Tools for Vigilance and Surveillance of Human Tissues and Cells

Vigilance and Surveillance Medical Advisory Committee

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Contents

1.0 Introduction

This document provides a collection of tools that can be used for the implementation of Vigilance and Surveillance in accordance with the requirements of

- Directive 2004/23/EC of the European Parliament and the Council of 31st March 2004 on setting the standards of quality and safety for the donation procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- 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 donation, procurement and testing of human tissues and cells
- Directive 2006/86/EC of the 24th 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.

It includes a glossary (Annex 3) describing the main terms used in this area, a number of tools derived from existing vigilance systems, a classification of the types of adverse events and reactions and examples.

2.0 The EUSTITE Project

All European Union (EU) Member States (MS) have recently implemented, or are currently planning to implement, systems for the inspection and certification of tissue establishments and for surveillance of adverse events and reactions related to the quality or safety of the tissues and cells provided by these establishments. There is currently wide variation both in the approaches being taken and in the stage of development of these initiatives in the various MS. The EUSTITE project aims to promote standardisation to good practice in the inspection of tissue establishments and to develop optimal systems for the notification and management of adverse events and reactions related to the quality and safety of tissues and cells applied to patients in the EU, whether they originate from within the EU or from third countries.

The project is being carried out by a consortium of organisations from 10 MS (see www.eustite.org for details) and the World Health Organisation (WHO) and is being led by the National Transplant Centre in Italy. The partners in the consortium have been selected to represent a broad cross-section of the current scope and level of development of tissue establishment inspection activity and vigilance and surveillance activity in the EU. They include organisations nominated as Competent Authorities (CA) for tissues and cells for transplantation (including haematopoietic progenitor cells) or for assisted reproduction, both with and without experience to date, and organisations with extensive experience in the provision of these services from countries where a competent authority has not yet been nominated. The WHO provides an essential link from the project to global developments in tissue and cell regulation and surveillance.

2.1 EUSTITE Inspection Guidance

A key specific objective of the project is to produce guidelines for the inspection of tissue establishments. A second edition of these guidelines has been finalized following an open consultation. From September 2008, a series of training courses for inspectors will be offered to EU CAs.

2.2 EUSTITE Vigilance and Surveillance (V&S)

In parallel with the activities related to guidelines and training for inspection, a group of experts in the clinical application of tissues and cells and the associated risks, notably of disease transmission, has reviewed existing systems for adverse event and reaction notification and management in MS and in related fields globally. The report of this review is available on the EUSTITE website.

Two meetings of the Vigilance and Surveillance Medical Advisory Committee of the EUSTITE project have taken place. The first meeting, held in Madrid in March 2007, identified several key areas which required further development. The second meeting took place in Rome in July 2007. At this meeting, systems for classification and reporting of Serious Adverse Reactions (SAR) and Serious Adverse Events (SAE) were discussed with the aim of developing a model for reporting and investigating SAE/SAR possibly related to the quality and safety of tissues and cells. This meeting was combined with a WHO meeting bringing together a global representation of experts in the field and representatives of national regulatory authorities in charge of cells and tissues. The European specific meeting was held independently, nested in this global meeting. This facilitated addressing the need for harmonized global understanding of adverse events and reactions and their reporting as well as agreement on aspects specific to the European Union. The synthesis of this meeting, with improvements brought through further exchanges between the EU participants, led to the drafting of the recommendations contained in this guidance and tools document.

This document aims to provide tools for the definition and classification of adverse events and reactions and a model for notification and management. The tools are designed to support compliance with the EU tissues and cells directives but an individual CA may require the reporting of events or reactions which fall beyond the scope of the European Directives. The tools will be applied in European Union Member States that participate in the EUSTITE Vigilance and Surveillance pilot which will run from July 2008 to July 2009. A final report and recommendations will be produced to contribute to future strategies for the surveillance of events and reactions related to the quality and safety of tissues and cells used in human applications, including clinical trials.

3.0 Roles and Responsibilities in the Management of Serious Adverse Events and Serious Adverse Reactions in the European Union

3.1 The principles of V&S for tissues and cells in the EU

The EU tissues and cells directives identify several types of key organization that must play roles in the management of serious adverse events and reactions within one Member State. The directives also describe how adverse events and reactions should be reported when associated with cells and tissues originating from another Member State or imported into the EU from a third country. The tissue establishment is the focal point for the receipt of reports of adverse events and suspected reactions.

The TE is first tasked with fostering the reporting of adverse events and reactions by providing detailed information in appropriate language to procurement organizations (PO), organizations responsible for human application of tissue and cells (ORHA), other relevant TEs or manufacturers using their tissues or cells to produce Advanced Therapy Medicinal Products (ATMPs) on how to report adverse events or reactions.

When receiving a report, the TE will investigate it in order to identify the cause and assess severity and imputability, in collaboration with the PO or ORHA as appropriate, notify as appropriate the CA and take any necessary actions, including preventive or corrective actions. The CAs must ensure that appropriate measures have been taken.

The EU tissues and cells directives require a mechanism to ensure appropriate circulation of information in the EU via the network of CAs for tissues and cells in the EU.

The directive makes it clear that the role of the TE does not preclude a PO or an ORHA from also directly notifying the CA if it so wishes.

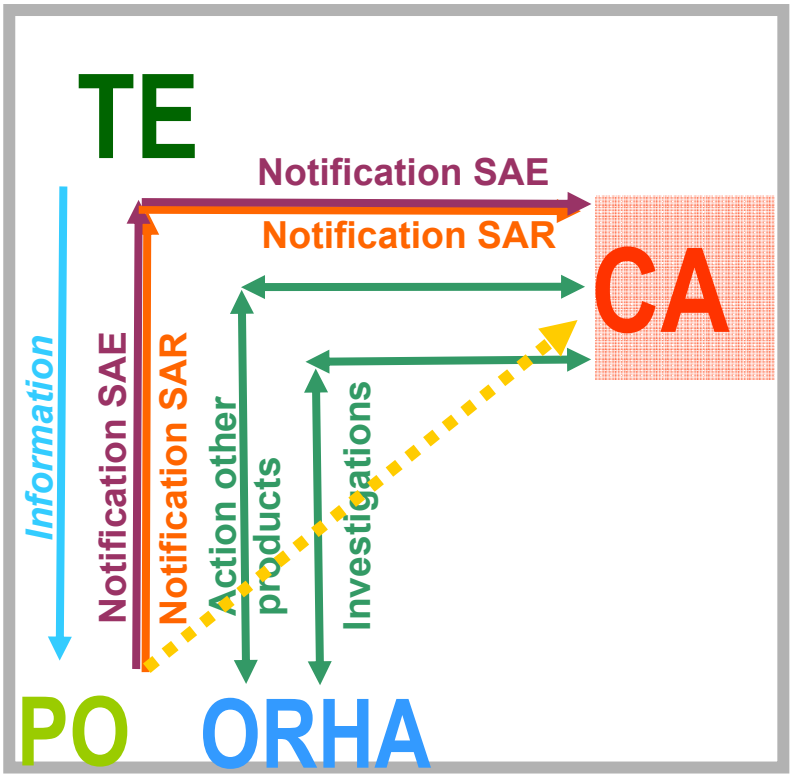
3.2 Responsibilities

Effective systems for the vigilance of cells and tissues are primarily dependent on reports by staff involved in the processing stages and clinicians in charge of donors and recipients. TEs, POs and ORHAs, together with CAs, should foster a culture of reporting and notifying SAE and SAR. Exposing the shortfalls of a process through identification and reporting of AE opens a potential source of learning and progress and should not be associated with blame. Likewise, identifying and reporting suspected adverse reactions needs awareness of the potential consequences they may have for others. Clinicians should be encouraged to be vigilant of clinical situations potentially caused by cell and tissue products and should track adverse reactions attentively.

The successive steps and flow of information between the different parties in the reporting and management of adverse events and reactions within one EU MS are summarized in Figure 1. Figure 2 outlines the roles of the different parties within one EU MS.

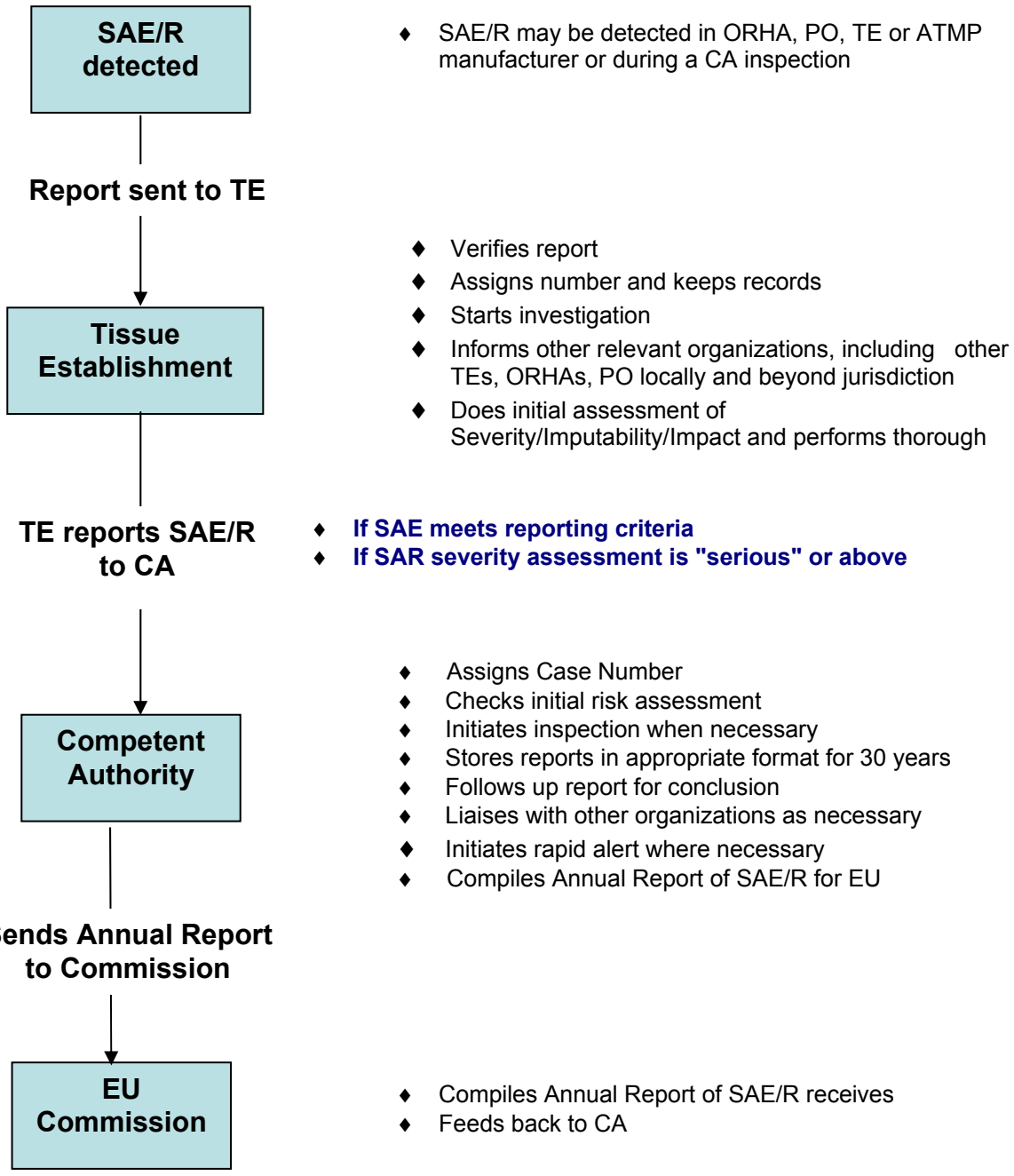
Note that the Directive describes responsibilities for functional entities, TE, PO or ORHA. Yet the efficacy of V&S relies on professionals whether for the appropriate reporting of adverse events and reactions or for their management. The questions at the beginning of each section of the following review of responsibilities underlines the necessary awareness of professionals.

Figure 1: Information flow within a Member State



Note:
It is possible that more than one ORHA or PO could also be involved where other tissues or patients are affected.

Figure 2: Responsibilities within a Member State



3.2.1 RESPONSIBILITIES OF POs

To whom should I report an adverse event or reaction that has occurred in my PO?

SAE/SAR should be reported wherever there is a suspicion that the cause was related to the donation process and where they may influence the safety or quality of the donated tissues or cells.

In most cases, tissues/cells will be supplied from a PO to a TE.; different situations are possible.

- I supplied tissues/cells to a TE in our **MS**: I should report the adverse event or reaction to that TE for onward reporting to the national CA.
- I supplied the tissues/cells to a TE in **another EU MS**: I should report the adverse event or reaction to that TE for onward reporting to their national CA and I should also report it to my national CA.
- I supplied the tissues/cells to a TE in **a third country** : I should report the adverse event or reaction to the receiving TE in the third country and to the CA in our MS.

In certain circumstances, tissues/cells may be supplied directly from a PO to an ORHA and no TE will be involved (see Article 6(5) of Directive 2004/23/EC). In these cases, adverse events or reactions associated with procurement (donor selection, testing, procurement) should be reported as follows :

- I procured tissues/cells and supplied them for use to an ORHA within our MS: I should report to the ORHA to which we supplied them and to my national CA
- I procured tissues/cells and supplied them for use to an ORHA in another EU MS: I should report to the ORHA to which we supplied them and to my national CA
- I procured tissues/cells and exported them to an ORHA in a third country : I should report to the receiving ORHA in the third country and to my national CA.

OTHER V&S RESPONSIBILITIES OF POs

Apart from reporting of adverse events and reactions, POs have the following responsibilities:

- Full collaboration with the TE or CA in the investigation of a suspected adverse events or reactions, and with an ORHA in the case of direct supply
- Implementation of any corrective or preventive actions arising
- Maintenance of records of suspected adverse events and reactions reported.

3.2.2 RESPONSIBILITIES OF ORHAS

To whom should I report an adverse event or reaction that has occurred in my ORHA?

Adverse reactions should be reported wherever there is a suspicion that the cause was related to the safety or quality of the tissues or cells applied.
Adverse events should be reported wherever there is a suspicion that there is a risk for the quality and safety of the graft and/or if there is a possible risk for recipient safety.

- I received the tissues/cells from a TE in our MS – (the tissues/cells may have originated at this TE or at a TE in another MS or a third country) : I should report to the TE in my MS that supplied the tissues/cells to us.
- I received the tissues/cells from a TE in another EU MS : I should report to this TE and also to my own CA.

In certain circumstances, tissues/cells may be supplied directly from a PO to an ORHA. No TE will be involved (see Article 6(5) of Directive 2004/23/EC).

- I received the tissues/cells directly from a PO in our MS : I should report to this PO and to my CA.
- I received the tissues/cells directly from a PO in another EU MS : I should report to this PO and to my CA.
- I received the tissues/cells directly from a PO in a third country: I should report to my CA and to the PO.

OTHER V&S RESPONSIBILITIES OF ORHAS

Apart from reporting of adverse events and reactions, ORHAs have the following responsibilities:

- Full collaboration with the TE or CA in the investigation of the suspected adverse events or reactions and with POs in case of direct supply
- Implementation of any corrective or preventive actions arising
- Maintenance of records of suspected adverse events and reactions reported.

3.2.3 RESPONSIBILITIES OF TES

As a TE, I receive a report of an adverse event or reaction from a PO, ORHA, ATMP manufacturer, another TE or there is an adverse event in my TE (including transport outside my TE by a contracted third party). To whom should I report it?

- If this adverse event or reaction meets the criteria for reporting to a CA (see below), I should report to my own CA and to any organisation in any country (TE / ORHA /ATMP manufacturer) to whom we have supplied implicated tissues/cells.
- Where the implicated tissues or cells originated from an organisation (TE or PO) **in another EU MS**, (and the incident has / may have implications for them), I should also report to this organisation.

Where the implicated tissues or cells originated from an organisation (TE or PO) **outside the EU** (and the incident has / may have implications for them) I should also report to this organisation who should take appropriate action in line with their own vigilance system.

OTHER V&S RESPONSIBILITIES OF TES

Apart from reporting of adverse events and reactions, TEs have the following responsibilities:

- Providing detailed information in appropriate language to PO, ORHA, other relevant TEs or ATMP manufacturer using their tissues or cells on how to report adverse events or reactions.
- Co-ordination of the investigation and evaluation of any reported suspected adverse reaction, involving appropriate stakeholders. This should include allocating grades for Severity (see the Severity Tool, 6.1), Imputability (see the Imputability Tool, 6.2) and Impact Assessment (see the Impact Assessment Tool, 6.3).
- Evaluation of any SAE in collaboration with appropriate stakeholders including allocating an Impact score (see Impact Assessment Tool) and reporting to the CA if the criteria at 4.3 are met.
- Investigation of the cause and outcome of any SAE/SAR, collaborating as necessary with other organisations involved and provision of the investigation report findings back to the CA
- Proposing a conclusion for each suspected adverse event or reaction and reporting this to the CA..
- Implementation of any corrective or preventive actions arising, including initiation and co-ordination of recall or quarantine of associated tissues and cells, as appropriate
- Maintenance of records of SAE and SAR reported and investigated.

3.2.4 Reporting Responsibilities of an ATMP manufacturer that received tissues and cells from a TE

To whom should we report an adverse event or reaction that has occurred in association with the tissues or cells provided to us by a TE for the production of an advanced therapy medicinal product

- We have received tissues or cells with a defect in safety or quality from a TE or PO: We should report it as an adverse event to the relevant TE or PO.
- We have received a report of an adverse reaction in a recipient: We should report it in accordance with the national requirements for **pharmacovigilance**. Moreover, if we suspect that this adverse reaction may have been caused by a defect of safety or quality in the tissues or cells, we should report it also to the supplying TE or PO.

Other V&S Responsibilities of an ATMP manufacturer that received tissues and cells from a TE

- Initiation and co-ordination of recall or quarantine of associated ATMP, as appropriate.

3.2.5 Responsibilities of CAs

To whom should we report an adverse event or reaction that relates to tissues or cells sent to my Member State from another country?

- We received an SAR/SAE report relating to tissues or cells sent to our MS **from another EU MS:** we should inform the CA of that MS (if the SAR/SAE has/may have implications for them). Our two CAs should share information and collaborate in the investigation. Moreover, we should inform the European Commission immediately (without waiting for the annual report) if there are likely to be consequences for other MS.

- We received an SAR/SAE report relating to tissues or cells imported **from a third country: we** should make all reasonable efforts to inform the appropriate authorities in the originating

country. We should inform the European Commission immediately (without waiting for the annual report) if there are likely to be consequences for other MS.

To whom should we report an adverse event or reaction that relates to tissues or cells supplied by my Member State to other countries? implicated tissues ore cells have been distributed?

- We received an SAR/SAE report relating to tissues or cells distributed from our MS **to another EU MS:** we should inform the CA of that MS (if the SAR/SAE has/may have implications for them). Our two CAs should share information and collaborate in the investigation. Moreover, we should inform the European Commission immediately (without waiting for the annual report) if there are likely to be consequences for other MS.

- We received an SAR/SAE report relating to tissues or cells exported **to a third country:** we should make all reasonable efforts to inform the appropriate authorities in the receiving country. We should inform the European Commission immediately (without waiting for the annual report) if there are likely to be consequences for other MS.

Other V&S responsibilities of CAs

Apart from reporting of adverse events and reactions, CAs have the following responsibilities:

- Assigning a CA reference number to each SAR/SAE report received
- Re-assessing the severity, imputability and impact scores allocated by the reporting organisation (or allocation of these scores if this has not already been done)
- Deciding on an appropriate regulatory response depending on the seriousness of the SAE/SAR reported and taking appropriate action (e.g. recall, inspection, rapid alert, regulatory notice.)
- Compilation of an annual report of SAE and SAR for submission to the European Commission before the end of June of each year.
- Making the European Commission summary annual report available to TEs in the MS.

3.2.6 THE ROLE OF THE EUROPEAN COMMISSION (EC)

The European Commission has the following co-ordinating functions:

- Receiving annual reports of SAEs/SARs from EU MS
- Publishing a summary of these annual reports and making it available to all EU CAs.
- Co-ordination of rapid alerts in the case of implications for more than one MS (according to 3.2.5).

- Communication with regulators outside the EU as necessary where SAE/SAR reported have implications for services in those countries

3.3 Information Flow

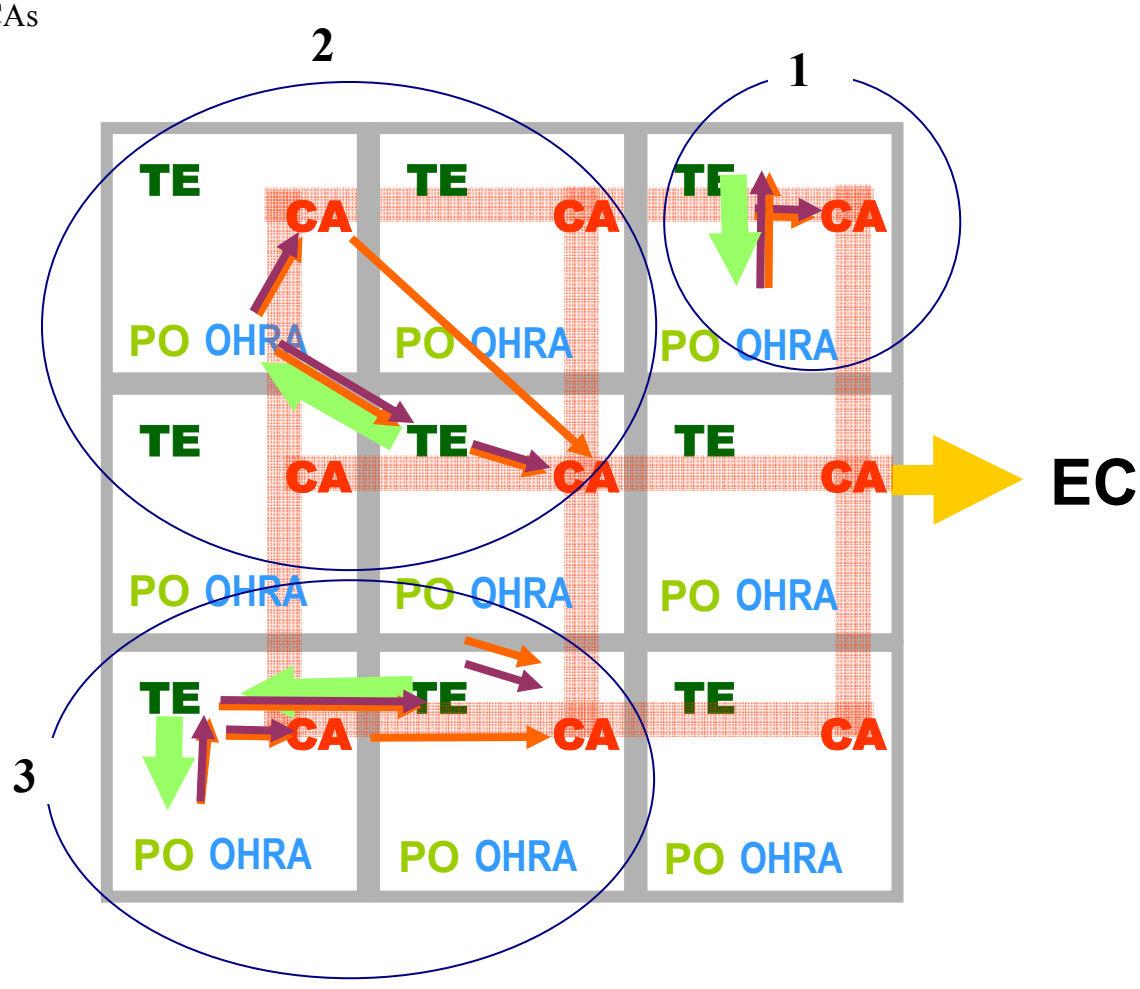
The key role at EU level of CAs to "*communicate to each other and to the EC such information as is appropriate with regard to SAR and SAE*." is represented in Figure 3 by the network of CAs in red. This network will allow for consistent access to relevant information in the EU. It is recommended, nevertheless, that as a general principle the CA in the MS where the SAE/SAR occurred should be informed in cases where cells and tissues from another MS are implicated, as shown in figure 3.

Figure 3: V&S information flow between EU Member States

The provision of a cells or tissues is shown by a green arrow

1. from a TE in the same Member State
2. from a TE in another EU Member State: report to this TE and to own CA.
3. from a TE in another EU Member State, through an importing TE: report to this TE and to own CA.

Purple and red arrows indicate SAE/SAR; orange arrow indicate communications between CAs



4.0 Triggers for Reaction/Event Reporting

4.1 Triggers for Reaction Reporting – Recipients

Although the minimum requirements described in Article 5 of Directive 2006/86/EC require ORHAs to notify to TEs 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 tissues or cells should be notified to TEs to allow trends in minor events and reactions to be monitored for continuous improvement purposes. TEs 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 CAs.

Clinical symptoms or situations suggesting that any of the following reactions might have occurred in a tissue or cell 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 (including mechanical failure) (**Failure**)
(f) Toxic effects from tissues and cells or associated materials (**Toxicity**)
(g) Unexpected immunological reactions due to tissue/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**)
(k) Other (**Other**).

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

4.2 Triggers for Reaction Reporting – Living Donors

Donor adverse reactions with a possible direct effect on the quality and safety of tissue/cells must be reported according to the guidance in section 3.2.1. . These may be immediate, i.e. occurring at the time of the donation or within 8 days of donation, or they may be delayed, i.e. identified after the donation (possibly even many years later).

Where allogeneic living donors have been harmed by a donation process but there is no detrimental impact on the quality or safety of the specific tissues or cells concerned; a serious threat to the

supply of those tissues or cells could result from the loss of public willingness to donate, or there may be implications for the safety of other living donors. On this basis, it is recommended that CAs include reporting of such donor adverse reactions in their tissue and cell vigilance programmes and in their annual reports to the EC. If such reactions are the result of an administered drug (e.g. OHSS for egg donors or a reaction to GCSF in peripheral blood stem cell donors) it will be reportable through the pharmacovigilance system. It should not be reported again through the tissue and cell vigilance system but appropriate communication links between responsible authorities should ensure that the tissue and cell CA is aware of these reactions.

4.3 Triggers for Serious Adverse Events Reporting

AE can be detected at any stage in the process from donation to transplantation. Competent Authorities will not want to be informed about every deviation from an SOP within a Tissue Establishment. Directive 2006/86/EC clarifies that only **'serious'** adverse events should be reported to the CA. Directive 2004/23/EC defines SAE in terms of the potential to cause a SAR. Seriousness might relate to potential severity of an adverse reaction if the event had not been discovered or to the severity of an adverse reaction that might occur due to a repetition of the event in another place or time.

EUSTITE proposes that deviations from Standard Operating Procedures in TEs, or other adverse events, which have implications for the quality and safety of tissues and cells should result in SAE reporting to the Competent Authority when one or more of the following criteria applies:

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

Thus, where the criteria listed above are met, the AE can be considered as posing a serious risk to patient health and in those circumstances it should be reported to the CA. Events that are commonly referred to as 'near misses' are included in the above categories. In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up is considered to be a serious adverse event and should be notified to the CA. See the table of examples at Annex 2 where various hypothetical or actual events are tested against these criteria.

5.0 Communication with Stakeholders

5.1 Clinical Users

Tissue Establishments have a key responsibility to inform clinical users (in POs and ORHA) regarding the procedures for the reporting of adverse events or reactions associated with the tissues and cells they receive or provide. Competent Authorities are also responsible for the general education of clinical users to ensure a high degree of awareness of the existence of the Vigilance System and to provide good quality feedback. The CA website and scientific and medical journals should be used to publicise the vigilance system and to educate users regarding the triggers that would indicate the need to report an adverse event or reaction.

Annex 1 provides a description of the categories of reactions and events that are reportable and **Annex 2** provides a series of illustrative examples. These tables may be useful for the education of clinical users of tissues and cells on the types of adverse events and reactions which may occur and are intended to provide background information on the triggers to look for. The examples list is not exhaustive. In any case all reactions and events, whether reported to the CA or not, should be investigated locally and documented in the TE.

5.2 Other vigilance systems

It is important that the tissue and cells vigilance system has in place appropriate communication channels with other health product vigilance systems. For example, Ovarian Hyper-stimulation Syndrome (OHSS) associated with egg donation or adverse reactions to GCSF administered as part of haematopoietic stem cell collection will be reported via the pharmacovigilance system. In both of these cases, an appropriate link between pharmacovigilance and tissue and cell vigilance systems will ensure that tissue and cell donation related risks are appropriately monitored. Similarly, links with medical device and blood vigilance systems will ensure better evaluation of risk to tissue and cell donors and recipients.

5.3 Testing laboratories

It is important that laboratories that test donor, donation or recipient samples participate in the adverse event and reaction reporting. They should be fully informed regarding procedures for reporting events to the clinician, the TE or the PO that requested the tests.

6.0 The Tool Box

This document provides the following tools for the evaluation and grading of SAE/R:

- The Severity Grading Tool
- The Imputability Grading Tool
- The Impact Assessment Tool

Adverse reactions in recipients or in living donors should be evaluated by the TE, in collaboration with clinicians in the PO or ORHA, applying all three of these tools as soon as they are reported to the TE. The grades allocated should be included in the initial report to the CA. The assessment of imputability, severity and impact should be repeated at the conclusion of the SAR investigation and any changes should be reported to the CA. The CA should independently apply the tools on receipt of the report (initial and final) to ensure consistent application.

Adverse events should be evaluated by the TE (or PO or ORHA if no TE involved), applying the Impact Assessment Tool only. An SAE is, by definition, reported if it could result or have resulted in a product that might be associated with a reaction of severity grade 2 or above if used in a patient. This potential severity is one element in the impact assessment matrix, graded with the same scale as reaction severity. In cases of SAE, a thorough investigation should be carried out. In this case also, the CA should re-assess the impact of the event.

6.1 The Severity Grading Tool

The following severity grading tool is only applicable for adverse reactions assessment.

A number of different grading systems are in use or under development in various settings. Following a review of severity grading systems, a classification system for describing the severity of an adverse reaction adapted from the ISBT severity classification is included in this tool kit... The ISBT grading is applied for non-infectious reactions while this adapted version is intended for application to all suspected adverse reactions. Suspected serious transmitted infections (e.g. bacterial, fungal, viral, prion, parasitic) should always be reported and their severity should never be graded as non-serious.

All adverse reactions apart from those graded as non-serious or insignificant should be reported to the CA.

Severity Grading Scale for Adverse Reactions

Insignificant	No harm to the recipient therefore considered as reportable as an event according to the EU Directives.
Non-serious	Mild clinical consequences which do not necessitate hospitalisation and/or result in long term disability or consequences for the recipient or living donor.
Serious	Adverse reaction resulted in: - hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - medical or surgical intervention to preclude permanent damage or impairment of a body function or - there is evidence of a serious transmissible infection
Life-threatening	The living donor or recipient required major intervention following procurement or the tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death or there is evidence of a life-threatening transmissible infection.
Death	Death.

6.2 The Imputability Assessment Tool

The assessment of imputability is limited to reactions only.

Imputability grading has been used for a number of years in blood vigilance systems as a tool to assess the causal relationship between a transfusion and an adverse reaction. In tissues and cells this should also be applied by the TE, in collaboration with clinicians at the PO or ORHA, for each SAR reported and reassessed on conclusion of the investigation. In the blood vigilance systems directive (2005/61/EC), an imputability grading is provided. This has been adapted for tissues and cells as shown in the following table:

Imputability level		**Explanation**
NA	Not assessable	When there is insufficient data for imputability assessment.
0	Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.
	Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells.
1	Possible	When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells or to alternative causes.
2	Likely, Probable	When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells.
3	Definite, Certain	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells.

The application of the imputability tool will involve a documented review of the evidence linking the reaction to the tissue or cell procurement or application. It should ideally be applied independently by individuals who review the evidence from different perspectives e.g. the clinician who detected and reported the reaction, the TE Nominated Registered Medical Practitioner and the TE Quality Manager. A score should then be agreed by discussion and reported to the CA if there is any suspicion that the reaction was related to the quality of the tissue or cells.

6.3 The Impact Assessment Tool

This tool assists in the assessment of the importance, or criticality, of a specific SAR or SAE and in the case of SAR, takes into account the severity. It includes the actual or potential effect on public health and on the broader system, including public support for donation and transplantation of tissues and cells and the risk to the supply of tissues and cells.

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The impact assessment tool should be applied by TEs and reassessed by the CA for each report. The outcome of the assessment should be linked to specified responses by the CA. A proposed version for a EUSTITE impact matrix (adapted from the HFEA risk matrix) is shown below. The response of a TE or a CA to a specific SAE/SAR should be proportionate to its impact as assessed by the matrix described.

STEP1 (Probability of recurrence):

Taking account of the current controls in place and their adequacy, how likely is it that this particular SAE/SAR will occur again either at this particular centre or all centres?

Level	**Descriptor**	
5	Almost Certain	Likely to occur on many occasions
4	Likely	Probable but not persistent
3	Possible	May occur occasionally
2	Unlikely	Not expected to happen but possible
1	Rare	Difficult to believe it could happen again

STEP2 (Consequences):

Again, taking account of the conditions and current controls in place and their adequacy, how critical are the consequences of this SAE/SAR? The score in the left hand column should be applied if any of the conditions in the impact columns applies.

Impact Description	**Actual or potential impact on individual(s) (SAE) Actual impact on individual(s) (SAR)** (as in severity tool)	**Actual or potential impact on Transplant or Fertility System**	**Actual or potential impact on tissue/cell supply**
Severe 4	Death	System destroyed – need to rebuild	All allogeneic applications cancelled
Major 3	Life-threatening	Major damage to system – significant time needed to repair	Significant number of procedures cancelled; importation required to make up shortfall
Significant 2	Serious	Damage to system; services will be affected for a short period	Many applications cancelled or postponed
Minor 1	Non-serious	Minor damage to system	Some applications postponed
Insignificant 0	Insignificant	No affect	Loss of tissues/cells which does not result in any significant change to supply for clinical use

STEP 3: Impact Matrix

Probability of recurrence → / **Consequences ↓**	Almost Certain 5	Likely 4	Possible 3	Unlikely 2	Rare 1
Severe 4	**20**	**16**	**12**	**8**	**4**
Major 3	**15**	**12**	**9**	**6**	**3**
Significant 2	**10**	**8**	**6**	**4**	**2**
Minor 1	**5**	**4**	**3**	**2**	**1**
Insignificant 0	**0**	**0**	**0**	**0**	**0**

Step 4: Response

The response of a TE or a CA to a specific SAE/SAR should be proportionate to the potential impact as assessed by the matrix described.

An SAE/SAR assessed as having a potential impact in the green area will generally require the CA to keep a 'watching brief', leaving the TE to manage the corrective and preventive actions.

An SAE/SAR assessed as having a potential impact in the yellow area will generally require a more proactive response from the CA. The CA may wish to conduct an inspection or to notify another authority if the inspection should be conducted at a site for which they are not the CA. An SAE/SAR related inspection should focus on the subject of the SAE/SAR. The CA may also request the supply of follow-up data to confirm that the corrective and preventive actions have been carried out effectively, including evidence of effective recall, where necessary. It may be appropriate for the CA to issue a Regulatory Action Notice (see section 8.0) to the field to ensure that the implications are considered at TEs not involved in the SAE/SAR.

An SAE/SAR assessed as having a potential impact in the orange area will generally require a very active response from the CA. The CA may wish to participate in the development of the corrective and preventive action plan, perhaps leading a task force that addresses the broader implications, with the participation of policy makers. It is likely that the CA would conduct an inspection that focuses on the subject of the SAE/SAR and would request the supply of follow-up data to confirm that the corrective and preventive actions have been carried out effectively. Depending on the details of the SAE/SAR, it may be appropriate for the CA to issue a Regulatory Action Notice to the field or a Rapid Alert (see section 8.0) and possibly to notify CAs in other Member States and the European Commission where there may be implications outside the Member State.

The effectiveness of the response can be assessed by re-applying the impact matrix following the implementation of the preventive actions. The impact can be reduced by reducing the probability of recurrence through preventive measures (e.g. excluding a particular group of potential donors, adding a decontamination or sterilization step, improving staff training) or by increasing the detectability of the risk (e.g. adding a new test, adding computer checks) or by reducing the severity of the consequences if it should recur.

7.0 Reporting Forms

The Forms from Directives 2006/86/EC of the 24th October 2006, Annex III and Annex IV may be used for SAR/SAE reporting. Alternatively CAs may wish to adapt specific forms to suit their own needs. It should be noted that any forms used should contain at least the information requested in the Directive. EUSTITE will use standard forms, incorporating the information required by Directive 2006/86/EC for the collection of SAE/SAR reports during the pilot of the tools. These will be adapted following the pilot and provided to the European Commission along with the final version of the proposed tools.

8.0 Competent Authority Responses and Notifications

Different forms of alerts and feedback mechanisms may be used by CAs to guarantee the safety of tissues and cells and in order to inform stakeholders involved in tissues/cells for human applications. These may be in response to a specific SAE/R, to a trend in the SAE/R reported or to information obtained from other sources such as other CAs, from the European Commission or from other sources.

8.1 Rapid Alerts

Rapid alerts are immediate urgent notifications by or through the CA in a MS to alert organizations to a potential threat. This may be as a result of information received from another regulator, the European Commission, an ORHA, TE, PO or industry. Rapid alerts should only be issued in exceptional circumstances. Rapid alerts are co-ordinated by the Competent Authority when issued nationally, or in collaboration with another CA, the European Commission and/or the World Health Organisation when issued across the EU or globally.

The following criteria must be satisfied for issuing of rapid alerts across Member States:

- SAE/SAR of a serious or potentially serious nature
- Potential risk to other individuals across member states
- Wider public health implications

A list of contact persons from CAs with responsibility for receiving rapid alerts is held by the Commission and is used for the dissemination of rapid alerts.

8.2 Regulatory Action Notices

Regulatory Action Notices are issued nationally to recommend change in practice to TEs based on SAE/SAR or trends in reports. Where there are broader implications, Regulatory Action Notices should be shared with other competent authorities in other MS. A Regulatory Action Notice system uses lessons learnt from investigations of adverse events and reactions and shares the information throughout the professional community in the MS to facilitate general improvements in safety and quality.

A Decision to produce a Regulatory Action Notice is made in circumstances where sharing the knowledge of contributory factors/root causes could reduce the incidence of similar SAE/SAR recurring elsewhere. Representatives of professional groups should be given the opportunity to comment and contribute to the content of the notice before it is issued. Regulatory action notices should be disseminated to all relevant stakeholders.

8.3 Routine Responses to SAE/R Reports

All SAE/R received by a CA should be acknowledged as soon as possible. The severity, imputability and impact assessments performed by the TE should be reviewed. If any grading is changed by the CA this should be notified to the TE. The response of the CA should reflect these gradings and could range from 'No action, file report' where it is considered that the SAE/SAR is being investigated and managed adequately locally to 'Urgent Inspection with the potential for the cessation of activity'. In all cases, CAs should consider the implications of SAE/SAR for other organisations in their MS and for other MS and should share information accordingly.

9.0 Evaluation of Vigilance Systems

Competent Authorities should review and evaluate their Vigilance systems to ensure that they are achieving the intended objectives. The following are performance indicators that could be used for the evaluation of a tissues and cells vigilance system.

- The core values of the system are agreed to and published
- There exists an Implementation Strategy and Plan for new V&S systems.
- Adequate resources have been allocated at EC, CA and TE levels
- Stakeholders are educated and understand their role in the system
- All relevant facilities have an SOP on how to feed into/manage the system and reports arrive on the correct forms
- Clinicians that apply tissues and cells to patients are engaged in the system – there are no published articles relating to SAE/SAR that have not already been reported via the V&S system
- Health professionals are not afraid to report – reports arrive in increasing numbers as the
- System is rolled out – indicates openness and transparency
- Reports arrive from a wide range of people in different places and different professional roles – (indicates good information dissemination and education about the system)
- System for documentation of SAE and SAR at the CA is expandable to cope with varied circumstances and occurrences
- Consistency between the SAE and SAR reported to the CA and those observed in the TE during routine inspection by the CA – indicates good knowledge of TE staff regarding what is notifiable to the CA
- High quality of reports submitted – all required data provided.
- CAs are receiving primarily **Serious** event and reaction reports – indicates appropriate filters in place at TE
- Responses by CAs are similar across the EU when they receive similar reports

- While the number of SAE/SAR reports may increase in response to increased awareness, the number of high risk reports should decrease in response to corrective measures which have been implemented. No instances of tissues or cells being released for clinical use **after** an SAE or SAR has been
  Reported – implies appropriate responses in the case of rapid alerts and recalls (although it is recognised that this would not apply to circumstances where tissues or cells may have to be released and used due to the lack of an alternative and their life-saving nature).
- The requirements of the EU technical directives (2006/17/EC and 2006/86/EC) change in response to lessons learned via the V&S system.
- The requirements of professional standards change in response to lessons learned via the V&S system.
- For each SAR received by a CA, there is at least one clearly identified hospital (or other clinical facility), one TE (if involved) and one CA.
- Scientific and Professional societies are actively involved in reviewing and discussing reported SAE and SAR.

Annex 1: Vigilance of Human Tissues and Cells – Categories of Events and Reactions to Notify (Adapted from AFSSAPS)

A -	EVENTS OR REACTIONS RELATING TO THE DONOR/DONATION			Vigilance notification to the CA	
				YES/NO	**TYPE OF REPOERT (IF REPORTABLE)**
	1.	**BIOLOGICAL AND CLINICAL SCREENING OF THE DONOR (after the tissues/cells have been released but before human application)**			
		a)	**biological** screening of the donor not in accordance with Directives	YES	SAE
		b)	**clinical** screening of the donor not in accordance with Directives	YES	SAE
		c)	discovery of a **positive** microbiological test results (virus, bacteria, fungi)	YES	SAE
	2.	**ADVERSE REACTIONS IN THE LIVING DONOR …at the time of procurement (within 8 days)**			
		a)	serious AR**,** unexpected or not, in the living donor, associated with procurement, with implications or potential implications for the quality and safety of the tissues and cells and potential implications for the safety of **other** patients, living donors or recipients	YES	SAR
	… following procurement (time lag post procurement)				
		a)	discovery or occurrence of a disease in the donor potentially related to the donation process	YES	SAR
B.	**EVENTS FROM PROCURMENT TO HUMAN APPLICATION**			**Vigilance notification to the CA**	
				YES/NO	**SAE/SAR**
	1.	**PROCESSING AND STORAGE**			
		a)	processing or storage event with implications or potential implications for the quality of the tissues/cells and for the safety of the recipient or other recipients	If criteria at 4.3 are met	SAE
	2.	**ANCILLARY PRODUCTS**			
		a)	poor quality of the product **before use**	If criteria at 4.3 are met	SAE
		b)	wrong use, wrong conservation, expiration	If criteria at 4.3 are met	SAE
		c)	positive microbiological test results on the ancillary product **WITH** AR	YES	SAR
		d)	positive microbiological test results on the ancillary product **WITHOUT** AR in the recipient	If criteria at 4.3 are met	SAE
	3.	**PACKAGING**			
		a)	packaging not consistent with current recommendations and **consequences for the quality of the tissues/cells**	If criteria at 4.3 are met	SAE

		b)	defective packaging **with consequences for the quality of the tissues/cells**	If criteria at 4.3 are met	SAE
	4.	**TRANSPORT**			
		a)	Transport event with implications or potential implications for the quality or availability of the tissues/cells	If criteria at 4.3 are met	SAE
	5.	**QUALITY OF THE TISSUES/CELLS**			
		a)	tissues/cells distributed out of specification	YES (unless exceptional release decision documented)	SAE
	6.	**TRACEABILITY**			
		a)	inaccurate traceability of tissues/cells (e.g. gamete or embryo mix-up)	YES	SAE
		b)	inaccurate traceability of an ancillary product	If criteria at 4.3 are met	SAE
C -	**EVENT OU ADVERSE REACTION OCCURING AT THE TIME OF HUMAN APPLICATION OR IN THE RECIPIENT**			**Vigilance notification to the CA**	
				YES/NO	**SAE/SAR**
	1 -	**LOSS OF TISSUES OR CELLS IN ORHA**			
		a)	after distribution (e.g. loss of sterility in theatre, inability to locate tissues or cells delivered to the hospital)	If criteria at 4.3 are met	SAE
	2 -	**HUMAN APPLICATION**			
		a) b)	human application to the wrong recipient human application after expiry date of the graft	Depending on whether this resulted in a reaction in the recipient	SAE or SAR
	3 -	**ADVERSE REACTIONS IN THE RECIPIENT**			
		… at the time of human application (e.g. within 8 days)			
		a)	**Adverse reaction,** unexpected	YES if severity 2 or above	SAR
		…after human application (time lag post human application)			
		a)	**Adverse reaction,** unexpected	YES if severity 2 or above	SAR

Annex 2: Examples of SAE/Rs

To demonstrate the use of the tools, they have been applied to these **hypothetical** cases. The scores allocated are indicative and might change considerably if more information were available about each case. In some cases, the scores are based on assumptions regarding corrective and preventive actions. The colour on the impact score should indicate the appropriate CA response (low level response, proactive response, vigorous response with follow-up and intervention as required).

Description	Report to CA?	Application of Assessment Tools	Comments
Equipment failure during haematopoietic stem cell collection resulting in abandoning of procedure. The procedure was carried out successfully at a later date.	Yes as an **SAE** if criterion No.2 applies (section 4.3)	Impact Score: **3** (Probability of Recurrence: possible Consequences: minor)	Reportable only if the equipment failure is something that other haematopoietic stem cell collection centres should be informed about. Link with medical device vigilance system if relevant
Positive microbial test result on stem cells detected at TE post transplantation. No adverse reaction detected in the recipient	Yes as an **SAE** – to own CA and to ORHA that received the cells	Impact Score: **6** (Probability of Recurrence: possible Consequences: significant)	Meets criterion 1 (Section 4.3)
A dry shipper containing an allogeneic bone marrow donation being transported for immediate transplant is stolen from the courier	YES as an **SAE**	Impact Score: **8** (Probability of Recurrence: unlikely Consequences: Severe)	Meets criterion No 3 (Section 4.3)
Cardiac valve mis-sized rendering it unusable. Error discovered in theatre prior to transplantation resulting in the use of a prosthetic heart valve for recipient resulting in the need for lifelong anticoagulation.	Yes as a suspected **SAR**	**Severity Score: Serious** **Imputability Score: 3 (certain)** Impact Score: **6**	Severity Score relates to long-term medical intervention

Description	Report to CA?	Application of Assessment Tools	Comments
		(Probability of Recurrence: possible consequences: significant)	
Embryos were mistakenly transferred into a Petri dish (unused) labelled for another couple. The error was detected (following issue) but prior to embryo transfer.	Yes as an **SAE**	Impact Score: **6** (Probability of Recurrence: possible Consequences: significant)	Meets criterion No. 1 (Section 4.3)
Liquid nitrogen container runs out of LN2, 120 heart valves thaw and are discarded.	YES as an **SAE**	Impact Score: **6** (Probability of Recurrence: possible Consequences: significant)	In this case the severity of the impact is related to tissue supply and the cancellation or postponement of transplant procedures
Pseudomonas detected in an incubator which contained tissues and cells.	Yes as an **SAE** if criterion No.1 applies (section 4.3)	Not possible to assess the impact without knowing the status of other tissues/cells in the incubator	Reportable if tissues or cells have been released for use which might have been contaminated.
2 corneas discarded in the TE due to technical error during dissection from the globe	No	Not applicable	Does not meet criteria at 4.3
Skin graft recipient tests positive for hepatitis B 6 months after the skin grafting procedure Donor was negative for HBsAg, HBc and NAT for hepatitis B	Yes as a suspected SAR	**Severity Score: Life-threatening** **Imputability Score: 0 (unlikely)** Impact Score: 4 (Probability of Recurrence: rare Consequences: severe)	Communication with other vigilance systems if relevant
Failure of remote alarm of temperature monitoring system of a fridge containing a large number of tissues and cells. Temperatures were	No	Not applicable	Does not meet criteria at 4.3 unless the defect in the alarm

Description	Report to CA?	Application of Assessment Tools	Comments
maintained within acceptable range.			system is inherent and the system is used by other TEs. In that case, the event may need to be passed to another authority (e.g. Device Vigilance)
Ruptured ectopic pregnancy following embryo transfer.	No	Not applicable	For capture in the quality system but does not fall within the scope of the legislation.
Sporadic CJD in a living femoral head donor several years after procurement	Yes as an **SAE**	Impact Score: 12 (Probability of Recurrence: possible Consequences: severe)	The TE must trace the fate of the donated tissue and follow-up the health of the recipient. This may become an SAR if there is evidence that the recipient has been infected.
Bone irradiated twice – grafts released for transplant – all recalled before use	Yes as an **SAE**	Impact Score: 2 (Probability of Recurrence: unlikely Consequences: minor)	Meets criterion 1 (Section 4.3)
A cornea is swabbed in theatre prior to being transplanted – subsequent culture shows growth of *Staphylococcus epidermidis* (previous cultures at the TE negative and no evidence of infection in the recipient)	No	Not applicable	Does not meet criteria in Section 4.3
Baby is born following donor sperm insemination with a genetic disease not present in the family of the mother	Yes – as a suspected **SAR**	**Severity Score would depend on the details of the disease** **Imputability Score: 2 (likely/possible)** Impact Score: 9 (Probability of Recurrence: possible Consequences: major)	

Description	Report to CA?	Application of Assessment Tools	Comments
Defective packaging results in exposure of a heart valve outside the sterile field in theatre – heart valve not implanted. Patient anaesthetized already. Surgery resheduled	Yes – as an **SAR**	**Severity Score: Serious** **Imputability Score: 3 (certain)** Impact Score: **8** (Probability of Recurrence: unlikely Consequences: severe)	Severity score relates to prolongation of hospital stay and need for intervention (second general anaesthetic) It is assumed that the TE immediately corrects the packaging problem so that it becomes unlikely that the event will recur.
Fracture in an irradiated massive allograft (femur) 2 months after transplant	Yes – as a suspected **SAR**	**Severity Score: Serious** **Imputability Score: 2 (likely/probable)** Impact Score: **4** (Probability of Recurrence: likely Consequences: Minor)	
Cryopreserved skin past its expiry date is distributed and used on a burned patient. Discovered after the procedure	Yes – as an **SAE**	Impact Score: **2** (Probability of Recurrence: unlikely Consequences: minor)	Meets criterion No 1 (Section 4.3) Patient should be followed-up. Assumed that TE puts effective steps in place to prevent recurrence.
Significant loss (80%) of stem cells in an allogeneic bone marrow graft following freezing/thawing (viability and CD34+ measured). Graft infused (no other option).	Yes as an **SAE**	Impact Score: **16** (Probability of Recurrence: likely Consequences: Severe)	Meets criterion No 3 (Section 4.3) High probability of recurrence relates to the strong evidence that the procedure in use is not effective. This case could become a SAR –

Description	Report to CA?	Application of Assessment Tools	Comments
			depending on the outcome in the donor/recipient.
All bone and skin tissue from a multi-organ, multi-tissue donor is contaminated with *Clostridium dificile* (organs transplanted, corneas and heart valves in other banks)	Yes	Impact Score: 12 (Probability of Recurrence: possible Consequences: Severe)	Meets criterion No 2 (Section 4.3)
A frozen femoral head is held by a courier company for 72 hours in a holding depot rather than being delivered immediately (Courier company used by many TEs in the country)	Yes as an **SAE**	Impact Score: 6 (Probability of Recurrence: possible Consequences: significant)	Meets criterion No 2 (Section 4.3)
Failed engraftment in an autologous recipient of peripheral blood stem cells (high viable cell numbers prior to freezing)	Yes – as a suspected **SAR**	**Severity Score: Serious** Imputability Score: data on cell numbers and viability prior to infusion required to assess imputability Impact Score: 12 (Probability of Recurrence: possible Consequences: Severe)	Although delayed engraftment might sometimes be expected, complete failure despite high numbers of viable cells might indicate a quality problem associated with freezing/thawing.
UK cornea recipient develops symptoms of vCJD 5 years after transplant – reported to TE	Yes as a suspected **SAR**	**Severity Score: Death** **Imputability Score: 1 (possible)** Impact Score:16 (Probability of Recurrence: likely Consequences: severe)	The impact score in this case relates to the high probability of recurrence if it happens once and the subsequent impact on the system in terms of supply.

Annex 3: Glossary

Advanced Therapy Medicinal Product (ATMP): a medicinal product which includes human tissues or cells and which meets the criteria defined in Regulation 1394/2007/EC.
Cells: individual human cells or a collection of human cells when not bound by any form of connective tissue
CJD: Creutzfeldt-Jacob Disease
Competent Authority: Organisation(s) designated by an EU Member State as responsible for implementing the requirements of Directive 2004/23/EC.
Distribution: transportation and delivery of tissues or cells intended for human applications
Donation: donating human tissues or cells intended for human applications
Donor: every human source, whether living or deceased, of human cells or tissues
Human application: the use of tissues or cells on or in a human recipient and extracorporal applications
Impact matrix: A feature of the Impact Assessment Tool in which the risk associated with a potentially recurring incident is assessed in terms of its potential consequences and probability of recurrence; it includes the actual or potential effects on the system, including impact on public opinion and tissue or cell supply.
Imputabilty: An assessment of the likelihood that a reaction is related to a safety or quality defect in the transplanted tissue or cell. **Incident:** a generic term for an adverse reaction or event
ISBT: International Society for Blood Transfusion
Near miss: an error or deviation from standard procedures or policies that is discovered before application of the tissues/cells and that could have led to an adverse reaction in a recipient. Near misses are considered as adverse events in this document.
Organ: a differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with an important level of autonomy;
Organisation Responsible for Human Application: (ORHA) means a health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells.
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
Processing: all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications
Procurement: a process by which tissue or cells are made available
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 tissue isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection
Recipient: person to whom human tissues or cells are applied.
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.
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 this document.
Storage: maintaining the product under appropriate controlled conditions until distribution
Surveillance System: A process at a local, regional or national level for the reporting of serious adverse events or complications related to organ/tissue/cell donation and transplantation.
Suspected Serious Adverse Reaction: an unintended response, including a communicable disease, in the donor or in the recipient which is suspected as being 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.
Third country: Any country that is not a Member State of the EU
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.
Tissue: An aggregate of cells joined together by, for example, connective structures which perform the same particular function, e.g. connective, muscle or nerve tissue or the cornea of the eye
Trigger: An unexpected clinical/laboratory/radiological finding in a recipient or living donor which may be related to the tissue/cell transplant.
vCJD: Variant Creutzfeldt-Jacob Disease.