GUIDELINES FOR HEALTHCARE PROFESSIONALS ON VIGILANCE AND SURVEILLANCE OF HUMAN TISSUES AND CELLS

DELIVERABLE 10

PART 1 – TISSUES

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GENERAL ISSUES

INTRODUCTION

These Guidelines for Health Care Professionals on Vigilance & Surveillance of Human Tissues and Cells were developed within a European Union-funded project entitled SOHOV&S (Vigilance and Surveillance of Substances of Human Origin). The broad aim of the SOHO V&S project was to support European Union (EU) Member States in the establishment of effective Vigilance and Surveillance (V&S) systems for tissues and cells used in transplantation and in assisted reproduction.

The three year project (2010 – 2013) was led by the Italian Competent Authorities for the Tissues and Cells (the Italian National Transplant Centre – Centro Nazionale Trapianti (CNT)) and a Steering Committee that includes a number of other Competent Authorities for Tissues and Cells in the EU as well as the World Health Organisation (WHO). A large number of other organisations, both regulators and professional societies from within and outside the EU, have participated as collaborating partners (see full list of project partners at Annex 1).

The SOHO V&S projects developed a number of output products (deliverables). This document is one of those deliverables. The other project deliverables are:

- A Survey of European Vigilance & Surveillance Systems for Tissues and Cells
- Guidance on Vigilance & Surveillance in Assisted Reproductive Technologies in the European Union
- The Detection and Investigation of Suspected Illegal and/or Fraudulent Activity (IFA) related to tissues and cells - report and guidance
- SOHO V&S Guidance for Competent Authorities - Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells
- A Training course model for investigators of Serious Adverse Events and Reactions .

SCOPE

These guidelines are addressed to health care professionals who, working in different organisations responsible for human application (ORHA) in the EU such as hospitals, clinics, doctors' and dentists' surgeries (offices) are involved in processes associated with the management and use of tissues and cells. They aim to define the roles and responsibilities of these health professionals in relation to supporting V&S of tissues and cells for transplantation.

The guidelines have been divided in 2, wholly self-contained parts.

Part 1 addresses all types of tissues, including:

- musculo-skeletal tissues (bones, tendons, ligaments, menisci, etc.)
- skin
- cardiovascular tissues (heart valves, blood vessels etc.)
- amniotic membrane
- ocular tissues (corneas in particular).

Part 2 addresses all types of hematopoietic stem cells (HSC) including:

- bone marrow
- peripheral blood stem cells (PBSC)
- cord blood.

Organs for transplantation, blood and blood components, advanced therapy medicinal products (ATMP) and tissues and cells used for in vitro research or teaching are excluded from the scope of these guidelines. Guidance on V&S in the field of Assisted Reproduction was developed in a different part of the SOHO V&S project.

Part 1 of these guidelines focuses on the key role of physicians in:

- maintaining tissue traceability
- recognizing, reporting and investigating serious adverse reactions and events (SAREs) associated with tissues
- recall and look-back management procedures where there is a need to contact all patients who received grafts from a particular donor, from a particular processing batch or from a particular centre.

Part 1 is also addressed to ORHA personnel who are responsible for ordering, receiving and storing of tissues prior to clinical application. It provides guidance on:

- choosing a tissue supplier
- the management of tissues, including ordering, receiving, storage, handling and disposal,
- management of recalls where the supplying tissue establishment (TE) requests the immediate return of distributed tissues for safety reasons.

Moreover the guidelines provide information on the legislative framework for the field of tissues and cells in the EU as well as risks related to donation and clinical application of tissue and cells.

METHODOLOGY

These guidelines were developed within Work-Package 9 (WP9) of the SOHOV&S project. The work-package was led by the Polish National Centre for Tissue and Cell Banking (KCBTiK – Krajowe Centrum Bankowania Tkanek i Komórek) with the support of a drafting group (see Annex 2) and the active participation of the key professional societies for the field in the EU (see Annex 2).

Part 1 draws on existing guidance from the United States in the form of a booklet entitled 'Hospital Tissue Management: A Practitioner's Handbook[1].The booklet was published jointly by the American Association of Blood Banks (AABB), the American Association of Tissue Banks (AATB), and the Eye Bank Association of America (EBAA). The authors of this document wish to acknowledge the importance of that publication for the development of this text.

The WP9 leader convened and facilitated the meetings of the partners participating in this WP as well as consultations with the European Eye Banking Association and the European Association of Tissue Banks.

Professional society consultations focused on the issues specific to the clinical use of that type of tissue. Issues explored during each consultation included:

- tissue management by the ORHA – tissue specific good practices regarding:
  - ordering
  - receiving
  - short-term storage
  - preparation before use
  - handling and management of unused tissues
  - recall
- maintaining traceability at the ORHA:

[1] Hospital Tissue Management: A Practitioner's Handbook, 1st edition, 2008, editors: A. Bradley Eisenberg, Ted Eastlund.

- responsibilities - who should be responsible at the hospital or clinic?
- recordkeeping - how/where should traceability records be kept?

- Serious Adverse Reactions and Events (SARE):
  - recognizing suspected adverse reactions
  - clinical triggers for reporting a suspected SAR
  - investigating the cause of an (S)AR
  - types of SAE that occur at the ORHA and how they should be managed;
  - reporting responsibilities of clinical staff.

This deliverable is made available to EU Competent Authorities for tissues and cells in an electronic version. Individual Competent Authorities may translate and adapt the document to the local conditions for subsequent national distribution to ORHA, either directly or via tissue establishments.

REGULATORY FRAMEWORK

EUROPEAN UNION TISSUE AND CELL DIRECTIVES

Directive 2004/23/EC[2], and its associated Commission Directives 2006/17/EC[3] and 2006/86/EC[4], regulate the field of human tissues and cells for clinical application in the European Union. These Directives have been transposed into national law in all 27 Member States and have been implemented by nominated Competent Authorities for Tissues and Cells in each country. The details of the authorities in each Member State can be found on the Eurocet Registry (www.eurocet.org). It is notable that EU legislation does not prevent a Member State from maintaining or introducing more stringent protective measures, provided that they comply with the provisions of the Treaty establishing the European Community.

The scope of the tissue and cell Directives extends from donation and procurement to testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications unless covered by other legislation.

In the context of this regulatory framework, ORHA should be aware that all tissues and cells (whether they are for autologous, allogeneic related or allogeneic unrelated use) must comply with the requirements of these Directives and, as such, they must be provided for clinical use by 'Tissue Establishments' that are authorized, accredited, designated or licensed by the Competent Authority in the Member State [see Section 'Tissue Establishments' below].

The Directives do not apply to:

- tissues and cells used as an autologous graft within the same surgical procedure;

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[2] 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 (OJ L 102, 7.4.2004).

[3] 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 (OJ L 38, 9.2.2006).

[4] 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 (OJ L 294, 25.10.2006).

- blood and blood components as defined by Directive 2002/98/EC;
- organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body;
- processing, preservation, storage and distribution of advanced therapy medicinal products (ATMP), which includes e.g. cultured *in vitro* cells such as chondrocytes, keratinocytes, limbal cells, endothelial cells and mesenchymal stem cells.

Moreover, the Directives do not regulate the clinical application of tissue and cells, which falls within national competence, but they do require ensuring traceability from donor to recipient and the reporting of adverse outcomes by clinical users:

"*All persons or establishments using human tissues and cells regulated by this Directive shall 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.*"

Article 11, paragraph 2, Directive 2004/23/EC

TREATMENT SELECTION

The application of human substances always carries some risk of adverse outcomes (see Section 'Risks Concerning Donation and Clinical Application Of Human Tissues ', below). Physicians should always give careful consideration to the decision to treat with a substance of human origin, considering the benefits, in the light of the risks and the availability of alternatives.

The risk associated with the application of human tissues is evidently very low, particularly where the donated tissues have been highly processed, with the removal of blood and other cells, or even terminally sterilized. The compendium of cases and their associated bibliography gathered by the experts worldwide in a searchable database on the Notify Library website (www.notifylibrary.org) demonstrates that although adverse outcomes are rare, viruses and bacteria have been transmitted by a wide range of tissue types and grafts have failed for various reasons, often associated with the quality or safety of the tissues provided for clinical use.

TISSUE MANAGEMENT IN AN ORHA

TISSUE ORDERING

When the application of human tissues is considered the most appropriate treatment option, the physician, and other health professionals involved, should be conscious of the exceptional nature of the human tissue to be applied, as material donated altruistically for the benefit of patients in need, often in short supply. Only the required amount should be ordered and wastage should be avoided.

TISSUE ESTABLISHMENTS

ORHA should be aware that all tissues (whether they have been removed from the patients themselves or they are of donor origin) come under the regulation of the above mentioned Directives (Directive 2004/23/EC, 2006/17/EC and 2006/86/EC). The only exception is tissues which are used as an autologous graft within the same surgical procedure.

ORHA routinely receive tissues from external suppliers. Tissues must be provided by centres defined as 'tissue establishments[5] that are authorized (the terms accredited, designated or licensed may also be used) by the Competent Authority in the Member State. The Competent Authority for tissues and cells may be national or regional (local). A registry of Competent Authorities with contact details is provided on the Eurocet website (www.eurocet.org).

CHOOSING AN APPROPRIATELY AUTHORIZED TISSUE ESTABLISHMENT

Choosing an appropriately authorized tissue establishment ensures that tissues meet the quality and safety requirements of the European legislation. The authorised tissue establishments are regularly inspected by Competent Authorities to confirm compliance with the legal requirements.

According to the Directives, Competent Authorities for tissue and cells must establish and maintain a publicly accessible register of tissue establishments specifying the activities for which they have been accredited, designated, authorised or licensed. Before choosing a tissue establishment, the ORHA should consult this register to ensure that the tissue provider is listed and authorised for the relevant activity. In the case that a tissue establishment is not listed and/or authorised, the ORHA should consult the Competent Authority for advice.

SERVICE LEVEL AGREEMENT (SLA) BETWEEN ORHA AND TISSUE ESTABLISHMENTS

Once tissues have been distributed by a tissue establishment for clinical use at an ORHA, the ORHA takes responsibility for their fate. It is highly recommended that a service level agreement (SLA) be put in place between the ORHA and the external tissue establishment.

The scope of the agreement should include:

- contact person details and possible forms of communication (by phone, by fax, by e-mail etc.);
- methods of tissue ordering and delivery, including liability for transport;
- conditions of tissue storage and preparation for use at the ORHA;
- procedures for tissue disposal at the ORHA;
- procedures for return of tissue to the tissue establishment, if permitted;
- responsibility and procedures for maintaining traceability;
- procedures for adverse reaction and event reporting and investigation;
- procedures for the management of tissue recalls and look-back procedures.

In the case of an ORHA which has a supplying tissue establishment within its own structure, all responsibilities should be described in written and approved Standard Operating Procedures within the Quality Management System.

TISSUE ORDERING FROM ANOTHER EU MEMBER STATE

The EU legislation does not consider the movement of tissues and cells between Member States as import or export. Any tissue establishment that is authorized in its own Member State may provide tissues direct to an ORHA in other Member States.

[5] 'Tissue establishment' means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells (Directive 2004/23/EC).

However, it should be noted that some Member States have implemented more stringent rules (as the legal basis for Directives allows) and do require a formal procedure to be followed even when the material is coming from another EU country. It is important, therefore, to be aware of the national legislation.

TISSUE ORDERING FROM OUTSIDE THE EU

The importation of tissues from outside the EU must be via an authorized tissue establishment within the Member State. The only exceptions to this are the case of 'direct distribution[6]' or in cases of emergency. In both of these cases, the Competent Authority must authorize the import directly.

The tissue establishment that imports and supplies tissues from outside the EU must take responsibility for ensuring that the standards of quality and safety that have been applied at the source organization are equivalent to those required in the EU. Importation of tissues from outside the EU by an ORHA is not permitted unless they have an exceptional authorization from the national Competent Authority.

EXCEPTIONAL RELEASE

In exceptional circumstances, an ORHA may agree with a tissue establishment that tissues which do not meet the normal release criteria should be released and used in a specific patient on the basis of a risk-benefit analysis, taking into consideration the alternative options for the patient and the consequences of not providing the tissues concerned. The risk assessment should be documented before acceptance of the exceptionally released tissue.

The recipient patient physician should, together with the Medical Director and the Responsible Person of the tissue establishment, conduct the risk assessment and the risk-benefit analysis for the particular recipient and the discussions and conclusions should be documented. The treating physician should, in written form, confirm his/her agreement with the exceptional departure from normal procedures. The patient should participate or be informed of the decision process and the conclusions before giving consent.

CENTRALISED VS. DECENTRALISED MANAGEMENT OF TISSUES AND CELLS AT THE ORHA

No specific model for the management of tissue distributed to an ORHA is mandated in the EU. Two main management models are applied: decentralized and centralized.

A decentralised model is a model whereby tissues are delivered directly to the relevant department (e.g. orthopaedic, cardio-surgical, ocular) or to the operating theatre. This model offers optimal control by the tissue users, however traceability of tissues becomes more difficult and compliance with the requirements for storage and handling is also problematic.

A centralised model is a model where an ORHA unit takes responsibility for all activities regarding administration of tissues. Centralised models greatly improve the ability to trace tissues and cells and can significantly improve inventory control and compliance with safety and quality standards. For these reasons, a centralized model for the receipt, short term storage and traceability of tissues and cells for human application is strongly recommended. In a hospital, the blood bank is likely to be the best option for this function. To ensure the traceability, the ORHA is

[6] 'Direct distribution' refers to an exception for some tissues and cells which may, with the agreement of the Competent Authorities for tissues and cells, be distributed directly for immediate transplantation to the recipient as long as the supplier is provided with an accreditation, designation, authorisation or licence for this activity. An example would be bone marrow donated for immediate transplantation without storage or processing.

required to designate oversight accountability for ordered, received, stored and applied tissues to named individuals and all the activities concerning tissue management should be recorded e.g. in a logbook (see section 'Tissue logbook' below). In the case of a larger ORHA, which has its own Quality Management System, all the above mentioned activities should be incorporated into this system and the roles and tasks of officially designated personnel should be clearly specified in Standard Operating Procedures.

TISSUE RECEIPT AT THE ORHA

Once tissues or cells have been distributed by a tissue establishment for clinical use, appropriate storage and handling becomes the responsibility of the clinical unit. The first step is to confirm that the tissues have been received with appropriate labelling and associated documentation.

According to the Directive 2006/86/EC, the label on the primary tissue container (the container in direct contact with the tissues) must provide:

a) type of tissues, identification number or code of the tissue, and a lot or batch number where applicable;
b) identification of the tissue establishment;
c) expiry date;
d) in the case of autologous donation, this has to be specified (*For Autologous Use Only*) and the donor/recipient has to be identified;
e) in the case of directed donations - the label must identify the intended recipient;
f) where tissues are known to be positive for a relevant infectious disease marker, it must be marked as: BIOLOGICAL HAZARD.

If any of the information in d) to e) above cannot be included on the primary container label, it must be provided on a separate sheet accompanying the primary container. This sheet must be packaged with the primary container in a manner that ensures that they remain together.

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

- description (definition) and, if relevant, dimensions of the tissue;
- morphology and functional data where relevant;
- date of distribution of the tissue;
- biological determinations carried out on the donor and results;
- storage recommendations;
- instructions for opening the container, package, and any required manipulation/reconstitution;
- expiry dates after opening/manipulation;
- instructions for reporting serious adverse reactions and/or events;
- presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc.).

Additionally, some tissue establishments require ORHA to return documentation providing details of the final disposition of tissues received. For this purpose, they enclose additional forms to be completed (see application report, disposal report).

INCOMING INSPECTION AT THE ORHA

The incoming inspection is an important step to be performed when tissues are first received and before they are placed into storage or delivered to the operating room.

ORHA personnel should verify and properly record that:

- Tissues received correspond to what was ordered and to the information in the accompanying documentation, which has to be complete and legible.
- Both shipping containers and primary containers are labelled with the information required (see above) and labels are affixed and legible. Separate accompanying documents should provide any information that is not included in the primary container label.
- Both the shipping container and the primary container are intact.
- Expiry dates of tissues have been not exceeded.
- The transport temperature range was monitored or adequately maintained and acceptable. For tissues that are transported frozen or at low temperatures, maintenance of the required transport temperature can be confirmed either by data readout from a temperature logger placed in the shipping container or by presence of residual coolant in the container (e.g. for refrigerated tissues – wet ice, and for frozen tissue – dry ice.) The supplying tissue establishment should be able to provide, on request, a validation study to show that the method of transport is adequate to maintain the required temperature for a certain period of time.

The ORHA should establish a procedure for situations where requirements described above are not met.

TISSUE STORAGE PRIOR TO CLINICAL APPLICATION

Instructions should be available in the package insert that accompanies the tissues or cells that describe the appropriate storage conditions and the proper handling procedures to be followed before clinical application. These instructions should be followed precisely. The tissue establishment will have validated the packaging system they have used to ensure that the required storage temperature is maintained for a defined period of time in the packaging in which the tissue arrives; this will be described in the accompanying documentation and should be strictly respected. If necessary, the tissue may be removed from this package and placed in a storage device that respects the temperature requirements described in the tissue accompanying documentation. It should be ensured that during short term storage, before clinical application, the material is stored together with its associated documentation or the documentation should be clearly linked to the tissues or cells and easily accessible.

The accompanying document specifies the presence of particular additives or reagents which may affect the recipient (e.g. antibiotic allergies); this information should be taken into account. If there is no package insert accompanying the tissues or cells, they should not be used.

STORAGE TEMPERATURE

Tissue grafts can be stored at various temperatures, depending on the type of tissue, their method of preservation and the nature of the packaging; the storage requirements will be defined in the accompanying documentation. The range of requirements for storage temperatures includes ambient, room temperature, refrigerated, and frozen. It should be noted that failure to monitor and maintain controlled temperatures can result in waste of a precious resource and, if the tissue is used, serious adverse outcomes due to deterioration in tissue quality.

STORAGE EQUIPMENT

Where a specific storage temperature is necessary from receipt to clinical application, the storage device (refrigerator, incubator etc.) should be monitored, maintained and calibrated and should be secure, with restricted access. It should be dedicated to the storage of healthcare products and should be cleaned according to a defined protocol and frequency. It should have functional alarms and there should be emergency backup storage capacity. All records pertaining to storage temperatures should be retained for a defined period of time, the American Association of Tissue Banks recommends a minimum of 10 years.

Storage procedures should address steps to be taken if the temperature is outside defined limits or in the event of equipment or power failure.

STEPS TO BE TAKEN BEFORE CLINICAL APPLICATION OF TISSUES

RECIPIENT CONSENT

It is highly recommended that patients who will receive a human tissue graft must be made aware of this fact and give their consent to the procedure, in compliance with prevailing legal requirements. This consent should be in written form and include a description of the tissue type which is going to be applied as well as any potential risks involved. The Notify Library database (www.notifylibrary.org) may be a useful tool for accessing risk information for a particular type of tissue.

The information given to a prospective recipient should include at least the following:

- The rationale for choosing human tissues rather than synthetic alternatives (where relevant), with a description of the associated clinical benefits;
- The risks associated with the use of the human tissues, with particular reference to adverse outcomes that are documented for the specific type of tissues or cells to be applied.

The patient should sign a consent form that should include at least the following elements:

- Confirmation that the recipient is aware of the use of human tissues in the procedure;
- Confirmation that the recipient was appropriately informed of any risks to their health associated with the planned application of human tissues;
- The acceptance by the recipient of the risks described above.

This form should be separate from the more generic consent to receive treatment or surgery but equivalent to any such consent for blood transfusion.

FINAL INSPECTION PRIOR TO CLINICAL APPLICATION

Tissues to be applied during the surgery should be specified in the surgical checklist.

Before opening the primary tissue container, the ORHA personnel should repeat the verification of the container, the label and the accompanying documentation and should record the outcome of the inspection. They should also confirm that the conditions of storage since receipt at the ORHA have been monitored, adequately maintained and acceptable in line with the instructions provided by the TE.

The tissue itself should be examined once the primary container has been opened to confirm that the anatomical characteristics are as shown on the label (e.g. left vs. right femur, medial vs. lateral left meniscus, aortic vs. pulmonary heart valve).

TISSUE PREPARATION BEFORE USE

Instructions for opening the container, package, and any required manipulation/reconstitution (e.g. thawing, washing, rehydration), as well as information concerning expiry dates after opening/manipulation and presence of potential harmful residues reagents which may affect the recipient (e.g. antibiotics, ethylene oxide), must be provided either on the label or in accompanying documentation of delivered tissues.

The handling instruction should be followed precisely. Any departure from the instructions provided is at the discretion of the clinical user who will take full responsibility for any adverse outcome resulting from not following the supplier instructions.

STEPS TO BE TAKEN AFTER CLINICAL APPLICATION OF TISSUES

TISSUE TRACEABILITY RECORDS

The ORHA is required to maintain traceability records from the point of receipt of the tissue until 30 years after clinical use or other final disposition. According to Directive 2006/86/EC (Annex VI B), these records must include:

- identification of the supplier tissue establishment;
- identification of the clinician or end user/facility;
- type of tissues;
- product identification;
- identification of the recipient;
- date of application.

Details of tissues applied should be placed in the recipient's hospital record as well as in the operating theatre log book if they were applied during surgery.

TISSUE LOGBOOK

It is highly recommended that the ORHA implements an electronic or paper 'logbook' where all activities concerning received, stored, transplanted and discarded tissues will be recorded in one dedicated place. Records should be accurate, comprehensible, and indelible, and should identify both the individual performing the work as well as the date on which it was carried out.

In the case of a larger ORHA, which possesses its own Quality Management System, all the above mentioned activities should be incorporated into this system and the roles and tasks of officially designated personnel should be clearly specified in Standard Operating Procedures.

Such a logbook would facilitate both tissue ordering as well as management of a 'recall' by the tissue establishment or the Competent Authority or a 'look-back/trace-back' procedure in the event that all recipient of tissues from particular donor or a particular process run must be contacted and monitored (see below). Careful consideration should be given to where and how this logbook will be archived for the required period.

HOSPITAL DISCHARGE REPORT

It is highly recommended that when patients who have been treated with human tissues are discharged from an ORHA, their discharge documentation should specifically mention this fact so that general practitioners looking after the patient in the longer term can also associate unexpected symptoms with a possible transmission or other reaction from the tissue applied. Moreover, general practitioners should be advised to report any suspicious / unusual findings to the ORHA.

TISSUE APPLICATION REPORT

Some supplying tissue establishments require ORHA to return documentation (e.g. a traceability form or card) providing details of the recipient for each tissue supplied. A copy of this information should be retained in the recipient medical record. The details should be enough to unambiguously identify the recipient, i.e. at least 3 points of identification including a unique identifier. It should be noted that returning the document does not release the ORHA from its responsibility to maintain the information to ensure traceability.

Where reports of clinical application are returned to the supplying tissue establishment, the manner of documentation should adhere to the data protection regulations of the country and should ensure that personal information is not visible or that the recipient's privacy is not compromised in any way.

ROUTINE RECIPIENT FOLLOW-UP

For most types of well-established and routine tissue transplantation, detailed clinical outcome reporting by the health care professionals to the tissue establishment is required only in those exceptional circumstances where there is an adverse reaction.

Case-by-case clinical follow-up and reporting of tissue recipient clinical progress is required, however, for all highly matched life-saving transplants or when novel tissue or cell processes have been applied or new types of tissues are being processed by a tissue establishment for the first time. This type of clinical follow-up is not generally considered as part of vigilance. In these cases, the follow-up protocol should be agreed in advance with the tissue establishment.

THE MANAGEMENT OF SURPLUS OR UNUSED TISSUE

It is not permitted that residue tissue be used in another patient. It should be discarded as clinical or anatomical waste, in accordance with national rules or returned to the supplying tissue establishment for appropriate discard. Similarly, a single unit of tissues or cells should not be used in two or more separate patients. Any additional processing of supplied tissue e.g. its division for use in two or more separate patients should be considered as an exceptional departure from normal requirements and should not be performed without a Competent Authority authorization and notification of the Responsible Person at the supplying tissue establishment. There may be nationally established rules for this situation. Tissues provided to one ORHA should not be sent to another ORHA. This action is defined as 'distribution' and it requires a Competent Authority authorization. Tissues that are received and not subsequently used in one department of ORHA may be sent to a different department or operating theatre in the same ORHA but, as a minimum, the supplying tissue establishment should be informed of the final disposition of the tissue according to tissue establishment procedures. There may be nationally established rules for this situation.

The documentation that accompanies the tissue should specify whether tissues can be returned to the tissue establishment if not opened or used, e.g. if the patient is not well enough for surgery or surgery is cancelled for another reason. Most tissue establishments will not accept tissues returned in these circumstances; those that accept the return of unused and unopened tissue packages will have to confirm that the conditions for maintenance of the required tissue properties were continuously ensured and documented and that the packaging was not exposed to risk of tampering.

DISPOSAL REPORT

Some supplying tissue establishments require ORHA to return a report providing details of the final disposal of any unused tissues.

MANAGEMENT OF TISSUE RECALLS AND LOOK-BACKS

There are various reasons why a tissue establishment may issue a **recall** of tissues that have been distributed to an ORHA. It may be related to new information received regarding the donor's medical or behavioural history that implies disease transmission risk or to the discovery of an error in processing or a fault or contaminant in a reagent or solution used in processing. A recall may be instigated by the tissue establishment or required by the Competent Authority.

When a tissue establishment issues a recall, it will be necessary to trace very quickly all the received tissues of the particular batch or donation implicated, as well as the recipients of these tissues. The existence of a centralized log-book or electronic database of tissues received with dates of application or disposal and identification of recipients will greatly facilitate the conduct of a recall. In many of the most important cases of disease transmission by tissue transplantation it was not possible to trace the fate of some of the tissue grafts supplied for clinical use. This could

leave patients at risk without the appropriate investigation and treatment. In this case, particularly, centralized management of tissues and cells in the ORHA will facilitate effective action.

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

RISKS CONCERNING DONATION AND CLINICAL APPLICATION OF HUMAN TISSUES

Tissues used in transplantation have some similar characteristics to those of blood and blood components used for transfusion. Their donation is voluntary and unpaid. They are sometimes in scarce supply and have a relatively short shelf life.

Although donors of tissue and cells are carefully selected and tested and tissues themselves are processed and stored within the framework of inspected and authorised tissue establishments, an element of risk remains due to their exceptional nature.

LIVING DONOR ISSUES

Donation of tissues by living persons is rare, and is usually associated with removal of the tissue for reasons unrelated to donation (sometimes referred to as 'surgical residue'); examples are bone donation during primary hip replacement or skin donation during skin removal for cosmetic purposes. In these cases, risks to the patients are normally associated with the surgery itself rather than the donation. Bone can also be removed from patients for autologous use and in some cases these procedures may be associated with adverse outcomes or complications.

THE NOTIFY PROJECT

In September 2010 the NOTIFY Project was initiated as a joint venture by WHO and the Italian National Transplant Centre (CNT). In collaboration with the SOHO V&S project a major global initiative was organized aimed at providing a global interface for the vigilance and surveillance of substances of human origin (organs, tissues and cells for transplantation and for assisted reproduction). Over 100 experts collaborated to gather documented cases of adverse reactions and events using published articles and vigilance system reports as their sources. The cases were used as the basis for developing draft guidance on detection and confirmation of reactions and events, with an emphasis on the key role of the treating physician. A meeting of experts from 36 countries took place in Bologna from February 7th to 9th 2011 to explore the work already carried out and agree on priorities for the future development of global V&S for organs, tissues and cells.

The work demonstrates that tissues and cells carry a small but significant risk of transmission of disease and that grafting procedures may fail due to processing or storage errors. The meeting report and didactic documents have been published[7]. Moreover the information was inserted in a searchable database on the Notify Library website (see below).

THE NOTIFY LIBRARY OF ADVERSE EVENTS AND REACTIONS

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

The database of vigilance information collected by the Notify Project was made publicly available on the WHO/CNT Global NOTIFY Library web site (www.notifylibrary.org). Currently the Notify Library contains over 1,700 bibliographic references and is kept updated by international expert groups. It is a useful resource for evaluating the risk of different types of donation and transplantation, based on the history of documented adverse outcomes.

SERIOUS ADVERSE EVENTS AND REACTIONS ASSOCIATED WITH TISSUE DONATION OR CLINICAL APPLICATION: TISSUE VIGILANCE

SERIOUS ADVERSE REACTION AND EVENT (SARE) DEFINITIONS

According to Directive 2004/23/EC, serious adverse incidents associated with human tissues and cells are defined as follows:

- **Serious Adverse Event (SAE):** *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 (SAR):** *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.*

Reporting of both of these types of incident is required. Consequently, even those cases where no patient was harmed but where there was, or still is, a risk of serious harm, the incident should be reported to the national vigilance system.

It should be noted here that these definitions are different to the definitions of SAE and SAR used in the field of medicinal products but are very similar to those for blood and blood components.

SERIOUS ADVERSE REACTIONS (SAR)

DETECTING SAR

It is obvious that adverse outcomes following transplantation can be caused by many diverse factors unrelated to the quality, safety or specific characteristics of the human tissues supplied by the tissue establishment and then applied in the ORHA. It is very important, however, that the possibility that transplanted tissues might be the source of a problem in a recipient be considered by the treating physician on every occasion.

The treating physician plays a pivotal role in detecting and then reporting adverse patient outcomes that might be, or that are clearly, associated with the tissues, such as transmitted diseases and graft failures, or quality related issues that could imply errors in processing, storage, transport or handling. Without this information, tissue establishments may continue to supply infected or otherwise unsafe tissues and cells to other ORHAs for multiple patients.

It should be noted that errors in storage or handling affecting the quality and safety of tissues may happen both at the tissue establishment and at the ORHA. For this reason, all the activities concerning tissue management at the ORHA should be performed by designated personnel according to standard operating procedures which incorporate instructions provided by the supplying tissue establishment.

There are many cases in the scientific literature where physicians did not report adverse outcomes such as patient infections, assuming that they were a complication of surgery when in fact they were transmitted by the tissues or cells. Reporting these incidents could have prevented further transmissions. In most cases, a short investigation (see

below) will establish imputability and, if the tissues and cells were not associated with the incident, the matter will be managed within the hospital's own patient safety system.

TRIGGERS FOR A SUSPECTED SAR NOTIFICATION

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

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

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

REPORTING OF SUSPECTED SAR IN RECIPIENTS

No punishments for reporting of adverse patient outcomes have been foreseen by the EU Directives. On the contrary, the lack of notification is a non-compliance with EU directives and the national laws which implement these directives.

According to the minimum requirements described in Article 5 of Directive 2006/86/EC:

- Tissue establishments that distribute tissue for human application must provide information to ORHA about how ORHA should report any adverse reaction observed during and after clinical application which may be linked to the quality and safety of tissues and cells (suspected SAR), in accordance with the national or local requirements.
- ORHA should have procedures (incorporating information provided by the supplying tissue establishment) in place to notify the tissue establishment, without delay, of any suspected SAR. Suspected SAR notification procedures in the ORHA should include specification of who will be responsible for initial notification of a tissue establishment of a suspected SAR (e.g. a treating physician) and who will be the designated person for further contacts with the tissue establishment (e.g. either a treating physician or an authorised member of ORHA staff).
- Tissue establishments must have procedures in place to communicate to the Competent Authority for tissues and cells, without delay, all relevant available information about suspected SAR including date, type of tissues or cells involved in the nature of the suspected SAR.
- Tissue establishments must have procedures in place to communicate to the Competent Authority for tissues and cells, without delay, the conclusion of the investigation to of the cause and the ensuing outcome.

The obligation of the ORHA to notify tissue establishments of any SARs does not preclude the ORHA directly notifying the Competent Authority if it so wishes. If there is a local vigilance contact point, they should, in parallel, be contacted without delay.

It should be noted that if the case concerns tissue processed in the other EU country and supplied directly to the ORHA, the suspected SAR should be notified to the tissue establishment in the other Member State. However, in those circumstances, the Competent Authority for tissues and cells in the Member State where the graft was applied should also be informed.

If the tissues were from another EU Member State or from a country outside the EU and were supplied via a local tissue establishment, the suspected SAR should be reported to the local tissue establishment, which should then proceed to contact the original tissue establishment and the Competent Authority for tissues and cells as appropriate.

Although Directive 2006/86/EC requires ORHA only to notify the tissue establishment of suspected adverse reactions when they are considered to be serious, it is highly recommended that any adverse reaction possibly associated with the quality and safety of the tissues should be notified to the tissue establishment to allow trends in minor reactions to be monitored for continuous improvement purposes.

It should be noted that incidents classified as 'serious' i.e. which '*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*' require notification to comply with the EU legislation. Notification of non-serious incidents is not obligatory but can help to improve both quality and safety of tissues as well as their effective utilisation.

REPORTING SUSPECTED SAR IN DONORS

Programmes of allogeneic tissue and cell transplantation rely entirely on the good will of donors and donor families; without them, there would be no transplantation. Living donor care and protection is of fundamental importance both from an ethical perspective and to ensure the continued willingness of society to donate for the benefit of others. Allogeneic living donors should be well informed of the risks they take when agreeing to donate and the collation of donor reactions provides concrete information on which this risk evaluation can be based.

However, the circumstances in which tissues can be donated by a living donor are very limited. The most common type of living tissue donor is the donor of 'surgical residue' where tissue is removed as part of surgery for the patient's benefit and can be donated, e.g. the head of femur removed during hip replacement surgery. These donors are not normally exposed to additional risk by agreeing to donate; no cases of harm to such donors were recorded in the Notify process. However some reactions associated with tissue removal for autologous transplantation have been recorded.

SERIOUS ADVERSE EVENTS (SAE)

According to Directive 2004/23/EC Serious Adverse Event (SAE) is any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity. So for this type of incident, no patient or donor has been harmed but a risk has been identified.

Activities such as processing, storage and distribution take place primarily at the tissue establishment but after delivery of tissues to ORHA there could also be storage, handling or other activities that could result in an SAE.

Examples of untoward occurrences at the ORHA which might be categorized as serious adverse events, and should be reported to the tissue establishment are as follows:

- incorrect storage temperature
- container damage
- improper preparation before application e.g. omission of one of step such as thawing, washing, rehydration
- preparation of wrong tissue (mix-up)
- re-freezing of thawed tissue
- contamination of tissue.

SARE INVESTIGATION

When receiving a notification from an ORHA of an adverse reaction or event, the tissue establishment will investigate it in collaboration with the notifying ORHA in order to assess its imputability as well as to identify its cause. Investigation is necessary whenever an SARE is suspected (rather than confirmed) and whenever the cause of an SARE (even if confirmed) is not known. It should be noted that in the majority of cases SAR are caused by undetected SAE.

Scientific or medical experts, specialist scientific laboratories or institutes and scientific and professional societies can play a crucial role in the investigation of a suspected SAR or SAE, providing testing services, advice and interpretation, relevant data from other sources etc. In the case of a particularly high impact SAR/E, the Competent Authority may participate in the investigation or follow-up with an inspection to review corrective and preventive actions. In some Member States Competent Authority representatives have the authority to investigate and inspect within hospitals or other clinical entities while in other this is not the case. In the latter situation, the tissue establishment personnel will collaborate with the clinical entity, investigating as advised by the Competent Authority. Clinical entities, including ORHA should collaborate fully with tissue establishments and Competent Authorities where appropriate to permit ruling out other possible sources of problems e.g. to confirm recipient infection by another route or to identify other potentially affected patients and provide appropriate treatment. The process of reporting and investigation is summarized in Figure 1.

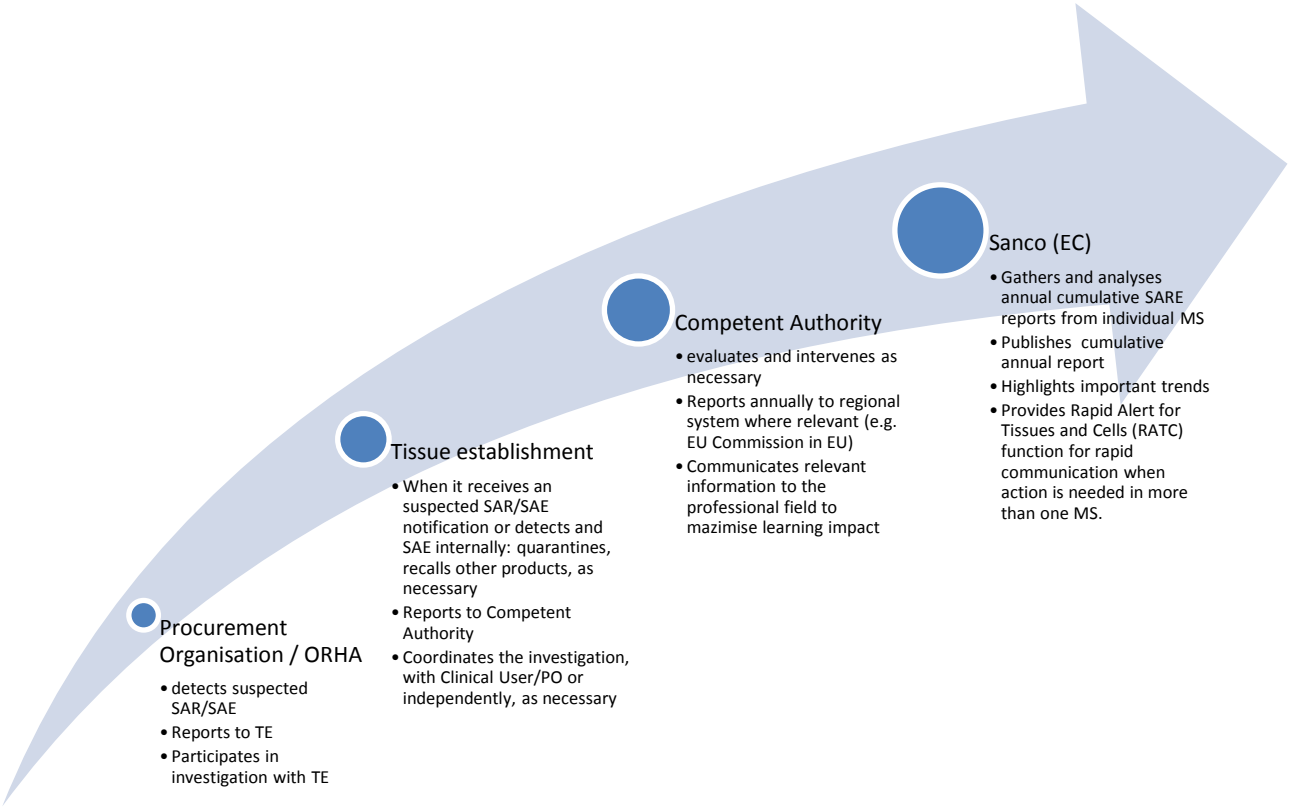

Figure 1: The Process of SARE reporting and investigation

Where a particular suspected SARE has implications or causes in more than one Member State, consideration should be given to the establishment of a multi-Member State investigation team. This should usually be organised by the tissue establishment that supplied the tissues or cells with the support of the Competent Authority.

INVESTIGATION METHODOLOGY

Investigation methodology will depend on the type of suspected SAR or the SAE that has occurred. In either case, previous experience of the type of SAR/E in other centres, or other countries, may provide important information for the investigation**.** The Notify Library (www.notifylibrary.org) is a useful source of information regarding previously documented cases, as well as the methodology followed for the assessment of imputability.

INVESTIGATION OF SUSPECTED SAR (OR AR)

The purpose of a 'suspected SAR' investigation is to establish imputability. **Imputability** is defined as:

'the likelihood that a serious adverse reaction in a recipient can be attributed to the tissue applied or that a serious adverse reaction in a living donor can be attributed to the donation process.' (adapted from Blood Directive 2005/61/EC).

Imputability of a suspected SAR may change in the course of the investigation, as evidence is gathered. In the case of suspected SARs in recipients, evidence may relate to establishing a link between the condition in the recipient and a characteristic of the tissue applied, or the identification of a similar condition in the donor. Alternatively, it may relate to the identification of other possible sources or causes for the condition in the recipient.

The following scale for imputability is included in the instructions for annual reporting to the European Commission.

NA	**Not Assessable**	Insufficient data for imputability assessment
0	**Excluded**	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes
0	**Unlikely**	Evidence clearly in favour of attribution to alternative causes
1	**Possible**	Evidence is indeterminate
2	**Likely, Probable**	Evidence in favour of attribution to the tissue
3	**Definite, Certain**	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells

ESTABLISHING IMPUTABILITY FOR SUSPECTED SAR INVOLVING POSSIBLE INFECTIOUS TRANSMISSIONS

SUSPECTED VIRAL, PARASITIC OR PRION TRANSMISSION FROM AN ALLOGENEIC DONOR

For the investigation of a suspected infectious transmission from an allogeneic donor, the tissue establishment and the ORHA that has detected the possible transmission should be involved, together with a testing laboratory with established specialist expertise for that infectious marker. The following steps would normally be included in the investigation:

- Full review of recipient clinical symptoms, test results and any alternative risk factors for the infection (life-style risk, relevant medical history, exposure to other substances of human origin such as blood etc.).
- If it is considered possible that the tissue donor is the source of the infection, the tissue establishment will:
  - check/test other recipients of tissues, cells and organs, where appropriate, from that donor;
  - review donor history for risk factors or other relevant information;
  - if the donor is deceased and an autopsy has since been performed, check whether there are results of relevance to this suspected transmission;
  - perform additional testing, as relevant, on biological material from the donor.

If the suspected infectious agent is one of those viruses for which testing is mandated, and NAT testing has not been performed on the donor sample prior to tissue release, it should be performed on an archive sample as part of the investigation[8]. **If the suspected infectious agent is not one of those included in the list of mandated donor tests**, the Competent Authority should support the tissue establishment in identifying a suitably specialist laboratory to perform tests on the recipient and on appropriate donor material as part of the investigation of imputability. This is particularly important in the case of new and emerging infections where many laboratories will not be equipped to test with appropriate sensitivity or specificity. In these circumstances, the most common approach to confirming imputability will be:

[8] It is noted that the EU Directives do not require the storage of an archive serum sample from each allogeneic donor. However, it is generally accepted good practice for testing laboratories to keep such a sample. In some cases, however, a serum archive might not represent the most appropriate material for testing for relevant agents.

- the identification of the same agent in the index recipient and in donor material;
- the identification of similar symptoms or clinical test results in other recipients of organs, tissues or cells from the same donor.

SUSPECTED ALLOGRAFT-ASSOCIATED BACTERIAL OR FUNGAL TRANSMISSION

The clinician must be suspicious that transmission of bacterial or fungal infection may occur in association with allograft implantation. In the setting of unexpected graft dysfunction, local signs (e.g., erythema, oedema, 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, 'rigors and tachycardia', 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.

Bacterial or fungal contamination of tissues may originate from the donor or from the process of procurement, processing or storage. As part of the investigation, any remaining samples of tissues from the donor should be similarly tested by the tissue establishment. If the donor is not identified as the source, then the tissue establishment will investigate whether the contamination was environmental or from reagents or additives used in processing or represented cross-contamination from other tissues.

In parallel, the ORHA should investigate whether the contamination might have originated from the hospital environment. Infections in other patients operated in the same operating room on the same should be investigated along with any environmental monitoring results that might be available.

ESTABLISHING IMPUTABILITY FOR SUSPECTED SAR INVOLVING POSSIBLE MALIGNANCY TRANSMISSIONS

There are very few documented cases of transmission of malignancy in the field of transplantation and none where the tissue has been rendered non-viable, acellular or sterile. Nonetheless, a history of malignancy is considered cause to exclude a potential tissue donor as a precautionary measure. An exception is cornea transplantation because of the avascular nature of the tissue.

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 immediately notify the tissue establishment so that other potentially affected recipients can be investigated. Donor transmitted malignancies should be suspected on the basis of clinical criteria. Clinicians should also take into consideration existing risk factors in the recipient's medical history. Even if imputability has not yet been determined, the suspicion of a transmitted malignancy should activate the alert, since preventive and therapeutic measures could be initiated for other recipients. The following steps would normally be included in the investigation:

- Full review of recipient clinical symptoms, test results and any alternative risk factors for the malignancy in the donor's medical history.
- If it is considered possible that the tissue donor is the source of the malignancy, the tissue establishment will:
    - check other recipients of tissues, cells and organs, where appropriate, from that donor;
    - review donor history for relevant information that might have been missed and, for living donors, check the donor's current health status;

- if the donor is deceased and an autopsy has since been performed, check whether there are results of relevance to this suspected transmission;
- perform histopathology on relevant biological material from the donor if possible.

The temporal sequence is an important factor in investigating imputability. 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.

Additionally, previous description of the transmission is important**.** A correct assessment of a case involves the analysis of the literature in order to understand whether the same tumor type was transmitted before by the type of tissue. The Notify Library (www.notifylibrary.org) provides important information regarding previous cases described, as well as the methodology followed for the assessment of imputability.

SAE INVESTIGATION

The investigation of a suspected SAE will normally be carried out by the tissue establishment although personnel at the ORHA may be asked to participate if the event occurred there.

The purpose of a suspected SAE investigation is to establish what caused the event. Wherever possible, a 'root cause analysis' process (RCA) should be followed rather than accepting superficial causes. Hence, rather than attributing a suspected SAE only to 'human error', efforts should be made to understand any contributing factors or circumstances that exacerbated the risk of the error occurring. The underlying causes might be understaffing, unduly long working hours, procedures that are not clear to staff, inadequate training etc.

INTERNATIONAL INVESTIGATIONS

Where a particular SAR/E has implications or causes in more than one Member State, consideration should be given to the establishment of a multi-Member State investigation team. This should usually be organised by the tissue establishment that supplied the HPCs, with the support of the Competent Authority.

V&S FEEDBACK FOR PRACTICE IMPROVEMENT

Data collected via vigilance and surveillance provides excellent material for training staff and improving practice. It is good practice to discuss any SARE that have occurred in the clinical entity at routine staff meetings. Discussions should include the details of the corrective and preventive actions taken at the clinical entity and, where relevant, at the tissue establishment or elsewhere. Clinical users are encouraged to publish cases of serious adverse outcomes, events or reactions, so that the didactic value of the cases can help to ensure that the field of tissue transplantation in general learns from the cases and changes practice to prevent their recurrence.

ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	DEFINITION
SOHO V&S	Vigilance and Surveillance of Substances of Human Origin
V&S	Vigilance and Surveillance
EU	European Union
WHO	World Health Organisation
ORHA	Organisation / Organisations Responsible for Human Application
SAR	Serious Adverse Reaction / Reactions
SAE	Serious Adverse Event / Events
SARE	Serious Adverse Reactions and Events

Glossary

Allogeneic: Refers to cells and tissues donated by one person for clinical application to another person.

Allograft: Tissues or cells transplanted between two genetically different individuals of the same species.

Autologous: Refers to cells or tissues donated by a patient for subsequent clinical application to themselves. . In ART, the terms 'autologous donors' and 'autologous use' apply to cases of preservation of fertility.

Cells: Individual human cells or a collection of human cells when not bound by any form of connective tissue.

Competent Authority (CA): Organisation(s) designated by an EU Member State as responsible for implementing the requirements of Directive 2004/23/EC.

Cross contamination: Transfer of micro-organisms from one material to another.

Direct use: Any procedure where cells are donated and used without any banking.

Distribution: Transportation and delivery of tissues or cells intended for human application.

Donor: Every human source, whether living or deceased, of human cells or tissues.

Error: A mistake or failure to carry out a planned action as intended or application of an incorrect plan that may or may not cause harm to patients.

Follow up: Subsequent examinations of a patient, living donor or recipient, for the purpose of monitoring the results of the donation or transplantation, care maintenance and initiating post-donation or post-transplantation interventions.

Human application: The use of tissues or cells on or in a human recipient and extracorporeal applications.

Human error: A mistake made by a person rather than being caused by a poorly designed process or the malfunctioning of a machine such as a computer.

Implantation/grafting: The process of inserting a piece of tissue or cells into a recipient.

Imputability: An assessment of the probability that a reaction in a donor or recipient may be attributed to the process of donation or clinical application or to an aspect of the safety or quality of the cells or tissues applied.

Incident: a generic term for an adverse reaction or event.

Preservation: The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.

Process: A series of related actions to achieve a defined outcome.

Processing: All operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human application.

Procurement: A process by which tissue or cells are made available for banking or clinical use.

Procurement Organisation*(PO)*; Means a health care establishment or unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue establishment.

Quarantine: The status of retrieved tissue or cells, or equipment that is isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection.

Recall: Removal from use of specific, distributed tissues and cells suspected or known to be potentially harmful.

Recipient: Person to whom human tissues, cells or embryos are applied.

Recovery or Retrieval: See Procurement.

Root cause analysis: A structured approach to identifying the factors that resulted in the nature, the magnitude, the location and the timing of a harmful or potentially harmful outcome.

Risk assessment: Identification of potential hazards with an estimation of the likelihood that they will cause harm and of the severity of the harm should it occur.

Serious adverse event*:* Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patient or which might result in, or prolong, hospitalisation or morbidity. In addition, the definition of SAE includes the total loss of germinal tissues, gametes or embryos for one cycle and any mix-up of gametes or embryos.

Serious adverse reaction: An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity. The definition of SAR should be extended to the offspring in the case of non-partner donation in ART, only for cases of transmission of genetic diseases.

Severity: Directive 2006/86/EC defines 'serious' as: fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity. A grading system for severity has been agreed and is presented in the Vigilance and Surveillance Tool.

Standard Operating Procedure: Written instructions describing the steps to be followed in a specific process including the materials and methods to be used and the expected result.

Surveillance: 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.

Tissue Establishment: A tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells. In the field of ART, TE applies to establishments performing ART activities: ART centres, ART laboratories, sperm banks, etc.

Traceability: The ability to locate and identify tissues or cells 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.

Transplantation: The transfer (engraftment) of human cells, tissues or organs from a donor to a recipient with the aim of restoring function(s) in the body. When transplantation is performed between different species, e.g. animal to human, it is called xenotransplantation.

Transport: To transfer or convey tissues or cells from one place to another.

Undue risk: Refers to the exposure of a patient or donor to a risk that was avoidable.

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

ANNEX 1: SOHO V&S PROJECT PARTNERS

Organisation (Abbreviation), Country
Co-ordinating Partner
Centro Nazionale Trapianti (CNT), Italy
Other Steering Committee Members
Agence de la Biomedecine (ABM), France
Agence Francaise di Sécurité Sanitaire des Produits di Santé (AFSSAPS) – now: Agence Nationale de Sécurité du Médicament (ANSM), France
Irish Medicines Board (IMB), Ireland
Krajowe Centrum Bankowania Tkanek i Komórek (KCTBiK), Poland
Organizacion Nacional de Trasplantes (ONT), Spain
Human Fertilisation and Embryology Authority (HFEA), UK
Human Tissue Authority (HTA), UK
Donor Action, Belgium
World Health Organisation (WHO), Switzerland
Collaborating Partners
Paul-Ehrlich-Institute (PEI), Germany
University Hospital Bratislava, Central Tissue Bank (CTB), Slovakia
Ministry of Health and Social Welfare (MHSW), Croatia
Executive Agency of Transplantation (EAT)
Centro operativo adempimenti legge 40/registro nazionale PMA
Danish Medicines Agency (DMA) now: Danish Health and Medicines Authority, Denmark
Inspectie voor de Gezondheidszorg Toezichteenheid Geneesmiddelen en Medische Technologie (IGZ), The Netherlands
Federal Ministry of Health, Austria
United States Food and Drug Administration (FDA), USA
Blood Safety Surveillance and Health Care Acquired Infections Division Centre for Communicable Disease and Infection Control Public Health Agency of Canada (PHAC), Canada
Tissue and Cell Inspectorate Cyprus
Slovenia-transplant, Slovenia

Transfusion Reactions in Patients (TRIP), the Netherlands
Office of Blood, Organ and other Tissue Safety Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (CDC), USA
Department of Pathology and Laboratory Medicine & McLaughlin Centre for Population Health Risk Assessment, University of Ottawa (UoO), Canada
European Association of Tissue Banks (EATB)
American Association of Tissue Banks (AATB)
European Society for Human Reproduction and Embryology (ESHRE)
European Eye Banking Association (EEBA)
European Society for Bone Marrow Transplantation (EBMT)
UK Public Health Agency (PHA), UK
International Haemovigilance Network (IHN), the Netherlands
Ministry of Health, Malta
American Association of Blood Banks
World Marrow Donor Association

ANNEX 2: WORK-PACKAGE 9 DRAFTING GROUP AND PROFESSIONAL SOCIETY COLLABORATION

Organisation (Abbreviation)
Drafting group
Krajowe Centrum Bankowania i Komórek (KCTBiK), Poland – Work Package Leader
Centro Nazionale Trapianti (CNT), Italy
Agence Francaise di Sécurité Sanitaire des Produits di Santé (AFSSAPS) – now: Agence Nationale de Sécurité du Médicament (ANSM), France
Organizacion Nacional de Trasplantes (ONT), Spain
Human Fertilisation and Embryology Authority (HFEA), UK
Donor Action, Belgium
Ministry of Health and Social Welfare (MHSW), Croatia
University Hospital Bratislava, Central Tissue Bank (CTB), Slovakia
Professional Societies
European Association of Tissue Banks (EATB)
European Society for Human Reproduction and Embryology (ESHRE)
European Eye Banking Association (EEBA)
European Society for Bone Marrow Transplantation (EBMT)
World Marrow Donor Association (WMDA)