a need for common terminology related to vigilance and surveillance of cells, tissues and organs.

Help is needed for molecular techniques:
Evaluation of the genomic profile is the best technique for ensuring the origin of the tumour. In cases of different gender transplantation, the interphase Fluorescence in situ Hybridization (FISH) for sex chromosomes can help identify the origin of a neoplasia.[11] In cases of the same gender transplantation the origin of the tumour can be identified by microsatellite analysis by polymerase chain reaction using different markers.[12] Paternity testing by genomic allelotyping investigation is another reliable technique to verify attributability. This test permits the analysis of 16 highly polymorphic loci (with the AmpF/STR identifier PCR amplification kit) for effective discrimination of donor/recipient tumour origin.[13]

Attributability of neoplasia origin after transplantation
a) **Donor transmitted tumour**: Malignant disease diagnosed in a recipient that may possibly, probably or definitely be present in the donor at the time of donation of SOHO.
This is the case in which a tumour in the donor is identified during or immediately after donation. The tumour can be transmitted with the graft (e.g. kidney with a neoplastic nodule) or can be identified at autopsy immediately after transplantation (e.g. lung carcinoma). The follow up of the recipients can reveal the presence of a tumour in the graft, or in a different organ.
For attributability of the origin, the following are necessary:
1) a detailed histological study of the primary tumour: histotype, grade, immunohistochemical profile
2) characterization of the neoplasia of the recipients.

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11 Haltrich, I., et al., *Donor-cell myelodysplastic syndrome developing 13 years after marrow grafting for aplastic anemia.* Cancer Genet Cytogenet, 2003. **142**(2): 124-8.
12 Kakar, S., et al., *Origin of adenocarcinoma in a transplanted liver determined by microsatellite analysis.* Hum Pathol, 2002. **33**(4): 435-6.^
13 Altimari A., Gruppioni E., Fiorentino M., Petraroli R., Pina A.D., Petropulakos K., Ridolfi L., Nanni Costa A., Grigioni W.F., D'Errico Grigioni A., *Genomic allelotyping for distinction of recurrent and de novo hepatocellular carcinoma after orthoptic liver transplantation*. Diagn Mol Pathol, 2005. **14**: 34-38.

Histology can provide the histotype of the tumour and the immunohistochemistry can help to identify a possible histogenesis. So if a kidney is used with a small papillary carcinoma (<4 cm) and the graft shows after few months from the transplant the presence of a papillary neoplasia, histology can recognize the histotype and immunohistochemistry can help to identify a kidney origin of the neoplasia. In the same way, the identification of a lung carcinoma in the donor during or immediately after transplantation needs a detailed investigation of the tumour (histotype, grade, immunohistochemical profile) and a careful follow up of the recipients. In the case of a tumour in one or more recipients, the morphological comparison between the tumour of the donor and the tumour arising in the recipients can allow the recognition of tumour origin.

b) **Donor derived tumour**: Malignant disease diagnosed in a recipient that may possibly, probably or definitely be derived from the transplanted SOHO. Some malignancies may develop in the organ or cell only after transplantation and not be present at the time of donation.

These cases represent a problem both for the management of the tumour in the recipient and for forensic medicine aspects. The attributability of a tumour can be defined as certain when, after SOHO transplantation, more than one recipient shows the onset of a tumour with the same histologic features. When a tumour arises in the recipient in the first months after transplantation it is necessary to establish the origin of the tumour. For these purposes the evaluation of genomic profile is the best technique to ensure the origin of the tumour.

During and since the meeting, the group developed a didactic paper on this topic which is published in the second part of this supplement.

6.3 Working group 8 – Characteristics and handling

Diego Ponzin (Facilitator), Scott Brubaker (Presenter),
Axel Rahmel (Rapporteur)

There were more than twenty attendees to this breakout group meeting and an overwhelming number expressed the desire to change the original title of this section (Product Property) but still retain the original scope. 'Product Property' caused confusion and both words connote negative thoughts in the context of human donation and transplantation (i.e. 'product' equates to manufacturing and sales; 'property' can infer ownership). Other words were selected to directly describe the focus of this section, which is to evaluate influences on outcome and risk that involves quality attributes and characteristics of, and handling activities involved with supplying, human cells, tissues, and organs (HCTO) for transplantation. These can all be generally referred to as 'allografts' and involve both living donors and deceased donors.

Each HCTO has specific quality attributes and characteristics determined by anatomy and usual function. For transplantation, 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 adverse event (SAE) or a serious adverse reaction (SAR) can occur.

The overall activity or process involves multiple steps in handling and is developed to maintain certain characteristics of the allograft so it serves a specific clinical need. Handling varies among the many different subtypes within general types of HCTOs but there are also general processes to which each HCTO is subject that can affect outcome. This work group specifically concerns those SAE/SARs relating to the physical properties 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 either viability of cells or other physical or chemical properties desired. To maintain desired allograft characteristics and clinical utility, controls should be in place for steps involving:

- consent/authorization;
- donor screening, testing and test kits;
- recovery, procurement or collection;
- preservation/processing (can include qualification of materials, reagents, equipment and facilities as well as maintenance where applicable, and validation of processes that incorporate process controls and/or verification of steps);
- storage, transport and distribution;
- selection for use and allocation (where applicable);
- preparation for use (or other final disposition);
- qualified personnel with sufficient training who are deemed competent; and
- documentation and maintenance of records for all the above.

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

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

During and since the meeting, the group developed a didactic paper on this topic, combining with the work of the subsequent group. It is published in the second part of this supplement.

6.4 Working group 9 – Clinical practice

Lorenza Ridolfi (Facilitator), Rene de Vries (Presenter),
Paula Nolan (Rapporteur)

The session opened with René de Vries setting out the aims of the session, describing how he carried out the work on his paper and presenting the outcomes. He explained that his paper should be viewed as a first chapter and asked for other members of the group to consider their own areas of practice to add to this paper. His paper uses examples of possible events that should be considered for a reporting system.

The three types of serious reactions discussed were: acute haemolytic reaction, Graft versus Host Disease (GvHD) and circulatory overload associated with the transfusion of cells (HPCs).

The group discussed where severe allergic/anaphylactic (unexpected/unknown) reactions should fit in this context? As well as acute haemolytic reactions due to ABO-incompatibility, wrong product infused/transplanted was discussed, though concerns were raised that this might fall under Working Group 10 (Genetic and donor). The group were also concerned that some issues might also be discussed by WG1 and WG6.
SARE resulting from clinical practice in ART was discussed. Severe adverse events could include: wrong sperm/egg used for in-vitro fertilization, wrong embryo implanted, severe bleeding following egg retrieval and severe or critical OHSS might be considered as an SAR due to clinical practice in some circumstances and might need to be reported (in cases where patient is admitted to ITU or dies).
In ART, clinical and laboratory practices are closely intertwined and it was considered it might be difficult to extract 'clinical practice' failures. In France, for example, a number of reports relating to patient bleeding post procedure could have been blamed on poor clinical practice but upon further investigation were shown to result from a fault in a type of surgical instrument.
The group did not consider that defining a narrow list of reporting criteria would be the right approach as it might discourage practitioners from reporting events or reactions not included in the list. With the objective of keeping vigilance data clear and useful, it was recommended that only situations that are critical, life-threatening, involving death, prolonged hospital stay or hospital readmission should be reported.
The group discussed how to minimise or prevent serious adverse events via quality management with SOPs, competent staff and audit.
The discussion was guided back to the purpose of the working group. The group felt that each discipline represented should provide a list of common adverse events/reactions (severe/critical) associated with clinical practice.
During and since the meeting, the group developed a didactic paper on this topic, combining with the work of the previous group. It is published in the second part of this supplement.

6.5 Working group 10 – Genetic and Donor

Emanuele Cozzi (Facilitator), Carolina Stylianou (Presenter), Dennis Confer (Rapporteur)

For the discussion on the transmission of genetic conditions and serious and unexpected reactions in living donors, information was sought from the literature reviews carried out by Working Groups 1 to 5, the World Marrow Donor Association (WMDA) and its Serious Events and Adverse Effects Registry (SEAR), from a global donor follow-up meeting that was held in Bern, Switzerland in August 2009 and sponsored by the Worldwide Network for Blood and Marrow Transplantation (WBMT) and WMDA, and from personal communications.
Adverse reactions (AR) in HPC Donors can be classified as:

- Collection-related
  - Mobilized peripheral blood – HPC(A)
    Mobilizing agent (e.g. filgrastim, lenograstim)-related
    Apheresis procedure-related
    Other
  - Conventional bone marrow – HPC(M)
- Late effects of donation
- Fatal adverse reaction

Adverse reactions in living donors can be classified according to their:

- Frequency – whether common, uncommon or rare;
- Seriousness – yes, often, occasionally, rarely, or no
- Sentinel events

HPC donor recommendations

Serious adverse reactions (AR) occurring between initiation of donation and 30 days after completion should be reported. However, some common AR that are rarely serious, e.g. nausea, vomiting, bone pain, may be exempted unless they are life-threatening or fatal. Long-term follow-up should occur annually or biannually for at least 10 years. The reports should address death, new onset malignancies with special attention to hematologic malignancies, and new onset autoimmune diseases.

Organ donor recommendations

Severe AR occurring between initiation of donation and recovery should be reported as should re-hospitalizations. Long-term follow-up should occur for life if there has been failure in the organ of donation, complications e.g. hypertension, in kidney donors, and quality of life data are lacking for liver and lung donors

Gamete donor recommendations

As ovarian hyperstimulation syndrome (OHSS) is under reported due to the fact that its occurrence outside of the ART setting is common, it should be better addressed in pharmacovigilance systems, operating in collaboration with the ART Competent Authority. Severe OHSS events that require intensive care treatment (i.e. are life threatening) should be reported to ART Competent Authorities so as to be investigated and provide analysis of event and guidance. Oocyte donors with life-threatening or fatal complications (e.g., haemorrhage) should be reported
During the discussion several issues were raised. Should there be a uniform schedule for donor follow-up and how long should it continue? As follow-up is probably organ-specific, it may be driven by regional/national guidelines but should be lifelong for organ donors and at least 10 years for HPC donors. For related HPC donors, follow-up systems are poorly developed in comparison to unrelated HPC donors. Therefore, better systems are needed. And what about autologous donors? Should these be included in a V&S reporting system? The answer is not clear but probably not since many AR will be related to an underlying disease and prior therapy.

Gamete donor adverse reactions and events

Events and reactions that can be associated with gamete donation include:

- Severe OHSS reported in partner (autologous) donation (where pregnancy is achieved immediately post-donation) (0.2-5%). This can potentially be life threatening
- Pelviperitonitis, Ovarian abscess (0,02%)
- Hemoperitoneum after oocyte retrieval (0,28%)

In cases of severe OHSS, the Alerting Symptoms are:

- Clinical Ascites
- Oliguria
- Elevation of haematocrit % over 45
- Hypoproteinaemia
- Requires hospitalisation (may require intensive care unit support)

Genetic transmission by HPC and gamete donors

All congenital diseases originating from bone marrow derived cells are transmissible. Genetic disease transmissions from sibling HPC donors that has been documented are Cyclic Neutropenia and Gaucher's disease. There have been no reports for transmission by volunteer donors (which could be due to adherence to strict medical history and medical assessment criteria).

Risk from cord blood unit donation

Genetic disease might not be recognised at birth or even some time later. The practice should be that cord blood banks request medical information on the child/donor usually within six months post donation.

Recommendations for HPC (Cord)

Volunteer donors originating from areas with a high incidence of certain genetic diseases should be screened, if the risk is identified during the medical assessment, and if found positive be deferred. Cord blood collection and storage from families with a genetic disease history should be avoided. If units are already in storage they should be screened prior to release or listing. The medical history questionnaire should cover maternal as well as family history and ethnic background information. If responses generate concern the collection should be cancelled. If cord blood units have already been collected, and the family history or future information on the newborn raises issues of genetic disease, they should be screened prior to listing. Stored units without an adequate history or that potentially carry the trait of a genetic disease e.g. beta-thalassemia, should be screened and this information should be available to requesting transplant centres. Cord blood from births originating through gamete donation should not be collected, unless the medical history of the gamete donor, and if an oocyte donor was used blood samples, can be provided. Families with a disease history that would present a risk to a transplant recipient should not donate

Genetic disease transmission from gamete donors

The cases of genetic disease transmission from gamete donors that have been documented are: Severe Congenital Neutropenia, Hypertrophic Cardiomyopathy, Fragile X Syndrome, Autosomal Dominant Cerebral Ataxia, Opitz Syndrome. There have been rare cases that have affected numerous recipients (offspring) from the same sperm donor.

Recommendations for gamete donation

The EU Directives on tissues and cells state that genetic disease transmission is a serious adverse event. Reporting to the Competent Authority is very important as more gametes from the same donor may be available for further use. Reporting should be as soon as the genetic disease is confirmed and the investigation proves that it is due to the use of donor gametes.

Challenges in third party reporting

As secrecy surrounds the use of gamete donors, couples with affected children may not report the condition. Genetic clinics should be alerted when new cases are presented and discuss the issue openly with parents in order to increase urgent reporting. Reporting is often too late for effective intervention. Cross-border care poses the problem which should be notified to the Competent Authority (It is recommended to report to the competent authority of the place of origin of the family and further investigation to be taken by the CA in the country that the ART treatment took place).

Issues

In addition to 'genetic transmissions', the transmission of acquired disorders, e.g. autoimmunity, cancer, should be considered.

During and since the meeting, the group developed this work further, dividing in two didactic papers which are published in the second part of this supplement.

7 Improving the efficacy of notification

Chair: Johann Kurz

This session aimed to address recommendations to clinicians that would enhance their ability to spot/report the unexpected.

7.1 Breakout Group 1. Recommendations to clinicians to help spot/report the unexpected

Ruth Warwick (Facilitator), Carolina Stylianou (Rapporteur)

The 16 participants in this break out group were asked to consider making recommendations to clinicians to help spot/report the unexpected in adverse event and reaction (AER) reporting. To scope out the work the group considered which clinicians would be involved in:

1 the short, long and very long term

2 for all sectors including organs, tissues, cells and the assisted reproduction sector.

It quickly became evident that the wide remit meant that almost any type of clinician could be involved in the recognition of AERs and that the only way to ensure that such practitioners could recognise and appreciate the significance of such a finding was to target clinicians in training. This would mean inclusion, at least at a basic level, of the use of donated materials for human application during medical school courses. In

further discussion with the wider congress it was fully appreciated that the introduction of an additional subject to the medical school curriculum meant competition with many other worthy subjects for teaching space on courses with limited time resource.
Also, even with patient based hospital clinicians present in the working group it was clearly difficult to find effective ways to reach individual clinicians and affect their knowledge base. It was suggested that one route to reach practising clinicians was to use hospital based committees, such as risk management groups, hospital transfusion committees or through hospital hierarchies through medical directors.
Different medical specialities are involved in the care of donors and recipients in either the short or long term. Development of partnerships with two-way dialogue between regulatory bodies and the relevant scientific and professional societies was considered a potentially useful way to disseminate information to the wide variety of clinical specialities, to nurses, hospital committees, scientific/professional societies, as well as to the regulators.
The subject of developing partnerships with recipients was also considered. Providing education to recipients about their allograft would require that the consent process for receiving an allograft is strictly formalised and this responsibility is clearly a clinical one. Patients and also living donors might usefully be given some form of identification to state what they had received or given. No single solution would fit all circumstances and it was recognised that in the assisted reproduction sector such information would sometimes be considered highly confidential for social or regulatory reasons.
For any partnership to function the relationship between patients, the medical community and regulators must be reciprocal, trusting, non-judgemental and non-punitive if there are to be improvements in patient care.
Good communication channels are required to reach individual clinicians, those working in organisations (e.g. hospital) and those working independently (e.g. dentists, individual practitioners), and those who might be reached through regional/national routes (e.g. CA, Scientific Society).
There needs to be a reward for reporting and encouraging clinicians to report which could be achieved through feedback and information from other clinicians in the local, regional, national and supra-national areas so that it is clearly appreciated that reporting is 'normal' and part of clinical care rather than something to be feared. Clinicians and their representatives should be included in analysing and collating outcomes so that their clinical judgement is seen to be appreciated and that reporting can improve patient care in a systematic fashion.
There also needs to be clarity and support for reporting in a simple way. The recommendations to encourage reporting are given in Table1 below.

7.2 Breakout Group 2. What would be the components and qualities of a V&S awareness tool for clinicians?

Günter Kirste

Twelve participants discussed the issue of how to install a tool for vigilance and surveillance and the pros and cons for people working in the clinical field.
A great part of the discussion was dedicated to problems related to lack of knowledge in the whole field. As an example, awareness amongst doctors working in the field is only possible if there is information about specific incidences, the number of cases, their significance etc. Without these data uncertainty remains amongst those working in the field about what aspects of awareness and surveillance are important.
At the end of the discussion, it was agreed that patients should be involved in the dialogue. It should be made clear to the patient that there is a lack of knowledge, even amongst experts, concerning specific situations as their occurrence might be extremely rare.
It is generally accepted that the informed consent of patients is needed. This is especially true for patients in need of a transplant. Informed consent, however, is constrained by knowledge in the medical field and, of course, limited by the personal experience of the doctor in charge.
Specific information about particular events that occur in the follow up of a transplant recipient needs to be made available to other clinicians and of course to other patients. This is not possible without a kind of registration of these events and reporting of the incidences. The follow up information has to be combined with expert opinion.

Table 1.

Build mutual trust by dialogue and education of tissue establishments, clinicians and regulators to expect the unexpected, to anticipate that AERs are 'NORMAL'
Non-punitive reporting,
Confidentiality,
Immediate and long term feedback of information to and from all key players
Analysis by expert groups, sharing of analysis report with other centres
Identification of trends, locally or internationally, all fed back to clinicians both individually and collectively
Clear, simple and rapid notification methods – with sieving
Hospital incidence reporting systems and development, where appropriate, of the model of hospital transfusion committees
Clear emphasis that lessons learned ultimately improve patient care and practices

Epidemiological data cannot be compiled and made available without a system of vigilance and surveillance. A surveillance system has to be put in place either at the hospital level or on a national level by health authorities. Some participants in the discussion expressed their fear that clinicians might not be willing to report cases and events because they fear prosecution or may even be penalised.
Doctors might even try to hide events or might not report them. This is underlined by the fact that most insurance companies contracted by clinicians do not allow the doctor to report an event or an accident which could lead to any kind of insurance payment to the patient involved.
Another important point for clinicians is that they need feedback to their reporting. Doctors in hospitals generally are bored with the number of reports they have to write and the documentation they have to prepare. Without any kind of feedback, the willingness to draw attention to problems and to report is minimal. Of course, there should be a kind of a 'no blame' culture. Ideally, vigilance and surveillance should turn into a learning opportunity.
To accomplish these goals, it is necessary to have an open website with open access and a peer review process about cases together with a kind of rapid alert system and a follow up of the cases. All this is extremely difficult to introduce in the clinical day to day environment. In an ideal world, this kind of reporting should be part of the routine work. Clinicians, however, need protection from accusations and of course they need time to report the follow up and to review problems.
At the end of the discussion, the whole group felt that both – awareness and surveillance – are important in the medical field in general. However, a number of problems concerning lack of time, openness of discussion, and specifically problems with insurance companies, and the possibility of losing their coverage, have to be solved beforehand.

7.3 Breakout Group 3. What are the key factors for an effective national vigilance and surveillance scheme?

Jun Wu

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

- Serious adverse event and reaction reporting must be required;
- Rapid alert systems, with 24/7/365 availability, are essential and should be developed;
- Standardized reporting by clinicians should be expected;
  - Clinicians are the first to acquire information when an SAE/SAR occurs and they are the ones 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 given providing them with clearly described and concise guidance for identification and reporting
  - Encouraging clinician reporting requires that there be feedback regarding the information collected and how it has been used to influence patient safety and changes to practice
- Cooperation between governments/competent authority, professional associations and clinicians is essential;
  - There is the need to identify a key contact for the reporting of SAREs. This may be an organization, or formal system, a coordinating body, or a registry which is responsible for the collection of information as it occurs (for evaluation by specialists)
- Human Cells, Tissue, and Organ V&S systems can be set up based on the extensive experience from the blood donation/transfusion V&S (haemovigilance) systems that already exists;
- Traceability requirements must be in place by all stakeholders and time-sensitive capabilities such as the use of quick and easy tracking systems should be promoted. These systems should make use of computerized data bases and machine-readable bar-code labeling that promotes unique identification on the CTO graft. The alternative is to rely on time-insensitive, laborious, manual searching of handwritten logs, donor records, distribution records, inventory records or individual recipient records;
- Although there may be different oversight bodies for cells/tissues and organs within a Member State, their vigilance and surveillance systems should be linked directly to optimize response;
  - Inspections for licensing, accreditation, certification, etc., must include evaluation of the V&S system in place.
  - Provision of training and education for all stakeholders is necessary
- Traceability and reporting systems must include consideration of compliance to the expectations in the country receiving/using the CTO as well as the country of origin of the CTO. Neither system should be compromised;
- A global V&S data collection system for CTOs is desirable and can be coordinated by WHO.

7.4 Breakout Group 4. What global value could the EU Experience add?

Beatriz Domínguez-Gil

The legislation of the European Union sets out requirements for the quality and safety of tissues and cells. The World Health Organization could add value to the EU's experience by:

- Establishing **harmonized terminology** to be applied to the field of vigilance and surveillance (V&S) including all organs, tissues and cells;
- Providing a **core framework and a practical basic V&S system**, with cases to be reported with examples;
  - This could be performed through an *aide-memoire*
- **Taking account of geographical and regional differences** through the WHO regional offices which could facilitate this process;
- Educating **all stakeholders** on the benefits of a comprehensive V&S system;
  - Physicians/health care professionals (i.e. with and through professional societies)
  - Patient groups
- Encouraging Member States to **develop and maintain follow-up registries** in which aspects relevant for V&S are addressed systematically and shared between all stakeholders involved. Ithis is in line with WHO GP 10; and
- Continuing to **foster the integration of all OTCs** under a common framework of V&S, where differences are respected.

7.5 Breakout Group 5. The role of WHO: feasible actions for and indicators of improvement of Global V&S for CTO products

Ines Alvarez Saldias

Taking account of

- the resolutions of the World Health Assembly WHO57.18, WHA40.13, WHA 42.5, the Executive Board Resolution 124.R13 in points 3 and 4, of the General Director's request to continue collecting and analysing global data on practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation of human cells, tissues and organs;
- The Global Vigilance and Surveillance Tools analysed in the Third Global Consultation on regulatory requirements for human cells and tissues for transplantation held in Geneva 10-12 February 2010, based on the accumulated experience gathered in the EUSTITE project pilot trial with 20 European countries, using the designed tools for V&S;
- The capacity of the SOHO V&S guidance on reporting, analysing and management of adverse events and reactions; and
- In order to facilitate Member States' access to appropriate and generic information on the donation and transplantation (D&T) process, including data on severe adverse events and reactions;

the analysis and discussion of the role of WHO on a Global V&S for CTO was developed with the representation of all stakeholders, searching for a match between commitment and compromise with the global purpose of patient safety.

The human transplantation of organs, tissues or cells is always based on a clinical assessment of risk versus benefit to the patient. Despite this, careful donor selecting criteria and a Quality Management System applied to the donation and transplantation process minimize the global risk of human transplantation. On the other hand, if a clinical risk decision is the only alternative for saving the patient´s life, it is necessary to obtain the patient's informed consent and acceptance of the risk.

Previous WHO – Stakeholders meetings and documents as:

– Guiding principles;
– Aide Memoir on key safety requirements for essential minimally processed human cells and tissues for transplant;
– Aide Memoir for National Health Authorities;
– Vigilance and Surveillance tools on human cells and tissues for transplant;
– Draft document on coding and traceability for cells, tissue and organs for transplant.

The enormous effort conducted by the pre meeting working groups in the Notify Project, collecting the existing data and summarizing the global vigilance on the field, pointed the reality of:

- the necessity to have equivalent criteria for reporting and classifying all the severe reactions and events (SAREs);
- The commitment of the stakeholders;
- The necessity to work with the clinicians and to improve the feedback to the professionals;
- Global knowledge of known/unknown/emerging risks, for patients and donors is imperative, in order to preserve the transparency of the D&T process.

The key and consensual ideas, emerging for the discussion were:

1. The core objective for this global consultation is to enhance patient care and safety.
2. The goals are:
   – to increase clinical commitment and
   – the Health Authority intervention needs to be based on reliable and validated data.
3. Patients need a global vigilance and surveillance system and WHO plays an important and substantial role.
4. There are enormous differences between the countries around the world with a wide range of capacity for transplantation therapies and regulatory practices. In the developed countries with capacity for donation and transplantation, there exists the motivation for voluntary reporting to the Scientific Societies and to the Authorities when it is required.

For developing countries, different capacity levels of exist, ranging from almost no transplantation system to fully developed donation and transplantation programmes. There are some countries (such as Nigeria) that are starting with the process; they need to know how to begin and what to report. In these cases the Breakout Group 5 believes that WHO can play a coordinating role with Governments, Scientific Societies and others stakeholders in developing countries, contributing to the building of the donation and transplantation process, including the V&S System, and helping with proven tools, in order to assure correct implementation. The tools that would support this process are:

– Protocols
– Global guidance
– How to report to the database, and what has to be registered
– Help with the accreditation process
– Recommended licenses

5. What needs to be reported?
   For the human transplant of organs, tissues, cells and assisted reproduction products, the consensus of the group was that the following should be reported:
   – All severe adverse reactions and events as previously defined
   – All unexpected clinical serious reactions.

For organ transplantation more discussion is required to obtain clear indicators of what severe adverse reactions have to be reported.

For Assisted Reproduction Products more discussion is needed for some indicators.

6. The Notify Project only will be successful with consistent data, and with the participation of all stakeholders. It is necessary that they be convinced that patient safety is the final objective and all relevant stakeholders should feel that they are partners in the project.

7. The National Authorities should do vigilance reporting to a central reference point so that lessons can be learned and shared.
8. Tools of communication: The consensus was that for the present current channels of reporting should be used but, in the future, new specific vigilance tools will have to be developed in order to have consistent and verifiable data.
9. Alert system: the group considered that the indicators for an Alert System probably will emerge from the working groups.

8 Conclusions and closing remarks

Luc Noel/Alessandro Nanni Costa

Dr Luc Noel spoke of the common responsibility to protect the health of citizens and of the importance of trust of the public in any SOHOs. Each profession must stick to its roles not only in providing care but in reporting when and where things may have gone wrong.

He remarked that this meeting – the Bologna Initiative – was just the first step in a process to develop a knowledge base of common experiences. It would become a collaborative effort bringing together the best of authorities, professional societies, and professionals themselves. Many quality management practices have already been implemented in the area of substances of human origin but an inherent risk remains. At the forefront is the transmission of infectious agents. Vigilance and surveillance of cells, tissues and organs will assist authorities in the delivery of better health care.

Dr Noel remarked that the CNT has been at the forefront of a global network for vigilance of substances of human origin. The NOTIFY project will build on this foundation. It will aim to improve access to information, provide guidance, establish collaboration, and facilitate communication.

Dr Noel described a number of important outcomes that will result from the meeting and the work that preceded it:

- The detailed report of the meeting would be published with the names of all participants included.
- The SOHO V&S project would develop instruments and guidance for tissue and cell V&S in the EU based on the data gathered and the recommendations developed by the Bologna Initiative.
- WHO will publish a booklet for clinicians that will summarise the guidance on detection and investigation of adverse reactions and events that was developed by project Notify. The booklet targeting professionals will be provided to WHO Member States to promote V&S in transplantation. It will be designed to be customized to meet national specificities and yet retain and promote a globally harmonized conception of V&S.
- A new dedicated site will be established by CNT, as part of a sustained collaboration with WHO, for the promotion of V&S. 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 will be publicly accessible and will be populated initially with the over 1,400 references to documented incidents already collected in the NOTIFY Google site. These cases, and new cases as they arise, will be posted on the site using key words and a minimum data set which will enable searching by, for instance, type of human substance, type of infectious disease transmission agent, type of logistical error etc. The tool will be a source of information for clinicians, potential donors and patients who wish to understand better 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 annual WHO consultation organized in collaboration with CNT will review progress, with regulatory and professional representatives from the fields of organs, tissues and cells, in particular oversee the work of the new website . Thus it is expected that the other outputs of the Bologna Initiative including the development of correspondence tables for terminology and agreement on common definitions will also be taken forward where possible.

This initiative will facilitate global sharing of V&S information and guidance for the enhancement of donor and recipient safety and for greater public transparency in transplantation and assisted reproduction. It will also support the development of internationally common, or corresponding, terminology for vigilance of organs, tissues and cells.

Dr Nanni Costa recognised the significant amount information that had been exchanged and the progress made in the course of the meeting. He acknowledged that adverse reactions and events, unfortunately, are part of the daily work of many of the participants. But he is convinced that through a cooperative effort, a sound knowledge base can be built that will be a source of valuable information for the enhancement of patient safety. With thanks to the participants for their huge contributions and enthusiasm, he declared the meeting closed.

LIST OF ABBREVIATIONS

AATB	American Association of Tissue Banks
ABM	Agence de la biomédicine (Biomedicine Agency) (France)
ABMTR	Autologous Blood and Marrow Transplant Registry
ALKV	Alkhurma virus
ALL	Acute lymphocytic leukemia
AML	Acute myelogenous leukemia
ANVISA	National Health Surveillance Agency (Brazil)
APABO	Pan American Association of Eye Banks
ART	Assisted reproduction therapy
ATMP	advanced therapy medicinal product
BOOT	Blood, organ and other tissue (of CDC)
CA	Competent authority
CAOD	Cost of avoiding one death
CBER	Center for Biologics Evaluation and Research (USA)
CDC	Centers for Disease Control and Prevention (USA)
CHIK	Chikungunya
CIBMTR	Center for International Blood and Marrow Transplant Research
CJD	Creutzfeldt Jacob Disease
CML	Chronic myelogenous leukemia
CNS	Central nervous system
CNT	Centro Nazionale Trapianti (Italian National Transplant Centre) (Italy)
CTO	Cell, tissue, organ
CTT	Cell- and tissue-based therapeutic products
CWD	Chronic wasting disease
D&T	Donation and transplantation
DBD	Donation after brain death
DCD	Donation after cardiac/circulatory death
DDDT	Donor-derived disease transmission
DHQP	Division of Healthcare Quality Promotion (CDC, USA)
DMSO	Dimethylsulfoxide
DTAC	Disease Transmission Advisory Committee (USA)
EBAA	Eye Bank Association of America
EBAANZ	Eye Bank Association Australia New Zealand
EBAI	Eye Bank Association of India
ECD	Extended criteria donor
ECDC	European Centre for Disease Control
EE	Expert elicitation
EEBA	European Eye Bank Association
EFRETOS	European Framework for the Evaluation of Organ Transplants

EIM	European IVF Monitoring programme
ESBL	Extended spectrum Beta lactamases ('s)
ESHRE	European Society of Human Reproduction and Embryology
EU	European Union
EUROCET	European Registry for Organs, Tissues and Cells
EUSTITE	European Union Standards and Training for the Inspection of Tissue Establishments
FDA	Food and Drug Administration (USA)
FISH	Fluorescence in situ hybridization
GCSF	Granulocyte colony stimulating factor
GMP	Good manufacturing practice
GTOR	Organs, Tissues and Cells Office (of ANVISA)
GvHD	Graft versus Host Disease
HAS	Health Sciences Authority (Singapore)
HBV	Hepatitis B virus
HCT/P	Human Cell and Tissue Products
HCV	Hepatitis C virus
HFEA	Human Fertilisation and Embryology Authority (UK
HHS	Health and Human Services (USA)
HIV	Human immunodeficiency virus
HOTA	Human Organ Transplant Act (Singapore)
HRSA	Health Resources and Services Administration (USA)
HSV	Herpes simplex Virus
HTA	Human Tissue Authority (UK)
IBMTR	International Bone Marrow Transplant Registry
ICCBBA	International Committee on Commonality of Blood Banking Automation
ITU	Intensive Therapy Unit
IUI	Intra-uterine inseminations
IVF	In vitro fertilisation
IWDT	Intervention without documented transmission
KCBTiK	Krajowe Centrum Bankowania Tkanek i Komórek (Poland)
LCMV	Lymphocytic choriomeningitis virus
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MMCT	Minimally manipulated cells and tissues
MOH	Ministry of Health
MRSA	Methicillin-resistant Staphylococcus aureus
MS	Member States
NAT	Nucleic acid test
NHSN	National Healthcare Safety Network (USA)
NMDP	National Marrow Donor Program
NNTKOP	Number needed to kill one person
NOTA	National Organ Transplant Act (USA)
NSRD	Non-standard risk donors
OARRS	Online Adverse Reaction Reporting System
OHSS	Ovarian hyperstimulation syndrome
ONT	Organización Nacional de Trasplantes (National Transplant Organisation) (Spain)
OPO	Organ procurement organization

OPTN	Organ Procurement and Transplantation Network (USA)
PBSC	Peripheral blood stem cells
PHMCA	Private Hospitals and Medical Clinics Act (Singapore)
PHS	Public Health Service (USA)
PTLD	Post-transplant lymphoproliferative disorder
QALY	Quality adjusted life years
SAE	Serious adverse event
SAR	Serious adverse reaction
SARE	Serious adverse reaction and event
SARS	Severe acute respiratory syndrome
SCD	Standard criteria donor
SCT	Stem cell transplant
SEAR	Serious events and adverse effects registry
SOHO	Substances of human origin
SOHO V&S	Vigilance and Surveillance of Substances of Human Origin
SOP	Standard operating procedure
SPEAR	Serious product events and adverse reactions registry
TTSN	Transplantation Transmission Sentinel Network (USA)
UBHEM	Bio and Haemovigilance Office (Brazil)
UD	Unrelated donor
UNOS	United Network for Organ Sharing (USA)
V&S	Vigilance and surveillance
VRE	Vancomycin resistant enterococci
WHA	World Health Assembly
WHO	World Health Organization
WNV	West Nile virus

Part B
Working Group Didactic Papers

The Transmission of Infections

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Summary

In this section of the document, issues related to infectious diseases transmissions through organs, cells, and tissues are reviewed. It is critical to recognize that this represents the first review of such data and hopefully there will be ongoing addition and revision of the document as additional information becomes available.

To complete this section of the document, reports of infectious disease transmissions aggregated by Groups 1-5 were reviewed as was the available literature by global experts by pathogen type (bacteria, fungi, parasites, viruses, and other pathogens). These were then analyzed to:

- Assess which tissue types were associated with transmissions
- Tabulate the number of transmissions by imputability category (Proven, Probable, Possible, Unlikely, IWDT, Excluded, or Not Assessable)
- Assess the average time of onset relative to implantation and presence of potential modulating factors (i.e. pathogen inactivation, immune suppression) that may have resulted
- Assess how the transmission presented, clinically, and how it was diagnosed

A summary of the findings with specific focus on the epidemiology of disease transmissions by pathogen type, risk factors for recognized disease transmissions, methods of testing for and mitigating disease transmissions, and limitations of the available literature was then drafted by the experts.

During the in-person discussion during the meeting in Bologna the goals and findings of the groups were summarized as follows:

- The overarching goal was to enhance patient care and safety.
- We recognize that it will be impossible to completely remove the risk of disease transmission from organ transplantation.
- There are still significant challenges to communications between organ-tissue-eye communities during the 'alert' phase of transmission events.
- There is a need to increased recognition by clinicians through education.
  - o Clinical syndromes associated with disease transmission differ in different hosts (e.g. immunocompromised organ recipients).
- There are differences in the epidemiology risk of transmission by region/geography/nation.
- There is a need to refine evaluation of donors screening based on accumulated data to minimize risk maximize donations recognizing:
  - o New pathogens, such as West Nile Virus, may emerge as new threats.
  - o The optimal microbiologic assays (i.e. cultures, NAT) should be studied for each pathogen type.
  - o New assays should be developed that are useful to those that will use them.
  - o Improved social or travel history through donor specific questionnaire.
  - o Improved interventions based on data (e.g., antimicrobials, resection) need to be developed.
- Improved recognition and screening for donor-derived disease will improved informed consent process and inform which patients may safely use organs from infected donors (i.e., Italian risk-specific consent forms, HCV donor's lungs).
- There needs to be better definition of what needs to be reported
  - o The concept of 'unexpected and/or clinically serious event in allograft recipient' should clearly prompt reporting of a potential event.
  - o The reporting process needs to maintain simplicity of reporting methods.
  - o Certain syndromes, particularly if they are occurring in an unexpected way or as a cluster should be reported (pneumonia, sepsis, graft dysfunction, meningo-encephalitis).
  - o Any unexpected pathogens that are detected as part of a microbiologic work-up of an infected recipient.

Additionally, the group identified the following gaps that warrant additional consideration:

- How to differentiate biovigilance from clinical research (i.e. should an HIV-infected tissue be allowed to be utilized in an HIV+ recipient?).

- Which conditions suggest the need for a "new" screening assay? And is such new screening part of vigilance, divided opinion but could inform screening?
- Novel communication systems are needed for use by the international community in such a way that data is shared freely.
- Assays for screening donors for common infections such as TB, Bacterial & Fungal (Candida, endemic) infections, resistant pathogens (e.g. VRE, ESBL gram negative bacteria, MRSA, azole-resistant yeasts) and parasites are needed.

1. Introduction

Section Authors

Jay A Fishman, Melissa A. Greenwald, Paolo A. Grossi

Viral, bacterial, parasitic, prion, and fungal infections have been transmitted via organ and tissue allografts (1-13, 44). Microbiological screening programs for organ and tissue donors are not standardized and vary with the intended use of the allograft, by national standards, and with the availability of screening assays. Analysis of allograft-associated disease transmissions (infection and malignancy) have been further hindered by incomplete reporting of these events, by difficulty in distinguishing recipient-derived infections from allograft-derived infections, and by the lack of standardization for the evaluation of donors and recipients. The number of tissue grafts implanted is unknown and transmission events are likely under-recognized and under-reported. One goal of this guidance document is to increase consideration by clinicians of the possibility of tissue-derived infections in graft recipients of all types. This document is designed to address the main clinical challenges of allograft-derived infections including screening, risks and clinical presentation.

2. General Considerations

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

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

3. Graft Recipient and Presentation of Allograft-Associated Infections

The efficiency of disease transmission is likely to be greatest in immunosuppressed transplant recipients (solid organs, hematopoietic stem cells) with enhanced susceptibility to infections of all types. As a result, these individuals act as sentinels for transmissible disease. In immunosuppressed hosts, symptoms of infection are often decreased and classic signs of infections (leukocytosis, erythema) are replaced by non-specific signs (altered mental status, elevation of blood liver function tests, wound dehiscence, unexplained hypotension). In immunosuppressed hosts, the transmission of blood or organ-derived infection due to West Nile Virus, for example, more often manifests as neurological disease with poor clinical outcomes than in normal hosts (14-17). Multiple clusters of infection associated with organ transplantation (multiple recipients from the same donor) have included tuberculosis, *Candida* and *Aspergillus* (and other fungal) species, herpes simplex virus (HSV) and human herpes virus 8, lymphocytic choriomeningitis virus (LCMV), rabies virus, Chagas disease, HIV and hepatitis C virus (1-18). Malignancies have also been transmitted via organ transplantation including renal cell carcinoma, glioblastoma, melanoma, hepatoma, lymphoma and others. Detection of these unusual transmission events is dependent upon the suspicion of the clinicians caring for the transplant recipients, access to advanced microbiologic testing including nucleic acid amplification technologies (NAT), recognition of epidemiologic risks, and assistance with investigation of the outbreaks by public health authorities.

Infections have also been reported uncommonly due to tissue and eye tissue transplantation. This lower frequency is likely a reflection of chemical or radiation processing (disinfection) of some tissue grafts as well as the normal inflammatory and immune function of the hosts, and possibly improved healing and vascular supply in many recipients of such grafts. Tissue transplants have been associated with transmission of *Candida albicans* and other fungi, *Chryseobacterium* meningosepticum, now *Elizabethkingia meningoseptica*, *Clostridium* species, HCV, Epstein-Barr Virus (EBV), and group A Streptococcus. These infections may present with local signs of graft failure, purulence, unexplained erythema, persistent pain, or systemic infection.

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

Despite screening and processing, hematopoietic stem cells (HPCs) have also been associated uncommonly with transmissions of a wide range of viral, bacterial, fungal, and parasitic infections; transfusion-transmitted prion disease has been described but transmission through HPCs have not.

Transmission of infections through gametes and other reproductive tissues have likewise been described but contemporary screening and processing seems to have reduced the risk of disease transmission from these tissues substantially. No cases of transmission of infection after

cryostorage of embryos and semen have been described. Likewise, substitution of human serum with serum substitutes in culture media appears to have reduced the risk of donor-derived disease transmission from embryo transfers.

4. Screening of organ donors for infectious risk to recipients

Organ and tissue 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 contacts and injection drug use) and physical examination, including by the surgical team during procurement to detect 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 organ procurement. Any such screening must be consistent with the requirements of the screening process as well as local and national policies and regulations (See Table 1).

Unfortunately, such donor history has limitations, including:

The medical and social history from deceased donor is inherently limited. Information is typically obtained from next of kin who may not be fully aware of all potential risk behaviors or conditions the donor may have (i.e. a mother may not know of recent experimentation with IV drugs in a child who lives away from home). There is often inadequate time or available information to know who all of the donor's providers are and obtaining a complete donor history may be incomplete; this is particularly true if there were unknown admissions to other hospitals or clinics in areas with non-centralized health care. Further, many organ procurement organizations may not be able to access existing registries to know if the donor has had prior infectious diseases (i.e. HIV, HCV, or tuberculosis) or if the donor has previously been deferred for blood donation.

The medical and social history obtained from living donors also may be incomplete. Donors may not be honest in completing their questionnaire, as was recently the case with transmission of HIV through blood products (42). Further, there is evidence that patients may not provide accurate data because of variable understanding of specific terms utilized in existing questionnaires (43).

Increased use of electronic medical records combined with limitations to procurement staff access to such records may result in missing outstanding tests that are not followed up upon.

Recent publications discuss guidelines for pre-transplant screening of organ donors and recipients (6-13). Some documented infections preclude organ donation (e.g. uncontrolled sepsis, HIV or, in some regions, HTLV infection, West Nile Virus, Rabies virus, LCMV). Other infections are routinely screened for pre- or post-transplant management purposes including syphilis, cytomegalovirus (CMV), EBV, HSV, varicella zoster virus (VZV), HBV, HCV; tuberculosis may also be screened for, particularly in living donors. In endemic regions, additional screening may be performed for endemic fungi (*Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides spp, Blastomycosis*), *Trypanosoma cruzi, Plasmodium spp., Strongyloides stercoralis*, Schistosoma spp, *Leishmania spp*, Chikungunya virus, WNV, and, in some regions, serologic assays for human T cell lymphotropic virus (HTLV-I/II). Screens of increased importance with transplantation of specific organs may also be performed (e.g. *Toxoplasma gondii* in cardiac recipients, although a potential for transmission exists for any organ. In addition, most donors have blood and urine cultures performed and a review of recent microbiological data and past infections when possible.

In the United States, for example, screening tests must be FDA-approved, licensed, or cleared for donor screening. To assure the quality of assay data, screening laboratories are generally certified by a national organization to perform testing on human specimens and must participate in routine proficiency testing generally on an annual basis (discussed below). The optimal utilization of nucleic acid testing in donor screening remains controversial given excellent sensitivity and concerns regarding false positive assay results. The serologic tests most frequently used for donor screening are reported in table 2.

False positive assays after blood transfusion, and false-negative serologic assays due to the haemodilution of blood samples after infusion of colloids and crystalloids must both be considered in the interpretation of serologic testing of organ donors (19-20). Similarly, testing of bloods for antibodies from newborns less than one month of age is unreliable given exposure to maternal antibodies and the inconsistent

Table 1. Suggested data to be collected regarding eligibility of organ or tissue donors.

- Medical history
- Previous infections
- Vaccinations
- Occupational exposures
- Travel history
- Transfusions with blood or blood products
- Contacts with people with HIV, HBV, HCV or other transmissible diseases
- Tattooing, ear piercing or body piercing
- Use of illicit drugs
- Sexual behavior
- Incarceration
- Contact with bats, stray dogs, or rodents (including pets)

From Grossi P, Fishman JA. Guidelines for Transplantation Infectious Disease: Donor-derived infections in solid organ transplant recipients. Am J Transplant. 2009;9(S4):S19-26.

Table 2: Standard Screening Tests for Organ Donors*.

- Human immunodeficiency virus (HIV) antibody
- Hepatitis B (HBV) serologies including HBV surface antigen, core antibody, surface antibody and Hepatitis delta antigen and or antibody in HBsAg positive donors
- Hepatitis C antibody
- Treponemal and non treponemal testing (TPHA or TPPA or FTA-Abs + Rapid plasma reagin [RPR])
- Human T cell lymphotrophic virus (HTLV-I/II) antibody (less common currently)
- Toxoplasma antibody (notably in cardiac donors)
- Cytomegalovirus antibody
- Epstein-Barr virus (EBV) antibody
- Herpes simplex virus antibody
- Varicella-zoster virus antibody
- Blood and urine cultures

* Many procurement organizations supplement these tests with additional assays based on local epidemiology and/or using nucleic acid-based assays (NAT). Modified from Grossi P, Fishman JA. Guidelines for Transplantation Infectious Disease: Donor-derived infections in solid organ transplant recipients. Am J Transplant. 2009;9(S4):S19-26.

antibody responses of the immature immune system. Likewise, testing platforms for some diseases that are transmissible (i.e. LCMV and rabies) are not commercially available or are not available in a format that is appropriate or validated for potential donors (i.e. tuberculosis). Further, some available test systems (i.e. Chagas and HTLV) are available but may frequently yield false positive results; since confirmatory testing is usually not available in real time, such assays may result in greater loss than is offset by reduction of disease transmission (i.e. HTLV) (44).

5. Donors at Increased Risk of Infectious Disease Transmission

In the evaluation of potential organ donors, the risk of HIV infection has been inferred from the donor's medical and social history in addition to the use of screening assays. These have been referred to in the past as 'high risk donors' but are considered at 'increased risk of infectious disease transmission' as organ or tissue donors. The epidemiological risk factors developed for HIV transmission in 1994 by the Centers for Disease Control and Prevention (CDC) have generally been applied also to HCV, HBV and other blood-borne viruses (Table 3). While these guidelines are under revision, they appear to have proven useful in the management of organ donor screening. The definition of 'increased risk donors' have not been updated to reflect the availability of highly sensitive NAT and protein-based assays for HIV, HCV, HBV and

Table 4. Estimated Risk of Undiagnosed Infection per 10,000 Donors by Risk Factor and Testing Modality.

Risk Factor	HIV ELISA	HIV NAT	HCV ELISA	HCV NAT
Window Period	22 days	9 days	66 days	7 days
Men who have sex with men	8.3	3.4	36.0	3.8
IV drug users	12.9	5.3	350.0	37.8
Hemophiliacs	0.05	0.02	0.46	0.05
Prostitutes	2.9	1.2	107.8	11.5
Partners with above	2.7	1.1	126.2	13.5
Blood product exposure	1.3	0.5	22.0	2.3
Incarceration	1.5	0.6	68.6	7.3

Adapted from Kucirka *et al.* American Transplant Congress 2010. Abstract LB22. Note: This data is predominantly derived from US data.

Table 3: Definition of Increased Risk Donors based on 1994 USPHS Guidelines.

General Behavior/History

- Factors
- Men who have had sex with another man in the preceding 5 years.
- Persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years.
- Persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates.
- Men and women who have engaged in sex in exchange for drugs or money in the preceding 5 years.
- Persons who have had sex in the preceding 12 months with any person described in items above or with a person known or suspected to have HIV.
- Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin, or mucous membrane
- Current or recent inmates of correctional systems.

Specific Factors for

- Pediatric Donors
- Children meeting any of the exclusionary criteria listed above for adults should not be accepted as donors.
- Children born to mothers with HIV infection or mothers who meet the behavioral or laboratory exclusionary criteria for adult donors (regardless of their HIV status) should not be accepted as donors unless HIV infection can be definitely excluded in the child as follows:
- Children >18 months of age who are born to mothers with or at risk for HIV infection, who have not been breast fed within the last 12 months, and whose HIV antibody tests, physical examination, and review of medical records do not indicate evidence of HIV infection can be accepted as donors.

Children ≤18 months of age who are born to mothers with or at risk for HIV infection or who have been breast fed within the past 12 months should not be accepted as donors regardless of their HIV test results.

Laboratory and Other Medical Factors

- Persons who cannot be tested for HIV infection because of refusal, inadequate blood samples (e.g. hemodilution that could result in false-negative tests), or any other reasons.
- Persons with a repeatedly reactive screening assay for HIV-1 or HIV-2 antibody regardless of the results of supplemental assays.
- Persons whose history, physical examination, medical records, or autopsy reports reveal other evidence of HIV infection or high-risk behavior, such as a diagnosis of AIDS, unexplained weight loss, night sweats, blue or purple spots on the skin or mucous membranes typical of Kaposi's sarcoma, unexplained lymphadenopathy lasting >1 month, unexplained temperature >100.5 F (38.6 C) for >10 days, unexplained persistent cough and shortness of breath, opportunistic infections, unexplained persistent diarrhea, male-to-male sexual contact, sexually transmitted diseases, or needle tracks or other signs of parenteral drug abuse.

From Guidelines for preventing transmission of human immunodeficiency virus through transplantation of human tissue and organs. MMWR. 1994;43 (RR-8):1-17.

Table 5. Recommended Follow-Up of Recipients of Organs from Increased Risk Donors*.

- Testing at least at 1, 3, 6, and 12 months after transplantation for:
  - — Serology: anti-HIV antibodies, Syphilis
  - — Nucleic Acid Testing for: HIV-RNA, HCV-RNA, HBV-DNA
- Mandatory storage of samples of donor and recipient blood, plasma and cells for future testing

*derived from U.S.A. and Italian guidelines.

other common infections (see Window Period above). The optimal use of organs from such donors remains controversial and generally these donors are excluded from other types of tissue donation. The CDC guidelines suggest that organs from these donors may be used if 'the risk to the recipient of not performing the transplant is deemed to be greater than the risk of HIV transmission and disease'. In those cases, specific informed consent is required. If organs from such increased risk donors are transplanted, close follow-up of the recipients and the storage of biological samples (serum, plasma and cells) form donor and recipient, is highly recommended.

Although many view the risk of disease transmission as dichotomous, there are significant differences in the risk of disease transmission based on the type of risk factor present in the donor and screening tests performed (Table 4). Understanding these relative risks are critical to understand when discussing risk with potential recipients.

Post-transplant evaluation of recipients of organs from increased risk donors is essential to detect disease transmission early and thus allowing institution of therapy as early as possible. These guidelines vary by the regulations governing organ and tissue procurement on a national and/or regional basis. Since patients who acquire infections from the donor may not seroconvert, especially in the case of HCV, assessment of serology plus direct assessments of infection, such as NAT/PCR are recommended. One approach to the use of such donors is described in table 5.

6. Pre-Procurement Donor Infections

Decisions regarding the use of tissues or organs from donors with active or suspected infection reflect the urgency of transplantation for the recipient and the availability of alternatives. Any active infections in the donor should be treated and, ideally, resolved prior to procurement (1, 34-40). Microbiologic data regarding donors must be communicated in a timely fashion to each of the clinical centers using those organs or tissues. There are no data on which to base a recommendation for the optimal duration of therapy or the interval between resolution of infection and procurement. Thus, clearance of infection should be documented to the degree possible. Special consideration must be applied to the potential donor with undefined infection (e.g. meningitis or encephalitis) or in whom resolution has not been documented (39). Given the frequent isolation in hospitalized or institutionalized donors of nosocomially-acquired organisms that are resistant to routine surgical antimicrobial prophylaxis (e.g. vancomycin-resistant *Enterococcus* [VRE], azole-resistant *Candida* species), routine surgical prophylaxis may be inadequate to prevent transmission. Data on the causative organism, including antimicrobial susceptibility patterns are essential. There needs to be developed a standardized approach to certain common donor issues including: current bacteremia, meningitis, pneumonia; prior tuberculosis; active or recent infections due to (e.g.) influenza, other respiratory viruses, West Nile Virus or Chikungunya virus; assays indicating exposure to Chagas' disease or hepatitis viruses (HBsAg positive, anti-HBc positive, or anti-HCV positive); anti-HHV-8 or HTLV- positive donors. These protocols will vary nationally, with the urgency of procurement, and the clinical condition of the recipient. These organs must be used with informed consent by the intended recipient and with a plan for careful microbiologic follow-up of the recipients. Formal guidelines, such as those established in Italy (http://www.trapianti.ministerosalute.it/imgs/C_17_normativa_1277_allegato.pdf), are needed for the use of organs from donors with infections. Such use is best guided by consultation with an expert in infectious diseases. (35)

7. The Assay 'Window Period'

A limitation to the screening of allograft donors is the relatively poor sensitivity of antibody-based serologic assays early after initial infection. Seroconversion may be delayed or may not occur during acute infections. Transmission of infection with organs and tissues may occur in the "window period" between infection and seroconversion (21-33). The window period for HIV exposure is approximately 22 days, but can be up to 6 months. The use of individual donor screening by nucleic acid testing can reduce the window period for HIV to 5.6 to 10.2 days (i.e. 4–15 days in which infection is detected by NAT but not ELISA. HBV surface antigen (HBsAg) ELISA assays have a window period of 38.3 to 49.7 days, with NAT in the range of 20.4 to 25.7 days (21-33). The use of HBV NAT testing may detect viral replication in hepatitis B core antigen positive who are HBSAg negative. The HCV ELISA assays have window periods of 38 to 94 days which is reduced to 6.1 to 8.7 days using NAT assays.

8. Considerations in Developing Programs for Laboratory Testing of Allograft Donors

Results of laboratory testing are only as useful as the quality of the assays performed. Incorrect assay results can occur due to: the assay (inadequate sensitivity or specificity, analyte below the limit of detection of the assay, innate error rate); the specimen (improper specimen handling, incorrect specimen type, interfering substances, hemolysis); or the laboratory technique in performing the assay (improper test procedures, poor lab technique resulting in contamination, improper specimen handling, expired reagent, improper maintenance or calibration of equipment). Organ and tissue programs, as well as laboratories, must be aware of the quality, performance characteristics and limitations of assays used, in order that results may be properly interpreted. Assay quality and performance characteristics can be reasonably assured when there is an available commercial assay that has been reviewed (or 'approved') by a regulatory agency/competent authority. It is incumbent upon the organ or tissue program to review and understand assay performance characteristics to develop optimal specimen handling protocols and to select appropriate assays for donor screening. This issue gains importance when an organ or tissue is imported from regions or countries using different assays than those that have been approved in the transplanting center. There must be a mechanism by which the organ or tissue program can be assured of the quality of laboratory procedures. In general, this requires that screening assays for organ and tissue donors have been examined critically by an external authority. As a result, 'approved' assays for donor screening are used preferentially over lab-developed ("home brew") assays. In the absence of approved commercial assays, more specialized or lab-developed assays may be used in evaluating donors or recipients, with appropriate controls used to ensure the quality of data obtained. Such

assays may be of importance when new or regional epidemiologic conditions require the introduction of a new assay as for, e.g. with the spread of West Nile Virus or Chikungunya virus.

Regardless of the assay used, adherence to good laboratory practices is required to obtain optimal assay results. For lab-developed assays, extensive validation studies must be performed and documented to assure that the assay performance is well characterized and can be communicated to regulatory authorities and to tissue or organ programs utilizing each assay. Standard protocols must be developed in each laboratory to assure that results are accurate and reliable. All laboratories should have both an internal quality program and be subject to routine external quality assurance audits to ensure that quality standards are adequate.

Adherence to good laboratory practices should be assured through accreditation, by either a regulator or other accreditation program, such as through a professional organization that sets laboratory practice standards (see Table 6).

The parameters for selection of assays used in testing samples from a potential donor or recipient in terms of sensitivity and specificity are determined by specific clinical circumstances. Increased sensitivity may incur false positive assay results result in discarding of uninfected donor tissues. However, the transmission of potentially fatal or life threatening diseases requires selection of an assay that optimizes sensitivity. Decisions must be based on the urgency of transplantation (elective versus life-saving), the availability of alternate therapies or grafts, and the availability of treatments for the disease screened. For tissue grafts, it may be possible to 'disinfect' the graft via various processing techniques. Highly specific diagnostic tests are used, in contrast, to guide therapeutic decisions. The performance of the assays used to screen donors should be evaluated in a relevant donor population (i.e., deceased and brain dead donors) by the competent authority. Tests for infrequent pathogens should be evaluated in a low-prevalence population to have relevance for donor screening.

Included among the parameters to consider when developing or selecting new screening assays are disease, host, and assay factors. These include: disease incidence and prevalence in the donor population; the rate and level of antibody formation; whether the pathogen antigen circulates in the blood, for how long, and at what levels. Antibody tests are more useful in evaluating prevalent disease, but have varying window periods (discussed above) of detection, and lack the sensitivity of molecular assays. Antibody testing may be supplemented with antigen or nucleic acid testing to shorten the false-negative assay window period and to provide signal amplification systems. Antigen or nucleic acid testing alone is preferable for detection of active infection (i.e. diagnosis) rather than past exposure to the agent. Determination of the selection of appropriate specimens for testing depends on whether the pathogen can be detected in blood samples; not all tests are optimized for non-blood specimens.

In the selection of laboratories for donor screening it should be noted that many assays are high-complexity tests that are subject to contamination, interpretation and other errors. Further, the equipment, reagents and personnel needed to validate, perform and maintain optimal

Table 6: Key Elements of Donor Screening Laboratory Programs*.

- Quality program independently reviewed by authority outside the chain of command
- Documented competencies for personnel with proficiency testing program
- Standard Operating Procedures (SOPs) for each assay written and routinely reviewed and adherence to assay SOP use is documented
- Test methods are validated
- Procedural or process changes evaluated and reflected in SOP when implemented
- Use of 'approved' donor screening assays when available and appropriate
- Laboratory facilities provide adequate space and are designed to provide function
- Environmental control and monitoring necessary to prevent contamination
- Proper installation, calibration and maintenance of equipment
- Use of proper, high-quality supplies and reagents
- Proper specimen handling and tracking
- Proper storage of all reagents and specimens
- Labeling controls
- Accurate, complete, legible and indelible recordkeeping with each significant step with adequate record retention (separate, duplicate records)
- Proper data handling, security and reporting

*For details see: 21 CFR 1271 [GTPs], 42 CFR 493 [CLIA], CAP Lab accreditation http://www.cap.org/apps/docs/laboratory_accreditation/checklists/laboratory_general_sep07.pdf

Table 7: Response to Possible Allograft–associated Transmission Event.

- The clinician must be suspicious that transmission of infection may occur in association with allograft implantation.
- In the setting of unexpected graft dysfunction, local signs (e.g., erythema, edema, pain) of infection or inflammation, fluid collections or bleeding, local samples must be obtained for microbiological analysis. These include 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 and differential counts should also be obtained.
- Systemic signs of infection or inflammation (fever, leukocytosis, hypotension, confusion, pneumonia, meningismus) merit blood cultures, and sputum or cerebral spinal fluid cell counts, glucose and protein, microbiological cultures as appropriate to the site of infection.
- Donor screening assays must be performed according to local requirements with consideration of the certification of the laboratory performing the assays, special testing based on the epidemiologic history of the donor, and laboratory quality control measures.
- Notification of the organ or tissue bank of the possibility or demonstration of infection in the allograft donor must be achieved within 24 hours of recognition of potential disease transmission.
- Notification of the appropriate public health authorities must be made to ensure appropriate investigation of transmission event.

screening assays are expensive. The performance of these assays is often not cost-effective and proficiency difficult to maintain if not used routinely. All such laboratories must be certified by an external, competent authority (regulatory authority, accrediting body) to assure adherence to a quality laboratory program. In countries lacking regulatory authorities to perform routine laboratory inspections, laboratories and procurement organization may develop systems for quality assurance and proficiency testing to assure optimization of laboratory practices.

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10. Definitions Related to Donor-Derived Infectious Disease Transmissions

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10.1 Differentiating Expected from Unexpected Infectious Disease Transmissions

Infectious disease transmissions can be categorized as either *expected* or *unexpected* disease transmissions. Since many infections are screened for in all or most donors (i.e. HBV, HCV, CMV, and EBV among others) and documented infection does not preclude use of organs or tissues for transplantation, these infections are frequently expected to be transmitted. Often, only certain recipients (i.e. use of HCV+ donors only in HCV infected recipients) are offered organs or tissues from such donors. While in other instances (i.e. CMV), pre-emptive monitoring or universal prophylaxis of recipients is utilized to mitigate the disease frequency and morbidity associated with such expected infectious disease transmissions. Likewise, a donor may be recognized to have a treated (i.e. culture positive *Streptococcal pneumoniae* meningitis) or ongoing but controlled (i.e. aspiration pneumonia, in a non-lung donor) bacterial infection that has been appropriately treated and organs or tissues are used, often with treatment of recipient for the recognized infection for a period of time post-transplant. As long as information about the infection was known prior to procurement by the clinician accepting the organ or tissue, any infectious disease transmission that occurred would be classified as *expected*.

If an infection was recognized to affect one or more recipients post-transplant but information about the infection in the donor was not known and/or not reported to the accepting clinician, any infectious disease transmission that occurred would be defined as *unexpected*. Frequently, the disease is not identified in the donor until an investigation of infections in recipients (i.e. rabies, LCMV, or tuberculosis) identifies the pathogen and subsequent retrospective testing of donor specimens confirms or suggests presence of the infection in the donor.

10.2 Definitions for Imputability of Donor Origin Infectious Diseases Transmission

For this document, potential donor-derived infectious disease transmission events are categorized, based on available information, as either: *proven*, *probable*, *possible, unlikely, excluded, intervened upon without documented transmission, positive assay without apparent clinical significance* or *not assessable* (Table 8).

The stringent definition of *proven* transmission should only be used if there is clear evidence of the same infection disease in the donor and at least one of the recipients. Absence of pre-transplant disease in the recipients should be documented. Variable involvement of different organs or tissues, different processing of organs and tissues, and recipient differences (i.e. pre-existing seroprotection or use of lymphocyte depleting induction in some but not all recipients) may contribute to variable disease transmission (e.g. transmission is not obligate in all recipients).

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

Four intermediate terms should be utilized when there is intermediate probability of donor-origin: *probable*, *possible, unlikely,* or *intervened upon without documented transmission*. It is recognized that there is some degree of subjectivity in how these individual definitions may be applied.

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

Possible transmission should be used for all situations where data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probable) and transmission cannot be formally excluded.

The term *unlikely* should be used for situations where it is possible that the disease in question could have been transmitted from the donor to at least one of the recipients but the available data suggests that donor origin is unlikely. It is recommended that this term is used exceptionally sparingly in classifying cases to better understand the epidemiology, prevention, and management of donor-derived infectious diseases. This term should not be used in lieu of attempts to complete a thorough investigation of a potential disease transmission event.

If all or some of the recipients received an intervention (i.e. antimicrobial therapy or organ removal) and no disease was recognized in any of the recipients, the term *intervened upon without documented transmission* (*IWDT*) was utilized. If some but not all recipients had an intervention but disease transmission was recognized in even one recipient, this category should not be used but one of the alternative categorization systems should be utilized.

If there are instances in which a donor assay is positive for infection (i.e. coagulase negative *Staphylococcus* in perfusate culture) which is felt by the clinicians not to be clinically significant, is not treated, and not associated with disease transmission, the term *positive assay without apparent clinical significance* should be used. If treatment was given that was active against the pathogen, IWDT should be utilized but those that would not be active against the pathogen can result in this definition.

If there is insufficient data available to assess imputability of the disease transmission, the term *not assessable* should be used. When reviewing the literature, such an imputability assessment may be appropriate, even if the authors have made stronger statements as to the imputability of the transmission event, if there is insufficient data presented for an independent reviewer to assess the definitive imputability of the case. Other potential challenges to assessing imputability include:

1. Inadequate donor specimens: lack of appropriate specimens to confirm or exclude the presence of the infectious disease in the donor prior to donation.
2. Inadequate recipient specimens: lack of appropriate specimens to confirm or exclude the presence of the infectious disease in the recipient prior to implantation of the organ or tissue.
3. Incomplete testing of infectious disease: Even when a pathogen is identified in both the recipient and the donor, available testing may not definitively determine if the two organisms are unique.

11. Bacterial Transmissions

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11.1 Epidemiology and Risk Factors

Donor-derived bacterial infection has been described for tissues (1-2), heart valves (3-6) bone marrow (7-10), and solid organ transplantations (11-19). At the beginning of the transplantation era, bacterial infection in the donor was considered an absolute contraindication for donation, as serious consequences (i.e. graft loss and death of the organ recipient) were observed in this setting (19-21). However, a growing number of publications show that although bacterial contamination of solid organs or bacterial colonization or infection in the donor is quite frequent (22-29) transplantation can be performed – with only a small number of recipients developing donor-derived infection- provided that transplant physicians are aware of the infection and donor and recipients are treated with appropriate antimicrobial therapy (30-37). Antibiotic prophylaxis was also effective in preventing infections in recipients of contaminated allogeneic bone marrow (7, 8).

Information about the epidemiology of bacterial donor-derived infections comprises three different clinical scenarios for solid organ and stem cell transplant recipients:

1. Donors with undiagnosed (and therefore untreated) bacterial infections, in whom the presence of infection is recognized when cultures become positive after transplantation are done. This situation poses the maximal theoretical risk. However, even in the presence of unrecognized bacteremia in the donor, wide spectrum antibiotic prophylaxis in the recipient has successfully prevented donor-derived bacterial infection, and a negative impact was not observed in the outcome of most organ transplant recipients (30). On the other hand, even with appropriate antibiotic treatment in the recipient graft loss and deaths have been described. Delay in the initiation of appropriate therapy may increase the risk of serious complications (12, 25). The risk also seems to vary according to the isolated microorganism, with some highly pathogenic or broadly antimicrobial resistant bacteria (i.e. *Pseudomonas aeruginosa*) posing the maximal risk (13, 16, 20, 22, 28, 39-43).
2. Donors with effectively treated (at least 48 hrs) bacterial infections, including, bacteremia, meningitis or endocarditis. The available information on this situation suggests that with appropriate treatment in both, donor and recipient, transplantation is almost always safe and successful, if the organ where an active bacterial infection is present is excluded from the transplantation procedure (i.e. heart in the case of endocarditis) (32-34, 44).
3. Contamination of the perfusion fluid (which may be due in a very small percentage to donor- derived bacteria): The lack of uniformity among the publications makes drawing an unequivocal conclusion difficult, although it seems that even highly pathogenic bacteria harbour no major consequences to the recipient due to the low inoculum and the use of routine (and adjusted) antibiotic prophylaxis, provided the regimen is adequate with regard to antimicrobial susceptibility (29).

Potential bacterial contamination of allograft tissues from an infected donor, such as musculoskeletal grafts, cardiac valves, and skin, pose different challenges. Although some tissues are extensively processed

Table 8. Definitions of Imputability for Donor Origin Infectious Diseases Transmissions.

Term	Definition
Proven	Clear evidence of the same infection disease in the donor and at least one of the recipients
Probable	Strong evidence suggesting but not proving a disease transmission
Possible	Used for all situations where data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probable) and transmission cannot be formally excluded
Unlikely	Used for situations where it is possible that the disease in question could have been transmitted from the donor to at least one of the recipients but the available data suggests that donor origin is unlikely
Excluded	Clear evidence of an alternative, non-donor origin of disease
Intervention without Documented Transmission (IWDT)	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
Positive Assay without Apparent Clinical Significance	Used for instances in which a donor assay is positive for infection (i.e. coagulase negative *Staphylococcus* in perfusate culture) which is felt by the clinicians not to be clinically significant, is not treated, and not associated with disease transmission.
Not Assessable	When there is insufficient data available to assess imputability of the disease transmission (either from insufficient data being provided in a published document or sufficient donor and/or recipient testing)

(e.g., bone), others cannot be processed to maintain the integrity of the tissues (e.g. ligaments, cardiac valves, corneas). Furthermore, recipients also are not routinely given broad antimicrobial prophylaxis, and are not followed closely after transplantation, increasing the risk of an adverse outcome. For these reasons, a tissue donor with evidence of active disseminated bacterial infection (e.g., sepsis, meningitis) would most often be excluded from consideration. When donor infection is unknown on recovery, transmission has been reported, resulting in disease clusters (1, 64).

11.1.1 Tuberculosis

M. tuberculosis transmission has been described from bone (2) , human heart valves (4), and lung (17, 45, 46) , liver (47) and kidney transplantation (47-54). Risk of transmission may be related to the incidence of tuberculous infection in the general population, as a higher proportion of donors may have dormant infection. Deceased donors pose an even more difficult situation, as past medical history regarding TB exposure may be difficult to obtain, skin tuberculin testing is impractical to perform, and interferon gamma-releasing assays have not been studied in this setting. Although presumed donor-derived TB cases were diagnosed up to 30 months after transplantation, solid organ transplant recipients with unequivocal (proven) donor-derived TB infection became symptomatic in less than 3 months after transplantation (50, 52, 55).

11.1.2 Syphilis

Although transmission of syphilis from an infected donor has been reported (56), transplantation from donors with syphilis has been performed without transmission of the infection, provided that adequate prophylactic treatment was administered to the recipient (57-59). In some geographic areas, the most important caveat in accepting such donors is the possibility that syphilis may be representing a high-risk donor, thus increasing the risk of transmitting other more severe infections (i.e. HIV, HTLV-1, HCV, and other infections). The decision to accept such donors depends on past medical history, the availability of NAT testing (to increase the sensibility to detect undiagnosed HIV and HCV infection), and finally, the evaluation from the transplantation team.

11.2 Testing and Disease Mitigation

The careful evaluation of donors for bacterial infection is of paramount importance, as effective antimicrobial treatment prior to ablation allows for safe donation. Cultures taken routinely from donors even in the absence of clinically apparent bacterial infections may allow detection and targeted prophylactic treatment in the recipients. Timely communication of relevant donor-related information to all transplantation teams involved is critical, specially when infection with highly pathogenic or multi-drug resistant pathogens are detected after the transplants have been performed, so adequate antimicrobial treatment can be initiated in all recipients (14).

The duration of prophylactic/therapeutic antibacterial treatment in the donor remains an unsolved issue, and has to be decided according to the sample which yielded a positive culture and the treatment received by the donor (perfusion fluid contamination with skin contaminants allows brief -1 week- antibiotic prophylaxis; positive blood cultures with highly pathogenic microorganisms from an untreated donor calls for close clinical observation of recipients and longer prophylaxis, ideally with bactericidal synergic antibiotic combinations).

11.2.1 Tuberculosis

In the geographic areas with high incidence of TB, discrimination of whether the infection is acquired from a donor with dormant infection or the result of reactivation or later acquisition by the recipient may be extremely difficult, and isoniazid prophylaxis to all recipients may be warranted (60). The recognition of active TB in an infected donor after transplantation was performed should lead to close clinical surveillance in recipients and in many cases to consider starting preemptive treatment.

11.3 Limitations of Existing Data

It is very difficult to know whether the published literature concerning donor derived bacterial infection mirrors the real rate of complications and success. Case series regarding transplantation from infected donors (donors with documented bacterial infection) suggests that with appropriate antimicrobial therapy, rates of infection in the recipients are very low (0 to 8 %) and serious complications are extremely unusual (30, 31, 35, 62-63).

However, many of the publications lack information about antimicrobial treatment in the infected donor prior to the ablation (35), and whether infections were detected before performing the transplantation (allowing optimal prophylaxis in the recipients). Many cases of catastrophic failures due to delay in the optimal treatment of unrecognized bacterial transmission have been published, mainly as case reports, but how many cases may have been successfully managed in this setting and the therapeutic approach that may have allowed such success it is unknown.

The systematized reporting of every detected situation that may imply the risk of bacterial transmission from donor to recipient, the preventive measures taken, and the outcome in each case, may allow for a more accurate estimation of the risk associated with transplants performed from donors with bacterial infections and the optimal approach to take this risk to its minimum (17).

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12 Fungal Transmissions

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12.1 Epidemiology and Risk Factors

Although a wide range of fungal pathogens have been demonstrated to be transmitted from donors to allograft recipients, endemic mycoses, Cryptococcus, and Candida clearly represent the most commonly transmitted fungal pathogens (1-39).

Among the endemic mycoses, cases of *Coccidioides imitis* and *Histoplasma capsulatum* have been described in the literature; no cases of *Paracoccidioides brasiliensis* or *Blastomyces* spp. infections have been documented to be donor-derived (5,8,11,12,15-17,20,21,23,24). Typically the donor had exposure, even if transient, to endemic regions. Coccidioidomycosis typically presented within 2 months of transplant with fever and pneumonia, while Histoplasmosis tended to present later (typically several months post-transplant) with pneumonia or unexpected positive cultures. One of the key challenges with these endemic mycoses is differentiating donor-derived disease from reactivation of latent infection in individual recipients. In most cases of donor-derived endemic mycoses, multiple recipients had documented infection.

Donor-derived Cryptococcal disease has been described following organ and ocular transplant (2,3,6,9,14). Donors often had a history of unexplained neurologic illness, immunosuppression, or high dose steroid treatment as part of donor maintenance (although this latter factor is common to many donors, currently). Disease typically presents early post-transplant (14-30 days) with fever and neurologic signs and symptoms. Several groups have noted that there have been a number of early-onset cases of Cryptococcus post-transplant; most of these have not been definitively evaluated to assess origin of infection. It is critical to note that asymptomatic cryptococcemia has been described in patients with advanced liver disease (40-42).

Candida species have been transmitted by a wide range of tissues, include corneas, heart valves, and solid organs (4,26-39). Presence of Candida in donor cultures, particularly donor corneal rim cultures, appears to be a risk factor for donor-derived Candida infections (33,43). None-the-less, presence of positive cultures does not guarantee disease transmission (43); likewise, disease can develop in the absences of positive cultures as well. Contamination during procurement and preservation is more common than donor infection, but donor infection tends to result in more severe disease in the recipient due to the larger organism inoculum. Contamination of tissues after procurement has been described and may be missed with routine cultures (33). Unfortunately, patients typically present early post-transplantation and may have a catastrophic event (i.e. rupture of mycotic aneurysm) as their presenting sign (34).

12.2 Testing and Disease Mitigation

Testing and disease mitigation is heavily reliant on assessment of exposure history (for endemic mycoses) and routine cultures. Rapid antigen assessment of many of the endemic mycoses (i.e. urine antigens) as well as cryptococcus are available and should be considered in at risk individuals. The role of serology is more controversial as a significant proportion of donors in an endemic region may have previously been exposed, and therefore seropositive, whereas the risk of disease transmission may be low or absent in the absence of active infection. The one exception is among lung transplant recipients who may reactivate even a latent infection since the lung and associated lymphatic tissue may harbor latent fungi. Retention of pre-transplant serum and urine from recipients would facilitate look-back testing but would likely be rarely needed. Routine pre-transplant screening of liver candidates for Cryptococcus warrants investigation to identify patients at higher risk of recipient-derived disease, whereas similar testing of high risk donors (those with neurologic abnormalities, immune suppression, or indwelling hardware) also warrants further investigation. Prompt initiation of antifungal therapy in all recipients after the identification of invasive fungal infection in a donor has successfully resolved subclinical undiagnosed as well as confirmed recipient infection. All recipients of infected donors should be immediately evaluated and preemptively treated once donor infection in documented (44).

12.3 Limitations of Existing Data

As with all sections, there is likely some under-recognition and under-reporting of cases. Clearly when an unusual pathogen presents (i.e. an endemic mycosis in a non-endemic region), it is likely to be recognized as unusual. Many of the pathogens, though, may be presumed to be reactivation of latent disease, often without pre-transplant testing, or a routine post-transplant complication (i.e. candidemia) and therefore not felt to be unusual. Seemingly innocuous exposures (i.e. connecting through an airport in an endemic region) may be sufficient to result in unrecognized active or latent infection in a potential donor and may therefore be easily missed even with a diligent exposure history. Lastly, even when exposure to an endemic region is recognized, testing for exposure (by serology) or active infection (i.e. antigen detection) may not be readily available to screen the donor.

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13 Parasitic Transmissions

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13.1 Epidemiology and Risk Factors

A wide range of parasitic infections have been documented to be transmitted from donors to allograft recipients; most of the reported transmissions have involved organ transplantation. Toxoplasmosis transmission in organ transplantation has been significantly reduced through the widespread screening of donors and recipients in conjunction with use of prophylactic strategies. Unfortunately, parasitic infections are often not considered when screening potential donors and recipients, and latent infection (which can either be donor-transmitted or reactivated in the recipient) may go unrecognized; as such, post-transplant parasitic infection may develop and subsequently cause morbidity and/or mortality. Transmission of malaria, *Strongyloides stercoralis*, *Schistosoma* spp., and *Trypanosoma cruzi* are among the more commonly recognized and reported parasitic infections among organ transplant recipients, although rare possible transmissions have also been describedd with such pathogens as *Balamuthia mandrillaris*, babesia, and Leishmania (1-41).

In general, living in an endemic region appears to be the most readily identifiable risk factor when screening donors for parasitic infection. Because of the ease of global travel and extensive global migration of individuals, an increasing proportion of donors and recipients have exposures to potentially endemic regions for many of the parasites that are recognized to be donor-transmissible. Even spending a brief period of time in an endemic region during travel may be theoretically sufficient to acquire certain transmissible infections. Eosinophilia may be present in some, but not the majority, of infected donors.

Most of the transmissible parasites remain latent and relatively asymptomatic in humans for an extended period of time, and therefore their presence may be missed without specific testing. As discussed below, testing for many of the parasitic infections is not widely available, and available tests often lack specificity. Serologic test results do not differentiate between acute and remote infections, or give information about parasitemia, so not all transplants from a seropositive donor will result in transmission. However, since most of the transmissible parasites do not cause persistent parasitemia, blood smears have a limited role in the assessment of parasite risk in donors. The utility of screening donor blood with NAT for parasitic infections is unknown, but the intermittent parasitemia may also limit the utility of NAT in donor assessment.

Although most parasitic infections present early after organ transplantation, this may be modulated by such factors as the parasitic load in the transplanted organ, degree and type of immune suppression used, and presence of pre-existing immunity. Presentation is variable and highly dependent on the parasite transmitted, although fever, rash, and mental status changes are commonly seen with many of the transmitted infections (See master table for details).

13.2 Testing and Disease Mitigation

Several documents provide guidance as to how to mitigate common parasitic transmissions in organ and hematopoietic stem cell transplantation (*Acanthamoeba*, *Trypanosoma cruzi, Babesia*, Echinococcosis, *Entameba* spp, Leishmaniasis, Malaria, Schistosomiasis, *Strongyloidiasis*, Toxoplasmosis) (39-41). Since many of the parasitic infections are problems of localized endemicity, all potential donors and recipients should have a detailed residence and travel history obtained. When a potential donor or recipient has identified exposure to a region of recognized endemicity to pathogens that have been recognized to result in disease transmission, appropriate testing should be performed, if available. Many assays lack specificity and require confirmatory testing to differentiate true exposure from false positive test results. Few of the assays have been assessed in large numbers of donors or recipients to fully understand the test characteristics in such populations. Many of the common parasitic infections are readily treatable; anti-parasitic therapy or prophylaxis can be considered while awaiting confirmatory testing. Unfortunately, few parasitic infections have sufficient data and/or clinical trials to determine the efficacy of such prophylactic/preemptive therapy. One notable exception is toxoplasmosis, where current guidelines suggest available prophylactic strategies are highly effective in preventing disease in hematopoietic stem cell recipients (39).

Additionally, there are isolated case reports suggesting that organs from donors with parasitic infections may be safely used; in such cases, it is critical to inform the recipients of the donor infection and have a plan for follow-up and management. For example, several South American studies have demonstrated that the majority of kidney transplant recipients of donors seropositive for *Trypanosoma cruzi* infection will not develop infection post-transplant and in cases of transmission, clinical disease can be thwarted by close post-transplant monitoring and treatment if infection becomes evident. Serial testing with blood smears and PCR should be performed in these cases and anti-parasitic therapy should be initiated if there is evidence of infection (7,10). A similar management strategy could be considered for *Trypanosoma cruzi* seropositive donors to liver transplant recipients, but is generally not considered for recipients of other organs. In certain cases *Clonorchis* infected organs have been reported to be used safely after macroscopic elimination of parasites and a long course of antiparasitic drugs in recipients (42). Isolated cases reports additionally describe the use of *Echinococcus granulosus* infected organs when recipients were 'preemptively' treated with praziquantel (43,44). Likewise, there have been two published cases in which organs from donors who died of *Naegleria* meningoencephalitis were used without transmission of the parasitic infection (45,46).

13.3 Limitations of Existing Data

There have been reports of parasitic infections via organ and hematopoietic stem cell transplantation, but no reports exist in the literature of transmission from tissues. There may be several reasons for the absence of reports. The association between the tissue transplant and the development of symptoms may not be recognized because there is often a long time between exposure to development of symptoms in immunocompetent individuals. It may be difficult to recognize a tissue transplant-transmitted infection in an endemic area, where exposure is presumed to be environmental. In general, tissue allografts undergo various degrees of processing and it is likely that some processing or handling methods may remove or inactivate parasites, although published data are not available to assess the effectiveness of processing in removing or inactivating parasites. Information about the distribution of parasites within various tissues is generally scant. Infectious disease transmission by tissues is complex and poorly understood; without active surveillance including testing of both donors and recipients, most disease transmission is likely to go unrecognized.

Only 5% of over 340 known parasitic infections have been reported in transplant recipients to date (9,24,39-41). Additionally, transplantation procedures are less available in resource-limited countries where, typically, several parasitic infections are highly endemic. Summary data from the literature are likely to be an underestimation, both for the absolute number of reported transmissions and for the potential transmissibility of a given pathogen. As such, the full range of potentially donor-derived parasitic infections may not be fully appreciated. A general increase in donor-derived parasitic infections should be expected with the increase of migration (globalization) and use of transplantation procedures in countries with a higher incidence of parasitic infections (39-41). Several guidelines exist for minimizing parasitic transmissions (39-41), but the recommendations may have limited utility for pathogens not commonly encountered in North America and Europe (9). Therefore, a high level of clinical suspicion should be maintained given that the incidence of parasitic transmission is expected to increase.

The reviewers encountered several limitations in analyzing published cases:

- Most cases were unable to exclude latent (pre-transplant) parasitic disease in the recipient.
- Transmission was commonly demonstrated only though epidemiological considerations (recipient or donor origin) without definitive serologic testing.
- Travel history was rarely provided and could have contributed to understanding risk of pre-transplant disease in the donor or recipient.
- In recipients living in a highly endemic area, exclusion of a latent infection before transplantation and/or re-infection after transplantation was frequently difficult, if not impossible, to determine, making it difficult to provide definitive imputability of individual cases.
- Transfusion of blood and blood products are a recognized source of transmission for several pathogens for which blood and blood products are rarely routinely tested (example: malaria, babesiosis, leishmania). Blood and blood products are commonly used during transplantation procedures, but often there were limited details provided of the blood lookback investigation, if it was performed at all.
- Not all donors had appropriate testing to determine if they were infected prior to donation; this could have resulted from lack of test availability or lack of appropriate type, quality, or quantity of specimen.
- Serology tests for parasitic diseases often lack in sensitivity and/or specificity.
- For many parasitic infections, there are either no available assays or is a lack of a single test that is internationally recognized as a 'gold standard', therefore limiting the ability to definitively exclude or diagnose infection.

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14 Viral Transmissions

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14.1 Epidemiology and Risk Factors

The risk of acquisition of blood-borne viruses (BBV) through organ transplantation is related to the prevalence of the virus in the donor population, the viral load in the donor, the type of organ allograft transplanted and the efficiency of virus transmission after contact with blood and tissues. The new standards on Quality and safety of human organs intended for transplantation released by the Council of Europe in July 2010 discuss viral transmission, including HIV, HBV and HCV particularly as these are of global risk, and potentially high impact in donor transplant services. There are multiple viruses of potential risk to organ and tissue recipients, and the review here addresses those of risk to the recipient from acute and chronic infection. DDI infection with ubiquitous, latent herpes viruses such as cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) are not dealt with in detail, as these are common, generally of lower clinical impact compared with others such as HIV, and addressing their transmission requires a separate document.

In general, two types of transmission are recognized:

- Expected transmissions in which routine screening of donors recognized the infection, allowing the use of interventions to minimize the impact of the transmission. Use of donors with CMV, EBV, HBV, and HCV is now standard in many transplant centers with expected donor-derived disease transmission.
- Unexpected transmissions occur when an infection is present in the donor but not diagnosed at the time of donation. This lack of recognition can be the result of incomplete history (i.e. family unaware of a donors IV drug history and therefore the donor is not flagged as increased risk), lack of available screening test (i.e. LCMV, arenavirus), or haemodilution of the tested specimen, resulting in a false negative result.

The recent campaigns in many countries to expand the donor pool have resulted in use of organs from increased-risk (also called marginal or high-risk) donors at greater risk of infection with BBV such as HBV, HCV and HIV. This further highlights the need for diligent screening, and surveillance to allow recognition of transmitted disease.

Human T-lymphotropic virus (HTLV) - 1 causes generally slowly progressive disease - either Adult T-cell leukemia (ATL), Tropical spastic paraparesis (TSP), or TSP associated Myelopathy. Many patients are diagnosed on a positive Ab test, although false positive serology occurs (1). The three recipients first diagnosed with donor-derived HTLV-1 infection were as-

ymptomatic initially (2), then developed subacute myelopathy two years later (3). Given the seroprevalence in some donor populations, the rates of detected HTLV-1 recipient infection seem low, compared with what might be expected. The modelling performed on UNOS database results suggests utilisation of organs from HTLV-1 seropositive donors is low risk for transmission and disease (4). This represents survey of previously infected, not necessarily actively infected donors.

West Nile Virus emerged predominantly in the USA as a significant problem since 1999. Infections of blood required rapid development of screening tools for blood and blood products. This has flowed to highly developed screening tools being available for organ donors, predominantly Nucleic acid tests (NAT) and serological screening with IgM for acute diagnosis. Previous exposure tested using specific IgG, with reference testing using haemagglutination inhibition (HAI) serological tests, and virus neutralization.

Organ donor infections are a small, but substantial number of overall infections, partly due to the asymptomatic nature of most infections (allowing unexpected transmission to occur), and the more severe symptomatic infections occurring in transplant recipients once infection has occurred. Infection from a single donor to multiple recipients has been recorded (5).

14.2 Testing and Disease Mitigation

Viral infections transmitted from donors to recipients may be (i) rare events with high impact for which screening is undertaken – predominantly HIV, HCV, HBV, and in countries such as the USA, WNV; (ii) rare events with high impact that are not screened for – including recent arenavirus transmission in Australia, rabies, or (iii) common and expected events, the impact of which is mitigated by pre-emptive monitoring and prophylactic interventions – this is predominantly viruses that are latent and/or endemic in the donor populations, such as Adenovirus, CMV, and EBV. Organ donor screening has usually been using serology, as it is well characterised, inexpensive, freely available, reproducible, and generally of high specificity. Although serology has been the major donor screening method utilized to date, it is limited by a prolonged window period between initial infection and sero-conversion (17-22 days for HIV, 35-44 days for HBV, and 70 days for HCV); with further haemodilution from donor resuscitation attempts occasionally resulting in false negative results in infected donors. Due to the limitations of serology - testing is dependent upon time to develop antibody, normal host immune function, and very low sensitivity for recent infection. High profile transplant related transmissions of HIV, HCV, and WNV have made the community aware of the limitations of serologic screening and have led to increased used of nucleic acid testing (NAT) to screen donors for BBV. Such testing will impact increasingly upon detection of donor-derived infections (DDI), and many of the references cited here are based upon the limited historical use of NAT assays in individual cases. The use of higher sensitivity tests such as NAT assays in low prevalence populations will result in identification of more DDI.

Screening techniques used for assessing viral infections in organ donors are based predominantly on assays designed for large-scale testing, such as screening blood donations. This results in some technical problems in terms of analyte assay design, turnaround time (TAT) and time constraints for confirmatory testing.

The current situation is that a combination of NAT (generally for HIV, HBV and HCV) are used, combined with serologic assays for HIV, HBV, HCV, HTLV, CMV and variably other viruses including EBV, WNV, Adenoviruses, and occasionally population specific testing. This is aimed at reducing the risk of transmission particularly of HIV, HBV and HCV, and the number of cases of transmission seen to date reflects mainly the situation prior to use of universal NAT screening of donors.

Mitigation strategies for reducing transmission of viruses from donor to recipient, and their results include:

- Recognition of individuals with special risks for infectious complications of transplantation will help to guide preventive, diagnostic and therapeutic steps in the control of donor-derived infections and complications and improve transplantation outcomes.
- Screening of donors with routine serologic, and more recently NAT assays as discussed above.
- Direction of infected grafts to infected recipients – particularly for HCV. No significant difference in survival is noted between recipients of HCV (+) livers & kidneys and HCV (-) livers and kidneys, although more advanced fibrosis has been found in HCV (+) liver grafts from older donors compared to HCV (+) liver grafts from younger donors.
- Histological assessment of the graft is advised, especially in older donors (22).
- Recipient (not donor) HCV (+) is an independent predictor of graft failure.
- Common infections (such as with human CMV) are mitigated by use of organ matching based on serology, prophylaxis (or pre-emptive) therapeutic strategies, and post transplant monitoring, often using testing surrogates for disease such as viral load.
- Development of improved surrogates for disease progression (viral load, viral diversity, genotyping, cellular proteomes) is aimed at providing additional testing strategies to inform clinical decisions.
- Enhanced surveillance globally for specific viruses (HIV, HBV, HCV initially) and use of enhanced detection with NAT assays.

14.3 Limitations of Existing Data

The current data are predominantly based upon passive acquisition of data from clinically detected infections. This limits much of the information to case report status – particularly as such transmission events in a global sense are fortunately uncommon. Further, the lack of relating the rates of DDI to population rates of infection means case to population ratios are not established for most (possibly all) countries, making accurate comparison globally impossible. The lack of consistent testing algorithms even within countries makes determining the rates of infection inaccurate, and inconsistent globally.

Clearly maximizing quality and safety in organ transplantation and prevention of donor derived viral infections represents an important opportunity to improve long-term transplantation outcomes, but requires multidisciplinary studies in basic quality assurance programs, viral screening, viral transmission, bio-vigilance, clinical care, and prevention research. The research will require basic studies on quality systems, main infecting agents and relationship of infections to immunosuppressive regimens together with strategies to manage at-risk donor populations. Transfer of existing diagnostic and therapeutic advances into clinical practice, and knowledge of how to introduce these changes optimally is a priority.

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15 Other Transmissible Pathogen (Prions) Transmissions

Section Authors

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15.1 Definitions

Prion diseases are neurodegenerative diseases that are caused by infectious proteins, called prion proteins (PrP^{C} is the benign, normal protein; PrP^{Sc} is the disease-associated conformational variant); unlike other infectious agents, prions lack nucleic acids. Prion diseases have long incubation periods and result in a progressive, and eventually fatal, decline in cognitive and neurologic function once symptoms develop. There are different forms of human prion diseases which can be classified according to etiology: unknown (and perhaps spontaneous): sporadic Creutzfeldt-Jakob disease (CJD), acquired: iatrogenic CJD, kuru and variant Creutzfeldt-Jakob disease (vCJD) and hereditary or genetic: familial CJD, Gerstmann-Straüssler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI).(1) Once PrP^{Sc} is introduced into the host, propagation of infection is thought to occur via the lymphoreticular system (especially the spleen) and then axonal transportation mechanisms eventually result in CNS infection.(2)

15.2 Epidemiology and Experimental Risk Models

According to 2006 WHO data, there have been 363 fatal cases of iatrogenic CJD reported; of these, 168 deaths occurred as the result of dura mater allografts and 2 confirmed cases (one proven and one probable) involving corneal transplantation. Additional cases possibly linked to corneal graft have been described but differentiation of donor-transmitted from sporadic disease has not been established.(3-14) Additionally, 1 case of possible donor-derived Creutzfeldt-Jakob disease developed 2 years after a liver transplantation.(15) For dura mater-associated transmissions, the median and mean incubation periods were 12.4 years and 11.8 years, respectively (range 1.2 - 24.8 years).(13) For the corneal transplant-associated transmissions, onset was 30 years and 18 months post-transplant for the proven and possible cases, respectively.(6, 7) Typically, affected recipients present with rapidly progressive mental deterioration (i.e. dementia, behavioral abnormalities, and deficits of higher cortical function) and myoclonus; presentation and clinical course is indistinguishable from sporadic cases of prion disease. Prevalence estimates in the United States suggest that there are approximately 0.045 prion-infected corneal donors annually in the US (about 0.005% of all donors).(16) Among sperm donors, consensus expert opinion estimates that the risk of transmission is <1:10,000,000, even for UK men.(17)

15.3 Risk, Donor Testing, and Disease Mitigation Methods

Disease-associated prion proteins have been identified in a range of tissues including: neuronal and non-neuronal (mostly glial) cells of the central and peripheral nervous system, lymphoreticular tissues (lymph nodes, spleen, tonsils, and thymus), B lymphocytes, T lymphocytes, monocytes, platelets, gastrointestinal epithelium, skin, and skeletal muscle (especially at the neuromuscular junction).(18) As such, transmission of infection from multiple tissue types is possible, although the risk varies between different forms of human prion disease.(19)

Processing of dura mater now universally involves individual processing of dura mater and treatment of each dura mater graft with 1.0 normal sodium hydroxide (NaOH); this practice is associated with a reduction in the risk of disease transmission.(13, 20) Additionally, most regulatory groups recommend screening potential donors for prior travel to or residence in a BSE-affected country. Depending on the duration and timing of the relevant residence a decision may be made to defer individuals as a blood donors. Additional donor exclusion criteria may include: a clinical diagnosis of CJD, a family history of CJD, prior treatment with human pituitary-derived hormones (including growth hormone pit-hGH), recipients of human dura mater grafts, donors diagnosed with any degenerative or demyelinating disease of the CNS (e.g. multiple sclerosis) or other neurologic diseases (e.g. senile dementia, Alzheimer's disease). The brain of donors should be assessed, by gross and histological examination, for prion disease when possible.

A number of assays are currently being developed as a potential screening test for prion disease in a potential donor.(21-25) Assays under investigation include tests of blood, urine, brain and lymphoid tissue. None are yet approved for donor screening but potential new tests continue to be reported.(26) A pilot of testing deceased tissue donor tonsil has been reported(27) and will shortly be extended to testing spleen and ocular tissue in England and Scotland (RW personal communication).

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The Transmission of Malignancies

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Summary

The therapeutic use of cells, tissues and organs of human origin has expanded progressively over the years, the number of procedures reaching a level that would have been unimaginable a quarter century ago. However, as the transplant community is well aware, certain risk of disease transmission is inherent in the transfer of biological material from one individual to another and may lead to morbidity and mortality and to adverse consequences on the public perception of the system. It is then essential to minimize the risk of disease transmission through the appropriate selection, testing and evaluation of donors, cells, tissues and organs, but it is also very important to gain evidence related to such risk. Hence clinicians and other professionals involved can identify, evaluate and manage this risk properly, being these three steps the main elements of a vigilance and surveillance system.

NOTIFY project intends to funnel current global endeavours to improve vigilance and surveillance for the benefit of patients in all countries, as a step toward building global vigilance and surveillance for organs, tissues and cells. The project, focused on the pivotal role of the clinician in the identification, reporting, and elucidation of each case, has established a series of working groups. In particular, the working group number seven was commissioned to review malignancy transmission through organs, tissues and cells, being the present document the outcome of such work.

The report is based on a review of the cases of malignancy transmission reported, of which the relevant information was synthesized in an *ad hoc* designed data base, and on experts' opinions expressed at a dedicated project meeting held in Bologna in February 2011. The authors have paid special attention to signals alerting on the possible transmission and how the latter was assessed. The *4th edition of the Guide to the Safety and Quality Assurance for the Transplantation of Organs, Tissues and Cells*, recently published by the *European Directorate for the Quality of Medicines and Healthcare* of the *Council of Europe*, has been an important reference for the design and conclusions of this report, as it is an international comprehensive reference.

For the purpose of consistency, the authors of the report have agreed upon some definitions on risk and disease transmission; however, deliberately, no specific nomenclature of the clinical, histopathological or diagnostic elements has been assumed. The terminology used by the various corresponding authors has instead been fully respected even though this has resulted in some heterogeneity. It should be pointed out that many cases have been reported on a voluntary basis; hence the lack of a report on the transmission of a particular cancer does not mean that it cannot occur.

Results show that the vast majority of reported malignancy transmissions correspond to the transplantation of organs, which have been classified by type of tumour. Conclusions, when possible, were added at the end of each section. Other units cover reported malignancy transmissions through tissues and cells and tumours not found to be transmitted. In most cases, a small description of the case is provided, including how it was detected by the clinicians, how soon after transplantation, the status of the patients at last follow-up, and how it was attributed to the donor, when available. In order to minimise the risk of transmission, conclusions and recommendations are provided in each section, and in the last part of the report, guidance is provided on a thorough characterisation of donors, on the basic steps of a vigilance system, and on the attributability of the malignancy to the donor.

Finally, the authors of this report acknowledge the support of the sponsors and the commitment of the working group task force, but overall, the vision of those professionals who suspected, investigated, and communicated the transmission of a malignancy through the transfer of organs, tissues or cells.

1 Introduction

The therapeutic use of cells, tissues and organs (CTO) of human origin has expanded progressively along the years. More than 100,000

patients receive an organ transplant worldwide annually and a larger number of patients receive tissues and cells for therapeutic purposes. (1) The high level of activity in the field is the consequence of the excellent outcomes achieved with these therapies saving many people who would have died of end stage organ failure.

However, the transfer of biologic material from one individual to another is inherently linked to a risk (hazard) of disease transmission. This risk is reduced through appropriate selection, testing and evaluation of both living and deceased donors and of the actual CTO, that are routine in clinical practice and encoded to a certain extent in different international and national legal and/or technical texts, to the extent that regulators and clinicians are aware of the risks associated with clinical transplantation of CTO.

Disease transmission can be considered in a number of different ways and its risk may be identified in three different circumstances:

- **A transmission risk might be identified before the transfer of CTO.** That risk may be accepted by both the recipient and the physician, when balanced against the risk of not proceeding with the transfer. This situation is routine in the fields of haematopoietic stem cells (HSC) and organ transplantation, because the unique nature of HLA matched HSC's or the shortage of organs to meet the transplantation needs of patients lead to a mortality risk from not proceeding that is usually far in excess of the risk of the transmission (this situation defines what the Italian Guidelines on organ donation name as 'non-standard risk donors(2)).
- A transmission risk or potential transmission in the donor and/or the CTO might be identified after the transfer of CTO has occurred.

These two situations might or might not lead to actual disease transmission to the recipient(s).

- **A disease might also be inadvertently transmitted from the donor through the CTO and become apparent when the clinical manifestations of such transmission appear in the recipient(s).**

The risk of disease transmission has to be considered in the light of the great benefits provided by the transfer of organs, tissues and cells. However, transmission of diseases through CTO can lead to a **significant morbidity or mortality** in recipients. Moreover, the adverse consequences on the **public perception** of donation and transplantation systems can itself be deleterious. Therefore, prompt identification of transmission risks and a high index of suspicion of transmitted diseases is essential and constitutes one of the critical steps in international 'vigilance and surveillance' (V&S) applied to CTO.

2 Objectives

The NOTIFY project intends to funnel current global endeavours to improve V&S for the benefit of citizens in all countries, as a step towards building global V&S for CTO. The project is focused on the pivotal role of the clinician in the chain of vigilance, clearly for the identification of reportable situations, but also for the elucidation of each case.

A series of working groups were established in NOTIFY with working group 7 specifically focused on transmission of malignancy through CTO and on understanding documented cases of malignancy transmission actually or potentially occurring with the transfer of CTO. The aims of this group were:

- to list donor malignancies known to be transmitted or known not to be transmitted, by cancer and CTO type;
- to provide guidance on early detection and prevention of malignancy transmission;
- to provide guidance on immediate steps to take for index recipient and other potentially affected recipients;
- to provide guidance on steps to investigate and confirm the attributability of malignancy transmission.

3 Methodology

3.1 Literature review

A review of the literature was performed to address the question of malignancies of donor origin through the transfer of human CTO. English language articles based on follow-up registries, single center follow-up of a cohort of recipients and case reports were selected. In the field of organ transplantation, data from national and international multicentre follow-up registries included the United Network for Organ Sharing (UNOS) Registry, the Israel Penn International Transplant Tumor Registry (IPITTR), the Centro Nazionale di Trapianti (CNT) Registry, the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), the Danish Registry and the Organización Nacional de Trasplantes (ONT) Registry. Excluded articles were reviews (unless they incorporated original data) and those focused on de novo or recurrent recipient malignancies following the transplantation. In addition, when any of the authors of the review were aware of a particular unpublished case relevant to the review, this was incorporated as personal contribution being cited the name of the contributor.

Information extracted from case reports included: general characteristics of the donor, cause of donor death (if deceased), relevant clinical and laboratory findings, description of the malignancy if known at the time of the transfer, how and when transmission suspicion was raised, how the attributability was assessed and the result of such assessment, status of other recipients potentially affected and situation of the patients at the last available follow-up. These data were then synthesized in a dedicated data base specifically designed for the working group (worksheet group 7). In particular, information was recorded on the malignancy and CTO involved and, in case of actual transmission, clinical symptoms and signs of transmission and data on the assessment of attributability to the donor/CTO in each particular case, when available.

As part of the common approach to the information collected, the authors have agreed upon some definitions regarding risk and disease transmission (section IV). However, no specific nomenclature of the clinical, histopathological or diagnostic elements of neoplastic disease has been assumed. The terminology used by the various corresponding authors has instead been fully respected, even though this has resulted in some heterogeneity being incorporated to the review. Due to the heterogeneity expected in the reported cases, it was not an objective of the work to estimate frequency measures or risks. In line with this, and as mentioned above, the estimates of malignancy transmission risks are those collected from multicentre registries, where available.

3.2 The Council of Europe Guide to Safety and Quality Assurance for the transplantation of organs, tissues and cells

An essential document taken as a reference for the preparation of this paper was the *Guide to safety and quality assurance for the transplantation of organs, tissues and cells* in its 4th Edition, recently published by the Council of Europe (hereinafter, the Council of Europe Guide) (3). Its chapter on neoplastic diseases is in itself based on the *Spanish National Consensus Document to prevent the transmission of neoplastic diseases in organ donation*(4). Detailed information, particularly with regards to the listing of malignancies having been transmitted (or not) through organ transplantation can be gathered from these two documents. Specific details from the above mentioned sources were taken and analysed for this report, as consulting original references is very important in the assessment of a particular case. The Council of Europe Guide will be translated into several languages and continuously updated in the future, incorporating new experiences shared by the medical community.

3.3 Experts Opinion: the NOTIFY Meeting in Bologna

Finally, some elements of the present report are based on expert opinions, agreed upon by participants in NOTIFY during a specific meeting on this project, held in Bologna (Italy) in February 2011.

4. Terminology and definitions

4.1 Transmission risk

The probability of transmission, which may or may not actually occur. It is a theoretical construct based upon knowledge of the donor and recipient. *E.g. A tumor curatively resected in the donor still has a theoretical chance of recrudescence in the context of an immunosuppressed recipient.*

Some classifications to rank this risk have been developed. Particularly in the field of organ transplantation, the Italian classification of donors with regards to their potential for disease transmission is worth summarising (table 1).

This classification became a milestone regarding the risk assessment of donors in the European setting. However, taking into account the case-by-case risk analysis process performed by clinicians and the specific characteristics of tumors, an adaptation of it has been proposed in the recent 4th Edition of the *Council of Europe Guide*, (3) being the resulting categories:

- Standard risk Donor: donor acceptable for all organs and all recipients;
- Nonstandard Risk Donor: donor acceptable for life-saving transplants, justified by the specific health situation of the recipient or the severity of their clinical condition, risk-benefit analysis;
- Unacceptable Risk Donor: contraindication, but acceptance may be discussed in exceptional cases and for some life-saving transplantation procedures in the absence of other therapeutic options on a case-by-case basis.

Quite lately, the US Disease Transmission Advisory Committee (DTAC) has suggested a classification for donor malignancy transmission risk assessment.(5) Based on a literature review and expert opinions and consensus, this classification is related to a quantitative approach to risk transmission. Moreover, the different types of malignancies are included in what the authors considered the appropriate risk category.

Table 1: Classification of organ donors based on their estimated risk of disease transmission.

Unacceptable risk	The donor is not suitable for transplantation.
Increased but acceptable risk	Transmissible organisms or diseases have been identified during the evaluation process of the donor, but organ utilization is justified due to the recipient specific health situation or the severity of his/her clinical condition.
Calculated Risk	Even in presence of transmissible diseases, transplantation is allowed for recipients with the same disease or with a protective serologic status, regardless of the severity of his/her health condition.
Not assessable risk	The evaluation process has not allowed an appropriate risk assessment for transmittable diseases.
Standard Risk	The evaluation process did not identify any transmissible disease.

4.2 Potential transmission

Donor cells capable of transmitting a known donor disease have been transplanted, but no disease has yet occurred in the recipient. *E.g. A donation that has transmitted renal cell carcinoma (RCC) to the recipient of one kidney has the potential to also transmit the tumor to the other renal recipient and to recipients of liver, lung or heart. Since RCC very rarely metastasizes to heart, but often to lung and liver, theoretically the recipients' potential transmission risks will be different and different decisions should be taken in each specific situation.*

4.3 Donor Derived Malignancy

A malignant disease diagnosed in a recipient which may be possibly, probably or definitely derived from the transplanted CTO and may or may not have been present in the tissues at the time of donation. Some malignancies may develop in the organ or cell only after transplantation and not be present at the time of donation, e.g. hepatocellular carcinoma after liver transplantation.

4.4 Donor Transmitted Malignancy (= Actual Transmission)

Malignant disease diagnosed in a recipient which may be **possibly, probably or definitely present in the donor at the time of donation** of CTO and thus transmitted through the donated CTO.

4.5 Levels of attributability in malignancy transmission

- **Certain / Definite Transmission:** The transmission (malignancy) cannot be explained by any other reason but the transfer of the CTO.
- **Probable / Likely Transmission:** The suspected transmission (malignancy) is unlikely to be attributed to a concurrent disease or to other exposure different from the transmission through the transfer of the CTO.
- **Possible Transmission:** The suspected transmission (malignancy) can be explained by the transfer of the CTO, but there are alternative possible explanations.
- **Unlikely Transmission:** Evidence clearly in favour of attributing the malignancy to other causes.
- **Excluded Transmission:** Conclusive evidence beyond reasonable doubt for attributing to alternative causes.

5 Listing donor malignancies known to be transmitted or known not to be transmitted by cancer, organ and cell type

The literature review performed in NOTIFY by working group 7 sought to review the current knowledge of risks of malignancy transmission through the transfer of CTO and to determine if the principles outlined below 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. The review of the published information (mainly case reports) also intended to serve for providing guidance on clinical manifestations of transmitted malignancies and on how to determine the likelihood of malignancy transmission. This section provides a summarized approach to these issues, with more extended and detailed information included in the worksheet of cases built by the mentioned working group.

It is important to understand that absence of a report of a transmitted cancer does not mean that it has not occurred, nor that it cannot occur. The assumptions inherent in the principles outlined above must take priority over the actual observed lack of transmission.

5.1 Risk of malignancy transmission

Although the risk of malignancy transmission has been understood since the first years of clinical transplantation,(6, 7, 8) the frequency of donors with malignant tumours and the risk of transmission of malignant diseases from donors to recipients are not known with precision. The limited information on such risks leads to the standard approach to consideration of individual / undocumented situations, based on a number of principles, as follows:

1. Diagnosis: A diagnosis of cancer in the donor which may be definite (known histology), or probable (histology reported by a third party).
2. Biological behaviour of the tumour: The characteristics of the expected biological behaviour and prognosis of the specific cancer in the normal population.
   a. A cancer that has the potential to metastasise to the CTO under consideration in the normal population should be a contra-indication to donation.
   b. Exceptions are made specifically to permit donation from donors with a history of malignancy: skin cancers that do not metastasise in normal population e.g. Basal Cell Carcinoma; and some central nervous system (CNS) malignancies that are known to be contained in the specific individual donor within the blood brain barrier through absence of intervention.
3. Tumour therapy performed / current follow-up: Consideration is made of specific cancers where the diagnostic evidence is explicit, but curative treatment and disease-free intervals are definitely observed such that the risk of metastasis in the normal population is minimal. Specific cancers that may behave differently in the immunosuppressed populations are excluded even if they meet this criterion e.g. Melanoma, Kaposi's Sarcoma.

5.2 Transmitted cancers by type and transplanted organ

5.2.1 General data derived from multicentre follow-up registries

The UNOS Registry

The first UNOS report (1994-1996) documented a frequency of 1.7 % (257 out of 14,705) organ **donors with a past history of cancer**. There were 28 post-transplant tumours in the 650 recipients transplanted from these donors. Cancer types were skin (18 cases), post-ransplant lymphoproliferative disorders (PTLD) (2) and solid tumours (8). None of the recipient cancers were of the same histological type than that in the donor's past history.(9) However, in a further publication, when reviewing the outcome of recipients transplanted from donors with a previous history of malignancy during 2000 to 2005 (1,069 donors with a history of cancer out of 39,455, resulting in 2,508 transplants),(10) the UNOS registry reported two cases of malignancy transmission. A donor with a **glioblastoma multiforme** (GBM) transmitted fatal tumors to two recipients (liver and bilateral lung transplantations). The recipient of one kidney had the graft removed, and it is not clear whether transmission occurred. The heart and contralateral kidney recipients remained without evidence of transmission at the last reported follow-up.(11) A donor with a history of **melanoma** 32 years earlier transmitted a fatal melanoma to a single lung recipient. Twenty four months after the transplant, none of the other recipients of this donor (contralateral lung, liver, heart and both kidneys) had developed a melanoma. Non melanoma skin cancer (776) constituted the largest group of histological malignancies. Within the central nervous system (CNS) neoplasia group (642), GBM (175) was the most common individual tumour type. The third most frequent donor history of cancer was carcinoma of the uterine cervix (336). The donor cancer type also included: melanoma (140), breast cancer (126), prostate (66), uterine endometrial (65), bladder (20), ovarian (75), testicular (28), kidney (15), colorectal (38), thyroid (34), tongue/throat (11), lung (10), leukaemia / lymphoma (51) and other (75).

Focused on the years 1994-2000, the UNOS registry also described **21 donor related malignancies** from 14 out of 34,993 deceased donors (4 *per* 10,000 donors) and from 3 living donors, being 15 tumours donor transmitted, and 6, donor derived (12). Tumour transmission occurred in 13 of the 108,062 recipients transplanted from deceased donors (1 transmitted tumour for each 8,312 transplanted organs) during this period. Another two cases were transmitted from living donors. The histology of the 15 transmitted tumours was (as named by the corresponding authors): **adenocarcinoma (1), breast cancer (1), lung cancer (2), melanoma (4)**, **neuroendocrine tumour (1), non-differentiated squamous carcinoma (1), oncocytoma (1), pancreas cancer (1), papillary tumor (1), prostate cancer (1) and small cell carcinoma (1).** As mentioned, 6 recipients developed a donor derived malignancy, i.e., leukaemia and PTLD. Among patients developing donor related malignancies, mortality rate was 38%. The time from transplantation to tumor diagnosis varied from 3 to 40 months (mean 14.2 months) post-transplantation.

Starting its work in 2005, the OPTN / UNOS **Disease Transmission Advisory Committee (DTAC)** is comprehensively collecting reports under the Organ Procurement Transplant Network policy on donor transmitted and donor derived diseases.(13) Reports from 146 donors with malignancies leading to transplantation were communicated to DTAC. **Twenty two cases of donor transmitted malignancies were reported: GBM (1), liver cancer (1), lung cancer (4), lymphoma (6), melanoma (2), neuroendocrine carcinoma (2), ovarian cancer (2), pancreas (3), prostate (1) and renal cell carcinoma (RCC) (8)**; each report may involve multiple recipients.(14) Donors with malignancy also lead to transplantation with no evidence of donor transmitted malignancies in a number of cases. There were additional reports on donor derived, but not donor transmitted malignancies, based on the time between transplantation and the diagnosis of the tumour (12.5 to 17 years).

IPITTR Registry

The IPITTR(15) has reported greater frequencies of **malignancy transmission** through organ transplantation than other follow-up transplant registries. During 1994-2001, of the 68 recipients of organs from donors with **RCC**, tumor transmission occurred in 43 (63%); of the 30 recipients of grafts from donors with **melanomas**, tumor transmission occurred in 23 (77%); and of the 14 recipients of grafts from organ donors with **choriocarcinoma**, there were 13 cases (93%) of tumor transmission. Over this same time period other tumors were also transmitted, including **Kaposi's sarcoma** (67%), **lung** (41%), **breast** (29%), **prostate** (29%) and **colon (**19%). No tumor transmission of head and neck, hepato-biliary, testicle or thyroid tumors or of lymphoma-leukemia from the donors was documented. The discrepancy between the results of the IPITTR registry and those of the other registries might be due to its voluntary nature and the resultant inherent biases. When reviewing all cases reported from both domestic and international sources that demonstrated a potential for donor transmitted malignances between 1965 and 2003, the IPITTR was able to provide new estimates of disease transmission.(16) From 296 high risk transplants performed using donors with known or incidentally discovered malignancies, 124 cases (42%) of confirmed donor transmission occurred. The incidence of malignancy transmission was uniform among allograft recipients: 45% kidney (99 cases / 222 transplants), 37% liver (14/38), 30% heart (8/27), 25% pancreas (1/4) and 60% lung (3/5). The mean time from transplantation to presentation of the donor malignancy

transmission was 2 months with a range of 2 days to 38 months. The malignancy transmission rate varied according to the tumor type:

- Very high transmission rates were identified for **choriocarcinoma** (93%, with a 64% mortality rate) and **malignant melanoma** (74% with 58% of related mortality).
- For **RCC**, information on two different series has been released: A first one reported the transplantation of organs from 14 donors with RCC (mean size 2.1 cm, ranging between 0.5 and 4.1 cm) and Fuhrman grades I-II) identified at procurement and excised prior to transplantation. No evidence of transmission was seen, suggesting that organs from donors with low grade RCC free of extracapsular or vascular invasion might be safely used with a minimal risk of transmission. In a second more recent study, 43 recipients of organs from 70 donors with a RCC suffered a transmission malignancy. This transmissions, the majority of which occurred as localized lesions in the allograft, were discovered either at the time of transplant or after transplantation, ranging between three to thirty six months. The resulting patient mortality was 15%.
- **Lung cancer** transmission from donors with a past or present history of this malignant disease was 43%, with a 32% mortality rate. **The overall** transmission rate for **colon cancer** was reported to be of 19% and 29% that of **breast cancer**.

Another relevant report derived from the IPITTR referred to **cases of errors** in the diagnosis of donor **brain death** due to intracranial hemorrhage from undiagnosed CNS tumors and where CNS metastases were misdiagnosed as primary brain tumors (melanoma, RCC, choriocarcinoma, sarcoma, Kaposi's sarcoma and others).(17) Forty-two organ recipients from 29 donors were reviewed. The transmission rate was 74%, the majority being identified in the allograft (71%). Sixty-four percent of recipients suffered diffused metastatic disease. Survival was poor, with 32% of 5 year survival rate.

Danish Registry

Birkeland reported on the risk of tumor transmission with organ allografts from data of deceased and living donors, collected throughout 27 years (1969-1996) in one single center in Denmark.(18) Out of 626 organ donors (491 deceased and 135 living donors), 10 had a carcinoma *in situ* or a dysplasia cervix uteri (non-malignant) and 13 had a malignant tumor, which were detected by linkage to the Danish Tumor Registry. This resulted in 17 recipients receiving a transplant from a donor with carcinoma in situ or dysplasia cervix uteri and 20 recipients receiving a transplant from a donor with a malignancy. Only one **donor-to-recipient transmission** of a **melanoma** was documented. This recipient died within one year. There was no evidence of transmission in the other kidney recipient. The authors quantified the risk for having a donor with an undetected malignancy in 1.3% (8 in 626) and the risk for transmitting a cancer in 0.2% (1 in 626).

The ONT Registry (Spain)

From 1990 until 2006, the frequency of donors with an undetected tumor has been 5.8 *per* thousand donors (117 donors with a malignant tumor out of 20,016 donors) in the ONT registry.(19) Of these donors, 5 transmitted the tumor to the recipient. Out of the 155 patients who received a graft from a donor with a tumor, 100 (65%) were followed up, and among those, only 10 recipients (10%) underwent tumor transmission, leading to a transmission rate of 6 per 10,000 transplants in a 17 year time period. Tumors transmitted from donors to recipients were: **soft tissue sarcoma (1), germinal cell carcinoma (1), undifferentiated carcinoma (1), and RCC (2)** (these latter two cases correspond to two kidneys that were transplanted and later presented with a renal adenocarcinoma and a papillary carcinoma; in both cases the diagnosis was made through a biopsy after transplantation).

The CNT Registry (Italy)

Since 2002, the CNT has put into practice a different strategy for evaluating the safety and acceptability of organ donors (20). This strategy analyses potential donors with infections and tumors and establishes donor risk categories, as previously summarized (2). The risks for neoplastic disease transmission for potential donors are classified as unacceptable, non-standard or standard. Analysis of the years 2001-2002 showed a frequency of 2.9% of potential donors with tumors, of whom almost half were deemed ineligible before procurement, in a quarter the tumor was detected between recovery and transplantation and, in the remainder a neoplasia was detected following transplantation.

New data show an improvement in the diagnosis capabilities before and during organ procurement. A further update of the results in applying this cancer screening protocol to a population of 7,608 potential donors in 2002 – 2005 has been provided. Suspicion of a tumor was raised in 337 cases (4.6%), leading to a pathological examination: 198 potential donors (2.6%) were considered to have an unacceptable risk of tumor transmission which thus excluded donation, 8 (0.1%) were considered standard risk donors, but were discarded because of other reasons, 80 (1%) were classified as pos-

- Key messages
- Information derived from transplant follow-up registries collecting relevant information on donor related malignancies have to be interpreted with caution, based on their voluntary nature, variations in reporting rates, epidemiological differences between donors populations, as well as disparities in the design and the quality and accuracy of the information recorded.
- Keeping in mind these limitations, the following conclusions can be provided:
- Donors with a previous history of malignancy are not rare (1.7% in UNOS registry).(10)
- Donors with malignancy at the time of donation or with a diagnosed neoplasia after donation is variable (5.8/1,000 deceased donors in ONT registry).(19)
- Donor transmitted malignancies are infrequent (approximately 2 cases per 10,000 organ transplant recipients).
- Rates of malignancy transmission vary depending upon the histological type of tumor, as well as on other factors, i.e. stage and grade. In general terms, donor transmitted malignancies usually involve clinically aggressive tumor types.
- There is an evident need for systematically collecting information on donors with a past or present history of malignancy and those in whom a malignancy has been diagnosed following the transplantation of at least one organ, as well as on the outcomes of related recipients.
- Cases of malignant disease transmission have to be evaluated with the perspective of the more than one million transplants undertaken worldwide to date. As detailed below, transmission of a broad spectrum of malignant diseases through the transfer of CTO has been published. Most of the reported cases have been transmitted through organ transplantation, followed by that of HSC. The review from the literature shows that the observed risk is very small when appropriate standards in donor selection are applied and an individualized risk-benefit analysis is performed.

ing a standard risk and 51 (0.7%) a non-standard risk, being utilized according to criteria in place. Two hundred and thirty one recipients transplanted from the two latest groups have not shown any evidence of malignancy transmission after a median follow up of 23.97 ± 16.7 months. In 14 additional donors (0.2% of potential donors) a tumor was diagnosed after the transplantation of at least one organ: esophageal cancer (2), gallbladder cancer (1), gastric cancer (1), hemangioendothelioma of the liver (1), lung cancer (6), lymphoma (1), pancreatic cancer (1) and malignant tumor of the CNS (1). Twenty three recipients were transplanted with 26 organs from these donors, only one liver having been removed after the knowledge about the tumor was gained. After 23 ± 14 months of median follow-up, no tumor transmission has been reported.(21)

5.2.2 Breast Cancer

Transmission of breast cancer through organ transplantation has been reported in follow-up registries. At least one case was transmitted through a live kidney donation from wife to husband. Six months after transplantation, the recipient developed osteolytic bone and CNS metastases due to ductal breast adenocarcinoma. Immunosupression was stopped, chemotherapy instituted and the graft left in situ. The patient rejected both the graft and the tumor, and in the last reported follow up (4 years), the patient was alive, tumor free, and in dialysis. (12)

Breast cancer has high potential for late and aggressive recurrences and metastases, even after many years of complete remission. Hence, donors with a present or past history of breast cancer have been considered as posing an unacceptable risk in general terms, but with exceptions pointed out in the *Council of Europe Guide*. Particularly, some countries consider as non standard risk, donors with a past history of breast cancer stage T1a or T1b, without lymph node involvement and in complete remission for ≥ 10 years.

Table 2 summarizes the suggestions for the utilization of organs from donors with a history of breast cancer after curative treatment at the ASTS Winter Symposium in 2003.(22, 23) As shown in the table, donation was also considered appropriate from donors with a recently diagnosed breast cancer stage 0, but only if low grade.

5.2.3 Central Nervous System neoplasias

In 1999, the Australian and New Zealand Organ Donation Registry published a series on 46 donors with a primary brain tumor (28 malignant and 18 benign) from whom none of the 153 recipients developed a neoplastic disease transmission.(23) The Czech Republic referred no cases of transmission either among 91 recipients transplanted from 41 donors diagnosed with this type of malignancies. Similarly, in 2002, the UNOS registry published a series of 397 donors with a history of a primary CNS tumor, from whom 1,220 organs were transplanted, which included 574 kidney, 293 liver, 192 heart, 76 lung, 60 kidney-pancreas, 16 pancreas, 6 heart-lung, and 3 intestine transplants. Among the donors with reported histological type of tumor, there were 2 donors with medulloblastoma and 17 donors with glioblastoma multiforme, the most common highly malignant tumors. These donors supplied a total of 56 transplanted organs: 26 kidneys, 2 kidney-pancreas, 15 livers, 10 hearts, and 3 lungs. After a follow-up of 36 months, no tumor transmission was detected among recipients.(24)

In line with the previous studies, a recent series of 448 recipients (495 organs) transplanted between 1985 and 2001 from 177 donors with CNS tumors was reviewed in the United Kingdom.(25) Type of CNS tumors were, with a variable grade according to the WHO classification, astrocytoma (astrocytoma unspecified, pilocytic, gemistocytic, fibrillary) gliomatosis cerebri, glioblastoma, giant cell glioblastoma, oligodendroglioma, ependymoma, glioma malignant, mixed glioma meningioma malignant, medulloblastoma, Ewing's sarcoma, primitive neuroectodermal tumor, pineoblastoma, neoplasm malignant (without any specific morphology identified), dermoid cyst with malignant transformation and haemangioblastoma. There was a wide range in timing of diagnosis in donor prior to death: 119 donors were diagnosed in the last 30 days before death, 23 donors between 31 days and 1 year, 16 between 1 and 3 years, and 19 had been diagnosed for over 3 years in relation to the time of death. Organs transplanted from these donors included: 279 kidneys, 1 double kidney, 72 livers, 1 combined liver-kidney, 12 heart-lung, 13 double lung, 51 hearts, 10 single lungs, 8 combined pancreas-kidney and 1 pancreas alone. Out of the 448 recipients with follow up assessment, none developed a malignancy transmission in a minimum follow-up of 5 years.

On the contrary, the IPITTR published data revealing that the risk of malignancy transmission does exist, on a series of 62 recipients transplanted from 36 donors diagnosed of CNS primary neoplasias (16 astrocytomas, 15 gliomas or glioblastomas, 3 medulloblastomas and 2 cerebellar tumors) between 1970 and 2002.(26) Twenty-four of the 36 donors received some form of cancer therapy before organ donation, including ventriculo-peritoneal or ventriculo-atrial shunts (n=12), craniotomy (n=6), radiation therapy (n=4), and chemotherapy (n=2). Grafted organs included 35 kidneys, 12 hearts, 10 livers, 2 pancreas and 3 lungs. Apart from primary tumor grades, histology and stage, donors with CNS malignancies were evaluated for potential transmission risk factors. Tumour transmission results reported were as follows:

- Out of the 25 organs transplanted from donors with astrocytomas, 14 were associated to at least one risk factor for tumor transmission (high grade tumor, ventriculo-peritoneal or ventriculo-atrial shunts, previous craniotomy, previous radiotherapy and chemotherapy). There was 1 case of tumor transmission of a high grade astrocytoma, identified 20 months after the transplantation. The sole factor associated with transmission was a high histologic (grade III) lesion in the donor.
- Out of the 26 organs from donors with gliomas (n=18) orgrade III-IV glioblastomas (n=8), 15 organs had at least a risk factor associated with the potential for malignancy transmission, including prior surgical intervention (n=10) or high-grade malignancies (n=9). There were 8 transmissions, being all identified between 2 and 15 months after transplantation.

Table 2: Suggestions for the transplantation of organs from donors with a history of breast cancer after curative treatment (ASTS Winter meeting 2003)(22).

Cancer	Stage	Specific characteristics	Survival (%)	Recommended disease-free interval for donation
Breast	0=CIS	Only if low grade*	5 years: 99-100	0 years
	T1a**/b***	-	10 years: 91	10 years
	T1c****	-	10 years: 78	Donation never to be realized

*High-risk characteristics (comedo histology, extensive or high-grade disease) increase the incidence of nodal disease from <1% to approximately 2%.
**0.1 cm < Tumor < 0.5 cm. ***0.5 cm < Tumor < 1.0 cm. ****1.0 cm < Tumor < 2.0 cm.

- Out of 7 recipients of the 3 donors with medulloblastomas (all with a previous ventriculo-peritoneal shunt), three suffered a tumor transmission between 5 and 7 months posttransplant.
- Tumor transmission also occurred in the two recipients transplanted with organs from donors with a cerebellum neoplasia. No transmission was detected from a donor with one unspecified primary brain malignancy.

Data provided by the IPTTR estimate a transmission rate of CNS neoplasias of 7% in the absence of the aforementioned risk factors, 36% if at least one is present, and 43% if two of them are met. As an independent factor, a high-grade malignancy was associated with a 43% of transmission rate.

The risk of transmission of CNS malignancies is corroborated by several published case reports, some of them being summarized below. Morse et al. reported the case of a malignant glial tumor transmitted to a liver transplant recipient.(27) The condition was known before donation, the donor having been diagnosed of a malignant glial neoplasia infiltrating pons, pituitary, spinal leptomeninges and spinal cord. No ventriculoperitoneal or ventriculovenous shunting had been performed. Nine months following transplantation, the liver recipient complained of abdominal pain (in right upper quadrant), severe headaches, nausea and vomiting. Liver chemistry tests were normal, but lesions were observed by image tests in the liver graft, biopsy revealing a poorly differentiated pleomorphic neoplasia and immunohistochemistry being consistent with a tumor of neural origin, similar to the donor's tumor. Laparotomy made evident an extensive tumor involvement of viscera and infrahepatic structures. The recipient died 1 month later despite the reduction of immunosuppression. Notably, the two kidney recipients did not show evidence of transmission 25 months after transplantation, although in both cases the transplanted organ had been removed in the first month because of acute rejection. The heart transplant recipient did not show evidence of malignancy transmission 25 months after the transplant procedure.

Frank et al described the transmission of a Glioblastoma Multiforme (GBM) through liver transplantation from a donor whose condition was known before the transplant (a frontal lobe glioma had been removed 4 months before death with later local recurrence and death after a second surgery).(28) Five months after transplantation, the liver recipient died following a rapid clinical deterioration. Necropsy showed multiple intrahepatic, adrenal gland, lymph node and leptomeningeal metastases of a gliomatous tumor. Both kidney recipients were doing well at 52 months after transplantation. Microsatellite DNA fingerprinting allowed the identification of all metastases as donor related.

In a more recent case report, five different recipients were transplanted from a donor diagnosed of GBM one year before death by stereotactic brain biopsy (he was known to have a 9- by 7-cm parietal mass for 3 years) and treated with steroids for 2 years and then with radiotherapy.(11) The lungs, heart, kidneys and liver were harvested and grafted into five different recipients. One enlarged hiliar lymph node was found and removed while the lungs were being transplanted, and its histology was consistent with a metastatic GBM of the small cell type. The bilateral lung transplant recipient had several posttransplant hospitalizations for dyspnea. A CAT scan 3 months after transplant revealed diffuse bilateral pulmonary infiltrates and pleural effusions. Bronchoscopy and transbronchial biopsy revealed metastatic GBM with identical histologic features of those seen in the lymph node removed at transplantation. No extrathoracic metastases were found but after rapid tumor progression the patient died, four months after transplant. The liver recipient also developed a metastatic GBM. One of the kidney recipients had his graft removed. The recipient of the contralateral kidney and the heart transplant recipient did not show evidence of malignancy transmission so far.

As mentioned above, the IPITTR had classically assessed a number of risk factors for transmission of primary CNS malignancies: high grade tumor, presence of ventriculo-peritoneal or ventriculo-atrial shunts, prior craniotomy, systemic chemotherapy and radiation therapy. It was recommended that donors with at least one of these factors were not considered for donation, except for recipients in a vital emergency.(26) Similarly, the *Council of Europe Guide* has classified CNS malignancies in three groups according to their related risk of being transmitted through organ transplantation:

- Group I includes WHO grades I and II tumors, which would not contraindicate organ donation;
- Group II includes WHO grade III tumors, which would not contraindicate donation, except if any of the risk factors described in the IPITTR are present;
- Group III includes WHO grade IV tumors, contraindicating organ donation regardless of the presence or absence of the aforementioned risk factors, except for vital urgencies.

5.2.4 Colo-rectal Carcinoma

Several follow-up registries have reported cases of transplantation from donors with a colo-rectal cancer. Kauffmann(10) described 38 organ transplants (19 kidneys, 17 livers and 2 hearts) from donors with a previous history of this type of malignancy during the period 2000 to 2005. Ison reported the case of a donor with colon carcinoma.(13) The CNT registry reported on one liver and two kidney transplants performed from a donor with colon carcinoma.(29) Finally, Birkeland reported two live related kidney transplants from donors with a history of colo-rectal malignancy and a disease free time of 5 and 8 years, respectively.(18) No malignancy transmission was reported to occur in patients transplanted from these donors in any of the previously mentioned series. On the contrary, the IPITTR has reported cases of transmission of colon carcinoma, providing an estimate of 19% risk of disease transmission.(16)

Whether or not organs from donors with colon cancer are suitable for transplantation is currently unknown. The *Council of Europe Guide* admits that there is an ongoing discussion on the acceptation of organs from donors with colorectal carcinoma stage T1. Regarding donors with a past history of colorectal carcinoma, those staged T1 and T2, with no lymphatic or distant metastases, may be considered as non-standard risk donors after adequate treatment and a disease-free interval of 5-10 years.

Table 3: Recommendations for the transplantation of organs from donors with a history of early stage colon cancer (ASTS Winter Meeting 2003).

Cancer	Stage	Specific characteristics	5 year survival (%)	Recommended disease-free interval for donation
Colon	0=CIS	-	99-100	Safe / 0 years
	T1/T2	Caucasian male	>95	>1 years
	T1/T2	Female	90-95	> 5 years
	T1/T2	African American male	<90	Donation never to be realized

At the ASTS Winter Symposium in 2003(22), similar recommendations were provided, as depicted in table 3, with considerations depending upon the ethnicity and gender of the donor and the malignancy recurrence free interval.

5.2.5 Choriocarcinoma

High rates of transmission of choriocarcinoma (93%) have been described in the IPITTR, with a high malignancy related death rate (64%). There are also different case reports detailing the features of such cases of malignancy transmission.(15, 16)

In a recent publication, the accidental transmission of a placental choriocarcinoma from a multiorgan donor to all four related transplant recipients was described.(30) The donor was a 26-year-old pregnant woman who died from a cerebral hemorrhage initially attributed to a vascular malformation. Macroscopic examination of the donor's heart, liver, pancreas or kidneys did not show any abnormality. Histological examination demonstrated the presence of a placental choriocarcinoma three weeks after donation. Diagnosis of choriocarcinoma transmission was established on the basis of an increase in human chorionic gonadotrophin hormone (hCG) levels in the combined pancreas-kidney recipient, who received chemotherapy and was in complete remission 2 years after, without removal of the grafted organs which showed optimal function. A transplant nephrectomy was performed in the single kidney recipient on day +35 following transplantation, when the risk of transmission was identified and after detecting elevated hCG levels. The patient also received actinomycin therapy. Notably, the explanted kidney did not disclose metastasis. The patient was in remission two years after the transplant. The liver recipient showed intestinal metastasis and died from digestive hemorrhage after an initial response to chemotherapy. After 80 days following transplantation, the heart recipient had increased hCG levels and a scan disclosed several pulmonary micro-nodules and lumbo-aortic lymph nodes. Treated with chemotherapy with an initial remission, he showed diffuse metastasis at the last available report.

Because of the high risk of transmission attributed to this malignancy, the *Council of Europe Guide* considers that donors with a past or present history of choriocarcinoma pose an unacceptable risk, regardless of the stage and the disease free interval.

5.2.6 Liver Cancer

As part of the DTAC experience, there has been only one published case of transmission of a liver tumour through organ transplantation. (13) However, because they are deemed very aggressive tumours, the *Council of Europe Guide* recommends considering donors with a past or present history of hepatocellular carcinoma as posing an unacceptable risk. Exceptionally, as applied in Italy, those persons with a past history of this malignancy could be considered for donation after a careful risk-benefit analysis, depending upon the stage and grade and if complete remission existed for more than 10 years.

5.2.7 Haematological malignancies

Three donor report cases of lymphoma were notified to DTAC, with one case of malignancy transmission which resulted in the death of the patient. (13)

Bodó et al described a case of a fatal acute promyelocyte leukemia diagnosed in a liver transplant recipient 24 months after transplantation, presenting with unspecific symptoms, ecchymosis, thrombocytopenia and disseminated intravascular coagulation.(31) The leukemic clone bore the genetic and phenotypic markers of the donor.

Königsrainer et al reported the transmission of a cerebral Non-Hodgkin's lymphoma, which at the time of organ procurement was suspected to be an astrocytoma, into two kidney recipients.(32) Postmortem examination of the donor revealed the high-grade of the CNS malignancy, but showed no distant metastases. Due to the missing metastases, the recipient centre had not been informed about the correct diagnosis. Both kidney recipients developed a malignant lymphoma at the site of the transplanted kidney.

Further case reports about donor derived and transmitted lymphomas are found in the literature. In all these cases there was no suspicion of malignancy in the donor, the lymphoma was first diagnosed in the recipient and the donor origin was then shown by immunohistochemistry or cytogenetics.

Cases of donors with haematological malignancies with no evidence of transmission are also known. There is a case report of a 24-year-old donor with no suspicion of malignancy, whose lymph node, extracted for tissue typing, was diagnosed with a low-grade follicular lymphoma two weeks after donation. The first kidney recipient kept his organ and did not show evidence of malignancy transmission 36 months after transplantation. The other kidney recipient underwent a transplant nephrectomy, was re-transplanted approximately 12 months later, and remained well and without tumor transmission at the last available follow-up (33).

In Germany there is one unpublished case of a liver donor after successful chemotherapy and autologous stem cell transplantation 4 years before donation due to a recurrent high grade B-cell lymphoma (DSO-Isys-Database, Germany). One year after the transplantation of his liver, the recipient did not show evidence of malignancy transmission (personal communication, Kirsten Moench, DSO, Germany).

Currently, there is no sufficient evidence to provide solid recommendations for the safe transplantation of organs from donors with a past or present history of haematological malignancies. Based on the current and limited information, the *Council of Europe Guide* recommends that persons with a present history or an accidental diagnosis of lymphoma/leukemia at the time of donation are considered as posing an unacceptable risk. Regarding donors with a past history of these malignancies, donation could be considered in cases of acute leukemia after a disease free interval of more than 5-10 years (this recommendation is provided in the French guidelines). Donors with a past history of chronic leukemia are considered to pose an unacceptable risk at any time and with any grade of disease.

5.2.8 Lung Cancer

Reports on transmission of lung cancers through organ transplantation are documented in the UNOS and the IPTTR registries, as previously described, with an estimated rate of donor to recipient transmission of 41% and a 32% of related mortality in the latest (15, 16). Several case reports on lung cancer transmission and on exposure with no transmission have been described in the literature, some of them being described below.

Lipshutz reported the case of a liver transplant recipient whose donor was diagnosed of a lung adenocarcinoma with metastatic mediastinal disease during autopsy (34). Retransplantation of the liver was carried out on day 7 after transplantation, despite which the recipient developed a metastatic lung adenocarcinoma 11 months after transplantation and died soon after. The explanted liver did not show evidence of malignancy. The patient underwent surveillance CT scan at 10 months after transplantation, with no evidence of disease. Six weeks later the recipient presented abdominal pain, vomiting, and early satiety. Abdominal radiography showed an adynamic ileus and ascites, and chest radiography showed a moderate pleural effusion. Two thoracenteses (in 5 days) and paracentesis yielded fluid with cells consistent with metastatic pulmonary adenocarcinoma. Analysis of short tandem repeat regions of chromosomal DNA from recipient, the 2 liver donors, and the post-transplantation tumour corroborates that the first donor was the source of the malignancy.

In 2001, a case of a lung cancer transmitted through live kidney transplantation was reported (35). The live donor was diagnosed of a small cell carcinoma of the lung 10 months after donation, while the transmission was detected 32 months after transplantation. Notably, the first clinical manifestation in the recipient was a Cushing syndrome. A mass was found in the kidney allograft, histology being compatible with a small cell lung carcinoma and having an extensive disease involving the kidney and the retroperitoneum. The donor origin of the tumour was confirmed by the demonstration of the donor HLA-type was expressed in the tumour but not in the tissue of the recipient. At the last follow-up, the patient was alive, without evidence of disease recurrence on CT scan 18 months after diagnosis, and in dialysis after graft removal and chemotherapy. On the contrary, Nair described the case of a live kidney donor being diagnosed of a metastatic small cell lung carcinoma 10 months after donation.(36) Recipient had no evidence of malignant transmission 36 months after transplantation and after having refused the removal of the transplanted organ.

Another case of a donor with lung cancer and no transmission was reported by Badia et al. (37) Seven days after the two kidneys of a donor had been transplanted, the forensic autopsy revealed a metastatic adenocarcinoma in the lung. After notifying the transplant team, both recipients underwent an early transplant nephrectomy. Fifteen months later, no signs of malignancy had been detected in the recipients, both having received a new transplant.

Morath described the case of a kidney transplant recipient with increasing back pain followed by hypercalcemia 10 months after transplantation.(38) Further studies revealed a small cell carcinoma with bone and liver metastases. Immunosuppression was stopped and the graft removed and 18 months after transplantation the patient was doing well. Donor origin was confirmed by DNA fingerprinting. Notably, the removed graft did not show any evidence of tumoural infiltration, suggesting that transmission of isolated solid organ tumoural cells was possible to occur through organ transplantation without manifestation of the original tumour in the transplanted organ. Only kidneys were allowed to be removed. The recipient of the other kidney was doing well with no signs of malignancy.

The high rate of transmission described in the aforementioned registries has led to consider persons with a past or present history of lung cancer as posing an unacceptable risk for donation. As described by the Council of Europe Guide, some countries would accept organs from donors with a past history of lung cancer, particularly those with adenocarcinoma or T1N0 squamous cell carcinoma and complete remission for 5-10 years, although they would be considered as nonstandard risk donors.

5.2.9 Malignant Melanoma

Melanoma is one of the malignancies related to the higher risk of transmission through organ transplantation. As a tumour likely to recur many years after a disease-free survival, cases of transmission of melanoma from donors with a past history of melanoma and a long disease free interval have been reported. In fact, this was the case put forward by the UNOS registry in its review of the outcomes of recipients transplanted from donors with a previous history of malignancy (10). The donor had a melanoma excised 32 years before donation. The lung recipient developed a melanoma, although the other 5 recipients of grafts from this donor did not show evidence of malignancy transmission. The results of this publication are however conflicting, because of only such case described out of 140 recipients transplanted from donors diagnosed of melanoma. Whether different histologies (lentigo melanoma, in situ tumour and malignant melanoma), stages and disease-free intervals are considered under such generic description justifying the low rate of transmission is a matter of discussion. Cases of melanoma being transmitted through organ transplantation have been also reported by the DTAC, the IPITTR and the Danish registry. The IPITTR estimated a 74% risk of malignancy transmission in cases of donors with melanoma with a resulting 58% mortality (16).

Different case reports on the transmission of melanoma through organ transplantation have also been published with detailed information on the clinical signs and symptoms and the assessment of attributability, as follows.

Suranyi et al. (39) reported the transmission of a melanoma through two kidneys and a liver. The multi-organ donor (heart, liver and two kidneys) showed no evidence of malignancy. Around 9 months after transplantation, one kidney recipient underwent renal transplant biopsy to investigate an unexplained rise in creatinine level, showing malignant melanoma infiltration which was extensively spread. Genetic investigation of the index case determined the donor origin. When notified, the immediate examination of the other kidney recipient, asymptomatic, revealed affectation of the graft, the abdomen and the lung fields. The index case spontaneously rejected both allograft and melanoma upon withdrawal of immunosuppression, but died shortly thereafter of other causes. With regard to the contralateral kidney recipient, prolonged immunotherapy eradicated the malignancy and the patient went on to a successful second renal transplant, with follow-up of over 24 months. The liver recipient succumbed to inadvertently transplanted melanoma, despite reduction of immunosuppression. The heart recipient never showed evidence of transplanted tumour.

Mackie et al. (40) reported the case of a donor who had been diagnosed of an excised melanoma 16 years before donation, in spite of which the tumour was transmitted to the two kidney related recipients. One of the kidney recipients underwent a routine mammography 18 months after transplantation, which showed a breast nodule, initially being diagnosed of a primary breast cancer. Afterwards, the patient complaint of pain and swelling of the graft and two subcutaneous nodules were detected, biopsy being compatible with a melanoma. The nodules were excised, immunosuppression was stopped and Interferon therapy started. Nevertheless, the patient died from a metastatic melanoma 22 months after transplantation. The second kidney recipient showed a palpable lump over the graft 24 months after the transplant, which biopsy revealed a melanoma. The patient was treated with interferon to reject the graft and the malignancy. The graft was removed showing large masses of necrotic melanoma cells. The recipient was doing well two years after transplantectomy.

Cankovic et al. (41) described the development of a metastatic melanoma in a liver transplant patient 9 months after transplantation, who died one month later. The autopsy revealed that the graft was extensively replaced by the tumour. Commercially available PCR–based microsatellite marker assay was used to perform tissue identity testing, strongly suggesting that the melanoma originated from the transplanted liver. A kidney recipient also suffered the transmission of the melanoma, whose donor origin was also confirmed through molecular genetic analysis.

Stephens et al. (42) reported a case of transfer of malignant melanoma from a single donor to four recipients, all of whom died from metastatic melanoma. The donor had no history or clinical evidence of such malignant disease. The first recipient initially did well, but 15 months after transplantation developed a urinary tract infection complicated by sepsis and poor renal function. The graft was removed and found to contain malignant melanoma. She died 17 months after transplantation, being widespread malignant melanoma documented by autopsy. The second recipient, 15 months after being grafted with the liver, developed shortness of breath. Image tests revealed multiple lesions in

lungs and liver. Melanoma was confirmed by biopsy. The patient died 16 months after transplantation. Extension was confirmed by autopsy. Multiple pulmonary nodules were found in the third recipient, in a routine x-ray examination, 10 months after heart transplantation. A CT scan also revealed liver lesions. The same malignancy was confirmed by biopsy. The patient died 13 months after transplantation. Regarding the fourth recipient, 17 months after the kidney transplantation, a CT scan revealed multiple masses in the kidneys, liver and lungs. He died 30 months after the transplantation. Immunohistochemical and PCR-based genetic analysis conclusively determined that the tumours were of donor origin.

Another case was reported by Milton et al. (43). Kidneys, lungs and heart were transplanted from a donor. Information on his personal history was limited. A mass was seen in the lung recipient's allograft on a routine x-ray 3 months after transplantation. Malignant melanoma was diagnosed by biopsy and donor origin confirmed by HLA-DR typing. The first renal recipient, undergoing his second deceased donor renal transplant, had his immunosuppression stopped 4,5 months after transplantation, when the disease was confirmed in the index case, he presented clinical rejection and graft was removed. Histology demonstrated vascular and cellular rejection as well as a 3 mm melanoma deposit with no evidence of tumor infiltrating lymphocytes which might suggest rejection of the melanoma cells. Three years post-transplant, the recipient remained with no evidence of melanoma. The other renal allograft recipient presented clinical rejection 6 weeks after cessation of immunosuppression. Histology of the graft removed did not demonstrate melanoma. The patient remained free of disease at 3 years post transplantation. The cardiac allograft recipient either did not show evidence of malignant melanoma 3 years after transplantation.

Morris-Stiff et al. (44) published a case report of another transmission of malignant melanoma from a multiorgan (kidneys, liver, and heart) as well as cornea donor, who had a diagnosis of grade II cervical intraepithelial neoplasia 8 years previously. The recipient of the first kidney, a female, had an emergency admission with severe abdominal pain and vomiting, followed by increasing confusion. Laparoscopy showed black plaques on the peritoneal surface. Biopsies were compatible with metastatic melanoma. No site of primary melanoma was found, and the patient died before starting immunosuppression. The recipient of the second kidney was a male and did well until his first annual review, presenting a pigmented lesion, which had developed over the preceding month on his forehead, that was identified as a malignant melanoma. Fluorescent in situ hybridation (FISH) analyses confirmed double X karyotype. Immunosuppression was stopped and the graft was removed. At 3 year follow up, the patient remains in stable partial remission. The liver recipient was clinically well until 2 years after transplantation, showing infiltration of the liver. The result of the biopsy was compatible with malignant melanoma, and she finally died. The recipients of the cardiac and corneal grafts were closely followed. Approaching 5 years of their follow up, no melanotic lesions have been found.

Another case, published by Kim et al., (45) reported the transmission of melanoma. At 6 months post-transplant, the liver recipient presented abdominal pain, ascites, and elevated levels of blood urea nitrogen, creatinine, liver enzymes and total bilirubin. CT scan showed and enlarged liver, which was biopsied, being the result compatible with metastatic malignant melanoma. No primary lesion was identified. Donor origin of the tumour was demonstrated through FISH and DNA sequence analysis. One kidney recipient decided to undergo a transplant nephrectomy and remained free of disease two years after transplantation. The second declined transplant nephrectomy and, although remained in reduced immunosuppression, 18 months post-transplant, developed widespread malignant melanoma and expired.

Because of its aggressiveness, a present or past history of malignant melanoma, regardless of the stage and disease free interval, is considered to be linked to an unacceptable risk for organ donation in the *Council of Europe Guide*.

5.2.10 Oesophageal carcinoma

Taioli et al.(29) reported two transplanted livers from patients with oesophageal carcinoma, who showed local lymph node metastases. However, no transmission of malignancy was reported in the recipients. In spite of the limited information available, because oesophageal carcinoma is an aggressive tumour, the Council of Europe Guide recommends considering donors with a past or present history of this malignancy as posing an unacceptable risk. Exceptionally, as applied in Italy, those persons with a past history of this tumour could be considered for donation after a careful risk-benefit analysis, depending upon the stage and grade and if complete remission for more than 10 Oropharyngeal cancer

The UNOS registry(10) provided information on 11 transplant recipients (7 kidneys and 4 livers) from donors with a previous history of oropharyngeal cancer with at least 5 years of disease free interval. No case of malignancy transmission was reported. With such limited evidence, the *Council of Europe Guide* recommends considering these donors as unacceptable for donation, although those free of disease for more than 5-10 years could be considered as non-standard risk donors. However this recommendation, caution is always needed because the clinical behaviour of this group of malignancies might be more aggressive in the immunosuppressed individual.

5.2.12 Ovarian Cancer

Lipshutz et al.(46) reported a case of transmission of metastatic ovarian cancer which was undetected in the female donor. Six months after kidney transplantation, the male recipient developed symptoms of a malignant disease and transplant nephrectomy revealed a poorly differentiated adenocarcinoma of ovarian origin. This recipient, as well as the recipient of the contralateral kidney, both died of metastatic disease shortly after.

In the Council of Europe Guide, ovarian cancer is considered to pose an unacceptable risk for organ donation. There are no data available about acceptance for donation after a recurrence-free survival of 5-10 years or more, but a very careful risk-benefit-assessment should be performed.

5.2.13 Pancreatic carcinoma

There are limited publications on organs transplanted from patients with a pancreatic *carcinoma. Kauffmann* (12) *reported the case of a transplanted liver from a patient with a* pancreas carcinoma (probably metastatic). The patient underwent hepatectomy and was retransplanted.

Gerstenkorn et al reported the transmission of a pancreatic adenocarcinoma to a renal transplant recipient (47). The tumour had been diagnosed in the donor on adrenal tissue removed from the donated kidney during bench preparation. At the time of the diagnosis, this kidney and the liver had been already transplanted. The liver recipient was urgently retransplanted in 24 hours. The renal recipient opted not to have a transplantectomy performed, developing a lymphangitis carcinomatosa of the lung 9 months after the transplant, likely contributing to the death of the patient 15 months after the transplant procedure. The contralateral kidney was discarded for transplantation.

One tumour transmission occurred in a patient who received live related kidney transplantation from her father, who had an unrecognized pancreatic carcinoma. The recipient died shortly after transplantation (personal communication, Thomas Breindenbach, DSO, Germany).

The *Council of Europe Guide* considers donors with a present history of pancreas cancer linked to an unacceptable risk of malignancy

transmission. As for other clinically aggressive tumours, the transplantation of organs from donors with a past history of this malignancy should be considered only after a careful risk-benefit analysis, depending upon the grade and stage, and after a disease-free interval of more than 10 years.

5.2.14 Prostate Carcinoma

As a disease of the aged man and the progressive increase in donor age, it is likely that many organ transplants performed nowadays are so from donors with an undiagnosed prostate carcinoma (48). In fact, the number of cases of prostate carcinoma transmission is quite limited.

Loh(49) reported the case of a heart transplant recipient developing a metastatic prostate cancer 10 months after transplantation, with a tumor related death despite reducing immunosuppression and chemotherapy. When the heart transplant procedure was about to be completed, a prostate adenocarcinoma was discovered in pelvic lymph nodes of the donor. A postmortem examination of the donor revealed a moderately to poorly differentiated adenocarcinoma of the prostate with extracapsular extension into the seminal vesicles and metastatic foci in pelvic lymph nodes and adrenal glands. This means that this case of malignancy transmission occurred with a high stage and grade prostate carcinoma.

Verran et al. reported two living kidney donors after R0 resection for localized prostatic adenocarcinoma. PSA showed normal levels. At last follow up, recipients remain free of malignancy (Abstract, ESOT 2007, Prague).

The *Council of Europe Guide* provides the following recommendations on the transplantation of organs from donors with a present or past history of prostate carcinoma:

- Some national guidelines consider donors with intra-prostatic, low grade (Gleason ≤ 6) as standard risk donors.(50) However, no international consensus exists in this regard.
- The acceptable disease-free time interval for donors with a past history of prostate carcinoma differs between countries (≧5 years, ≧10 years or never) and depends on the stage and grade of the tumor. The presence of small, low-grade prostate carcinomas under 'active surveillance' may be acceptable for organ donation, even in the absence of surgical therapy and a disease-free interval. The donor-selection procedure should be individualized, assessing the characteristics of the tumor and the donor, and the conditions of the recipient. Donors with extra-prostatic tumor extension or metastatic disease must be excluded from the donation process.

5.2.15 Renal Cell Carcinoma

Cases of transmission of RCC through organ transplantation have been reported to the mentioned above registries. Some series have provided information on the follow-up of recipients transplanted from donors with RCC diameter<4 cm and Fuhrman I-II with no evidence of transmission of malignancy, (51) this information representing the safety limits provided by some national and international guidelines when considering suitability for organ donation.

There are also case reports in the literature on the transmission of RCC to kidney, liver, heart and lung recipients. Sack et al reported the transmission of a RCC to a heart transplant patient with death due to metastatic RCC 12 months after transplantation (52). Barrou referred to a contralateral kidney and a heart transplant from a donor with a 17 mm tubulo-papillary RCC (53). The kidney recipient underwent transplantectomy due to tumoural infiltration of the graft 4 months after the transplant and the heart transplant recipient died 7 months after the procedure due to a metastatic RCC. Buell et al. (54) described two transmitted RCC in a heart and a heart/lung recipient both dying of metastases 11 and 14 months after transplantation, respectively. The RCC had been found in the donors shortly after the transplantation of the organs and both showed evidence of vascular extension. Three further donor RCC had been detected during organ recovery, being confined within the renal capsule. The three heart recipients from these donors were without evidence of tumor transmission at 36-70 months of follow-up.

Cases of RCC in live kidney recipients detected after transplantation have also been reported. Neipp et al. (55) described the case of a father to daughter live kidney donation with the wall of a prominent cyst excised prior to transplantation. Histology was available 10 days after, revealing a high grade RCC. Partial nephrectomy and sirolimus based immunosuppression was attempted in the recipient, with no evidence of malignancy transmission one year after transplantation.

The current guidelines of the European Association of Urology state that the therapy of small, localized RCC<4cm in a regular, non-transplanted patient is an effective nephron-sparing surgery of the diseased kidney. Recurrence-free and long-term survival rates are similar compared to patients treated with radical tumour nephrectomy. This implies that, in selected cases and after a risk-benefit assessment of the recipient, even the diseased kidney may be transplanted after tumour resection. In fact, Brook et al reported the follow-up of 43 recipients who received kidneys from mostly live-unrelated donors with small (<3 cm) RCC from 1996-2007.(56) Tumours of 41 kidneys had been excised before transplantation. In two cases, the contralateral kidney had also been transplanted. One tumour recurrence was observed 9 years after transplantation at the initial tumour resection site. All other recipients were tumour-free after a median follow-up of 25 months.

Based on the above, the *Council of Europe Guide* provides the following recommendations on the transplantation of organs from donors with a present or a past history of RCC:

- Donors with a RCC diagnosed at the time of organ recovery could be considered suitable if the newly-diagnosed tumor is <4 cm (stage pT1a), the margins of the resection are tumor-free and the Fuhrman grade is I-II. In general, the affected kidney will not be accepted for transplantation, but all other organs may be considered. Donors with RCC Fuhrman grade III should be considered Nonstandard Risk Donors. In these cases, the decision to transplant the organs should be made on the basis of an individual risk-benefit analysis for emergency recipients (heart, lung and liver recipients). Some countries will not accept a donor with a newly diagnosed RCC at all.

Limits for the transplantation of organs from donors with a history of RCC vary between European countries. Some countries accept a donor only after >10 years of complete remission, whilst others may accept the organs after shorter follow-up times, always depending on tumor staging and grading. Tumors <4 cm (stage pT1a) with a Fuhrman grade I-II might be accepted as Nonstandard Risk or even Standard Risk Donors. Donors with RCC>4 cm (at the time of initial diagnosis) are typically not accepted for organ donation.

5.2.16 Sarcoma

Transmission of sarcoma through organ transplantation has been reported to multicentre follow-up registries. Based on the IPITTR registry, Buell reported two lung recipients who received their grafts from donors with a sarcoma detected during autopsy (54). Both recipients were re-transplanted without any evidence of tumour transmission at the latest assessment 3 and 36 months after transplantation, respectively. The ONT registry also has reported the case of a sarcoma transmitted through organ transplantation (19).

Chan et al. (57) reported the case of a liver transplanted patient who showed a 6 cm tumor in the right posterior sector of the graft in a control image test 3.5 years after transplantation. A right hepatectomy of the tumor was performed, histology being compatible with a high

grade sarcoma. The patient was well 1.5 years after the described resection and reduction of immunosuppression. Only the liver recipient was affected, despite the fact that the two kidneys, skin (two recipients), bone (11 recipients) and corneas had been used. Microsatellite analysis was performed on the DNA of the donor (liver allograft), recipient (peripheral blood) and tumor tissue, the study determining the donor origin of the tumor.

Detry et al. (58) reported the transmission of an undiagnosed sarcoma to a liver and a kidney recipient. The donor was a Maastricht type III donor after circulatory death who led to the transplantation of both kidneys and the liver. The liver recipient developed cholestasis 13 months after the transplant, an ultrasound evaluation revealing a large necrotic lesion within the left liver. Surgery showed a tumour, resection of which was impossible and histology revealing a sarcoma. The patient died 5 days after the surgical intervention because of a multi-organ failure. One year after the transplantation, the kidney graft was removed from one of the recipients due to a malignancy proven to be a spindle cell sarcoma. The contralateral kidney was removed shortly after transplantation because of a primary non function and the recipient remained well 15 months later. Attributability to the donor of sarcomas found in the two recipients affected was based on a comparable histology and the kariotype mismatch in the liver recipient (the donor was a female).

As pointed out by the *Council of Europe Guide*, due to the aggressive clinical behaviour of sarcomas in the general population, persons with a past or present history of this malignancy should not be considered as organ donors, regardless of the stage of the disease and the disease-free interval.

5.2.17 Thyroid carcinoma

The UNOS registry (9) provided information on 11 transplants performed with organs from donors with a history of thyroid carcinoma (7 kidneys, 3 livers and 1 heart). Later on, the same database reported 34 cases (22 kidneys and 12 livers) (10). In the Italian registry, one donor with a thyroid carcinoma led to the transplantation of three organs (2 kidneys and one liver) (29). No cases of malignancy transmission were reported in both registries.

Based on the limited information available and the clinical behaviour of these tumours in the non-transplanted population, the *Council of Europe Guide* considers as standard risk donors those diagnosed of a thyroid carcinoma during procurement in case of a capsulated papillary and minimally-invasive follicular thyroid carcinoma (T1a). Donors with a past history of thyroid carcinoma (particularly those with anaplastic carcinomas) are considered as non-acceptable in most countries. Exceptions may be made also in cases of capsulated papillary and minimally invasive follicular thyroid carcinomas (T1a).

5.2.18 Uterus and uterine cervix cancer and cancer of the urinary bladder

Data published about uterine or cervical carcinoma transmission through organ transplantation have not been found.

There is one case report of an urothelial carcinoma transmission via kidney and liver transplantation.(59) In the 37-year old female donor no malignancy was suspected. The transmitted urothelial carcinoma was first diagnosed in the 21-year old kidney recipient, who died of metastatic disease. The child who received the donor liver was also diagnosed with tumoural nodules in the graft within the first year after transplantation.

Active presence of these cancers is considered an Unacceptable Risk for organ donation. Only cancer of the urinary bladder stage T1 might be accepted as Standard Risk (21). The Council of Europe Guide summarizes that, after a disease-free interval of more than 5-10 years (depending on national guidelines), patients with these tumors might be considered as Nonstandard Risk Donors. Only cancer of the urinary bladder stage T1 might be accepted as Standard Risk.

5.3 Transmitted malignancies through tissues and cells

Most published cases of malignancy transmission through the transfer of CTO are related to organ transplantation, with less profuse information in the field of tissues and cells. In this area, the quantitatively most relevant information is related to HSC transplantation. Malignancies transmitted through HSC are typically hematologic malignancies, which become clinically evident through tumor-specific symptoms (abnormal blood counts/differential) and in late stages.

Regarding the recommendations on the utilization of tissues and cells from donors with a history of malignancy, donation is not to be realized. An exception is cornea transplantation because of its avascular nature. Salame et al. (60) reports a comparison of the incidence of cancer in recipients of cornea coming from donors with malignancies with recipients of cornea from donors without malignancies, concluding no statistical or clinical evidence to suggest the transmission of cancer from donors with malignancies via corneal transplantation. As previously described on organs (see section on Malignant Melanoma), Morris-Stiff et al. (44) reported a case of transmission of malignant melanoma from a multi-organ and cornea donor. However the corneal recipients did not show any evidence of melanoma after 5 years of close follow-up. López-Navidad(61) published a series of 204 cornea donors with history or active malignancy. A total of 325 recipients received 325 corneas from cancer donors. Among those 305 (93.9%) were transplanted from donors with solid tumors (64% of them had died with systemic dissemination) and 20 (6.1%) from donors with malignant hematological disease. After an average follow-up of 64.1 month, there was no tumor transmission. However, limits in cornea transplantation are yet unclear. Yao et al reports a case of a metastasis of cholangiocarcinoma in a cornea which was grafted in the corresponding recipient (62). Moreover, certain tumors (i.e. retinoblastoma, hematologic neoplasias and malignant tumors of the anterior segment of the eye) exclude cornea donation in the European Union setting(63). Transmission of hematological malignancies through cell transplanta-

Key messages

Regarding malignancies transmitted through organ transplantation:

- Most cases have been diagnosed within the first 14 months following the transplant procedure. This occurs in 75% of the cases included in this NOTIFY review. However, time between the transplant and the diagnoses ranged from 1 to 108 months. Such difference is likely due to the fact that cases of donor derived malignancies are also included in some series and reports. The differentiation between donor-transmitted and donor-derived malignancies is however important both from a conceptual and a practical point of view. In donor-derived malignancies, the organ was transplanted without bearing malignant cells, which means that other recipients from the same donor are not necessarily exposed to the risk of developing a donor related malignancy.
- Clinical symptoms and signs of malignancy transmission are heterogeneous, depending upon the type of tumor and organ transplanted. Usually, the transmitted malignancy is identifiable in the transplanted organ with or without extra-graft metastases, reflecting a tumor borne by the allograft. Exceptionally, the graft does not show evidence of malignant infiltration, which reveals that isolated tumor cells might be transmitted through the organ (E.g. leukemia and Kaposi's Sarcoma).

tion has been reported. Niederwiser et al. (64) reported a case of transmission of a donor's acute leukemia in bone marrow transplantation for chronic myelocytic leukemia. A patient with Philadelphia chromosome-positive chronic myelocytic leukemia in a phase of accelerated growth received bone marrow transplantation from his HLA-identical brother, whose peripheral blood revealed no abnormalities. However, the graft showed the features of acute myeloid leukemia. Six months after transplantation, the recipient developed leukemia with morphologic, immunohistologic and cytogenetic features of the donor's leukemia. Berg(65) published a transmission of a T-cell lymphoma by allogeneic bone marrow transplantation. Donor and recipient were sisters. After three years of the procedure, the donor developed eczematous dermatitis, a nodule on one arm and fever, and was diagnosed of subcutaneous panniculitic T-cell lymphoma. Despite treatment, the donor died. One month before her sister's death, the recipient was seen for a one-year history of skin lesions, presenting eczematous plaques and nodules on the legs. Histologic examination revealed many similarities, raising the suspicion of a transmission from donor to recipient during bone marrow transplantation. Posterior analyses showed the donor's neoplastic T-cell clone persisted in the recipient for five years before clinically evident disease appeared. In line with this case, Hart et al. (66) reported a case of a patient with acute myeloid leukemia, for which he received allogeneic bone marrow stem cells from his father. Three years later, the patient's father was diagnosed with a follicular lymphoma stage IV. Eighteen months after he developed a bulky lymphadenopathy, he was given treatment, and another lymph node revealed diffuse large B-cell lymphoma. He died of the disease 6 years after the transplantation. Eleven years post-transplant, the patient developed bulky retroperitoneal lymphadenopathy, and was diagnosed of follicular lymphoma. The authors found that the recipient's lymphoma was donor cell derived.

5.4 Specific Donor Cancers for which no reports on transmission have been found

5.4.1 Central nervous system neoplasias

See corresponding section (Central Nervous System neoplasias) on organs

5.4.2 Non-melanoma Skin Cancers

No reports have been found on the transmission of non-melanoma skin cancers through organ transplantation. In fact, these donors are considered as posing a standard risk of disease transmission in different national and international guidelines.

5.4.3 In-situ cancers (breast, cervix, colon)

Carcinoma in situ is a non-invasive epithelial tumour which has not crossed the basal lamina. Therefore it has no potential for metastases, but can transform into an invasive tumour after some time. As summarized in the Council of Europe Guide, donors with in situ carcinomas may be considered, except for high grade in situ breast cancer, choriocarcinoma, melanoma, lung cancer and sarcoma at any time after treatment. Some authors consider donors with stage Tis colon carcinomas for donation if they have received adequate treatment for their tumour (67). Other authors consider that donors with thyroid carcinoma in situ can also be considered for donation.

There is a view that patients with aggressive tumours like the above mentioned ones should not be considered as donors, regardless of the stage of their neoplasia (22).

5.4.4 Curatively treated cancers

There is no consensus on the time free of malignancy to consider a donor as a standard risk. It also depends upon tumour type, grade and stage and the situation of the recipient. Some authors agree that, after 10 years of a strict follow-up with no evidence of disease recurrence, organ donation can be considered, with a few exceptions: breast tumour, sarcoma and malignant melanomas. However, for other authors, donors with a previous history of malignancy should never be considered organ donors, while others agree that a time free of disease from 3 to 5 years is enough. As a general statement, time free of malignancy to consider donation should be individualized depending upon the particular characteristics and behaviour of the corresponding neoplasia (see previous sections), and the particular case of an individual recipient.

It is highly recommended to have a proper staging in donors with curatively treated cancers (risks of recurrence, metastasis or secondary malignancies).

6 Providing guidance on early detection and prevention of transmission

6.1 Deceased donors

Strategies to minimize the risk of malignancy transmission related to donor evaluation through the transfer of CTO are summarized in table 4 and discussed below.

6.1.1 Specific medical history of the donor

For every donor of CTO, a complete clinical history of the donor should be collected, with special emphasis on these three points:

- Dangerous life style habits related to neoplastic diseases, such as smoking.
- Records of any previously diagnosed neoplasia (or tumors removed without documentation of the definite diagnosis) should be reviewed. Information to be collected: date of first diagnosis, detailed histologi-

Table 4: Strategies to minimize the risk of malignancy transmission through CTO.

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 tumor recurrence at any time • **Life style habits** related to neoplastic diseases (i.e. smoking behavior) • **Menstrual irregularities after pregnancies and/or miscarriages** in women
Physical examination
Laboratory tests: • **Standard** • **Tumor markers:** HCG, PSA, both in selected cases
Image tests: • **Chest X-ray** • **Abdominal ultrasound** • **CT or other in selected cases**
Inspection of all intra-thoracic and intra-abdominal organs, regardless of their eligibility for transplantation, including bowel and genital organs
Histopathological examination of any mass or lymphadenopathy identified during evaluation or recovery-including ISOL*
Recommended autopsy when possible
Guidelines for donor evaluation, testing and selection

*ISOL: intracranial space occupying lesions

cal report, stage, grade, type and date of surgery, chemotherapy and/or radiotherapy, regular follow-up conducted, latest follow-up and results, complete remission and tumor recurrence at any time.

- History of menstrual irregularities after pregnancies and/or miscarriages in women of a fertile age, as clinical signs of a suspected metastasized choriocarcinoma.

In case of deceased donors and if possible, the donor's general practitioner and the relatives of the deceased should be contacted to provide detailed information.

Relatives might provide useful and valuable information on the medical history and lifestyle habits of the donor. When no clinical record is available, they can be asked and even provide clinical reports of much help to assess the risk to make the decision whether proceeding or not with the transplantation. Still bereaving donor relatives are under stress and they may not be able to report all details.

6.1.2 Physical examination

A careful physical examination should be always conducted, paying particular attention to the skin, looking for potential neoplasias or scars of previous surgical procedures.

6.1.3 Investigations

1. Laboratory tests. Tumour markers

Standard laboratory tests should be conducted in all potential donors with the objective of detecting specific diseases that may contraindicate donation, including malignancy.

Routine screening of tumour markers is not recommended in potential organ donors, since false-positive determinations may lead to the unnecessary discard of otherwise suitable organs or donors. However, there is no universal consensus on this statement:

- Some commentators recommend routinely determining specific tumour markers (i.e. PSA, βhCG).
- Others recommend determining some of these markers just in specific circumstances. *E.g. βhCG in females in fertile age dead due to an intracranial bleeding, since a small proportion of choricarcinomas present for the first time with a cerebral haemorrhage; other tumour markers appropriate for monitoring malignancies known to be present in the donor's history*.

It is highly recommended to store a sample of serum or plasma from every donor should any laboratory test and/or tumour marker needed to be explored in the future.

2. Radiological tests

Abdominal ultrasound and chest X-ray must be carefully inspected. Further radiological tests (E.*g*. CT-scans), may be required for a thorough donor evaluation, especially in patients with suspected malignancies.

In patients with any history of neoplastic disease, CT-scans of the thorax and abdomen should be carried out to evaluate current disease status and to ensure the highest possible safety for organ recipients.

3. Histopathological evaluation

- Three situations are to be considered in detail:
- Any mass or lymphadenopathy with a malignant appearance found during donor's evaluation or during recovery (see below) should be subjected to histopathological testing before transplantation, by using a cytological smear and/or frozen sections.
- A histological diagnosis should be carried out on intracranial space occupying lesions (ISOL). Furthermore, for tumors in which different histological degrees of malignancy may co-exist, a complete histopathological test of the tumor should be performed. In some cases, the extraction of the CNS, its *in situ* macroscopic study and the performance of frozen sections to determine the histogenesis and the histological degree of malignancy, can be performed within 2-3 hours. Nevertheless, this is not always the case and it might be necessary to embed the tumor material in paraffin for 24 hours, so that its histogenesis and malignancy degree can be more accurately determined. If a histological diagnosis of the ISOL cannot be performed, the risk of proceeding with the transplantation should be balanced against the risk of not proceeding with the transplantation.
- In cases of suspected malignant prostate tumor, it is recommended to recover the entire prostate and to proceed with its pathological study through frozen sections, followed by a complete pathological study, prior to acceptance of the donor.

6.1.4 Cause of Death

For donors whose cause of death is an intracranial bleeding without an evident underlying aetiology, the possibility of an intracranial tumour should be considered on a case by case basis.

For the evaluation of donors with ISOL, see section 'Investigations' on deceased donors in the unit 'Providing guidance on early detection and prevention of transmission'.

6.1.5 Recovery. Laparotomy and examination of each organ for transplantation

During organ recovery, surgeons should examine all intra-thoracic and intra-abdominal organs (including complete intestine and genital examination) regardless of whether the corresponding organs are being considered for transplantation, to detect possible unrevealed tumors or pathological lymphadenopathies. Any lesion must be investigated immediately by frozen sections by an experienced pathologist. Particular care should be taken when examining the kidneys, due to the relatively greater number of tumors that have been found in kidneys following procurement.

6.1.6 Formal Post-mortem

The performance of an autopsy in every deceased donor is recommended. Should it be carried out, professionals in charge should collect the results and immediately inform the transplant teams of any findings that potentially affect the safety of recipients.

6.1.7 General risk profile of the donor

Based on a careful evaluation of potential donors, a past or present history of malignancy might be identified before the transfer of CTO. Donors with a past or present history of malignancy are being considered for transplantation, particularly for organs, in a universal scenario of shortage, which has made to reconsider the boundaries of organ donation. Donors with a previous or present known history of malignancy, with a few exceptions, fall under the category of non-standard risk donors, as outlined in previous sections. Because some of them have not been reported to be transmitted through transplantation, still some may be considered to pose a standard risk for malignancy transmission.

However, the use of organs from donors with a past or present history of malignancy is usually based on a set of principles sustained on limited evidence. Therefore the appropriate and systematic follow-up of recipients transplanted from these donors in currently available or newly developed registries would be highly beneficial. Only by systematically recording information on recipients transplanted from these donors, the safety limits in transplantation can be clearly defined. Moreover, such an approach would benefit from an international initiative with data sharing and exchange of experiences.

6.2 Living Donors

6.2.1 Investigations

As for the deceased donor, potential live donors should be carefully evaluated to identify a previous history of malignancy or an active neoplasia, based on a thorough medical history, a physical examination and image tests. It should be noted that the risk of clinical and

subclinical malignancy increases markedly with age and that the risk of different cancers differs between countries. Hence, screening for prevalent malignant diseases in the population should be based on national cancer screening protocols. Some guidance on the evaluation of live kidney donors with regards to the screening for malignancy was provided in the Amsterdam Forum (68).

6.2.2 Donor Follow up

The follow-up of the living donor to detect and treat any complication related to donation and appearing in the short, mid or long term is a recognized international standard (*WHO Guiding Principles, Directive 2010/53/EU, Convention of Human Rights and Biomedicine, Amsterdam and Vancouver Forums, Istanbul Declaration on Organ Trafficking and Transplant Tourism*). Recording information on the follow-up of living donors and on donation-related complications in the short, mid and long term is a recommended practice carried out systematically by some countries.

On the other hand, during the follow-up of the living donor, potentially transmissible diseases, including malignancies, might arise which were not detected during the donor evaluation preceding the transplantation. Cases of malignancies appearing in living donors shortly after donation have been described in the literature. This situation should lead to alerting the concerned teams. Needless to say, the procurement/transplant team, as established in international standards, should take care / responsibility of the live donors in terms of treatment and follow-up care.

7 Providing guidance on immediate steps to take for index recipient and other potentially affected recipients

7.1 Tracing, alerting and notifying

Clinicians diagnosing a malignancy after transplantation that might be donor-transmitted should always consider other recipients from the same donor might be affected and should activate the corresponding mechanisms to alert the teams in charge of other potentially affected recipients. Donor transmitted malignancies should be suspected on the basis of clinical triggers briefly summarized before. Even if attributability has not yet been determined, the suspicion of a transmitted malignancy should activate the alert, since preventive and therapeutic measures might start on other recipients. Moreover, the collective investigation started by each team is required to study comprehensively the case and if the malignancy can be attributed or not to the donor.(69)

Tracing is the step previous to alerting other teams concerned in the corresponding case. Traceability is defined as the ability to locate CTO at any stage of the chain from donation to transplantation or disposal. Tracing should include all CTO, which implies that link between the different tracing systems should be ensured. Usually, a team is not able to trace all recipients of CTO from one donor on its own. The corresponding body in each country, i.e. allocating body, responsible procurement organization, etc. should hence participate in tracing and in alerting the other teams, as foreseen in the corresponding jurisdiction.

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

7.2 Graft removal and cessation of immunosuppression

A substantial part of therapy in kidney transplant recipients developing a donor transmitted malignancy is represented by cessation of immunosuppression, added to graft removal (although no systematically) with the subsequent return of the patient to renal replacement therapy with dialysis. In some of the reported cases, the sole cessation of immunosuppression has led to the rejection of the transmitted malignancy, by recovering the immunocompetent status of the recipient.[12,27,38,39] Added to other therapeutic strategies (see below), the outcome of kidney recipients with this approach has been successful in many cases, contrary to what occurred with non-kidney organ transplanted patients.

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

7.3 Immunotherapy

Cases of transmitted malignancies have been also treated by stimulating rejection of both the allograft and the tumour, through the use of Interferon[40], tumour vaccines, pooled allogeneic cell vaccination, and adoptive immunotherapy using lymphokine-activated killer cells.

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

Usually in combination with the aforementioned strategies, conventional therapy (i.e. chemotherapy) might be used based upon cancer type. This might be an important strategy, especially when the CTO concerned cannot be removed.

8 Providing guidance on steps to investigate and confirm the attributability of disease transmission

Except for the scale developed by the DTAC committee(13), no common and objective criteria are being applied to consider whether attributability in the context of malignancy transmission is definite (certain), likely (probable), possible, unlikely or excluded. Developing an objective and universal scale to assess attributability is needed. However, this does not preclude the description of the steps that should be followed in case of a suspected malignancy transmission occurs, in order to assess attributability.

8.1 Suspected transmission malignancy

Clinical manifestations of transmitted malignancies as reported in the literature have been comprehensively reviewed in the worksheet produced by our group. 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, as mentioned above, some reports have exceptionally described a different clinical picture where the malignant tumor is not involving the allograft itself.

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

Previous description of the transmission: A correct assessment of a case involves the analysis of the literature in order to understand whether the same tumor type has been transmitted before. Registry reports and case reports provide information regarding the type of transmission and the methodology followed for the assessment of attributability.

8.2 Traceability from donor to recipients. Alerting and assessing.

Traceability is necessary to identify other recipients at risk and to assess attributability:

- It is a duty of the teams to alert the suspect of transmission to the teams in charge of patients at risk, so they can manage the case appropriately.
- Presence of the malignancy in the donor and the recipients is of much help for determining transmission, and the more of them affected the more likely transmission took place. Finding the recipients is additionally of help, as quite often a tumor stayed unrevealed in the donor and is not easy to determine if the tumor was developed by the donor in the transplanted organ or the tumor was developed by the donor and transmitted to the recipient. The same tumor type in at least two recipients from the same donor practically excludes other explanation but malignancy transmission.

Team working between centres and coordinating agencies / authorities (according to the administrative organization of each setting) is necessary for alerting other teams regarding a potential risk that should be carefully monitored but also for determining the level of transmission in a lineage of recipients.

8.3 Tumour histology in donor and recipients

When a neoplasia is known in the donor before the transplant or immediately after transplantation, histology can provide the histotype of the tumor and immunohistochemistry can help to identify a possible histogenesis. Therefore, if a kidney with a small papillary carcinoma (<4 cm) is transplanted and a few months after transplantation the graft shows a papillary neoplasia, histology can recognize the histotype and immunohistochemistry can help to identify the donor origin of the neoplasia. Similarly, the identification of a lung carcinoma in the donor during or immediately after transplantation needs a detailed investigation of the tumor (histological type and grade, immunohistochemical profile) and a careful follow up of the recipients. In the case of a tumor in one or more recipients transplanted with organs from this donor, the morphological comparison of the tumor in the donor and the tumor arising in the recipients can allow the recognition of the tumor origin.

8.4 Kariotype of donor and recipient

Several reports on transmitted malignancies of those reviewed in NOTIFY project have relied totally or partially on the investigation of a kariotype mismatch between the tumor cells with respect to that of the recipient for assessing attributability. This strategy is obviously limited to those cases where a gender mismatch exists between the donor and the recipient. Careful attention should be paid on the interpretation of results and accurate molecular diagnosis might be necessary as tumor cells might lose their kariotype and express a different one.(70) The interphase Fluorescence In Situ Hybridization (FISH) for sex chromosomes has been used in these situations.(44, 71)

8.5 Genetic testing of sample from cancer, eg HLA testing

Other strategies applied rely on genetic testing of the cancer compared to that of donor and recipient tissue. Different gene sequences and polymorphysims have been studied in the process of assessing attributability. The origin of the tumor can be identified by microsatellite analysis by PCR using different markers.(28, 41, 71) Paternity test by genomic allelotyping investigation is another reliable technique to verify attributability. This test permits the analysis of 16 highly polymorphic loci (with the AmpF/STR identifiler PCR amplification kit) for effective discrimination of donor/recipient tumor origin.(73)

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Adverse Outcomes Associated with Characteristics, Handling and Clinical Errors

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Summary

Each cell, tissue or organ (HCTO) allograft intended for transplantation, implantation, infusion or transfer has specific quality attributes and characteristics determined by anatomy and usual function. Handling activities that support the maintenance of desired efficacy or utility of the organ, tissue or cells can affect clinical outcome. When a gap exists or a step or process fails, a serious adverse event (SAE) or a serious adverse reaction (SAR) 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 HCTOs, but there are also general processes to which each HCTO is exposed that can affect outcome. This work group specifically addressed those SAE/SARs relating to the physical properties (characteristics) of organs, tissues and cells and to changes in the properties due to events surrounding procurement, storage and processing or other aspects that may alter viability or other physical or chemical properties desired. To maintain desired allograft characteristics, clinical utility, and availability for use, controls should be in place for steps involving:

- consent/authorization;
- donor screening, testing (including controls regarding the blood sample) and test kits;
- recovery, procurement or collection;
- preservation/processing (this can include qualification of materials, reagents, equipment and facilities as well as maintenance, where applicable, and validation of processes that incorporate process controls and/or verification of steps);
- storage, transport and distribution;
- selection for use and allocation (where applicable);
- preparation for use (or other final disposition);
- qualified personnel with sufficient training who are deemed competent; and
- documentation and maintenance of records for all the above.

Some allograft outcomes and risks are anticipated (expected) while some may be unanticipated (unexpected). Additionally, steps taken to report or notify are critical when an unexpected adverse outcome occurs (i.e. an SAE or SAR). There is value to collection, analysis, and sharing this type of information because there may not only be national or regional implications, but also concerns on an international scale. The process surrounding the handling of an allograft so it performs as expected involves careful development and execution of protocols. The well-being of living donors is also included in protocol development and evaluation.

This section, 'Characteristics, Handling and Clinical Errors', includes functions in the outline above and addresses hematopoietic progenitor/stem cells, ocular tissues, tissues other than ocular, organs, gametes and embryos.

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

Traditional (conventional) tissues transplanted include skin, bone with or without cartilage, musculoskeletal soft tissues, and cardiac and vascular tissue types. While these tissues can be gifts provided by deceased donors, some are also provided by living donors. Steps in allograft donor screening, tissue recovery and handling throughout production can be discovered to be the root cause of an SAR or SAE. Tissue allografts made available for transplantation that come from one donor can number a few to over 100, and these can be used to alleviate pain and/or restore function in as many recipients. Tissue risk reduction measures include: obtaining valid consent/authorization for donation; qualification of donors through standardized donor screening and testing; applying controls to recovery/procurement procedures; use of tissue treatment (processing) steps that reduce, eliminate, or inactivate contaminants; selecting equipment and materials that are qualified for their intended use; properly validating tissue culture methods and other procedural steps; establishing controls for tissue storage environments that are conducive to the tissue preservation method selected; establishing tissue tracking measures to be able to (quickly) trace each tissue allograft from the donation event through final use or other disposition; and, evidence of all steps taken are maintained via detailed recordkeeping. In the event that, after a thorough investigation, a tissue allograft is implicated to be the cause of a serious adverse reaction, all of these risk mitigation measures may need to be reviewed.

In the case of hematopoietic progenitor/stem cells (HPC), 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 HPC 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 HPC donation requires there to be an expectation for a high level of cell viability. There are specific critical aspects relating to the quality of banked HPCs 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. Dependant on the indication for use, the recipient may receive conditioning therapy prior to transplant, and immunosuppression afterwards.

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

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

As will be described in more detail later in this document there are quite a number of incidents that might fulfil the criteria above and it is of central importance that selection of incidents to be reported is organized in such a way that it can be readily managed by stakeholders (organ procurement organizations, organ exchange organizations, transplant centres).

A section deals with serious reactions resulting 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 will be discussed: 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, respectively as acute haemolytic reaction, transfusion associated GvHD (TA-GvHD) and transfusion associated circulatory overload (TACO). The extensive experience with these reactions taken from the haemovigilance literature is referenced.

1 Introduction

Data pertaining to corneal tissues were obtained from the Notify Group 4 Worksheet – Corneas (sheet Adverse Events), the Group 8 Master Worksheet for corneas and traditional (conventional) tissues, and the Worksheet from Group 9. Further literature searches contributed to some information pertaining to traditional (conventional) tissues.

2 Organs

2.1 General aspects

Organ transplantation has become an established worldwide practice, bringing immense benefit to patients with end-stage organ failure. With the improvement of the results of transplantation the use of human organs for transplantation has steadily increased during the last decades. Organ transplantation is currently the most cost-effective treatment for end-stage renal failure. For patients with end-stage failure of liver, lung and heart it is often the only available therapeutic option in a live-threatening situation.

The process of organ transplantation can be divided into several phases:

Consent/Donor screening (Donation) → Testing → Characterisation → Procurement → Preservation → Allocation → Transport → Transplantation / Disposal

These phases are not necessarily ordered in time sequence, as processes may run parallel or in different order. In the following section examples for events in each phase will be given.

In order to prevent overlap of this document with topics covered by Group 6 (infectious disease transmission), and Group 7 (Malignancy), it is suggested to distinguish several possible scenarios delineated in the following example:

Transmission of an infectious disease from a donor to a recipient can be a/an:

1. 'Estimated risk' taken by the transplant team as described above, in case there was no time to perform the necessary testing of the donor (organ) and it was decided to transplant the organ anyway because the clinical situation of the recipient was critical.
2. 'Product property' problem (Group 6) for example if:
   a. A test to identify the infectious disease was not done, although it should have been done according to existing operating procedure (OP) and could have been done in the time available;
   b. The test to identify the infectious disease was performed in an inappropriate way resulting in missing the diagnosis of an infection of the donor;
   c. The test result was not, or incorrectly, transmitted to the organ exchange organization and/or the recipient centre, etc.
3. All required tests were done according to existing OP but the diagnosis of the infection was nevertheless missed, because of an unknown/new infection not covered by the OP (Group 6, in case of a tumour Group 7).
4. Test result was known but ignored or not correctly included in the decision making process in the transplant centre (Group 6).

2.2 Specific events

Most of the following (categories of) events are not limited to one specific organ, but could occur with any of the vascularized organs transplanted (kidney, liver, pancreas, intestine, heart, lung). Therefore organ specific aspects are only mentioned were appropriate. The events are linked wherever possible to the different steps in the transplantation process based on but not limited to the examples given by group one:

2.2.1 Donation

Not asking for consent for the transplantation of a specific type of organ or not reporting the consent for transplantation to the organ exchange / allocation organization could result in the loss of this organ for transplantation. No such incident was entered in the database, indicating that this either never happens or it is difficult to identify this possible problem.

Incomplete collection of the patient clinical history might result in omitting specific test that otherwise could have prevented disease transmission (travel into areas where specific diseases are endemic (malaria) prior to becoming a donor). The same would be true for missing history of a tumour disease, etc.

2.2.2 Testing/Donor characterization

Typical examples for events falling into this phase of the transplant process are:

- Omission of a mandatory test according to the operational procedures (OP) of the organ procurement organization
- Test not performed according to standards resulting in:
  - Incorrect determination of donor blood group;
  - Wrong determination of HLA-typing;
  - False positive or negative crossmatch result;
  - Missing detecting of donor infection, tumour or other disease;
  - Etc..
- Wrong communication of test result, this can have the same impact as not performing or incorrectly performing the test.

All incidents of this category can have a severe impact on transplantation. The outcome of the transplant could be negatively affected, resulting in graft loss, disease transmission or even (immediate) patient death for example if an organ is transplanted to a blood group incompatible recipient.

Another result of the incidents listed above could be the allocation of the donor organ to a recipient that according to the allocation rules should not (yet) have received the donor organ thereby skipping another recipient. This change in allocation sequence could in the worst case result in the death of the skipped patient, if he does not receive a suitable donor organ in time.

A wrong test result can also lead to the loss of donor organs, for example if the donor was incorrectly identified as being HIV-positive and offering is stopped or no suitable recipient can be found.

2.2.3 Procurement

Incidents in this period of the transplant process can be categorized as follows:

- Inadequate perfusion of the donor organ with preservation fluid;
  - Long first warm ischemic time
  - Incomplete / inhomogeneous perfusion of the donor organ
- Technical problems during the surgical procedure;
  - Damage to the parenchyma of the donor organ
  - Damage to the vessels, ureter etc. of the donor organ
- Contamination of the donor organ during procurement.
- The events listed above might involve a single organ or several/all organs from one donor. They can potentially result in organ loss because the donor organ is not transplantable any more. Another consequence could be impaired results of the transplantation (including donor organ loss, transmission of disease or even death of the recipient).

2.2.4 Preservation

Organ preservation, procurement and transport are closely linked in several regards. Some of the interaction can be derived from the following examples. Preservation can be hampered at different stages of the transplant process. Incidents during the procurement procedure, e.g.:

- Wrong/contaminated preservation fluid;
- Incomplete/inhomogeneous perfusion of the donor organ (as. above);
- Inadequate temperature of the preservation fluid.

Other events related to preservation can be linked to the transport or the donor organ, e.g.:

- Rise in temperature of the donor organ due to different reasons like;
  - Technical problem with the transport box
  - Too long transport time/Not enough ice
- To low temperature resulting in freezing of the donor organ for example by to close contact of the donor organ with ice.

The above mentioned problems with preservation relate to cold organ preservation. With the recent increased interest and use of machine perfusion a whole new set of problems that are associated with the use of these devices have to be considered:

- Damage to the donor organ when connecting it to the preservation machine;
- Unintended disconnection of the donor organ with loss of preservation;
- Technical problems of the perfusion device resulting in inadequate perfusion of the organ etc..

2.2.5 Transport

Organizational problems of the transport can result in substantial prolongation of the ischemic time with the associated risks mentioned above. In case cold ischemic time gets too long, organ loss can occur even in case of adequate initial preservation.

Several other types of events related to organ transport have been reported, like:

- Problems with transport logistics;
  - Sending the donor organ to the wrong place (wrong city, hospital or department)
  - Delay of transport due to missing/wrong information of directly or indirectly responsible (security personal at the airport) persons in the transport chain)
  - Accidents in the transport chain
- Damage to the transport box resulting in contamination/warming up etc. of the donor organ;
- Missing crossmatch material etc. for testing at the recipient site;
- Mixing up of donor organs at the time of packing/wrong labelling.

All of the above mentioned events might result in organ loss, impaired function of the donor organ and/or disease transmission.

2.2.6 Allocation

Several of the problems described above can also result from wrong allocation. For example if testing is done incorrectly the organ of an HCV-positive donor might be allocated to a patient not suitable for such a donor organ. The same adverse event can result from incorrect allocation in spite of accurate donor information.

A structural mistake in the allocation algorithm used/programmed can entail systematic deviation from the intended allocation sequence. This might have an influence on (long-term) transplant outcome (for example of HLA-matching is not correctly considered in the allocation algorithm).

2.3 Reporting of serious adverse events and reactions

According to the EU directive *'serious adverse event'* (SAE) means any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that *might* lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity;

A *'serious adverse reaction'* (SAR) means an unintended response, including a communicable disease, in the living donor or in the recipient that *might* be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity.

This definition is very broad and includes not only events that did in fact result in serious adverse events or reactions but also all events that *might* have led to these events. Such a broad definition could easily result in a huge burden both for those parties, responsible for reporting SAE/SAR as well as the recipients of this information.

Losses of donor organs along the process of donation and transplantation imply indirect health risks to potential recipients due to the lost opportunities for transplantation. However, these losses may fall under the scope of a quality, but not of a safety management system. In the framework of the EFRETOS (European Framework for the Evaluation of Organ Transplants) project it was decided to limit the recommendations to those situations in which at least one patient has been exposed to a direct health risk derived from the donor or the process.

In a similar way it might be more appropriate to report incidents that are related to non-compliance to existing standards to a quality control system than to a vigilance system.

Other incidents might not have to be reported at all, if they occurred after careful assessment of the risk of organ donation and transplantation. There are situations in which the clinician weighs up a risk derived from the donor or the process of transplantation with the risk derived of not proceeding with the transplantation. Reporting such cases to a vigilance-system would generate a remarkable load of work. In order to avoid burdening professionals unnecessarily, the EFRETOS consortium decided not to consider such situations of risks known and taken by the clinician ('calculated risk') unless an unexpected (or expected to occur infrequently) serious adverse reaction appears in the recipient.

3 Composite Tissue Allografts (CTA)

With advances in surgery and immunosuppressive regimens, complex grafts can also be used in face, hand and uterine transplantation. In these cases the tissues share many of the features associated with organ transplantation in that they must be transplanted fresh, not preserved, used almost immediately after donation and the recipient requires lifelong immunosuppressive therapy. Currently no clear standards are established for these types of transplants as they are in most countries neither regulated nor identified as a 'tissue' or 'organ'. The approach taken in the 'organ' section above for the categorization and reporting of SAE and SAR might also be applicable for composite tissue allografts (CTA), because in many respects the procurement and transplantation procedures of CTAs are more similar to organs than to tissues. Note: CTAs may also be referred to as vascularized composite allografts (VCAs).

4 Tissues other than corneas

4.1 General Aspects

The allograft tissue types covered in this section include cardiac tissue, vascular tissue and various bony and soft tissue musculoskeletal tissues as well as skin and other tissues. Autologous tissue, such as parathyroid glands, bone skull flaps and skin, can also be collected and banked (handled) before re-implantation and are included.

The types of cardiac tissue allografts banked and used in transplantation include the aortic valve with conduit, pulmonary valve with conduit, ascending aorta, thoracic aorta, pulmonary artery, and small sections of each of these. The mitral valve can also be used but the complexity of the anatomy of this valve means use of this allograft is not common. Vascular tissues, such as greater saphenous veins, infra-renal aorta, iliac arteries, and the femoral arteries and veins, are also banked and used clinically. Musculoskeletal allograft tissue can include: bone, cartilage, osteochondral and osteoarticular grafts containing bone plus cartilage, meniscus with or without bone, and soft tissues such as tendons (with and without bone attached) and ligaments. Skin is a life-saving tissue used extensively in burns surgery but it can also be highly processed and supplied as a decellularized dermal matrix that is used for applications inside the body. There are numerous other tissues used in clinical applications; a non-exhaustive list includes the sural nerves, fascia lata, pericardium, dura mater, and amniotic membrane and many other innovative grafts (tissue engineered forms) can be applied in many types of surgery.

Maintaining the natural characteristics of a tissue may be desired by the surgeon in order to promote aspects required for clinical use, however, in some respects, maintenance of certain components in their natural state may not be ideal. For example, cardiovascular surgeons may use heart valves, cardiac conduits, or vessels and expect to be supplied with an elastic matrix that is durable, and has a smooth, non-thrombogenic surface since these are hallmarks of the successful functions of these tissues. Tissue banking professionals consider gentle handling and mild treatment as goals to retain these essential properties. Likewise, orthopedic surgeons expect the articulating surfaces of a joint allograft, or an osteochondral or osteoarticular allograft to have smooth cartilage covering a bony surface, or a smooth surface to the intervening meniscus, if supplied. Within the bone are bone marrow and blood cellular components as well as mesenchymal stem cells, small blood vessels and fats/lipids. There are bone elements at the matrix level that contain molecules important for the induction of new bone growth, and bone morphogenic proteins and collagen are also important components of the matrix, and there is an expectation these will promote a successful outcome for patients. Whilst the ability of a bone to sustain its graft strength and structure are desirable, in other regards the removal of marrow elements (e.g. blood, lipids) is also desirable because they are antigenic and the marrow can be contaminated by viruses or other transmissible agents. These elements can be removed by applying tissue processing methodologies.

Tissue handling, from recovery through processing, packaging labelling, storage and distribution, has evolved in many ways and, although steps to mitigate contamination and other risks have also evolved, the potential for errors to occur has exponentially increased. The SARS and SAEs reported below are examples of what can happen when gaps in protocols or other influences affect allograft quality.

4.2 SARs Associated with Tissue Handling or Characteristics (tissues other than ocular)

The relevant types of SARs (defined as an AR that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization) documented by the Notify working groups are summarised in the following table. Some occurred at the level of the end user/clinician.

Note: In Project Notify listings there appears to be mixed use of the terms 'adverse event' and 'adverse reaction'. This may be due to variation in definitions between countries. In this table the term 'reaction' is used where there was an actual impact on the recipient even if it is only because a graft was not available and the intended recipient was already anaesthetized.

Table 1. SARs Proven to Be Caused by Tissue Handling or Characteristics *(tissue other than ocular).*

Problem	When it was identified	Latency	Outcome; other information	Reference - Literature or other source (e.g. Project Notify (PN))
Heart valves				
Cracks in walls or valves	Just prior to use (at thaw/prep)	Months to years; time from cryopreservation to thawing for use (storage, distribution, preparation)	Can be repaired, used anyway, or not used and returned to tissue bank	Newman-Gage, et al, 1994 Strong, et al, 1996 Miller et al, 1990; PN number 2
Structural failure	After use	Months to years		Nowicki, et al, 2008
Valve Calcification	After use	Months to years		PN
Determined to be unusable due to excess tissue attachments, not used	Just prior to use (at thaw/prep)	Months to years; time from cryopreservation to thawing for use (storage, distribution, preparation)	Caused delay in patient treatment, loss of allograft	Internal tissue bank adverse incident report reported to PN
vascular conduit cracks	Just prior to use (at thaw/prep)	Months to years; time from cryopreservation to thawing for use (storage, distribution, preparation)		Internal tissue bank adverse incident report reported to PN number 24. Classified as reaction as OR repair time would lengthen anaesthetic time
Wrong size heart valve package opened by mistake resulting in loss of tissue graft	Just prior to use (at thaw/prep)	Months to years; time from cryopreservation to thawing for use (storage, distribution, preparation)	Delay in patient treatment and loss of graft	Reported by hospital to tissue bank
Bone				
Spongiose bone	After use	1 day post-op, presence of febricula	Oedema, face, chills, fever, asthenia	EUSTITE V&S, 2010
Cranium autograft failure	After use	Days to months post op	Inflammation, non-incorporation; Failure of function of autoclaved cranium autografts (skull flaps); Failure due to non-viable and mechanically and biologically impaired due to autoclaving.	EUSTITE V&S, 2010
Fractures of large bone grafts, osteochondrals	After use	(Not reported)	Stored frozen	Freidlaender et al, 1999; Strong, et al, 1996
Mislabelling of femur, left labelled as right	Just prior to use in OR	(Not reported)	Patient under anaesthesia without proper graft, operation had to be rescheduled	Internal tissue bank adverse incident report reported to PN
Only half as many bone chips in package as labelled	Just prior to use in OR	(Not reported)	Required delay to retrieve a second deposit; delay in patient treatment; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
Anatomic abnormality of meniscus graft	Just prior to use in OR	(Not reported)	Discarded, delay in patient treatment; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
meniscus fractured	Just prior to use in OR	(Not reported)	Discarded, delay in patient treatment; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN

Skin				
Cultured skin autograft failure	After use	2 weeks	Within 2 weeks of applying a sheet of autologous cultured, expanded skin, the site became inflamed and ulcerated. Uncertain cause. Possibility of recipient tissue reaction to residues of chemicals used during autologous skin culturing. Infection was not thought to be the cause.	EUSTITE V&S, 2010
Skin torn upon thawing and implanting	Just prior to use in OR	(Not reported)	Discarded; delay in patient treatment and loss of graft; reported by hospital to tissue bank	PN
Skin graft not measured properly and not acceptable	Just prior to use in OR	(Not reported)	Discarded; delay in patient treatment and loss of graft; reported by hospital to tissue bank	Internal tissue bank adverse incident report
Tendon and bone, meniscus				
ETO reaction - Freeze-dried ETO-treated bone-patellar ligament-bone graft	After use	Occurred over 4 year time span	Persistent intra-articular reaction; persistent synovial effusion with collagenous particulates and cellular inflammatory response, loss of graft	Jackson et al 1990 USA, Jackson DW, Am J Sports Med. 1990;18:1-10;
Tendon determined to be split upon opening package	Just prior to use in OR	(Not reported)	Discarded by surgeon; delay in patient treatment; reported by hospital to tissue bank	PN
Error in packaging with 2 menisci in one package	Just prior to use in OR	(Not reported)	One graft was discarded; loss of usable tissue; reported by hospital to tissue bank	Internal tissue bank adverse incident report
Tendon graft too small and too short	Just prior to use in OR	(Not reported)	Discarded by surgeon; delay in patient treatment; reported by hospital to tissue bank	Internal tissue bank adverse incident report
Bone on bone-tendon-bone graft fragile and poor quality	Just prior to use in OR	(Not reported)	Graft used but delay in surgery due to need for repair	Internal tissue bank adverse incident report
Reaction to preservatives				
DMSO hypersensitivity - cryopreserved allografts	After use	(Not reported)	Testing before and after grafting; No further details mentioned	Nelson, et al, 1994; Strong and Friedlaender, et al, 1996 Clin Ortho Relat Res; Friedlander and Strong et al 1999 Orthop Clin North Am
Cryopreserved tendon discarded due to odour	Just prior to use in OR	(Not reported)	Surgeon did not read the package insert and was unaware of expected odour due to DMSO. Delay in surgery and loss of graft; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
Immune response				
Antibody Response	After use	(Not reported)	Anti-HLA (no other details provided)	Nelson, et al, 1994; Strong and Friedlaender, et al, 1996 Clin Ortho Relat Res; Friedlander and Strong et al 1999 Orthop Clin North Am

Latex allergy	Just prior to use in OR	(Not reported)	No reaction because graft not implanted; surgeon wanted to know whether the allograft was 'latex-safe' because his patient is known to be allergic	No documented case in the literature for tissue implants; however, documented cases in kidney transplants; AORN recommends 'latex-free' tissue retrieval for implants dedicated to allergic patients. Stevens et al., 2004; see also: http://www.redorbit.com/news/science/413449/recommended_practices_for_surgical_tissue_banking/; USA & Canada
Tissue not specified. Quality, thawing, labeling and traceability issues				
Tissue determined to be of unacceptable quality by surgeon and discarded	Just prior to use in OR	(Not reported)	Delay in patient treatment and lost graft; reported by hospital to tissue bank	PN. PN classified this as SAE but as delay in patient treatment re-classified here as SAR
Loss of shipped tissue which when located, had thawed, and thus unusable	Before use	(Not reported)	Delay in patient treatment and loss of graft	Internal tissue bank adverse incident report reported to PN
Irradiated tissue discarded due to discoloration and odor	Just prior to use in OR	(Not reported)	Surgeon did not read the package insert and was unaware of the effects of irradiation on tissue appearance. Delay in surgery and loss of graft	Reported by hospital to tissue bank
Inability to identify recipient of tissue during recall	After use	(Not reported)	Contaminated tissue may have caused infection that could not be diagnosed in the recipient due to lack of records; Tissue Bank investigation	Internal tissue bank adverse incident report reported to PN
Poor graft quality made surgery more difficult	Upon use in OR	(Not reported)	Delay in patient treatment; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
Inner package label and outer package label not matched	Just prior to use in OR	(Not reported)	Delay in patient treatment, loss of graft; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
Staples on package instructions penetrated inner package.	Just prior to use in OR	(Not reported)	Delay in patient treatment; graft discarded due to potential contamination; reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
Brittle upon opening container	Just prior to use in OR (found at rehydration step)	(Not reported)	Delay in patient treatment proven, sometimes used anyway, sometimes returned	Miller et al, 1990;
Improper sizing of allograft resulting in surgeon discarding tissue	Just prior to use in OR	(Not reported)	Patient under anesthesia without proper graft Operating delay and loss of otherwise usable graft; Internal tissue bank adverse incident report. Seen on visual inspection Reported by hospital to tissue bank	Internal tissue bank adverse incident report reported to PN
Improper rehydration of bone graft resulted in graft fracture at time of implant	Just prior to use in OR	(Not reported)	Prolonged Operating time, surgeon had a backup; internal tissue bank adverse incident report	PN

Tendon graft mislabelled with improper expiration date and graft discarded at hospital	Just prior to use in OR	(Not reported)	Delay in patient treatment	Reported to PN
Broken bottle of bone graft	Just prior to use in OR	(Not reported)	Loss of inventory and delay in surgery	PN

4.2 Table 2: SAEs Proven to Involve Tissue Handling or Characteristics *(tissue other than ocular).*

Problem	How failure was recognized and "other information"	Where event recognized	Reference - Literature or other source (e.g. Project Notify (PN))
Bone			
Fractured graft	Visual	Tissue bank	Internal tissue bank adverse incident report The PN report does not indicate the type of allograft.
Package broken (type of graft not specified)	Visual; Requires replacement; graft could be contaminated.	(Not reported)	Internal tissue bank adverse incident report. Included as product property could be altered
Thawed graft	Visual (temperature indicator); Could be contaminated or graft integrity compromised	(Not reported)	Internal tissue bank adverse incident report
Positive microbial culture post graft release	Report; Potential graft contamination; Failure of QC release procedure	(Not reported)	AFSSAPS, Le rapport annuel Biovigilance 2009, France reported to PN
Package broken on massive bone graft	Visual; Potential graft contamination	(Not reported)	AFSSAPS, Le rapport annuel Biovigilance 2009,
Osteoma; Chondrosarcoma; lymphocytic lymphoma; Paget's disease; rheumatoid arthritis	Reports; Histological exam reports of femoral heads, tissue not placed in distributable inventory	Tissue bank	Palmer, et al., 1999
Decontaminated Achilles tendons were distributed as irradiated Achilles tendons	(Not reported); surgeon considers he is implanting irradiated tissue presumably it met criteria for release and was safe; Patient not reported as harmed	Tissue bank	EUSTITE Pilot Report reported to PN
Amniotic Membrane. Loss of significant quantity of amniotic membrane due to improper monitoring/storage.	Records; Possible loss of opportunity or delays in patient treatment	Tissue bank	EUSTITE Pilot Report reported to PN
Femoral Heads. Electrical power supply to storage freezer switched off by contractors. Some material disposed of.	Records; Possible loss of opportunity or delays in patient treatment	Tissue bank	EUSTITE Pilot Report reported to PN
Massive bone graft had rupture in freezer bag	Visual; occurred during thawing stage at transplant centre; No report of patient impact so reported here as SAE; Possible contamination of bone and infection of recipient	Hospital	EUSTITE Pilot Report reported to PN
Graft lost in hospital, Large osteochondral graft lost by FedEx, Tendon graft mislabelled with improper expiration date and graft discarded at hospital, Transplant record returned with tissue not used but not with tissue. Upon investigation, tissue used but no record made	Reports; Possible loss of opportunity; lost matching graft, possibility for lack of traceability	Hospital inventory manager discovery, Transportation service, Identified at Tissue bank	Reported to PN
Tendon returned from hospital with no refrigeration, graft discarded	Loss of inventory for a high demand tissue.	Tissue bank	PN
Vacuum pack tested and loss of vacuum determined, graft discarded	Visual; Potential contamination of graft due to air leakage	Hospital	PN

4.3 SAEs Associated with Tissue Handling or Characteristics (tissue other than ocular)

The relevant types of SAEs (defined as an AE that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity) documented by the Notify working groups are summarised in the following table. Some occurred at the level of the end user/clinician.

Note: Wherever a Project Notify report documented a delay to patient treatment as a consequence of the 'event' it has been re-classified as a 'reaction'.

4.4 Further reading

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5 Haematopoietic Progenitor/Stem Cells

5.1 Types of Hematopoietic progenitor cells

In the case of haematopoetic progenitor/stem cells (HPC) the donations may be from the patient (autologous), family members (related) or from unrelated donors (adult stem cell registry donors or umbilical cord blood bank). Donors are screened and tested according to donor evaluation criteria. The products are collected with or without an intermediate storage and then infused into recipients.

5.1.1 Autologous HPC

In the autologous setting the bone marrow or peripheral blood progenitor cells are collected and cryopreserved in advance of transplantation. The product is then thawed and infused after conditioning therapy. Some cord blood products may also be banked in a private/ autologous/ family setting. These products are 'owned' by the family and rarely used. Most 'autologous' clinical treatments thus far have occurred in families with an existing illness treatable by HSC transplant, primarily between siblings. If families select a private cord blood bank to hold the product temporarily, these may also be called 'autologous cord blood products' despite the related donor use. For the scope of this project, autologous products are not included. It is noteworthy, however, that some 'adverse events' related to product handling, storage and administration may be applicable to the autologous setting.

5.1.2 Allogeneic HPC

For allogeneic hematopoietic progenitor/stem cell transplantation, the donor may be either related or unrelated to the recipient. Related donors are family members and the donor/recipient details are often handled by the recipient's physician or treating facility. Family members are HLA typed and once a suitable match is found, the donors may donate the HPC as either bone marrow or mobilized peripheral blood progenitor cells. In the unrelated donor setting, the tissue matched recipient is identified from either an adult stem cell registry or a cord blood registry. HLA typing of adult donors (or cord blood products) are stored in a searchable database to facility identification of a potential match. For cord blood products, the registry database also includes details such as cell dose, viability and volume.

5.1.3 Bone marrow – HPC-M

Bone marrow is also called HPC-M and is obtained with the patient under some form of anaesthesia. The donor generally undergoes bone marrow collection until an amount close to a desired cell dose is reached, with a maximum amount cut off of 20ml/Kg of the donor's weight.

5.1.4 Peripheral blood stem cells (HPC-A)

Peripheral blood stem cells are also called peripheral blood progenitor cells or HPC, Apheresis. Donors are given pharmaceutical grade cytokines that 'mobilize' the stem cells from the marrow into the peripheral blood circulation. The cells are then collected by apheresis.

5.1.5 Umbilical cord blood products (HPC-C)

Cord blood products, or HPC-Cord blood, are collected at birth and would normally be discarded. As previously mentioned, this project is limited to publicly banked cord blood products. The 'donor' is the biological mother for the purposes of infectious disease screening, testing and consent. The product is collected immediately via the umbilical cord blood vein. It is shipped to a cord blood bank where it is processed for cryopreservation and storage until needed.

5.1.6 Other Cell Products

The nature of cellular therapy is such that potential applications are expanding almost daily. Other products may be therapeutic and are called 'therapeutic cells'. Examples include donor lymphocytes, mesenchymal stem cells, pancreatic islet cells and other novel therapies. Donor lymphocyte infusions (called DLI or TC-T for Therapeutic Cells, T-cells) are collected by apheresis from the original HPC donor. These products are generally nonmobilized and can be used for several reasons including to induce remission during relapse from a hematologic malignancy. The other cells types have been used less clinically and therefore, adverse events and reactions are protocol specific and less reported.

5.2 Sourcing and Recovery

Most of the events related to the product properties surrounding recovery or collection of the product fall into one of these categories: a) donor infectious disease transmission potential b) microbial contamination during the collection process and c) inadequate cell count, progenitor cell content or volume. Products for HSC transplantation are generally 'dosed' at either a target or minimal level of a desired cell type (nucleated cells or CD34+ cells). CD34 is a surrogate marker for progenitor cells and represents a subpopulation of nucleated cells in the product. In the cord blood setting, the birth mother serves as the surrogate for infectious disease screening and testing. Cord blood products must meet minimal quality specifications before the units can be banked and approximately one third of the cord blood units collected for public banking fail to meet these minimal requirements, leading to their discard or donation for research. Peripheral blood stem cell collection is normally limited to collection by apheresis that occurs over two days, even if the desired dose may not be reached. Product samples are generally collected partway through the collection process so that a final target volume is calculated. Not all products meet the target requirements and errors in cell counting or calculations are possible owing to human error. All cellular products are collected into an anticoagulant and failure to mix properly can result in a clotted or unusable product.

5.3 Processing and Storage

HSC products may be infused fresh or cryopreserved and stored for potential use at a later time as previously described. Whether to be cryopreserved or not, products are transported to a laboratory where test samples are removed for assays such as cell count, microbial testing, ABO typing for confirmation, viability assessment and volume de-

termination. These procedures are generally performed inside a biologic safety cabinet (BSC) using good aseptic processing techniques. The following events have been reported in the literature upon initial receipt:

- Product mix-up and mislabelling
- Positive sterility results indicating contamination
- Miscalculation of cell dose or volume

HPC-M and HPC-A products with positive sterility tests are often infused by the time the test result is known or issues with a declaration of urgent need/deviation/medical exception. HPC-C products with positive sterility results would not meet specifications for public banking or would be designated as such in the registry.

Products undergoing subsequent processing are subjected to additional manipulations. These manipulations may include procedures to remove tumour cells or other certain cell populations (such as T cells), volume reduction, red blood cell removal or plasma removal. Some products including therapeutic cells may be cultured and expanded *in vitro*. Products which are cryopreserved are mixed with a preservative solution, most commonly 5-10% dimethylsulfoxide (DMSO). Reported adverse reactions include allergic reactions to DMSO and constitutional symptoms, which often increase in severity as volume increases. Reactions to other materials or reagents used in processing are also possible as are events associated with human error. Potentials for human error include incorrectly performing a specific procedure, resulting in progenitor cell loss or damaged or contaminated product; incorrect measurement of a test article or calculation resulting in incorrect product dosing or a near miss; and product mix-up and contamination.

Cryopreserved products are stored in temperatures below -90C and most commonly in the vapour phase or liquid phase of liquid nitrogen. Events include external/environmental events such as fire, flood, theft and power failure. Internal events include accidents such as nitrogen overfill, running out (dry tank) or dropped or damaged product. Products are stored in specially designed storage bags (and less often vials). These containers are brittle and break easily upon impact. Products are thawed rapidly at 37C either in the laboratory or adjacent to patient care area and infused immediately into the recipient's IV line. Progenitor cells eventually home to the marrow space and engraftment occurs in 10-30 days depending on product type, preparative regimen and cell dosing.

5.4 Administration

As previously described, both non-cryopreserved and cryopreserved products are handled by humans, transported (fresh or thawed) and infused. Potential events include administration with an incorrect solution, product mix up, contamination or container incident (spill, leak, puncture, bag breakage). Results of infectious disease screening and testing should be complete before product is administered. Events related to the latter component include incomplete or incorrect test results, transcription errors and incorrect labelling of high-risk product or missing informed recipient consent when applicable.

5.5 Events in common

All HSC products undergo some degree of transport, whether down a corridor or across international borders. Test samples are removed for product assessment and dose calculations and final release criteria must be met before a product is released for infusion. At any point during the spectrum of steps from collection to infusion (administration), a handling, storage or human error could occur. Reported examples include product mix-up and mislabelling, loss or damage during shipment and equipment failure or malfunction. Since these products are selected based on tissue typing, an acceptable back up product may not be suitable or available.

The previous descriptions serve as a background and snapshot of HPC collection, processing and infusion. HPC products are generally administered as part of stem cell transplant (SCT). This procedure carries significant morbidity due to the recipient's clinical situation, disease status, preparative regimen by chemotherapy and/or radiation, and duration of immunocompromised condition. Thus, a consensus was reached at the February 7, 2011 meeting that those reactions and events which are expected to occur in the transplant setting should be excluded from the V&S system unless they are life threatening. Examples include dimethylsulfoxide (DMSO) toxicity, constitutional symptoms, etc. The rationale was that common, transient reactions would inundate the system with somewhat useless data and possibly obscure important and more rare reactions and events. Issues related to the biology of the disease and efficacy such as graft versus host disease (GVHD) should not be captured by the system. If an adverse event occurred, such as product mix-up (i.e., a patient received the wrong product), that would be reported.

5.6 HPC Donors

For donors of HPC products, the following serious adverse reactions are expected to be reported:

- Reactions related to donation that are life threatening or fatal;
- Unexpected or serious reactions (e.g., bleeding from the spleen); and
- Significantly debilitating reactions.

Expected events (e.g., nausea, pain) should NOT be reported unless life-threatening or fatal.

It was group consensus that long-term follow up through adult registries was essential and donor follow up should be performed at a minimum of one, five and ten years. The follow up and reporting should include donor malignancies and autoimmune diseases for mobilized donors. Regarding related donors, the incidence of malignancy may be increased above the general population due to motivational factors that bias donors to donate HPC products and due to familial/genetic predisposition. Routine and expected donor reactions such as headache and bone pain would not be reported.

5.7 HPC Recipients

The consensus was that immediate reactions that occur within 24 hours of product infusion that are unexpected or life threatening should be reported. As previously mentioned, DMSO toxicity (e.g., hives, flushing, transient bradycardia, etc.) would not be reported. However, life-threatening anaphylaxis would be reported. Avoidable, serious adverse events associated with the infusion of the incorrect product, near misses such as 'wrong product thawed,' and events related to processing error during manufacture and storage of the product would also be reported. Other examples include, but are not limited to, clinically significant human errors, transportation errors, and equipment failures that result in the damage or loss of product. Regarding microbial contamination, the system should capture those reactions and events that are probably or definitely related to disease transmission by the product. Untreated sepsis that is serious and related to transmission by the product would be reported as SCT patients are routinely place on antibiotics during the transplant procedure and untreated sepsis is avoidable. Unexpected infectious diseases having a high probability that the source was the donor or product would be reported.

For long term follow up, all donor-derived malignancies (i.e. malignancies that develop from donor cells but no malignancy is present in the donor) would be reported. In this regard, unexpected CMV transmission and EBV related PTLD would be excluded from reporting since this is a common occurrence. Donor-transmitted malignancy (i.e. malignancy present in donor at time of donation) would be reported as well as genetic changes of donor origin.

Table 3: Summary of Events by Category.

Table 3.1 Product Administration Events.

Event	Symptom	Confirmation	Treatment/ Prevention	References
Incompatible plasma transfusion	Hematuria			Shanwell, et al 1991;
Wrong unit infused / product mix-up	Ranges from selecting less desirable back up to non-engraftment/ GVHD; Wrong UCB unit shipped	ABO did not match record; HLA typing did not match record	Class I HLA typing on cryopreserved units prior to infusion	McCullogh, McKenna, et al 2009.
Haemolytic reaction (ABO mismatch)	Red cell aplasia fulminant haemolysis and acute renal failure	ABO type on product does not match donor		Cockerill, et al, 1989; Labar, et al, 1992; Mueller, et al, 2006; Curtin and Schwarer, 2005; Lopez, et al, 1998; Worel, et al, 2003;
Allergic reaction (DMSO)	Fever; back pain; tachycardia; shock; haemoglobinemia; haemoglobinuria Red cell aplasia fulminant haemolysis and acute renal failure	ABO incompatibile red cells in product		Cockerill, et al, 1989; Labar, et al, 1992; Mueller, et al, 2006; Curtin and Schwarer, 2005; Lopez, et al, 1998; Worel, et al, 2003; TRIP annual report 2009, Tissue vigilance
Allergic reactions other than DMSO	Flushing; pruritis; urticaria; wheezing; nausea; fever, vomiting, high or low BP, chest pain	Large volume, high percentage of DMSO in the final product, not washed post thaw, patient sensitivity?	Administer antihistamine; infuse product more slowly if possible or space bags apart during administration; consider washing (cell loss may prevent this)	EUSTITE V&S, 2010
	Mild or severe: hives, urticaria; wheezing; rash; pruritis; bronchospasm; hypoxemia; hypotension	Reaction during or within minutes after infusion in absence of other causes		Internal facility reports; anecdotal

Table 3.2 Product Transport Events.

Event	Symptom	Confirmation	Treatment/ Prevention	References
Delayed or lost in transit (failure to engraft)	Flight diverted/delayed. Courier lost units	Arrive 8 days later at TC		EUSTITE Pilot
Improper storage conditions	Product stored short term or transported at incorrect temperatures	Upon discovery		Internal reports of centers; anecdotal
Improper transport conditions				EUSTITE Pilot

Table 3.3 Product Specific Events.

Event	Symptom	Confirmation	Treatment/ Prevention	References
Product clotted		Discovered at TC		EUSTITE Pilot
Unlicensed collection facility	Missing appropriate registration/license/ controls			EUSTITE Pilot
Incomplete ID testing/ transcription error	ID testing result error discovered; Positive recorded as negative test result			EUSTITE Pilot
Donor malignancy discovered during collection	Increased B cells during collection	Diagnosed as hairy cell leukemia	N/A	EUSTITE Pilot
Product contamination during storage	Bacterial or viral infection from product (source)	Lookback identified single source patient and contaminated LN2	Process controls; sterility results prior to release; double bagging in liquid; store in vapor phase	Hawkins et al 1996 + Tedder et al 1995; Mele, et al, 2005;

Key: ID = Infectious disease TC = Transplant centre LN2 = Liquid nitrogen N/A = Not applicable DMSO = Dimethylsulfoxide
BP = Blood pressure

5.8 General comments

It was confirmed that the system would capture certain events related to the biology of SCT such as efficacy issues causing non-engraftment (e.g., low viability, clotted sample, etc.). Clinicians should specifically be encouraged to report anything in their clinical judgment that is unexpected and life threatening or fatal, or results in significant disability. Specific attention should be paid to how the data are analysed at the national and international level to ensure optimal utility of the V&S system.

5.9 References

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6 The Cornea

The human cornea is an avascular tissue, approximately 0.5-mm (centrally) and 1-mm (peripherally) thick, which is highly specialized to refract and transmit light. It is delimited externally by a squamous, non-keratinized epithelium, which rests on a homogenous stroma relatively poor in water. The inner monolayer of exagonal cells, forming a regular mosaic and bordering the aqueous humor of the anterior chamber of the eye, is termed endothelium.

Human corneal endothelium has virtually no mitotic activity and consequently the cell number decreases with age. Despite this loss of endothelial cells, corneal thickness and transparency are maintained. It is only when cell number and viability are drastically reduced that the cornea swells and corneal decompensation occurs.

6.1 Events and reactions related to cornea transplantation

In this review we collected events linked to organizational or structural dysfunctions of the tissue establishment, which caused a significant loss of product. We also documented events or reactions linked to

intrinsic property of the product and related to its recovery, processing (evaluation, storage), and distribution, as defined above.

1. Procurement of cornea without adequate consent

The retrieval of tissues without appropriate consent/authorization by the donor's relatives can be considered an Unlikely Event. The typical alerting signal can come from the hospital's staff, or the chart review in the eye bank. It may produce a moderate impact on system, if not managed with a proper communication with the family. Calls for an educational intervention on the procurement's staff.

2. Corneas transported to eye bank but information not communicated in time so corneas kept beyond specified limit before being received into eye bank

Loss of tissue results from problems in the logistical organization. Typical alerting signal: chart review in the eye bank. Unlikely event, no effect on individuals. Calls for an educational intervention on the eye bank's staff.

3. No transport medium available for cornea

This event produced a loss of suitable corneal tissues because of lack of OC transport medium. The typical alerting signal should come from the storehouse records. An appropriate supplier management (as defined by the ISO quality management system), or planning of the production (in case of the in-house preparation of media) should prevent its recurrence. Can be considered Unlikely and of Minor/ Moderate impact, depending on the amount of lost tissues, and on the effect on the surgery schedule (interventions could have been cancelled because of the event).

4. Detection of a failure in the sterilization process of rubber stoppers for cornea vials

Typical alerting signal: the indicator for sterilization did not changed in colour and was inspected after some corneas had already been released. Tissues had to be recalled and re-tested. One tissue was already transplanted, so this is a typical event in which inappropriate tissues were distributed for clinical use. The transplanted tissue may increase the risk of infection (keratitis, endophthalmitis) after corneal transplantation, even though the correlation between a positive microbiology and post-operative infection is poor. Follow up of recipient was necessary. Unlikely/Possible event, no effect on individuals. Calls for an educational intervention on the eye bank's staff.

5. Problems in the temperature during transportation

Typical alerting signal: graft failure (defined as: presence of a diffusely oedematous penetrating corneal graft on the first postoperative day, failure of the cloudy graft to clear at any time postoperatively). Imputability certain if the problem in the temperature has been established. Unlikely, Serious reaction, in which inappropriate tissues were distributed and transplanted. Moderate effect on recipient (needs a re-graft). Calls for a control in the transportation procedures.

6. Primary graft failure

Typical alerting signal: presence of a diffusely oedematous penetrating corneal graft on the first postoperative day, failure of the cloudy graft to clear at any time postoperatively, lack of an identifiable cause of corneal graft failure. Imputability sometimes difficult to ascertain. Unlikely, Serious reaction, may be due to distribution and transplantation of inappropriate tissues. Moderate effect on recipient (needs a re-graft). Calls for a control of the mate tissue, and a double check in the tissue selection procedures.

7. Late endothelial failure

Typical alerting signal: progressive graft oedema, no apparent cause, unresponsiveness to corticosteroids, no recent history of a rejection episode. Primary cause of graft failure after the first 5 postoperative years. Accounts for over 90% of failures between 5 and 10 years after PK. Can be elicited by complications during follow up (previous ocular hypertension, rejection episodes, etc). Imputability difficult to ascertain. Serious reaction, may be due to distribution and transplantation of inappropriate tissues. Moderate effect on recipient (needs a re-graft).

8. Evidence suggestive of donor corneal dystrophy after transplantation

Evidence of guttae in the donor cornea during the early post-operative period, could have been missed by the eye bank. Typical alerting signal: can be detected either by specular microscopy or slit lamp examination. May increase the risk for late graft failure. Imputability may be difficult to ascertain. Unlikely/Possible event, inappropriate tissues could be distributed and transplanted. No effect on individuals. Calls for an educational intervention on the eye bank's staff.

9. Evidence suggestive of prior refractive surgery in the transplanted cornea

The use of corneal tissues from donors previously operated with laser intrastromal keratomileusis (LASIK), photorefractive keratectomy (PRK) may result in significant ametropia and anisometropia, abnormal anterior curvature, abnormal low thickness following penetrating keratoplasty. Typical alerting signal can be the following evidences in the transplanted corneas: central, mild scar in the anterior stroma, an interface, abnormal ametropia and/or anisometropia, abnormally low thickness, abnormal anterior corneal curvature. Imputability certain in the presence of objective findings, may be confirmed by a thorough donor history. Unlikely Reaction, Minor impact on recipient. Calls for a control of the mate tissue, and a double check in the tissue selection procedures.

10. Lymphoma found in donor by pathology after cornea had been transplanted

Typical alerting signal: evidence in the donor's history, previously neglected by the procurement staff. Typical event in which inappropriate tissues were distributed and transplanted. The transplanted tissue may increase the risk of transmission of malignancies via corneal transplantation. Follow up of recipient is necessary. Unlikely event, no effect on individuals. Calls for an educational intervention on the procurement and eye bank's staff.

11. Donor not tested for MAT although donor history showed residence in malarial area

Typical alerting signal: evidence in the donor's history has been neglected by the procurement staff. Typical event in which inappropriate tissues can be distributed and transplanted. The transplanted tissue may increase the risk of transmission of malaria via corneal transplantation. Follow up of recipient is necessary. Rare event, no effect on individuals. Calls for an educational intervention on the procurement and eye bank's staff.

12. Weak positive serological test result for HBsAg in donor. Previously negative in another lab

Typical alerting signal: evidence in the donor's screening tests. Typical event in which inappropriate tissues can be distributed and transplanted. The transplanted tissue may increase the risk of transmission of HBV via corneal transplantation. Follow up of recipient is necessary. Rare event. Transmission of HBV via corneal transplantation has been documented. Calls for an educational intervention on the eye bank's staff.

13. Evidence of microbiologic growth in 2 de-swelling medias from same batch contaminated with Pseudomonas aeruginosa

Typical alerting signal: microbiologic test performed in the eye bank or microbiology laboratory. Only loss of media if the solutions have not been used for tissues. Loss of tissues if used for de-swelling and transportation. Storage. Can be considered a Rare event of Minor impact, depending on the amount of lost tissues, and on the effect on the surgery schedule (interventions could have been cancelled because of the event).

14. Evidence of microbiologic growth in the donor cornea during storage, before the tissue is released

Typical alerting signal: laboratory finding of positive microbiologic culture of media samples during corneal storage. No event, no reaction, the tissue can be disposed by the eye bank before being released, part of the conventional eye bank procedure.

15. Evidence of microbiologic growth in the donor cornea after the tissue is released, before it is transplanted

Typical alerting signal: laboratory finding of positive microbiologic culture of media samples after the corneal storage, in the last medium sample taken before the tissue is dispatched. Event, no reaction, the tissue can be recalled before being transplanted. Can be considered a Possible event of Minor impact, depending on the effect on the surgery schedule (the intervention must be cancelled unless the eye bank can provide another tissue).

16. Evidence of microbiologic growth in the donor cornea after the tissue is transplanted

Typical alerting signal: laboratory finding of positive microbiologic culture of any media samples taken during or at the end of the corneal storage. Possible event which may increase the risk of infection (keratitis, endophthalmitis) after corneal transplantation. The correlation between a positive microbiology and post-operative infection is poor. Follow up of recipient is advised. Calls for a control of the mate tissue.

17. Surgeon returned cornea to eye bank as cornea appeared hazy with numerous stromal folds suggesting oedema and poor endothelial function

Typical alerting signal: communication from the surgeon. Can be considered a Possible event of Minor impact, depending on the effect on the surgery schedule (the intervention must be cancelled unless the eye bank can provide another tissue).

18. Donor cornea with characteristics not suitable for the ultimate use

Typical alerting signal is a communication from the surgeon about evidences of: a poor *in situ* inspection before retrieval, inadequate recovery technique, irregular or insufficient scleral rim, uveal tissue or lens residues, a contact lens still present, precut corneal lenticule sent for Lamellar Keratoplasty of inadequate thickness or diameter. Can be considered a Possible/likely event of Minor impact, depending on the effect on the surgery schedule (the intervention must be cancelled unless the eye bank can provide another tissue).

6.2 Conclusions

Identification of reportable Serious Adverse Events, attributable to the donor tissues characteristics, could be found in the whole process of donation, eye banking and transplantation of corneas.

The recent evolutions of corneal transplantation have increase the involvement and responsibility of eye banks in the preparation of suitable tissues for keratoplasty. Sound validation procedures, good communication between eye banks and surgeons, and a reliable reporting system are essential in order to identify trends and opportunities for process improvement.

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7 Gametes and embryos

7.1 General

European Directive 2006/86/EC indicates that in the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered to be a serious adverse event.

It is proposed, in line with the recommendations of the EU SOHO V&S project recommendations, that in addition, the definition of SAE should include the total loss of germinal tissues, gametes or embryos. Gametes and embryos are particularly susceptible to unsuitable temperature, humidity, osmolarity or PH and to exposure to toxic substances.

Serious adverse events leading to complete loss of gametes and embryos can happen in the different phases of an assisted reproductive technology technique: procurement (oocyte and semen collection), manipulation in the different ART phases, preservation in the incubator, cryopreservation and thawing of gametes and embryos, and manipulation before embryo transfer.

7.2 Recorded SAEs

The following events have been described:

- Damage to gametes and embryos due to inappropriate freezing technique;
- Loss or damage to stored gametes and embryos due to e.g. equipment failure (controlled rate freezer, storage vessel, vapour refrigerator, dry shipper failure) or failure of electric power supply;
- Damage due to warming / premature thaw of gametes and embryos during audit of the cryobank;
- Missing gametes and embryos due to: loss or misreading of labels, loss of straws due to floating, failure to keep accurate records;
- Damage to samples due to failure of containment and contamination risk;
- Loss of any irreplaceable gamete or embryo or gonadal tissues (equipment failure, culture infection);
- Loss of any irreplaceable gamete or embryo or gonadal tissue due to inappropriate handling.

7.3 Recommendations

When a couple loses the chance of pregnancy because gametes or embryos were rendered non-viable due to one of these factors, it should be reported as a serious adverse event.

When a mix-up results in the wrong embryo being implanted in a patient or the wrong sperm being used to fertilise an egg, these incidents should also be reported as serious adverse events.

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8 Reactions resulting from errors/ inadequate procedures at the level of the clinical user

8.1 Introduction

This section addresses serious reactions resulting from errors/inadequate procedures at the level of the clinical user as opposed to reactions due to product-related causes.

For organ transplantation, a few problems at the transplant centre are explored and for tissues other than corneas, examples are provided in tables above.

Three types of serious reactions are discussed for HPCs: acute haemolytic reaction, Graft versus Host Disease (GvHD) and circulatory overload associated with the transfusion of cells (HPCs). All three are known from Haemovigilance, respectively as acute haemolytic reaction, transfusion associated GvHD (TA-GvHD) and transfusion associated circulatory overload (TACO). The first two reactions (acute haemolytic reaction and TA-GvHD) are certainly not always due to errors or inadequate procedures but may also be a calculated risk of the transplantation. So it needs special vigilance to detect and careful investigation to categorize them as being due to errors or inadequate procedures.

8.2 Organ transplantation

Events at the level of the transplant centre can include problems related to:

- Acceptance of a donor organ based on incorrect or misunderstood information (available donor information not correctly evaluated or logistical problems occurring inside the transplant hospital.
- Surgical problems resulting in prolongation of cold and/or warm ischemic time, contamination of the donor organ, other damage to the donor organ etc.

8.3 HPCs

8.3.1 Acute haemolytic reactions

A haemolytic reaction due to tissue transplantation is one in which symptoms and clinical and laboratory signs of increased red cell destruction are produced by transplantation of organs or transfusion of hematopoietic cells. Haemolysis can occur intravascularly or extravascularly and can be acute (immediate) or delayed. Acute (immediate)

and delayed are defined as respectively occurring < 24 hours or > 24 hours after transplantation/transfusion.

In this chapter we will only discuss acute haemolytic reactions due to ABO-incompatibility because they are the most common serious haemolytic reactions following transplantation of organs or HPCs. These may be defined as: all serious acute haemolytic reactions where an organ or tissue was transplanted or transfused which was ABO incompatible.

These reactions may occur if an ABO incompatible organ or tissue was transplanted or transfused

- Unintentionally, or
- not according to the existing procedures, or
- in the absence of an adequate procedure.

Early detection and prevention

Common signs are

– Fever
– Chills/rigors
– Facial flushing
– Chest pain
– Abdominal pain
– Back/flank pain
– Nausea/vomiting
– Diarrhoea
– Hypotension
– Pallor
– Oligoanuria
– Diffuse bleeding
– Dark urine

Common laboratory features are

– Haemoglobinemia
– Haemoglobinuria
– Decreased serum haptoglobin
– Unconjugated hyperbilirubinemia
– Increased LDH an AST levels
– Decreased haemoglobin levels

Not all clinical or laboratory features are present in cases of an acute haemolytic reaction (conform to ISBT definitions of transfusion reactions).

Prevention

– procedures for checking that the right product is given to the right patient;
– procedures for slower transfusion or transfusion in 2 aliquots/2 days of ABO-incompatible HPCs.

Immediate steps for index patient

– stop transfusion (if still applicable);
– perform administrative checks (ABO patient and product);
– take blood samples for haemolysis investigation, renal function tests and DIS, and repeat compatibility testing. Test urine for Hb;
– control blood pressure and diuresis (> 100 ml/hour), iv fluids, consider furosemide, dopamine.

Immediate steps to prevent reactions in other recipients

– consider identification or administrative error and warn the tissue establishment that has issued the product if a possibility exists that another ABO-incompatible product may be administered to another patient.

Further investigation

– investigations are usually sufficient to establish the cause or exclude acute haemolysis and/or ABO-incompatibility.
– depending on the error identified (e.g., incorrect product transfused, no adherence to procedures or no adequate procedures) further analysis may be needed to improve the quality of the clinical part of the transplantation chain.

8.3.2 Transfusion Associated Graft versus Host Disease (TA-GvHD)

GVHD is a clinical syndrome characterised by symptoms of fever, rash, liver dysfunction, diarrhoea, pancytopenia and findings of characteristic histological appearances on biopsy that may occur after transplantation of HPCs. TA-GvHD very rarely occurs 1-6 weeks following transfusion and should be reported when the cause was due to infusion of the wrong product (i.e., use of non-irradiated product when irradiated product was indicated). . GvHD is caused by T lymphocytes and NK cells from the graft attacking organs and tissues of the (immunodeficient /compromised) recipient (host). GvHD may also occur due to an identification error or inadequate identification procedure..

1) Early symptoms and signs: see above
2) Prevention: procedures for checking that the right product is given to the right patient

Immediate steps

– To prevent reaction in other patients: warn the tissue establishment that has issued the product if a possibility exists that an 'incorrect' product may be administered to another patient.

Further investigation

– Biopsy of affected organ(s): identification of donor lymphocytes

8.3.3 Circulatory overload associated with the transfusion of cells

We know this reaction also from haemovigilance where it is called transfusion associated circulatory overload (TACO). Circulatory overload may occur associated with the transfusion of HPCs. Like TACO, a circulatory overload associated with the transfusion of other cells is characterized by any four of the following:

- Acute respiratory distress
- Tachycardia
- Increased blood pressure
- Acute or worsening pulmonary oedema on frontal chest radiograph
- Evidence of positive fluid balance occurring within 6 hours of completion of transfusion.

Early detection and prevention

– Early signs and symptoms: see above. An elevated BNP is supportive of TACO

Prevention

– slow infusion and diuretics (furosemide) when large volume HPC products are given to patients with decreased cardiac function.

Immediate steps

– for index patient: administration of furosemide

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Adverse Reactions in Donors

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1 Donor Reactions – Hematopoietic Progenitor Cells

Dennis L. Confer

1.1 Introduction

Living donors provide an estimated 25 - 30,000 HPC products annually for use in related- and unrelated-donor allogeneic hematopoietic cell transplantation (HCT) (1, 2). These are donations of bone marrow (HPC, Marrow or HPC(M)) and peripheral blood stem cells (HPC, Apheresis or HPC(A)). Not included in these numbers are an estimated 200,000 newborn infants whose umbilical cord blood (HPC, Cord Blood) is collected and evaluated for potential storage in public cord blood banks (2). Adverse reactions (AR) and serious adverse reactions (SAR) are not known to occur among cord blood donors, so they have been excluded from this report. Also excluded from this report are autologous HPC donations.

Today, HPC(M) donations from children and adults are much less frequent than HPC(A) donations, which comprise about 80% of the total. Preparation for HPC(A) donation almost always involves mobilization of HPC from the bone marrow space into the peripheral blood stream through administration of a mobilization agent. Most often the mobilizing agents are filgrastim or lenograstim administered subcutaneously, once or twice daily for 4 to 5 days prior to apheresis (3). Biosimilars of these mobilizing agents are entering some markets, but experience with them is very limited. Plerixifor is a recently developed agent that mobilizes cells by blocking CXCR4 binding receptors on HPC (4-6). Experience with dosing and administration-scheduling of plerixifor in allogeneic HPC donation is also very limited.

After an appropriate duration and dose of the mobilizing agent has been administered, HPC(A) are collected by apheresis, which is most commonly performed as a single procedure processing 3-5 blood volumes over a period of several hours (3). Occasionally a second apheresis procedure is performed on the following day, either by design or because of low HPC yield from the first procedure. A third or fourth apheresis collection from allogeneic donors is rare.

HPC(M) products are almost always collected in surgical suites with donors having received general or regional (epidural or spinal) anaesthesia (7-10). Red cell transfusion with autologous or allogeneic products is common. In some countries the standard of care for HPC(M) donors is hospitalization for 1 or 2 days, but in many others 'day surgery' without overnight hospitalization is the usual practice.

Allogeneic HPC donations by children are common in the related donor setting. The use of children as HPC donors has been the subject of ethical discussions and occasional controversies (11-13). The wisdom and safety of HPC(A) donation by children has been debated, but it appears these donations are safe (14-16).

1.2 Therapeutic Cells (TC)

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 AR among TC donors (17, 18). The most common procedure for TC donation is unstimulated leukapheresis and thus similar to apheresis procedures for platelet or red cell donation. Considerable information exists on the risks of these unstimulated apheresis procedures. A detailed review of AR in unstimulated apheresis donors was deemed to be beyond the scope of this investigation.

1.3 Sources of Information

Project Notify: Groups 1-5. Substance-specific Groups 1 – 5, Organ, Tissues (other than ocular), HPC, Ocular Tissues, and Gametes and Embryos, respectively, conducted reference collection activities that produced more than 850 references. Of these, 55, mostly concerning HPC donors, were identified as related to Group 10. These references were reviewed and a handful was removed because they contained no information on donor experiences.

Literature search. Additional searches of the literature, specific to HPC donors, were conducted using Ovid Medline and Science Citation Index. These searches produced about 100 additional relevant publications. The final database of 193 references includes over 150 concerning HPC donors.

World Marrow Donor Association (WMDA). The WMDA is an international association of HCT unrelated donor registries and public cord blood banks. Seventy-six registries and 132 cord blood banks participate with WMDA, which provides a forum for international information exchange and collaboration. Among its activities, WMDA promulgates standards, provides for registry accreditation, conducts annual surveys of registry/cord blood bank activities, and maintains a registry of unrelated-donor SAR, termed the Serious Events and Adverse Reactions Registry (SEAR). SEAR was established in 2001 and suffered from underreporting during its early years. This has improved, however, with 126 reports filed in calendar year 2010 when total donations were estimated to exceed 12,300 (2, 19). A second registry, SPEAR (Serious Product Events and Adverse Reactions Registry), is also maintained for product-specific issues. The WMDA SEAR was reviewed to identify SAR reported by the registries. In some instances, rare events might also have been reported in peer-reviewed publications, which will confound efforts to accurately determine the total number of occurrences.

Global Donor Follow-up Meeting, August 27-28, 2009. A meeting sponsored by the Worldwide Network for Blood and Marrow Transplantation (WBMT), a 'society of societies' that has 17 members including the WMDA, was held in Bern, Switzerland to establish agreement on minimal requirements for short- and long-term follow-up of related and unrelated HPC donors. Twenty-five representatives from WBMT, WMDA, registries, donor centers and transplant programs participated in this two day meeting. Recommendations from Bern have been incorporated into the final recommendations of this report.

Personal Communications. Isolated occurrences of very severe events, particularly fatalities, are often not reported in the medical literature. A few events are known only through personal communications and each has been verified by direct conversations with knowledgeable physicians who were directly involved in the cases.

1.4 Definitions and approach

We have used the following definitions in the preparation of this report.

Adverse Reaction (AR): an unintended response in the donor associated with the procurement of organs, tissues and cells.

Serious Adverse Reaction (SAR): an AR that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization.

Imputability: AR and SAR that were clearly not related to donation activities have been excluded. To be included, the AR or SAR must be at least 'possibly' related to the donation activity. The distinction between 'not related' and 'possibly related' can be difficult. For example, we are aware of three adult HPC donors who experienced sudden death in the days prior to actual initiation of the donation procedures (personal communication, 20). Although the relationship between these deaths and HPC donation may be sheer coincidence, it is certainly possible that stresses of impending donation may have contributed to sudden death. These cases are deemed possibly related. Similarly, donor suicide after HPC donation may be related to the donation procedure, especially if it is seen in relatively close proximity to donation.

Early AR: Any AR possibly related to the donation process, which includes all events leading up to the actual donation and continues for 30 days after the completion of the donation.

Late AR: Any AR possibly related to the donation process with onset more than 30 days after completion of the donation.

1.5 Findings

AR for HPC donors have been grouped into categories. Early AR have been separated from late AR (Table 5). Early AR have been also separated into those associated with HPC(A) donation and those associated with HPC(M) donation (Table 4). Early HPC(A) AR have been further subdivided into those related to mobilizing agents (Table 1), those related to the apheresis procedure (Table 2), and 'others' (Table 3).

An additional section has been devoted to known fatalities.

1.6 Fatal AR in Living HPC Donors

Rarely, HPC donors suffer fatal AR. Several of these are known to have occurred in the U.S. A 40 year old man suffered sudden death from cardiac arrest a few days prior to a planned HPC(M) donation to his son (20). He had no prior cardiac history. A 57 year old woman who had donated HPC(A) to her sibling suffered a fatal stroke 3 days after completing donation (49). Her platelet count had been documented to be adequate following donation. A previously healthy 47 year old woman with sickle/beta thalassemia received filgrastim in preparation for HPC(A) donation to her sister. After 4 days, she experienced a severe sickle crisis, which ultimately proved fatal (38). A 35 year old woman died from myocardial infarction during an HPC(M) donation for her sister (87). She had no prior cardiac history.

In addition to these reports, Halter, et al, surveyed programs in Europe and Japan (88). Respondents reported five known deaths, one during marrow donation and four in association with HPC(A) donation. In 2010, the death of a 7 year old child was reported (50). He had received 6 mcg/kg of filgrastim twice daily for 5 days. He underwent apheresis on the 5th day, but suffered a fatal cerebellar haemorrhage that evening.

Additional deaths have likely occurred. We are aware of at least one other that is well-documented. Still, given the numbers of related- and unrelated-donor collections that have been performed, the existence

of so few documented fatalities suggests that HPC donation is very safe with a fatality incidence far less than 1 in 10,000.

1.7 Commentary

HPC donation is most often a safe procedure. AR occur, but life-threatening or fatal AR are rare. Most common AR can be readily managed with symptomatic interventions. In long-term follow-up, new-onset cancers and autoimmune disorders are encountered, but there is currently no evidence that these occur at higher-than-expected rates (22, 64, 80, 82).

1.8 Recommendations

These recommendations are largely based upon conclusions from the global donor follow-up conference held in Bern, Switzerland, in 2009. SAR occurring at any time between initiation of the donation procedure and 30 days after completion of the collection should be reported. Reporting of hospitalization-related SAR that result from common donation-associated AR, e.g. nausea, vomiting, pain, headache, may be excessive because the distinction between AR and hospital-related SAR in these cases is highly dependent upon geographical differences, practice standards, and regulatory requirements. Life-threatening or fatal AR in the context of common donation-associated AR should always be reported.

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.

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1.10 References

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Table 1. Early adverse reactions reported with mobilizing agents administered to living HPC(A) donors.[1]

Adverse Reaction	Freq#	Serious#	Sentinel Event	Prevention	Treatment	Refs
Allergic reaction	U	Rarely	Local site irritation, rash, or anaphylaxis	History of allergy	Topical or systemic glucocorticoids, antihistamines	(19, 21)
Anorexia	C	No	—	None	Reduce dose or stop if severe	(22, 23)
Arrhythmia, atrial or ventricular	R	Occ	Palpitations, lightheadedness, syncope	—	Symptomatic, may reduce dose or stop	(19)
Arterial vasculitis	R	Occ	Pain, tenderness	None	None or systemic glucocorticoids	(19)
Autoimmune disease flare	R	Occ	—	Risk Assessment	Symptomatic, Reduce dose or stop if severe	(24)
Bone Pain	C	Rarely	—	Non-aspirin, non-narcotic analgesics	Narcotic or non-narcotic analgesics	(3, 10, 22, 23, 25-35)
Chills	C	No	—	—	Symptomatic	(22)
Deafness	U	No	—	—	?None	(19)
Fatigue	C	No	—	—	Symptomatic	(3, 10, 22, 23, 25, 27, 28, 30, 31, 33, 35)
Fever	C	No	—	—	Symptomatic	(22, 31, 32)
Headache	C	Rarely	—	—	Symptomatic	(3, 22, 23, 25, 26, 28, 30-35)
Hematuria	R	No	—	Risk assessment	Symptomatic	(10)
Hyposphagma (subconjunctival hemorrhage)	U	No	—	—	Symptomatic	(19)
Insomnia	C	No	—	—	Symptomatic	(22, 23, 31)
Leukocytosis	C	Rarely	—	—	Reduce dose or stop if severe	(22, 26, 29, 30, 33, 36)
Myalgia	C	No	—	—	Symptomatic	(22)
Nausea	C	No	—	—	Symptomatic	(3, 22, 23, 25, 31-33, 35)
Ocular inflammation	U	Rarely	Eye pain, redness, visual change	—	Symptomatic, Reduce dose or stop if severe	(19, 37)

Other flu-like symptoms	C	Rarely	—	—	Symptomatic	(22)
Pulmonary embolism	R	Often	Dyspnea, chest pain, anxiety, collapse	Risk assessment	Standard Medical Care	(19)
Sickle crisis	R	Yes	Pain	Hemoglobin-opathy assessment	Standard Medical Care	(38, 39)
Skin irritation/eruption	U	No	—	—	Symptomatic	
Splenic rupture/bleeding	R	Yes	Abdominal pain, hypotension, shock	None	Medical management usual, surgery may be needed	(19, 28, 40-43)
Splenomegaly	C	No	None	None	None	(44-48)
Stroke	R	Yes	Headache, numbness, weakness, visual change, altered mental status	Risk assessment	Standard Medical Care	(49, 50)
Sweats	C	No	—	—	Symptomatic	(22, 34, 35)
Thrombosis/thrombophlebitis	R	Occ	Extremity pain, redness, swelling, edema	Risk assessment	Standard Medical Care	
Thrombocytopenia	C	Occ	Petechiae	Risk assessment	Usually none required, but may include transfusion or glucocorticoids	(22, 30, 35, 51)
TIA	R	Occ	Transient unilateral blindness, numbness, weakness	Risk assessment	Standard Medical Care	(19)
Vertigo	U	Occ	—	None	Symptomatic	
Vomiting	C	Rarely	—	None	Symptomatic	(22, 23, 35)

[1]Codes for Tables: Freq: Frequency: C = common, U = uncommon, R = rare, Serious (e.g., fatal, life-threatening, hospitalization, disability): Occ = occasionally.

Table 2. Early adverse reactions reported with the apheresis procedure in living HPC(A) donors.

Adverse Reaction	Freq#	Serious#	Sentinel Event	Prevention	Treatment	Refs
Anemia	C	Rarely	Fatigue, light-headedness, hypotension	—	Rarely transfusion	(22, 52)
Cardiac arrest	R	Yes	—	Risk assessment	Standard Medical Care	(19, 53)
Cardiac arrhythmia	R	Yes	Light-headedness, chest pain	Risk assessment	Standard Medical Care	(19)
Central line thrombosis	U	Occ	Line failure	—	Standard Medical Care	
Chest pain, cardiac	U	Often	—	Risk assessment	Standard Medical Care	(19, 54)
Chest pain, non-cardiac	C	Occ	—	—	Symptomatic	
Citrate toxicity	C	Occ	Perioral numbness, tingling, tetany	Calcium infusion, Heparin supplementation to citrate	Calcium infusion	(22, 55-58)
Generalized seizure	U	Often	—	Risk assessment	Standard Medical Care and Evaluation	
Headache	C	Rarely	—	—	Symptomatic	(22)
Haemorrhage from central line site	U	Occ	—	Skilled physician	Symptomatic	
Horner's syndrome from central line	R	Occ	—	Skilled physician, imaging assisted placement	Symptomatic	

Hypertension	U	Rarely	—	Risk Assessment	Standard Medical Care	(19)
Hypotension	C	Rarely	—	—	Standard Medical Care	(19, 58)
Infection at peripheral line site	U	Occ	—	Skilled care	Standard Medical Care	
Infection at/of central line	R	Often	—	Skilled care	Standard Medical Care	
Leukopenia	C	Rarely	—	—	None	(22, 23, 49, 59, 60)
Misplacement of central line	U	Often	Line failure, syncope, hypotension	Skilled physician, Imaging assisted placement	Standard Medical Care	
Nausea	C	No	—	—	Symptomatic	(19, 34)
Peripheral access reactions, e.g., line infiltration, site hematoma, inflammation	C	Rarely	—	—	Symptomatic	(19, 22, 57, 58)
Pneumonia	U	Yes	Dyspnea, chest pain, cough	Risk assessment	Standard Medical Care	(19)
Pseudo-aneurysm from central line	R		Pain, swelling	—	Surgical repair	(19)
Seizure	U	Yes	—	Risk assessment	Standard Medical Care	(19)
Syncope	C	Occ	—	—	Symptomatic	(19, 58)
Thrombocytopenia	C	Occ	Petechiae, bleeding	Risk assessment, Laboratory monitoring	Rarely transfusion	(22, 23, 29, 30, 34, 49, 51, 52, 59, 61-63)
Vomiting	C	Rarely	—	—	Symptomatic	(22, 34)

Table 3. Other early adverse reactions reported with HPC(A) donation.

Adverse Reaction	Freq#	Serious#	Sentinel Event	Prevention	Treatment	Refs
Acute cholecystitis	R	Occ	Abdominal pain, N & V	—	Standard Medical Care	(19)
Generalized edema	R	Rarely	—	—	Symptomatic	(19)
Cardiac arrhythmia	U	Occ	Palpitations, hypotension, cardiac arrest	—	Standard Medical Care	(19)
Elevated liver enzymes	C	Rarely	—	—		(19)
Leukopenia (prolonged)	R	Rarely	—	—	—	(26)
Pneumonia	U	Rarely	Dyspnea, fever, cough	—	Standard Medical Care	(19)
Pulmonary embolism	R	Often	Dyspnea, chest pain, anxiety, collapse	—	Standard Medical Care	(19)
Subdural hematoma	R	Often	Headache, altered consciousness	—	Standard Medical Care	(19)
Suicidal Ideation	R	Yes	—	—	Psychiatric card	(19, 64)
Syncope	U	Occ	—	—	Symptomatic	
Thrombocytopenia (prolonged)	U	Occ	Petechiae, bleeding	—	Rarely transfusion, systemic glucocorticoids	(10, 65)
Thrombosis/thrombophlebitis	U	Occ	Pain, redness, swelling	—	Standard Medical Care	(19)
Transfusion reaction	R	Often	—	—	Symptomatic	(19)
Vomiting	U	Rarely	—	—	Symptomatic	

Table 4. Early adverse reactions reported with the bone marrow donation procedure in living HPC(M) donors.

Adverse Reaction	Freq#	Serious#	Sentinel Event	Prevention	Treatment	Refs
Anemia	C	Rarely	Fatigue, dyspnea	Risk assessment	Transfusion, limiting collection volume	(10, 66)
Apnea	R	Yes	—	Risk Assessment	Medical Intervention	(66)
Aspiration site infection	U	Occ	Pain, swelling, redness	—	Standard Medical Care	(19)
Autoimmune disease flare	R	Occ	—	—	Standard Medical Care	(67)
Air embolism	R	Yes	—	—	Standard Medical Care	(68)
Back pain	C	Occ	—	—	Symptomatic	(7-10, 27, 66, 69)
Cardiac arrest	R	Yes	Collapse	Risk assessment	Standard Medical Care	(9)
Cardiac arrhythmia	U	Often	—	Risk assessment	Standard Medical Care	(19)
Cauda equina compression	U	Often	Pain, numbness, weakness, bladder & bowel function	Skilled physicians	Standard Medical Care	(19)
Chest pain, cardiac	U	Often	—	Risk assessment	Standard Medical Care	
Chest pain, non-cardiac	U	Occ		—	Symptomatic	(19)
Commotio cerebri (concussion)	U		Post-fall	—	Standard Medical Care	(19)
Fat embolism	R	Yes	Dyspnea, low O2 Sat	—	Standard Medical Care	(70)
Fatigue	C	Rarely	—	—	Symptomatic	(10, 27, 66)
Fever	C	Rarely	—	—	Symptomatic	
Headache	C	Rarely	—	—	Symptomatic	(10, 71, 72)
Hematoma	U	Rarely		—	Symptomatic	(19)
Hypotension	C	Occ	Light-headedness, syncope	—	Symptomatic	(19)
Ileus	R	Yes	Pain, N&V	None	Standard Medical Care	(73)
Iliac fracture	R	Rarely	Pain	None	Symptomatic	(74)
Laryngospasm	R	Yes	—	—	Intubation	
Malignant Hyperthermia	R	Yes		Risk assessment	Medical Intervention	(75)
Nausea	C	No	—	—	—	(71)
Osteomyelitis	R	Often	Pain, fever	—	Standard Medical Care	(76)
Pancreatitis	R	Yes	Abdominal Pain		Standard Medical Care	(77)
Peripheral access reactions, e.g., line infiltration, site hematoma, inflammation	C	Rarely	Swelling, redness, pain	—	Symptomatic	
Pneumonia	U	Occ	Fever, dyspnoea, chest pain	—	Standard Medical Care	(7) Personal Communication
Pulmonary embolism	R	Often	Dyspnoea, chest pain, anxiety, collapse	—	Standard Medical Care	(7) Personal Communication
Retained collection needle fragments	U	Rarely		—	Usually non	(19)
Sacroilitis	U	Rarely	Pain	—	Symptomatic	(19)
Sciatica	U	Rarely	Radicular pain	—	Symptomatic	(19, 78)

Sepsis	R	Often	Fever, vascular collapse	—	Standard Medical Care	Personal Communication
Seizure	U	Often	—	—	Standard Medical Care	(10, 79)
Sore throat	C	Rarely	—	—	—	(10)
Syncope	C	Occ	—	—	—	(19)
Thrombocytopenia	U	Occ	—	—	Rarely transfusion	
Thrombosism / thrombophlebitis	U	Occ	Pain, swelling, redness	—	Standard Medical Care	(19, 64)
Transfusion reaction	R	Occ	—	—	Standard Medical Care	
Vomiting	C	Rarely	—	—	Symptomatic	(71)

Table 5. Late adverse reactions reported after HPC donation including possible causal relationships.

Adverse Reaction	Freq#	Serious#	PBSC or Marrow	Causal Relationship	Treatment	Refs (Pro and Con)
Acute myelogenous leukaemia	R	Yes	Both	None evident	Standard Medical Care	(19, 80-84)
Chronic myelogenous leukaemia	R	Yes	Both	None evident	Standard Medical Care	(19, 80)
Acute lymphocytic leukaemia	R	Yes	Both	None evident	Standard Medical Care	(80)
Chronic lymphocytic leukaemia	R	Yes	Both	None evident	Standard Medical Care	(80, 83)
Myeloma	R	Yes	Both	None evident	Standard Medical Care	
Amyloid	R	Yes	Both	None evident	Standard Medical Care	(19)
Myelodysplastic syndrome	R	Yes	Both	None evident	Standard Medical Care	(19, 80)
Myeloproliferative disease	R	Yes	PBSC	None evident	Standard Medical Care	(31)
Hodgkin disease	R	Yes	Both	None evident	Standard Medical Care	(19, 83)
Non-Hodgkin lymphoma	R	Yes	Both	None evident	Standard Medical Care	(19)
Auto-immune disease, new onset[1]*	R	Often	PBSC Marrow	Unclear	Standard Medical Care	(19, 31)
Cauda equina syndrome	R	Often	Both	Unclear	Standard Medical Care	(19)
Chronic pain	U	Often	Marrow	Often unclear	Standard Medical Care	(85, 86)
Endocarditis	R	Yes	PBSC	Unclear	Standard Medical Care	(19)
Foot pain	R	Yes	PBSC	Unclear	Standard Medical Care	(19)
Leukopenia (prolonged)	R	No	PBSC	Unclear	None	(51)
Non-hematologic malignancy[2]**	R	Yes	Both	None evident	Standard Medical Care	(26, 31)
Pulmonary embolism	R	Yes	Both	Unclear	Standard Medical Care	(19)
Stroke/TIA	R	Yes	Both	Unclear	Standard Medical Care	(31)
Suicide	R	Yes	Both	Unlikely	—	(64)

1 *Reported diagnoses include for PBSC: Multiple sclerosis (3), rheumatoid arthritis (4), ankylosing spondylitis, De Quervain thyroiditis, alopecia areata and Grave's disease. For bone marrow: Systemic lupus erythematosis and sarcoidosis.

2 **Reported non-hematologic malignancies include Breast (6), prostate (6), testicular (7), melanoma (6), thyroid (2), colorectal (2), bladder (2), hapatoma (2), Lung (3), esophagus (2), gall bladder, pancreas, cervix/uterus, sarcoma, thymus and appendix. Benign tumours are also reported.

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2 Donor Reactions – Gametes

Carolina Stylianou, Mauro Costa

Europe leads the world in Assisted Reproductive Technology (ART) with 500,000 reported cycles annually which is more than half of the cycles reported worldwide. Sperm and oocyte donation is a practice adopted in many countries.

The European IVF monitoring consortium of the European society of reproduction and embryology (ESHRE) reports yearly the data from these cycles.

The most serious and potentially fatal iatrogenic event due to an ART cycle is ovarian hyperstimulation syndrome (OHSS). It is recognized since 1943 and has been extensively studied. OHSS is an iatrogenic disorder associated with the procurement of oocytes and can potentially affect donors as well as patients (autologous donors). It occurs during the luteal phase of the stimulated cycle and in early pregnancy. OHSS development is normally observed only after exogenous HCG administration for the final triggering of ovulation (early form) or after endogenous HCG production if the pregnancy is obtained (late form) (1, 2).

The cardinal event of this syndrome is a third space fluid shift related to the ovarian production of substances that increase vascular permeability. Recent observations from animal studies suggest that vascular permeability factor (VPF) / vascular endothelial growth factor (VEGF) plays a pivotal role in increasing vascular permeability in hyperstimulated subjects. In fact, the inactivation of VEGF function by a specific antibody can reduce ascites by about 70% in gonadotropin stimulated animals. A relationship between VEGF production and HCG administration has been described.

OHSS may be mild, moderate, or severe:

Mild OHSS

Abdominal distension and discomfort (grade 1)

Plus nausea, vomiting and/or diarrhoea, ovarian diameter 5-12 cm (grade 2)

Moderate OHSS

Grade 2 and ascites (grade 3)

Severe OHSS

Grade 3 plus clinical ascites and/or hydrothorax with dispnea (grade 4)

Grade 4 plus hemoconcentration, coagulation abnormalities, diminished renal perfusion (grade 5)

OHSS is considered a self-resolving condition with a spontaneous remission of usually 10-14 days or longer if pregnancy is achieved. If the syndrome persists there is deterioration of the patient's health which leads to hospitalisation, usually in intensive care units. It causes morbidity and potentially mortality in 1-45,000 to 1-50,000 cases.

The condition that is considered serious for the health of the donor / patient is the severe OHSS. Clinical ascites, pleural effusions, oliguria, increase in haematocrit level over 45%, reduced renal perfusion, thrombotic complications and hypoproteinaemia are the main symptoms that alert physicians. It is estimated that 0.2-5% of donors / patients are affected. The European IVF monitoring consortium reports that in a total number of 459.170 ART cycles 2,753 cases of OHSS were recorded, corresponding to a risk of OHSS of **0.8%** of all stimulated cycles (3).

As there is no curative treatment, apart from symptomatic treatment in Intensive care units, prevention remains the option of choice.

Strategies for prevention, during the patient selection phase can include identification of risk donors/patients i.e. women under the age of 35, low body mass index, hyperinsulinaemia, polycystic ovary syndrome and previous history of OHSS.

The identification of donors / patients at risk may direct the treating physicians to make changes in the protocols used i.e. use of protocols with lower doses of gonadotrophins or gonadotrophin antagonist, and coasting.

Once the ovarian stimulation has been carried out the syndrome occurs only if HCG is administered for the final triggering of ovulation, so the only secure prevention in this phase is cycle cancellation (because without exogenous HCG administration oocytes retrieval is not possible) and its reprogramming with a different stimulation approach. If the patients and the physician decide to go on in the cycle, some strategies are available to minimize the risk, but none has been demonstrated absolutely secure to completely prevent OHSS. The proposed strategies are the following: coasting (withholding gonadotrophins while maintaining gonadotrophin analog administration until Estradiol levels drop to a safe level and then administration of gonadotrophin), intravenous albumin administration around the time of oocyte retrieval, GnRH agonist as an oocyte trigger in GnRH antagonist cycles, natural-cycle IVF or in vitro oocyte maturation, administration of the Dopamine agonist cabergoline (4).

2.1 Other complications

According to the European IVF Monitoring Consortium by ESHRE other events associated with ART are complications with oocyte retrieval, severe bleeding and infection. In the 2010 report on the 2006 cycles, the following complications to oocyte retrieval are reported: all complications 938 (risk 0,2%), bleeding 544 (risk 0,1%), infection 42 (risk 0,009%).

2.2 Recommendations

a. Severe OHSS, severe bleeding that requires transfusion/hospitalisation and infection that requires hospitalisation should be reported as Serious Adverse Reactions.
b. Any of the events that lead to the death of the donor/patient should be reported as Serious Adverse Reactions.

Despite the evidence that OHSS is not properly an Adverse Reaction (AR), because it is a well known complication of ART and not an unintended response in the donor, there are some reasons to report the severe cases. As it is not completely clear which donors/patients are at high risk of developing severe OHSS, as well as which is the best protocol to be used, it is evident that reporting of severe OHSS cases to the ART Competent Authority or to the Tissue and Cell Authorities that have the means of analysing the data and provide guidance, is of outmost importance especially when donors are involved. Reporting of these events will assist in recognising the 'high risk patient' characteristics as well as the development of ovarian stimulation protocols that can be well tolerated by donors/patients.

Events related to bleeding as well as oocyte retrieval complications and infection are all related to clinical practise and reporting of these occurrences will assist in improving and redefining the services provided. Events occurring in high frequency in certain IVF centres will guide the Competent Authorities to investigate the methods used and provide guidance for minimising the recurrence.

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3 Donor Reactions - Organs

Emanuele Cozzi

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

However, for living donation to progress successfully and possibly further expand, all the steps must be put in place to ensure that these procedures take place in the respect 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 between 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 but also with later complications that may be mis- or underdiagnosed and, ultimately, be inadequately treated with health consequences to the donors.

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

Taken together, these observations unquestionably demonstrate that living organ donation is inextricably associated with some degree of risk to the donor health. In this light, the development of a set of recommendations to timely identify and correct any health issue in living organ donors is eagerly encouraged to enable to safe expansion of living donation programmes world-wide.

3.1 Recommendations

1) National Living organs donor Registries should be developed in each country with on-going transplantation programmes 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 (possibly located at the WHO?)
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 that clearly indicate timing and type of investigations to be conducted after live organ donation.
5) The donor follow up should be conducted throughout the donor lifespan and should continue with the same meticulousness irrespective of the outcome of the transplant itself. A strategy should be identified to ensure that no patient is lost during follow up.
6) Donor follow up should be provided free of charge and without 'logistic burden' (i.e. if the donor will move to another area or country, access to free healthcare in the new location should be provided).
7) Identification of adverse events should be thoroughly documented. If severe, they should be timely reported to national health authorities, the [organ-] specific task force of international experts, and to those responsible for updating registries. If deemed necessary, the task force of international experts may decide to convene to specifically analyse the problem arisen.
8) In conjunction with the WHO, the task force of international experts may release reports or documents to be distributed to National Health Authorities to possibly recommend measures that may have to be put in place as a consequence of the reported adverse event.

The Transmission of Genetic Diseases

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1 Genetic Transmissions – HPC

Dennis L. Confer

1.1 General

Until relatively recently, bone marrow grafts from sibling donors were the only stem cell source available to patients needing 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 nowadays mandatory. Donors are considered eligible for the donation when all medical data conclude that they are healthy. This assessment has truly 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 might not be manifested until much later in life.

Theoretically, all congenital diseases originating from bone marrow-derived cells are transmissible. Very few cases of genetic disease transmission through haematopoietic cells have been reported. Cyclic neutropenia and Gaucher´s disease were transmitted via sibling HPC transplantation (Krance et al. 1982).

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

1.2 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 collection of cord blood from families with a genetic disease should be avoided, if such units were collected in the past, they should be screened prior to release.
3. 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.
4. 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.
5. Cord blood banks that have stored cord blood units that are not found to carry a genetic disease but 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.
6. The cord blood from babies that were conceived through the use donor gametes should not be collected and stored unless the medical history of the sperm donor is available and if an oocyte donor is involved, blood samples from the oocyte donor can be collected.

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2 Genetic Transmissions - Gametes and Embryos

Carolina Stylianou, Mauro Costa

2.1 General

Conditions such as Severe Congenital Neutropenia (SCN)[1], Hypertrophic Cardiomyopathy[2,3], Autosomal Dominant Cerebellar Ataxia (ADCA)[4], Opitz Syndrome[5], Neurofibromatosis type 1 (NF 1), Autosomal recessive Polycystic Kidney Disease (ARPKD)[1], Congenital adrenal hyperplasia (CAH)[1], Fragile X syndrome (from the soho doc) and Phenylketonuria (PKU)[1] have been reported in offspring originating from gamete donation. 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[6].

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 a 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[1]. Another donor transmitted Hypertrophic Cardiomyopathy to 9 children[2]. 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 Sydrome, with a 50:50 chance of inheritance[5]. 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[5]. 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.

2.2 Recommendation(s)

The following recommendations are based on discussions within an ART vigilance working group of the EU-funded project 'Vigilance and Surveillance of Substances of Human Origin'.

1. The birth of a child with a genetic illness following donation of gametes or embryos should be reported as a suspected Serious Adverse Reaction (SAR). 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 a Serious Adverse Event (SAE) so that stored gametes, or stored embryos created from that donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
3. Sperm banks should have access to clinical genetic expertise for advice in developing donor screening policies and in investigating suspected genetic transmissions to offspring.

   To facilitate the effectiveness of vigilance reporting in these circumstances, the following is recommended:
4. Couples having ART treatment with donated gametes or embryos should be strongly advised to inform any doctors subsequently treating the resulting child(ren) of the donor origin. They should understand that, in the unlikely event that a child will manifest an inherited condition, informing the clinic could protect further families. Consideration could be given to the development of a carefully worded standard leaflet explaining these issues that could be provided to all couples. In the analogous situation of allogeneic cord blood banking, some banks provide the donor mother with a leaflet

asking her to contact the bank in the unlikely event that the donor child manifests a genetic or other illness, so that the transmission of the illness by transplantation of the cord blood can be prevented.

5. Gamete and embryo donors should be strongly advised to inform the clinic where they donated, in the event that they are subsequently diagnosed with any genetic condition. In this case also, a standard information leaflet for donors might be considered.
6. Specialist genetic centres should always consider whether a child manifesting a genetic condition might have been conceived with donor gametes or embryos. This issue should be raised immediately and openly with the parents in the interests of other potential offspring and when parents acknowledge the involvement of a donor, they should be strongly urged to contact the ART centre. The issue should be included in the appropriate professional standards and guidance for specialist genetic centres.

2.3 Pre-implantation Genetic Diagnosis

Some couples with a high risk of transmitting an inherited condition, cystic fibrosis, Beta-thalassemia, sickle cell disease and many others, opt for ART with the objective of preventing the transmission of the disorder. In these cases, Pre-implantation Genetic Diagnosis (PGD) is used to select embryos for implantation that do not carry the condition.

An error in the process of PGD might lead to the birth of a child with the particular condition. However, the test has an expected error rate so it could be argued that this type of outcome should not be considered as an issue for vigilance reporting.

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

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

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