

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



DELIVERABLE 10

PART 2 – HAEMATOPOIETIC STEM CELLS

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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 2 of these guidelines focuses on the key role of HPC transplant physicians and supporting personnel in:

- maintaining HPC traceability
- recognizing, reporting and investigating serious adverse reactions and events (SAREs) associated with HPCs
- recall and look-back management procedures where there is a need to contact the patient(s) who received cells from a particular donor from a particular processing centre.

Part 2 is also addressed to ORHA personnel who are responsible for ordering, receiving and storing of HPCs prior to clinical application. It provides guidance on:

- the management of HPC products, including ordering, receiving, storage, handling and disposal,
- management of recalls where the supplying centre requests the immediate return of distributed HPC 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](#)).

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 their hospitals and clinics, either directly or via tissue establishments.

REGULATORY FRAMEWORK

EUROPEAN UNION TISSUE AND CELL DIRECTIVES

Directive 2004/23/EC¹, and its associated Commission Directives 2006/17/EC² and 2006/86/EC³, regulate the field of human tissues and cells for clinical application in the European Union. These Directives have been transposed into

¹ 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).

² 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).

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 authorised, accredited, designated or licensed by the Competent Authority in the Member State.

The Directives do not apply to:

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

HPC MANAGEMENT IN AN ORHA

ORHA routinely receive cells from external suppliers. Once HPC have been distributed by a tissue establishment (or a Procurement Organisation in the case of 'direct distribution', where a Competent Authority may authorize a collection

³ 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).

centre to send a donation directly to a transplant centre⁴) for clinical use, appropriate storage and handling becomes the responsibility of the ORHA. To ensure traceability, the ORHA should designate oversight responsibility for requested, received, stored and applied cells to named individuals. It is highly recommended that all activities concerning HPC management such as requesting, receiving, storing, clinical application or disposal and SARE reporting and recall management should be systematically documented e.g. in a logbook (see below). In the case of larger ORHA, which possess their own Quality Management System, all the above mentioned activities should be incorporated into this system where the roles and tasks of officially designated personnel should be clearly specified in Standard Operating Procedures. The procedures should take into account the guidance of the Joint Accreditation Committee-ISCT (Europe) & EBMT (JACIE)⁵.

SUPPLIERS OF HPCS

Hospitals or clinics that transplant HPCs should be aware that all HPCs (whether they are of unrelated donor origin, they have been removed from the patients themselves or provided by relatives of patients) come under the regulation of the EU tissues and cells Directives. As such, if they are recovered, processed and stored (where applicable) in the EU, they must be provided for clinical use by 'tissue establishments'⁶ that are authorized (the terms accredited, designated or licensed may also be used) by the Competent Authority in the Member State, apart from particular circumstances of 'Direct Distribution' described above Competent Authorities may be national or regional. A registry of EU Competent Authorities for Tissues and Cells with contact details is provided on the Eurocet website (www.eurocet.org). Authorised tissue establishments are regularly inspected by Competent Authorities to confirm compliance with the legal requirements.

Transplant centres should ask to see an authorization certificate from the appropriate Competent Authority for any HPC processing centre or cord blood bank that is supplying HPC to them from the EU. The certificate should specify the types of tissues or cells and the general activities for which the centre is authorized. The centre should be regularly inspected by the Competent Authority to confirm compliance with the legal requirements.

SERVICE LEVEL AGREEMENTS BETWEEN ORHA AND TE OR HPC DONOR REGISTRY

It is recommended that a service level agreement be signed between the ORHA and the HPCs donor Registry for allogeneic transplantation, or TE for autologous transplantation. The agreement should define responsibilities of each party regarding traceability, adverse reaction and event reporting and investigation and patient follow up. Moreover, the scope of the agreement should include contact person details, the procedures for requesting and delivery (including liability for transport), the need to comply with specific conditions of storage and preparation for use, as well as the management of recalls.

As, theoretically, the number of registries a single ORHA is collaborating with could be high, it is recommended to make an agreement at least with the most frequent collaborating register.

For situations where an ORHA and supplying TE are within the same health care institution, responsibilities should be specified in the Quality System documentation.

⁴ Article 6 Directive 2006/17/EC

⁵ JACIE standards reference

⁶ '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 (EU Directive 2004/23/EC)

Written agreements should be signed, dated, reviewed, and renewed regularly and must be in compliance with applicable laws and regulations.

RECEIVING HPCS FROM ANOTHER EU MEMBER STATE

The EU legislation does not consider the movement of tissues and cells between Member States to be import or export. The Directives indicate that any tissue establishment that is authorized in its own Member State may provide tissues or cells direct to clinical units in other Member States. However, it should be noted that some Member States have implemented more stringent rules (as the legal basis for these Directives allows) and do require a formal import procedures to be followed even when the material is coming from another EU country. It is important, therefore, to be aware of the local legislation.

RECEIVING HPCS FROM OUTSIDE THE EU

The importation of tissues and cells from outside the EU must be via an authorized HPC facility within the Member State. The only exceptions to this are the case of 'direct distribution'⁷ or in cases of emergency. In both these cases, the Competent Authority must authorize the import directly. The authorised centre that imports and supplies HPCs from outside the EU must take responsibility for ensuring that standards of quality and safety have been applied at the source organization that are equivalent to those required in the EU. Importation of tissues or cells from outside the EU by organizations that will apply them clinically is not permitted unless they have an exceptional authorization from the national Competent Authority. HPC donor registries, and particularly the World Marrow Donors Association (WMDA), play an important role in supporting this process of establishing equivalent safety and quality when importing from outside the EU.

RECEIVING HPC UNDER CONDITIONS OF EXCEPTIONAL RELEASE

In exceptional circumstances, a transplant centre may agree with a HPC centre or cord blood bank that cells 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 cells concerned. The risk assessment should be documented before acceptance of the exceptionally released material. The recipient patient's physician should participate with the Medical Director of the HPC supplying centre or cord blood bank in the conduct of the risk assessment and the risk:benefit analysis of the particular recipient and the discussions and conclusions should be documented. The treating physician should sign 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. Examples of cases where there might be an exceptional release would include: donor and recipient are both HBV or HCV positive, the donor has Thalassemia minor, the donor had skin cancer successfully removed, there is known bacterial contamination in the donation.

CENTRALISED Vs. DECENTRALISED MANAGEMENT OF HPCS IN THE ORHA

No specific model for the management of HPCs received by ORHA for transplant is mandated in the EU. The most prevalent model is that the material is delivered direct to the department where they will be used; i.e. a decentralized

⁷ 'Direct distribution' refers to an exception for some tissues and cells which may, with the agreement of the competent authority or authorities, be distributed directly for immediate transplantation to the recipient as long as the supplier is provided with an accreditation, designation, authorisation or license for this activity. An example would be bone marrow donated for immediate transplantation without storage or processing.

model. The control of the process by the users is the greatest advantage of the decentralized model, but traceability of cells is difficult in such a model and compliance with the requirements for storage and handling is also problematic. Centralised models greatly improve the ability to trace tissues and cells and can significantly improve inventory control and compliance with safety and quality standards. For these reasons, a centralized model for the receipt, short term storage and traceability of HPCs for human application is strongly recommended; the blood bank is likely to be the best option for this function.

TISSUE RECEIPT AT THE ORHA

INCOMING INSPECTION

Once HPC products have been distributed by a tissue establishment for clinical use, appropriate storage and handling becomes the responsibility of the ORHA. There should be written procedures for the incoming inspection. The inspection should include the following:

- Verification that HPCs received correspond with those ordered by examining the container labels and the accompanying documentation, which has to be complete and legible;
- The packaging should be inspected for any signs of damage during transport and for any evidence that the required transport temperature was not maintained. For cells 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 cells – wet ice). The supplying centre 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.
- There should be verification that both shipping and primary containers are labelled with the information required. According to Directive 2006/86/EC, the primary cell container label (the container in direct contact with the cells) must provide:
 - type of cells, identification number or code identification of the supplying centre;
 - expiry date (if applicable);
 - in the case of autologous donation, this has to be specified (*For Autologous Use Only*) and the donor/recipient has to be identified;
 - in the case of directed donations - the label must identify the intended recipient;
 - if HPCs are known to be positive for a relevant infectious disease marker, the container must be labelled as: BIOLOGICAL HAZARD.

If any of the above information 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.

- The following information must be provided either on the label or in accompanying documentation:
 - description (definition) and critical characteristics of the HPC product;
 - morphology and functional data where relevant;
 - date of distribution of the cells;
 - biological determinations carried out on the donor and results;
 - storage recommendations;
 - instructions for opening and any required manipulation/reconstitution;
 - expiry dates after opening/manipulation;
 - instructions for reporting serious adverse reactions and/or events;
 - presence of potential harmful residues.

The accompanying documentation should highlight any specific identified risk factors, for example, side effects could occur with a product rich in granulated cells. There should also be included a transplant follow-up form.

ADDITIONAL QUALITY TESTING

When applicable, critical characteristics of the product should be verified (e.g. viability, CD34, HLA etc.) in line with the procedures in place at the ORHA and agreed with the supplying centre.

HPC STORAGE PRIOR TO CLINICAL USE

STORAGE CONDITIONS

Storage conditions before use should assure sterility and potency of the cell transplant as well as minimise deterioration of physical damage. Access to the storage device should be restricted and controlled. Each type of HPCs, non-cryopreserved and cryopreserved, should be stored according to package insert information. It should be ensured that during short term storage, before clinical application, product associated documentation is clearly linked to the HPC product and easily accessible. Temperature and/or liquid nitrogen level should be continuously monitored. Monitoring data should be recorded.

STORAGE EQUIPMENT

Where a specific storage temperature is necessary from receipt to clinical application, the storage device 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.

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 TRANSPLANTATION OF HPCS

RECIPIENT CONSENT

It is necessary that patients who will receive a HPC transplant give their consent to the procedure in compliance with prevailing legal requirements. It is highly recommended that this consent should be in written form and include a description of the cells to be transplanted as well as any potential risks involved. The Notify Library database may be a useful tool for accessing risk information for particular HPC types. The information given to a prospective recipient should include at least the following:

1. The rationale for choosing the selected therapy;
2. The risks associated with the use of the human cells, with particular reference to adverse outcomes that are documented for the specific type of HPCs to be transplanted and any alternative therapies available.

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

1. Confirmation that the recipient has been appropriately informed of any risks to their health associated with the planned transplantation;
2. The acceptance of the recipient of the risks described above.

This form should be equivalent to any such consent for blood transfusion.

HPC PREPARATION BEFORE USE.

Any specific preparation instructions included in the package insert should be followed precisely. These might include instructions for thawing, and/or particular cell preparation processes. 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. Thawing of frozen products should be performed in monitored conditions and using designated and maintained equipment. Dilution, when necessary, should take a place in aseptic conditions and with biocompatible isotonic solutions.

FINAL INSPECTION PRIOR TO CLINICAL APPLICATION

Immediately before attaching an infusion device to a bag of cells, the label should be checked finally to ensure that the correct product has been allocated to the correct patient. Inspection should include checking of unique product identification code, product type, name and identification code of the intended recipient, visual inspection of the bag(s) for any signs of damage and visual inspection of the product. It is recommended that the confirmation of the product and intended recipient is done by two persons, and identification of the intended recipient is made from at least two identifiers.

STEPS TO BE TAKEN AFTER HPC INFUSION

TRACEABILITY RECORDS

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

- (a) Identification of the supplier tissue establishment
- (b) Identification of the clinician or end user/facility
- (c) Type of tissues and cells
- (d) Product identification
- (e) Identification of the recipient
- (f) Date of application

TRACEABILITY LOG-BOOK OR DATABASE

Details of the cells applied should be in the recipient's hospital record. On its own, this is not adequate to permit rapid retracing of patients who might be at risk from a particular donation or processing batch. Transplant centres should also have an electronic or paper 'log' where all received, transplanted and discarded HPC products are recorded, for quick and easy action in the case of a 'recall' by the tissue establishment or the Competent Authority or a 'look/trace back' in the event that all recipients of cells from a particular donor or a particular process run or laboratory must be contacted and monitored. Careful consideration should be given to where and how this log will be archived for the required period.

HPC TRANSPLANT REPORT

Transplant centres should return traceability information to the supplying HPC centre or cord blood bank to confirm the identity of the recipient. A copy of the 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 information does not release the transplant centre from its responsibility to maintain the information to ensure traceability. Where reports of transplants are returned to the supplying 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.

RECIPIENT FOLLOW-UP

Case-by-case clinical follow-up and reporting of recipient clinical progress is highly recommended for HPC transplantation. For each transplant patient, the time to neutrophil and platelet engraftments should be filled in and sent to the Cell Therapy Unit responsible for the graft production. This routine clinical follow-up is not generally considered as part of vigilance. The follow-up protocol should be agreed in advance with the tissue establishment or the national registry or professional society that is collecting the data. It is strongly recommended that follow-up protocols include ORHA obligations to report to TEs the death of patients for whom the TE is storing autologous or allogeneic matching HPC product. Procedures for follow-up should be the part of the ORHA's QA documentation.

Additionally it is recommended that a process be established to obtain feedback from patients and their representatives.

MANAGEMENT OF RECALLS AND LOOK-BACKS

There are various reasons why a tissue establishment may recall cells that have been distributed to an ORHA. It may be related to new information received regarding the donor's 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.

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

RISKS ASSOCIATED WITH HPC DONATION AND TRANSPLANTATION

Although donors of tissues and cells are carefully selected and tested and the material itself is processed and stored within the framework of inspected and authorised centres, an element of risk remains due to the exceptional nature of the material. The process of donating HPCs can also present risk to donors.

LIVING DONOR ISSUES

Donors of HPCs, both bone marrow and peripheral blood stem cells, should be thoroughly informed regarding the risks posed by these procedures. It is noted that the World Marrow Donors Association (WMDA) already collects, records and publishes all cases of serious adverse reactions in allogeneic, unrelated donors reported by its members. Worldwide, unrelated bone marrow donor registries must participate in this vigilance programme, sending quarterly reports, to maintain their accreditation. The results are made publicly available.

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 published⁸. Moreover the information was inserted in a searchable database on the Notify Library website.

THE NOTIFY LIBRARY OF ADVERSE EVENTS AND REACTIONS

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 including those working on the WMDA's S(P)EAR vigilance programme for HPCs. The library is a useful resource for evaluating the risk of different types of donation and transplantation, based on the history of documented adverse outcomes, evaluated by experts in the field.

SERIOUS ADVERSE EVENTS AND REACTIONS ASSOCIATED WITH HPC DONATION OR TRANSPLANTATION: HPC 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.*

⁸Notify. Exploring Vigilance Notification for Organs, Tissues and Cells. Organs Tissues & Cells, 2011, November, 14, 3: Suppl.

It should be noted here that these definitions are different to definitions of adverse incidents used in the field of medicinal products.

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

SERIOUS ADVERSE REACTIONS (SAR)

DETECTING SAR IN RECIPIENTS

The treating physician plays a pivotal role in detecting adverse patient outcomes that might be associated with the HPCs infused, such as transmitted diseases or graft failures or quality related failures that imply errors in processing, storage or handling. Without this information, tissue establishments may continue to supply unsafe or ineffective products to other centres.

When patients who have been treated with human tissues or cells are discharged from a clinic or hospital, 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 tissues or cells applied.

TRIGGERS FOR SUSPECTED SAR IN RECIPIENTS

Clinical symptoms or situations suggesting that any of the following reactions might have occurred in a HPC recipient (**abbreviated descriptions in brackets**) should be seen as triggers for an adverse reaction report. Note 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, cells or associated materials from procurement to clinical application (**Infection – Tissue/cells**)
- (c) Hypersensitivity reactions, including allergy, anaphylactoid reactions or anaphylaxis (**Hypersensitivity**)
- (d) Malignant disease possibly transferred by the tissue/cells (whatever the origin, donor or process) (**Malignancy**)
- (e) Unexpectedly delayed or absent engraftment, graft failure (**Failure**)
- (f) Toxic effects from the HPC or associated materials (**Toxicity**)
- (g) Unexpected immunological reactions due to mismatch (**Mismatch**)
- (h) Aborted procedure involving unnecessary exposure to risk e.g. wrong HPC supplied, patient already subjected to immuno-ablative therapy (**Undue Risk**)
- (i) Suspected transmission of a 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 donation).

TRIGGERS FOR SUSPECTED SAR IN BONE MARROW DONORS

The literature review conducted in NOTIFY summarised the various types of reactions that bone marrow donors might experience. All cases recorded relate to the allogeneic setting, mostly unrelated and in the immediate or short-term.

Reactions included constitutional symptoms such as nausea, vomiting, anorexia, insomnia, fatigue (most common) and site-related localised pain and injury to bone and soft tissue. Cytopenias (anemia, thrombocytopenia) and more serious reactions such as DVT, thromboembolism, CVA and subdural bleeding have also been documented in the literature. Post-donation septicaemia and anaesthesia-related complications have also been described, as well as respiratory complications such as pulmonary alveolitis and oedema.

TRIGGERS FOR SUSPECTED SAR IN PERIPHERAL BLOOD STEM CELL DONORS

While DVT and thromboembolism have also been described in peripheral blood stem cell donors, the more common reactions in these donors are related to mobilisation agents or to the apheresis procedure. Documented mobilisation related reactions include pain and constitutional symptoms such as malaise, insomnia, nausea and vomiting, sweats, other flu-like symptoms and fatigue. Reactions associated with the apheresis procedure include catheter-related pain, Ca, Na and K alterations and ACD-related bleeding, as well as ACD-related seizure/neurologic/cerebral events. Cytopenias (other than thrombocytopenia) and leukocytosis have also been described. All cases recorded relate to the allogeneic setting, mostly unrelated and occurring in the immediate or short-term. Failure of the apheresis procedure can result in the need for a second apheresis; this places the donor at additional risk and many would consider that it should be reported as an SAR.

SERIOUS ADVERSE EVENTS (SAE)

In accordance with its definition, no patient or donor has been harmed in this type of incident, but a risk has been identified. Most SAE occur during activities such as processing, storage and distribution that take place primarily at the tissue establishment. However, after delivery of HPC to the ORHA, storage, handling or other activities could also 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 washing
- preparation of wrong product (mix-up)
- re-freezing of thawed cells
- contamination of cells.

REPORTING OF SUSPECTED SARE

A physician suspecting or confirming an adverse event or reaction related to the donation or application of HPC should immediately contact the tissue establishment that distributed the tissues or cells to them, even if they were procured and processed in another country. If there is a local vigilance contact point in the clinic or hospital, they should, in parallel, be contacted without delay. Further contacts with the TE that provided the HPC should be led by a designated person. No punishments for reporting of adverse patient outcomes have been foreseen by the EU legislation. On the other hand, lack of notification is a non-compliance with the EU directives.

Although the minimum requirements described in Article 5 of Directive 2006/86/EC require ORHA to notify to tissue establishments only **serious** adverse events and reactions, it is recommended here that all adverse events and reactions that are suspected of being related to the quality and safety of the HPCs supplied should be notified to tissue establishment. This reporting will allow trends in minor events and reactions to be monitored for continuous improvement purposes. Tissue Establishments should then apply the tools described here to assess the severity, the imputability and the impact, in collaboration with appropriate stakeholders, and to identify those **serious** adverse events and reactions that should be notified to Competent Authorities. Moreover it is highly recommended that even those incidents where no patient has been harmed but there was, or still is, a risk of serious harm, should be reported to the tissue establishment.

If the case concerns HPC processed in another EU country and supplied directly to the ORHA for human application, the suspected SAR/E should be notified to the tissue establishment in the other Member State. However, in those circumstances, it is strongly recommended that the Competent Authority in the Member State where the tissues or cells were used is also informed. If the material was from another EU Member State or from a country outside the EU and was supplied via a local tissue establishment, the suspected SAR/E should be reported to the local establishment which should then proceed to contact the original tissue establishment and the Competent Authority as appropriate.

The tissue establishment should provide detailed information in appropriate language to procurement organizations and ORHA on the procedure to follow in the event that an adverse event or reaction is suspected or confirmed. When receiving a report, the tissue establishment will investigate it in order to identify the cause and assess severity and imputability and, in collaboration with the reporting organisation, will notify as appropriate the Competent Authority. It will take any necessary actions, including preventive or corrective actions such as recalling other implicated tissues or cells or quarantining implicated donations. The competent authorities will ensure that appropriate measures have been taken and that other Member States have been informed where relevant. The directives makes it clear that the key role of the tissue establishment in reporting to the Competent Authority does not preclude a procurement organization or an ORHA that has applied tissues or cells from directly notifying the Competent Authority if it so wishes. The process is summarized in Figure 1.

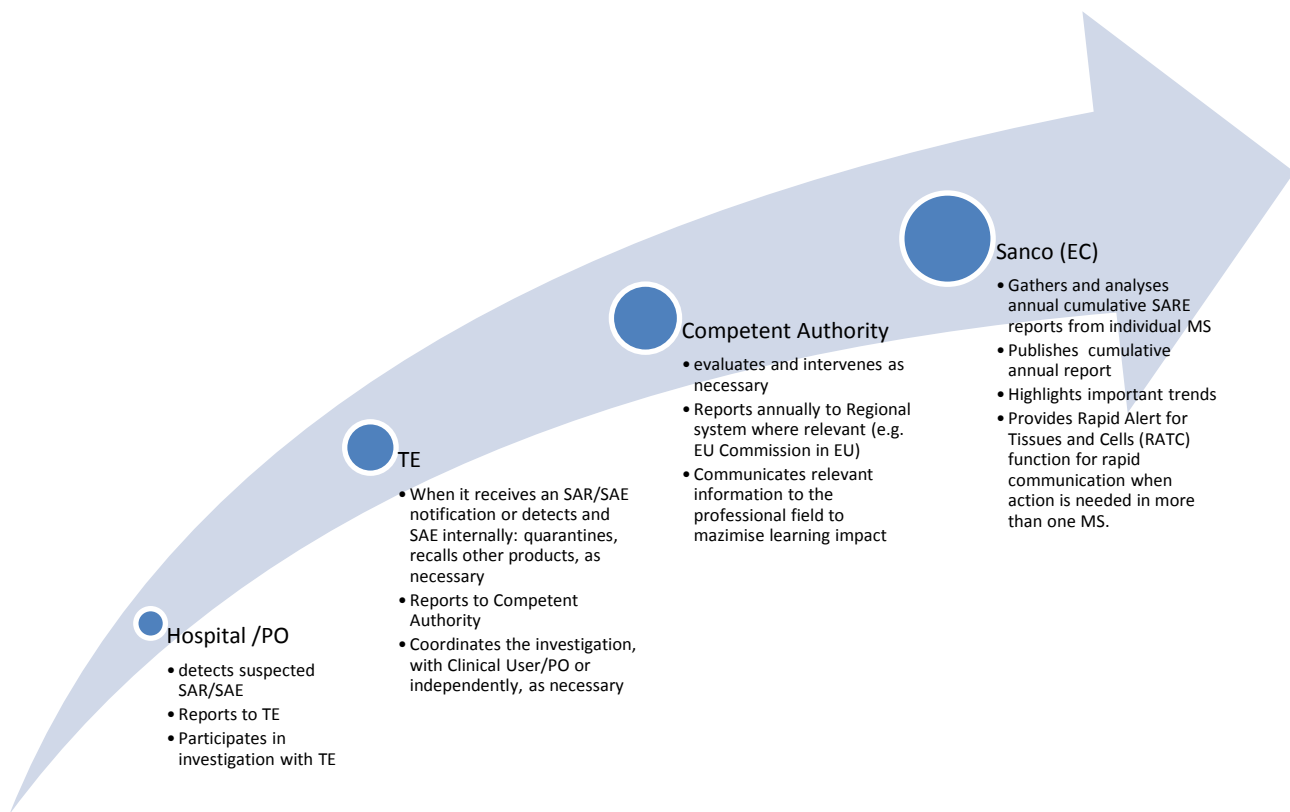


Figure 1: The Process of SARE reporting and investigation

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 a 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.

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

The purpose of an 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 or cells 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 an SAR may change in the course of the investigation, as evidence is gathered. In the case of SARs in recipients, evidence may relate to establishing a link between the condition in the recipient and a characteristic of the HPC 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 to Member States for annual vigilance reporting to the European Commission.

NA	Not Assessable	Insufficient data for imputability assessment
	Excluded	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes
	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 tissues/cells
3	Definite, Certain	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells

When assessing imputability of an SAR, an important aspect to consider is whether the incident has ever happened before with the same or similar clinical procedures. The Notify Library of Adverse Events and Reactions is a useful resource for establishing this. The project was developed by the World Health Organization (WHO) and the Italian National Transplant Centre (CNT) and the EU-funded SOHO V&S project with the collaboration of experts and regulators across the globe. The scope of the project included organs, tissues and cells for transplantation and for assisted reproduction. Expert groups, including those in the World Marrow Donor’s Association (WMDA) vigilance group, worked collaboratively to gather and review 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 1,700 published references have been collected and new cases continue to be added. The expert analysis includes information regarding how the imputability was established for specific SAR types. The information is now available in a searchable database on a public website www.notifylibrary.org.

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 clinical unit 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 HPC donor is the source of the infection, the tissue establishment will

- Review donor history for risk factors or other relevant information
- 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 /cell release, it should be performed on an archive sample as part of the investigation⁹. If the suspected infectious agent is not one of those included in the list of mandated donor tests, the tissue establishment and/or the ORHA should identify 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

- 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 HPC infusion. In the setting of unexpected symptoms of infection, 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.

Bacterial or fungal contamination of HPC may originate from the donor or from the process of procurement, processing or storage. As part of the investigation, archived biological samples of 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 another donation.

⁹ 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.

ESTABLISHING IMPUTABILITY FOR SARS INVOLVING POSSIBLE MALIGNANCY TRANSMISSIONS

There are very few documented cases of transmission of malignancy in the field of tissues and cells. Quantitatively, the most relevant information is related to haematopoietic stem cell (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. In general, a history of malignancy is cause to exclude a potential tissue or cell donor. Transmission of hematological malignancies through cell transplantation has been reported in a number of well described cases.

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. The following steps would normally be included in the investigation:

- Full review of recipients 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 HPC donor is the source of the malignancy, the tissue establishment will
 - Review donor history relevant information that might have been missed and, for living donors, check the donor's current health status
 - Perform histology on relevant biological material from the donor if possible.

The temporal sequence is an important factor in investigating imputability. Most transmitted tumours appear within the first 14 months after transplantation. Therefore, it is unlikely that an aggressive tumour diagnosed in the recipient 5 years after transplantation is donor-transmitted.

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 tumour type has been transmitted before by the type of tissues or cells. 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 purpose of an SAE investigation is to establish what caused the event. Wherever possible, root causes should be sought rather than superficial causes. Hence, rather than attributing an SAE only to 'human error', efforts should be made to understand any contributing factors or circumstances that exacerbated the risk of the error occurring.

Investigation is necessary whenever an SARE is suspected (rather than confirmed) and whenever the cause of an SARE (even if confirmed) is not known.

The investigation of SAEs will normally be carried out by the tissue establishment although personnel at the ORHA may be asked to participate if the SAE occurred there. SAE investigation essentially comprises a 'root cause analysis' process (RCA). It is easy to conclude that mistakes are caused by 'human error' but this error often has an underlying cause that must be identified and addressed if repetition of the error is to be avoided. The underlying causes might be understaffing, unduly long working hours, procedures that are not clear to staff, inadequate training 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 HPC 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

Term	Definition
Organisation Responsible for Human Application (ORHA)	
Vigilance & Surveillance (V&S)	
Traceability	
Serious Adverse Reaction (SAR)	
Serious Adverse Event (SAE)	

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.

Disinfection: A process that reduces the number of viable microorganisms, but does not necessarily destroy all microbial forms, such as spores and viruses.

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.

Haematopoietic Cell: Cells capable of self-renewal as well as maturation into any of the haematopoietic lineages, including committed and lineage-restricted progenitor cells, unless otherwise specified, regardless of tissue source.

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.

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.

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 and 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 de 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 Toezichtseenheid 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 de Sécurité Sanitaire des Produits de 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)