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## **Vigilance and Surveillance EUSTITE Pilot Report**

**Stephanie Sullivan**

**Pilot Co-ordinator**



**On behalf of the EUSTITE Vigilance and Surveillance Medical Advisory Committee**

THE EUSTITE PROJECT WAS CO-FUNDED BY THE EUROPEAN COMMISSION  
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## EXECUTIVE SUMMARY

### Background:

Vigilance and Surveillance (V&S) tools specifically designed for the reporting, evaluation and management of Serious Adverse Reactions (SARs) and Serious Adverse Events (SAEs), as defined in Directive 2004/23/EC related to tissue and cells for human application, were developed as part of the EUSTITE project. A Pilot scheme to test these tools involved 22 competent authorities from 20 Member States across the European Economic Area. It was commenced on 01 July 2008 and ran for one year.

### The aims of the pilot were:

- i) to test the feasibility of the tools and identify any necessary improvements,
- ii) to reduce the likelihood of disease transmission by promoting vigilance,
- iii) to improve quality and safety by sharing information learned and supporting the added value of consolidated data and expertise from across the EU,
- iv) to promote openness, transparency and learning within the field, and
- v) to promote advocacy of patient safety and donor motivation for human cell and tissue vigilance and surveillance.

### Methods:

Each Competent Authority (CA) was issued a code number to facilitate anonymisation of the information. Tissue Establishments (TE) or other establishments reported Serious Adverse Reactions and Serious Adverse Events (SARE) to their CA in the normal way in their country. Each SAR was scored using the Severity Grading Tool and the Imputability Tool and then the Impact Tool was applied. Evaluation of SAEs used the Impact Tool only. A report of SARE notifications received, the scores applied, and information regarding their investigation and any relevant corrective or preventive action, was sent to the pilot co-ordinator each quarter by the identified contact person in each participating CA. SARE were grouped according to the stage of activity at which the incident occurred, in line with the requirements of Directive 2006/86/EC. The scope of reporting included the recognised activities of procurement, , testing, processing, preservation, storage and distribution of human tissues and cells. The relevant tissue and cells included within the scope of the pilot were: vascular, reproductive, ocular, haematopoietic stem cells from peripheral blood and bone marrow, haematopoietic stem cells from cord blood, skin, musculo-skeletal and amniotic membrane. A quarterly report drawing together the results was prepared by the pilot co-ordinator and sent to each participant CA together with an anonymised spreadsheet containing details of all SARE reported to the pilot for that quarter.

### Results:



Between 12 and 19 reports were received each quarter (average of 16 reports). Eight countries reported no SARs or SAEs during the operation of the pilot scheme. A total of 152 SARs and 149 SAEs were reported during the year. These were evaluated and, in some cases reclassified, to meet EU Directive and EUSTITE SARE reporting criteria giving a final number of 71 SARs and 150 SAEs.

Classification of SARs: Hypersensitivity 25%(18), Other 25% (18), Infection – tissue & cells 27% (19), toxicity 1% (1) infection - donor 4% (3) Failure - 16% (11) and Mismatch 2% (1).

**Severity - SARs:** Serious - 85% (60) Life-threatening - 11% (8) Death - 4% (3).

**Imputability:** N/A – 1%(1), excluded/unlikely – 14% (10), possible - 30% (21), likely/probably - 41% (29), certain- 14% (10).

**Impact Grading SARs :** ≥12 - 6% (4), 9 - 7% (5), 8 - 8% (6), 6 - 34% (24), 4 - 34% (24),3 - 3% (2), 2 - 7% (5), 0 - 1% (1).

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**Stage at which SAE occurred:** Procurement 23% (34), Testing 7% (10), Processing 29% (43), Storage 17% (26), Distribution 19% (28), Transport 2% (4) and Other 3% (5).



**Classification of SAEs:** Tissue & Cell defect 19% (29), Other 11% (16), Equipment Failure 23% (35), Human Error 47% (70).

**Impact Grading SAEs:** ≥12=1% (2), 9=3% (4), 8=3% (5), 6=29% (43), 4=23% (35), 3=27% (40), 2 – 11% (17), 0=3% (4).

### Conclusions:

The pilot demonstrated the feasibility of multi-national co-operation in vigilance and surveillance in the area of tissue and cells for human application. The tools developed during the EUSTITE project were tested in multiple countries on a large number of real SARE and were found to be easily applied by CA vigilance officers, although some reservations were expressed in relation to their direct applicability in the field of Assisted Reproduction. Many CAs will consider extending their application to the tissue establishment level. A willingness to share vigilance information was clearly demonstrated and a network of CA personnel working in this field was established. The potential for learning from consolidated data was demonstrated. The greatest level of reporting was in the fields of haematopoietic stem cells and the assisted reproduction sector. Approximately 50% of SAEs are classified as human error.

A final meeting of the Vigilance & Surveillance Medical Advisory Committee (V&SMAC) was held in Warsaw in December 2009. Several proposed changes to the EUSTITE V&S tools are listed here and have been incorporated in the Final Recommendations for Vigilance and Surveillance (Project Deliverable 11) submitted to the European Commission along with this report.

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## 1.0 INTRODUCTION

This is the final report of a year-long European pilot programme on the use and feasibility of a specially designed model and selection of tools to support the implementation of Vigilance and Surveillance (V&S) programmes in the EU, in compliance with the requirements of Directive 2004/23/EC and 2006/86/EC. The pilot commenced on 01 July 2008 and ended on 30 June 2009. The programme covered human tissues and cells for human application, for both allogeneic and autologous. The tools support a common approach to the reporting, measuring and management of SARE encompassing the processes of procurement, processing, testing, storage, distribution of human tissues and cells.

All countries in the European Economic Area were invited to participate. Eighteen countries involving 20 Competent Authorities (CAs) joined the pilot scheme at the beginning and commenced in Quarter 1 (Q1). Ten of these countries were EUSTITE project partners. In Q2, 2 further countries joined the programme, increasing the number of participant countries to 20 with 22 CAs (some countries have more than one CA for the field of human tissues and cells). In Quarters 3 and 4 participating countries remained at 20 with 22 CAs.

Recommendations arising from this pilot programme, including modifications to the vigilance tools, have been included in the Final Vigilance Recommendations (Deliverable 11) of the project, submitted to the European Commission together with this report.

### 1.1 The aim of this pilot was to:

- validate and improve the tools developed in EUSTITE (Project Deliverable 10),
- enable improved quality and safety by sharing information learned from incidents,
- demonstrate the value of both numbers of cases and expertise from across Europe,
- promote advocacy of patient safety and donor motivation for cell and tissue donation,
- promote openness, transparency and learning with colleagues across Europe,
- support added value of consolidated data from many countries,
- support the implementation of the EU Directives on tissues and cells.



### 1.2 Background to pilot

The EUSTITE project ([www.eustite.org](http://www.eustite.org)) partnership comprised a consortium of organisations from 10 Member States and the World Health Organisation (WHO) and was led by the National Transplant Centre in Italy. The other project partners were: Austria, Bulgaria, Denmark, France, Ireland, Italy, Poland, Spain, Slovakia and the UK. The purpose of the EUSTITE project was:

- a) to promote standardisation to good practice in the inspection of tissue establishments and
- b) 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 within the EU, regardless of whether the tissues and cells originate from within the EU or from third countries.

Vigilance was recognised as a fundamental instrument for improving safety in tissue and cell transplantation and Assisted Reproduction Technology (ART) by the European Union in its recently adopted legislation.<sup>1</sup> A Vigilance and Surveillance Medical Advisory Committee (VSMAC) was

<sup>1</sup> European Parliament and Council Directives 2004/23/EC, 2006/17/EC and 2006/86/EC

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constituted as part of the EUSTITE project. The VSMAC was chaired by the World Health Organisation because of their worldwide mandate for vigilance in transplantation and in recognition of the need to consider vigilance in the global context.

### 1.3 Vigilance and Surveillance Medical Advisory Committee (VSMAC)

The Vigilance and Surveillance Medical Advisory Committee (VSMAC) first met in 2007 in Madrid. The meeting was attended by representatives from project partner organisations, together with international experts in the clinical application of tissue and cells and experts in the risks associated with transplantation and assisted reproduction. The meeting outcomes were documented in a full report. On behalf of the VSMAC, a contracted expert reviewed existing vigilance systems in place in EU Member States and internationally, together with models for reporting and managing of adverse reactions and events within related fields, and produced a full report which was provided to the European Commission and was made available on the project website. A second VSMAC meeting was held in Rome later in the same year with an extended global attendance supported by WHO. The discussions and outcomes of the 3 day meeting were documented in a detailed report provided to the European Commission and made available on the project website.

### 1.4 The Vigilance and Surveillance Tools and Guidance



On the basis of discussions at the VSMAC meetings, and consultation with individual experts, a toolkit and guidance document for use across the EU to support the reporting and management of donor and recipient related SARE was developed, submitted to the European Commission (Project Deliverable 10) and made available on the EUSTITE project website. The V&S Toolkit contains flow-charts and guidance on reporting, together with information exchange responsibilities within MEMBER STATE. Criteria for the reporting of SAEs, and scales for grading of severity and imputability of SARs, are defined. A risk tool, the Impact Assessment tool, for quantifying the broader importance or criticality of SARs and SAEs is also described. Guidance for the management of SARE is provided in the document. Suggested levels of response in proportion to different grades of assessed impact of SARE are described. A summary of the tools as they were applied during the pilot is shown at **Annex 1**.

## 2.0 PILOT METHODOLOGY

Figure 1 summarises the steps undertaken in the pilot programme.

- Each participating Competent Authority (CA) was given a code number known only to the CA and the pilot co-ordinator to reduce any risk of patient or donor identification. All incidents reported to the co-ordinator were filed by CA number together with any local incident number provided by the CA.
- For the purposes of the pilot a vigilance officer at the relevant CA in each participant country was responsible for reporting and liaising with the V&S coordinator.
- All adverse reactions were scored against the Severity Grading Tool and the Imputability Tool and then the Impact Assessment Tool was applied by the CA.
- Adverse events were matched against the SAE criteria for reporting and scored against the Impact Assessment Tool.
- After an investigation of the incident and provision of a report by the Tissue Establishment (TE) the CA used the toolkit and compared their own evaluation of the incident then checked the investigation and results. If necessary the CA investigated with the TE.

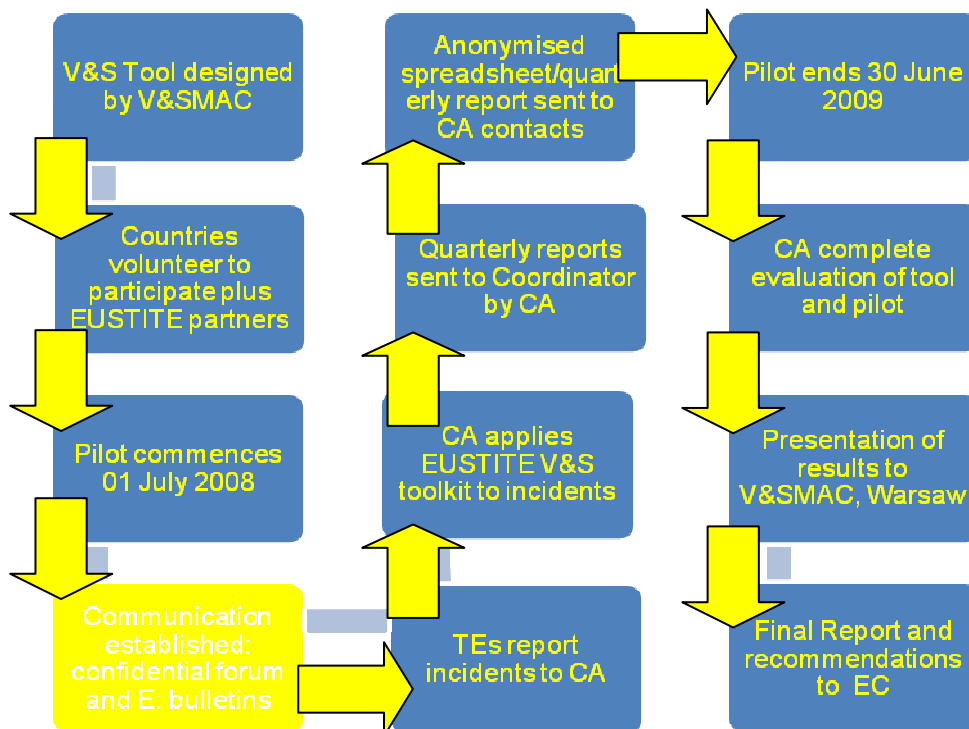


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- Each CA sent a quarterly report of all their SARE meeting the requirements of the European Directive to the V&S co-ordinator using the form shown at **Annex 2**.
- Any incident for which the investigation was not yet completed was included in their report and the status of the investigation marked as ‘Pending’. The results of the completed investigation were then reported in a subsequent quarterly report, with scores altered as necessary.
- Individual reports could be sent between quarterly reports if advice was required or if it was considered immediate lessons needed to be shared among the participants.
- All participating CA received a quarterly report from the co-ordinator. Attached was a spreadsheet containing all the previous quarter’s anonymised SARE received by the co-ordinator.
- Communication with participant Vigilance Officers and the co-ordinator was via a confidential forum on the EUSTITE website, regular E-bulletins and telephone.

Some CAs sent in SARE which did not meet the pilot specifications for reporting and so were excluded from the data analysis in this report although they are referred to in the discussion.

**Fig. 1 Pilot Process**





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### 3.0 PARTICIPATING COUNTRIES

At the beginning of the project, it was intended that the pilot participants would be the 10 project partner EU Member State organisations. The European Commission subsequently asked that other EU Member States be given the opportunity to participate. Consequently, the pilot was opened to all EEA countries and 8 non-partner countries accepted the invitation to participate. As the pilot progressed, two further countries joined as a result of inspectors attending the EUSTITE Inspector training course and reporting back to their offices on this work programme. By the end of the pilot the participant countries were:

Austria	Italy
Belgium	Lithuania
Bulgaria	Netherlands
Croatia	Poland
Denmark	Portugal
Estonia	Spain
France	Slovakia
Germany	Slovenia
Greece	Switzerland
Ireland	United Kingdom

Two countries, France and the United Kingdom, had two participating CAs, the CA for Assisted Reproduction and the CA for tissues and cells for transplantation; all other participants had one, for the purpose of the pilot.

Of the participant countries: Austria, Bulgaria, Denmark, France, Ireland, Italy, Poland, Spain, Slovakia and United Kingdom were EUSTITE project partners. In the UK, one of the two CAs participating was a project partner.

### 4.0 RESULTS - GENERAL

#### 4.1 Reporting Rates

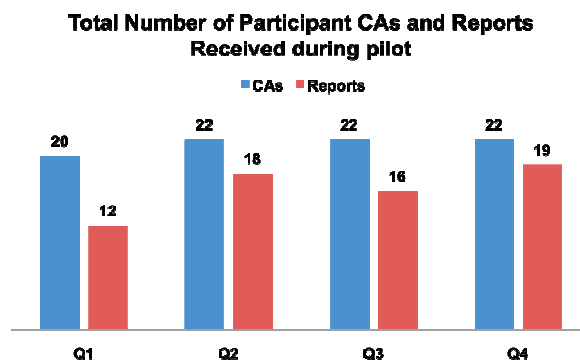


Fig. 2



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Fig. 2 shows the number of participating CAs together with the number of quarterly reports sent to the Pilot. In total, the CAs submitted 65 quarterly reports – an average of 16 per quarter. There was a gradual increase in reporting over the year. Six CAs did not send reports, or sent nil reports, during the pilot. Some CA only reported SARE involving specific tissues or cells e.g. Greece only reported cord blood, France (ABM) and the UK (HFEA) both only reported incidents involving reproductive cells, in line with their specific designated competency. Croatia and Germany only reported incidents involving haematopoietic stem cells.

#### 4.2 SARs Vs SAEs

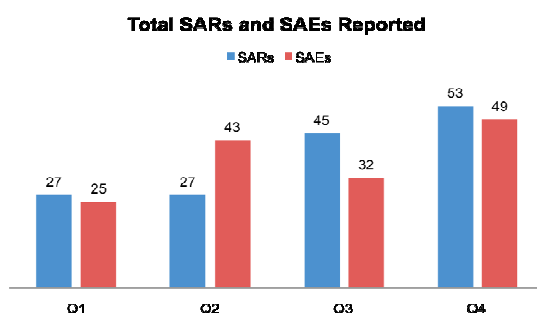


Fig. 3

In total, 152 SARs and 149 SAEs were reported during the one year programme. Fig. 3 shows a steady increase throughout the pilot in the number of SARE reported. This correlates with the expectation prior to the start of the pilot and reflects the fact that many of the national vigilance systems were in the early stages of development.

#### 4.3 SARE by Tissue/Cell Type

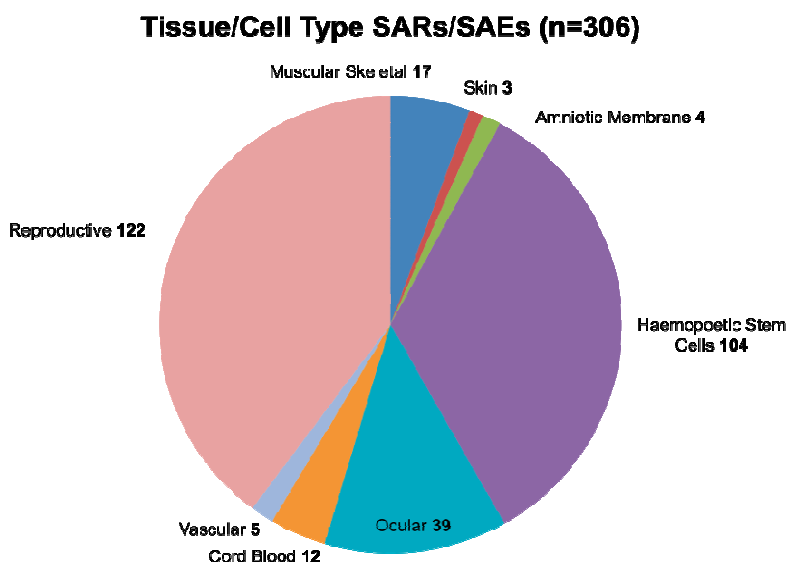


Fig. 4



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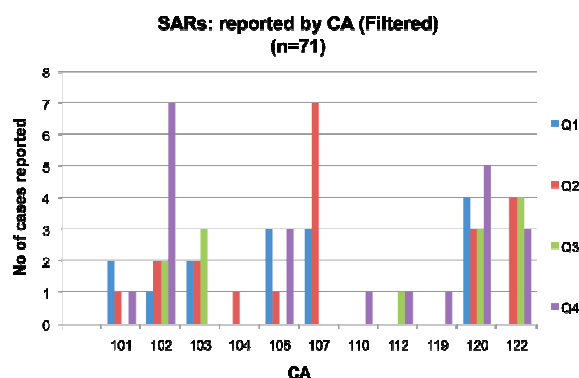
Fig. 4 demonstrates the number of SARE reported during the pilot by tissue and cell type, using broad categorisations. Reproductive tissue and cells, primarily oocytes and embryos were associated with a higher number of incidents reported, followed by haematopoietic stem cells and ocular tissue, primarily cornea. This pattern remained constant through the pilot. The nomenclature used in reporting by different participants varied initially making it difficult to group by different tissue types. Skull flaps, bone, tendon, chondrocytes, femoral head grafts were classified as ‘musculo-skeletal’ and oocytes, sperm, semen, blastocysts, embryos, reproductive cells and ovarian tissue were all classified as ‘reproductive’. It was agreed to show cord blood separately from other haematopoietic stem cells due to the very different organisation of cord blood banks compared to peripheral blood stem cell and bone marrow collection and processing centres.

## 5.0 RESULTS - SERIOUS ADVERSE REACTIONS (SARs)

### 5.1 Filtration of Reported SARs



The provision outlined in Article 5 of Directive 2006/86/EC requires that serious adverse events and reactions to be reported to the national CA; this does not prevent Member States from requiring reporting of non-serious incidents on a national basis. Many of the CA reported adverse events and reactions that were not classified as serious according to the Severity Scale in the V&S toolkit. At the end of the Pilot, a filtering (or reclassifying) process was carried out and those SARs which were considered to be reactions to medication, or were considered to have been inappropriately classified according to the tools, were either removed or changed from SAR to SAE, as appropriate. During the filtering process many of the SARE involving reproductive cells and HPC were reclassified. Following this exercise, the total number of SARs decreased to 71 and the number of SAEs increased to 150. The reporting of incidents outside the strict EU or EUSTITE criteria was encouraged during the pilot as it was considered a source of learning for participants.

### 5.2 SARs by Competent Authority



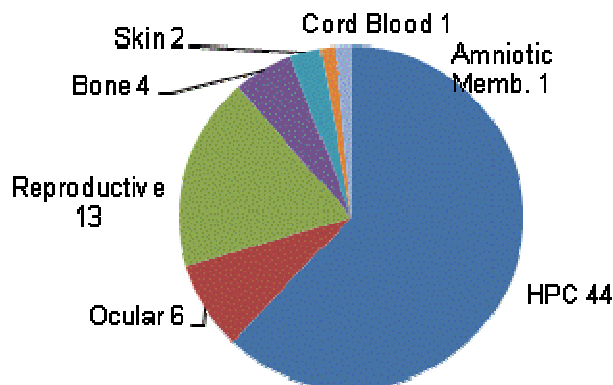
**Fig. 5**

Fig.5 shows the number of SARs reported in each quarter by CA. The 71 SARs notified during the pilot, and compliant with the reporting criteria, were reported by 11 of the 22 participating CAs. Many of the 11 have well established vigilance systems. The greatest number of CA reporting SARs was in Q4 when 8 CAs reported 22 SARs and in Q2 when 8 CAs reported 21 SARs. Two CA reported SARs in each of the four quarters. Three CAs reported just one SAR over the entire year.

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### 5.3 SARs by Tissue and Cell Type

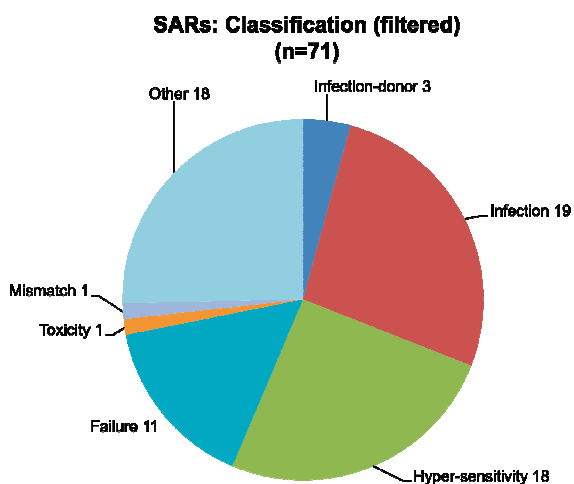
#### SARs: Tissue & Cell Type (filtered) (n=71)



**Fig 6**



As shown in Fig. 6, the SARs remaining following the filtration process involved most tissue and cell types but there was a predominance of HPC-related reactions.

### 5.4 SARs by Reaction Category



**Fig.7**

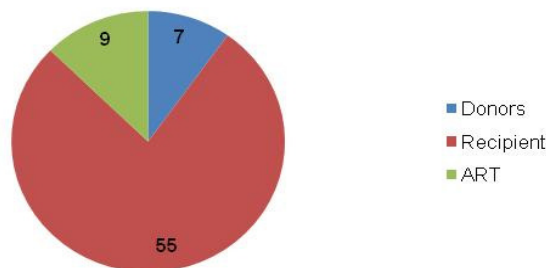
Fig. 7 shows the SARs grouped according to the reaction types, as categorised in the Tools and Guidance document. Recipient infection closely followed by *Hypersensitivity* and *Other* were the most common types of reaction. **Annex 3** shows all of the reported SARs, following filtration according to these reaction type categories. Reaction types that were included in the Tools and Guidance document such as *undue risk*, *genetic abnormality*, *malignancy* and *other transmission* had no SARs meeting the criteria during the pilot. The Tools and Guidance document had indicated that all suspected transmitted infections e.g. bacterial,

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fungal, viral, prion, parasite should always be reported and their severity should never be graded as non-serious or insignificant. As the examples in Annex 3 demonstrate, the imputability in many of these cases is low; the infections may have originated from other sources.

### 5.5 Donor Vs Recipient SARs

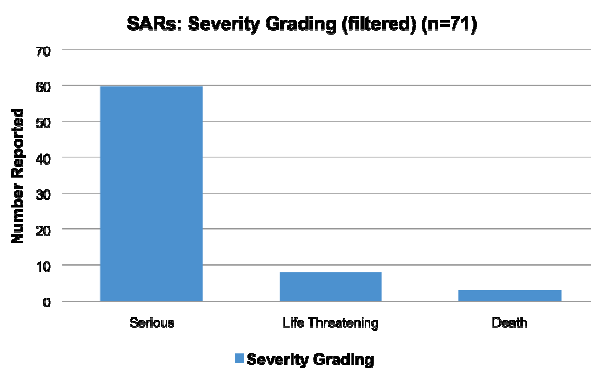
**SARs: donor/ART donor-recipient reactions (filtered)**





**Fig. 8**

Fig. 8 shows the breakdown of donor vs. recipient reactions from the filtered SARs. Both the donor (7) and ART (9) cases refer to donor reactions whereas the 55 cases concern SARs in the recipient. Donor adverse reactions with a possible effect on the quality and safety of tissue and cells must be reported according to EU legislation. There is no EU legal requirement to report donor reactions where the quality or safety of the donated tissues or cells have not been affected. The imputability of the donor reactions varied between 0 (*excluded*) and 3 (*certain*). Most of the donor reactions involved HPC and included hypersensitivity involving peripheral blood stem cells with the donor becoming unwell during apheresis, imputability was 3 (*certain*) with an impact of 6. There is also difficulty with donor reactions in ART cases and they have been separated from other tissue and cell types. The above cases, apart from one, refer to infection post oocyte retrieval or embryo transfer. None of the above are OHSS cases and all are in the context of partner treatment where the use of the term ‘donor’ is perhaps not appropriate. It is possible that some did not impact on the safety or quality of the gametes and should have been excluded from the analysis according to the mandatory EU Directive reporting requirements.

### 5.6 SAR Severity Grading



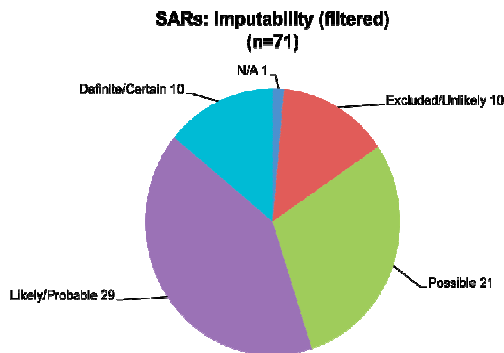
**Fig. 9**

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The EUSTITE Severity Grading tool facilitates an evaluation of actual harm using a consistent approach. Any reaction graded serious or above must be reported to the national CA according to the EUSTITE guidance. Primarily the evaluation of severity should enable the appropriate response to be taken following the SAR. This is important clinically for the patient but also for lessons to be learned and shared from SARs and to enable clear priorities to be set for a reactive and proactive approach to harm. The toolkit suggests that only serious and above incidents should be reported to Competent Authorities. During the Pilot several adverse reactions falling outside this criterion were reported i.e. insignificant and non serious and subsequently were filtered out. All suspected transmitted infections e.g. bacterial, fungal, viral, prion, parasite should always be reported to the TE and CA and their severity should never be graded as non-serious or insignificant, according to the EUSTITE guidance.

Fig. 9 shows that 60 of the filtered SARs were graded as Serious, 8 were considered life-threatening and 3 resulted in death. The deaths reported during the pilot all followed transplantation of haematopoietic stem cells and the rate observed is not unexpected given the high mortality observed in association with haematopoietic stem cell transplantation.



### 5.7 SAR Imputability Grading



**Fig. 10**

The Imputability tool was adapted from the imputability grading tool used over a number of years in blood vigilance. The scores should be applied in collaboration with clinicians/scientists working in the Procurement Organisations and/or Organisation Responsible for Human Application. The tool enables the causal relationship between the procured or applied tissue and cells and the SAR to be assessed.

Fig. 10 shows that the majority of the SARs reported were evaluated as either likely/probably (29) or possible (21) with certain (10) to have a causal relationship between the tissue and cells transplanted and the reaction.

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### 5.8 SAR Impact Grading

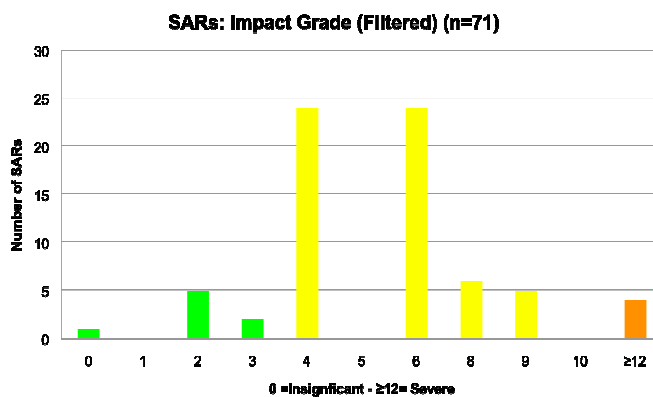


Fig. 11

The Impact Assessment Tool supports the evaluation of the criticality of a specific SAR or SAE. In the case of SARs, the severity is also taken into account. The impact takes into account the actual or potential effect on the individual patient and also on public health and on the broader system, including public support for donation and transplantation of tissue and cells and risk to the supply of tissue and cells. The impact grade for SARE is calculated by multiplying the probability of recurrence by the consequences of this particular recurrence. The impact matrix is colour coded: 0-3 = green, 4-9 = orange and >9 = red. The colour coding makes it easy to see the suggested level of response necessary, as described in the Impact Tool (**Annex 1**).



In Fig. 11 a comparison of the grades from the impact matrix given to SARs during the pilot is shown. Not every participant notified the pilot of the breakdown of their calculation. However all gave the total impact score. The highest score reported during the pilot was 12, given to three SARs. [See **Annex 3**]

- i. a bone marrow sibling allograft in which the recipient died (Q2)
- ii. two hypersensitivity cases following transfusion of HPC in which the recipient made a full recovery (Q3).

### 5.9 SAR Frequency by Tissue Type

Most CAs were not yet in a position to provide detailed data relating to numbers of tissues/cells of particular types which have been clinically applied at the national level. Such data, if they were readily available, could have provided denominators to allow calculation of risk associated with these procedures by tissue/cell type and by country. An approach applied to estimating SAR frequency was to select some participating Member States that provide activity data to the Eurocet CAs platform ([www.eurocet.org](http://www.eurocet.org)) or to the Council of Europe Transplant Newsletter and to present their SAR rate for particular tissues/cells per number of transplants of this type of tissue/cell. Using this approach, reaction rates of SARs were estimated for some of the tissue and cell types included in the scope of the pilot, using the activity data published for 2008 in the Eurocet platform ([www.eurocet.org](http://www.eurocet.org)) and in the Council of Europe Transplant Newsletter for the same year. Eurocet and Council of Europe data were used as the data provided to the European Commission in the Member States Annual Vigilance Reports were not yet available. Only those countries that had provided activity data to Eurocet or Council of Europe **and** had participated in the pilot were included in the analysis. The following estimates were calculated:



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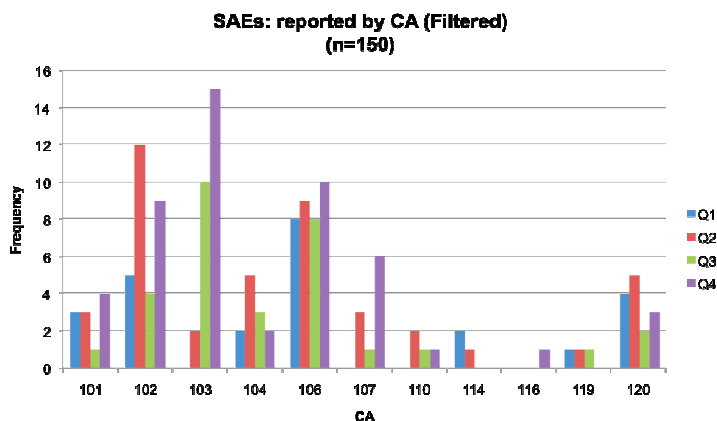
:

- 17,096 cornea transplants were performed in 2008 in 15 countries that were participating in the pilot. During the pilot (a one year period from the middle of 2008 to the middle of 2009) there were 6 serious adverse reactions reported for corneas in those countries; this implies an approximate SAR rate of 1 in 3,000. However, it should be noted that in the country with the most well established reporting system, there was a serious adverse reaction reported for approximately each 1,000 corneas transplanted.
- Approximately 71,000 bone transplants were performed in 2008 in 15 countries that were participating in the pilot. During the pilot, there was 1 bone-related SAR reported in those countries; this implies an approximate SAR rate of 1 in 71,000.
- Approximately 21,811 HPC transplants (of which 8,710 were allogeneic and 13,101 were autologous) were performed in 2008 in 13 countries that were participating in the pilot. During the pilot, there were 34 HPC-related SARs reported in those 13 countries; this implies an approximate SAR rate of 1 in 650.

## 6.0 RESULTS - SERIOUS ADVERSE EVENTS (SAE)

Directive 2006/86/EC clarifies that “serious” adverse events should be reported to the CA and defines an SAE in relation to its potential to cause an SAR. 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 of which might result in, or prolong, hospitalisation or morbidity is the definition of a Serious Adverse Event. EUSTITE proposes that deviations from Standing Operating Procedures (SOPs) 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 CA when one or more of the criteria listed in **Annex 1** applies.

### 6.1 SAEs by Competent Authority



**Fig. 12**



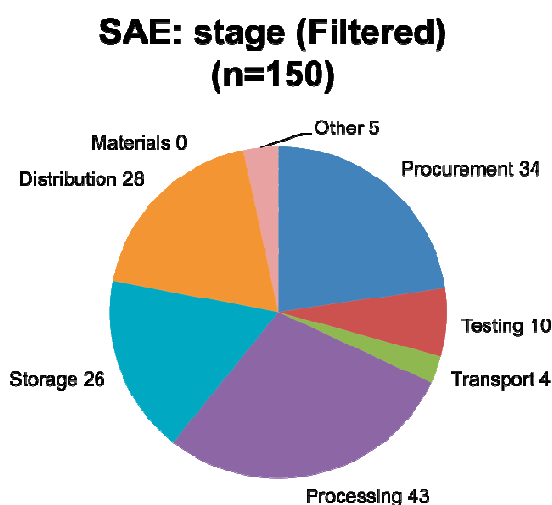
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Fig.12 illustrates the number of SAEs reported during the pilot by CA. 11 CAs reported SAEs in at least one quarter. 6 CAs reported at least one SAE in Q1; this increased to 10 in Q2 and then decreased to 9 in Q3 and Q4. The highest number of SAEs reported by a CA was 15 during Q4 by one CA. Only 4 CAs reported SAEs in each of the quarters. The average number of SAEs reported over the pilot by the 11 CAs was >13.5. Over the 22 CAs the average was >6.

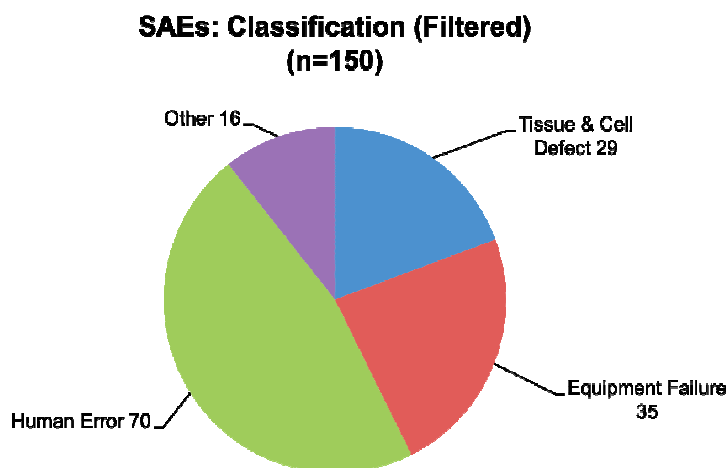
### 6.2 SAEs by Stage of Occurrence





**Fig. 13**

Fig. 13 shows the stage at which the reported SAEs occurred. Events commonly known as “near misses” are included in the SAE category. **Annex 4** shows a series of examples of SAEs reported by stages of occurrence.

### 6.3 SAEs by Event Category



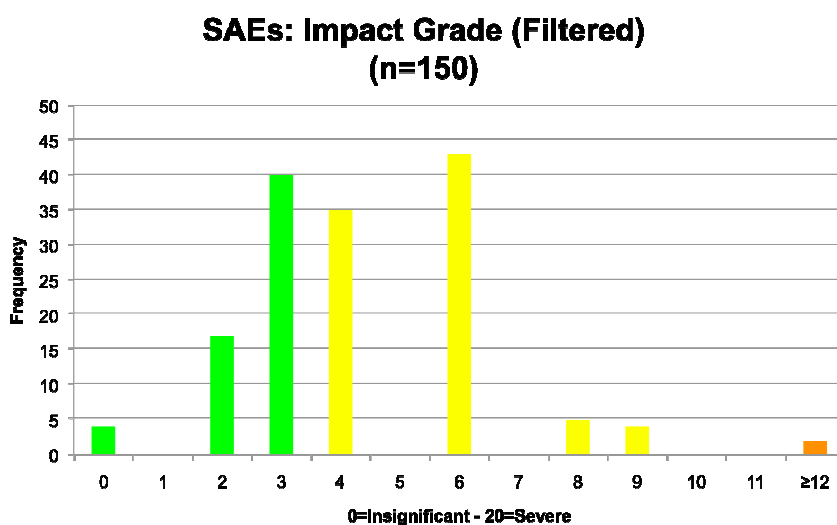
**Fig. 14**

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When completing their quarterly report, participants were asked to classify SAEs into one of 4 categories, which are those defined in Directive 2006/86/EC: tissue and cell defect, equipment failure, human error and other.

- **Tissue and cells** defect - when the quality of the tissue or cells is compromised. The defect may have been present in the tissue when first retrieved or may have been introduced prior to transplantation. This could be due to inadequate testing, procurement or processing or to the way it was distributed or transported. An example would be a lesion found at autopsy that is not obvious on visual examination and is not notified until after distribution has taken place. [See **Annex 6** for further examples]
- **Equipment failure** is a cessation or breakdown of the normal operation of a piece of equipment leading to process not being performed as intended. Failure of equipment may also be linked to failure to follow maintenance instructions and guidelines supplied by the manufacturer. Alternatively there may be poor protocols in place e.g. failing to check levels of liquid nitrogen in storage tanks or over reliance on alarm systems. [See **Annex 5** for further examples]
- **Human error** may suggest active failure on behalf of an individual – there is inconsistency between what the professional intended to happen and what actually happened or what s/he meant to do and what they actually did. Examples of human error, as classified by the participant countries involved in the pilot included: use of expired equipment and failure of a required witnessing step. As Fig. 15 shows, in almost 50% of the reported SAEs Human Error is declared as the main component. Some of the SAEs classified in other categories may also have a component of human error in them. [See **Annex 5** for further examples]
- **Other** is used when the defect is of unconfirmed origin or does not fit the previous three categories. Examples include: contamination (e.g. *E.coli*) caused by contaminated culture or freeze media and activity in unlicensed premises.) [See **Annex 5** for further examples]

#### 6.4 SAE Impact Grading



**Fig. 15**

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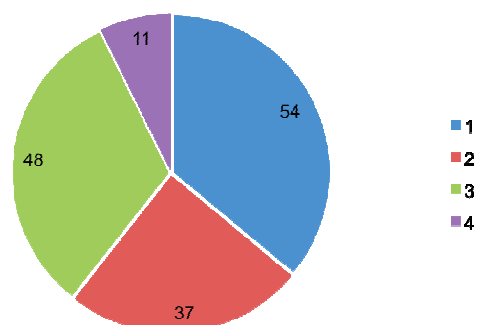
The Impact Assessment Tool assists in assessing the criticality of a specific SAE or SAR. The impact takes into account the actual or potential effect on public health and on the broader system, including public support for donation and transplantation of tissue and cells and the risk to the supply of tissue and cells. The impact grade for SAEs is calculated by multiplying the probability of recurrence by the consequences of this particular SAR (see **Annex 1**). The impact matrix is colour coded and 0-3 = green, 4-9 = yellow and >9 = orange. The colour coding makes it easy to see the suggested level of response necessary.

A comparison of the grades from the impact matrix given to SAEs is shown in Fig. 15. The majority of SAE Impact scores during the pilot were 3, (40) 4, (35) and 6 (43). Those that scored 3 were in the green zone and all others were in the yellow zone apart from two SAEs which were scored as 12 (orange):

- i. Late fungi growth on last culture. Corneas already transplanted but no reports of any harm to the recipient
- ii. Multi-organ plus eye donor. To clarify cause of multi-organ failure many tests were performed before procurement, among them HSV-1 DNA. No information about this test was given to the Eye Bank before the results were available: positive. Corneas were still in culture and were discarded.



### 6.5 SAEs by EUSTITE Reporting Criterion

**SAE: EUSTITE criteria for reporting (n=150)**



**Fig 16**

Fig. 16 shows that 54 SAEs involved inappropriate tissues/cells were distributed for clinical use, even if not used (Criterion 1). 48 events resulted in loss of irreplaceable autologous tissue or cells or highly matched (i.e. Recipient specific) allogeneic tissues or cells (Criterion 2). 37 events could have implications for other patients or donors because of shared practices, services, supplies or donors (Criterion 3). Finally, in 11 cases, the event resulted in the loss of a significant quantity of unmatched allogeneic tissue or cells (Criterion 4).

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## 7.0 ANALYSIS AND DISCUSSION

### 7.1 Reporting

22 Competent Authorities in 20 countries from the European Economic Area participated in the pilot. 10 of the 20 countries were project partners in EUSTITE. 65 quarterly reports were received during Pilot. 8 countries reported no SARE during the Pilot. There was a gradual increase in reports received as the Pilot progressed. The greatest number of SARE was reported in the final quarter (22 SARs and 51 SAEs).

### 7.2 National Regulatory systems

In some countries where more than one regulatory CA is responsible for various aspects of tissue and cells, there can be some confusion with V&S reporting leading to the possibility of SARs being missed. Many of the CAs participating in the Pilot are responsible for only one or a few tissue/cell types. This may be because some countries are still developing their vigilance systems and have not yet incorporated all types of tissue and cell activity in their national monitoring programmes.

### 7.3 SARs or SAEs

Some SARs were reported that did not meet the EU Directive criteria for reporting to the CA in that they were evaluated as non-serious or insignificant or were donor reactions to medical treatment. Some SARs classified as serious were given an Impact score of 3 or less. There may be a need to review the Impact tool to ensure that if the severity is 'serious' then the impact must be at least significant which would require scoring >3.

### 7.4 Procurement



A relatively high number of corneas were rejected by surgeons immediately prior to transplantation due to inadequate 'procurement' procedures. There was a similar picture with heart valves which were rejected just before transplantation. Quality control and ongoing training may be issues in some procurement organisations.

### 7.5 Nomenclature

The different nomenclature applied to the various tissue and cells was identified as a key issue in Q1. The importance of reaching agreement on common terminology was acknowledged by the project group to allow data analysis and comparison. The tissue and cell categories defined by the European Commission in the guidance document provided in 2009 to CAs is a first step in this direction. Appropriate, common coding will also help to overcome this barrier. The description of the types of reaction categories also requires harmonisation. *Hypersensitivity*, *Toxicity* and *Other* were common reaction types reported for HPC. These categories from the toolkit caused some confusion with some participants in different Member States who used them interchangeably for apparently similar SARs. Clarification is necessary in this regard.

### 7.6 Impact Scores

When reporting Impact scores, some CAs gave just the total Impact score, some gave consequences x likelihood/probability = Impact score and some gave likelihood/probability x consequences = Impact score. An agreement should be reached to clarify reporting: perhaps consequences x likelihood/probability = impact. This will help in ensuring better understanding of the consequences of a particular SARE and how likely it is that a similar SARE will occur again either at the same establishment or all establishments. Occasionally scoring of similar events seems to differ between the various CAs. Some contacts at CAs communicated that they had not received specific training. It is clear that the application of a common set of tools will require a common training basis for vigilance officers.

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### 7.7 Severity Grading

A number of SARs which were infections were graded as non-serious or insignificant. The tool states that ‘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’. This requires review as there were some transmitted bacterial infections that were considered to be of minor clinical importance. Nonetheless, it is noted that there is the possibility that an infection that initially seems to have a low severity could later prove to be serious but would not have been reported if initially classified as non-serious.

### 7.8 Imputability

The assessment of the causal relationship between the tissue and cells and the adverse reaction proved a useful tool during the pilot. However, there were difficulties with the Imputability level 0, defined as ‘Excluded’ or ‘Unlikely’. Imputability may be excluded because of direct evidence to the contrary. However, if it is scored as ‘unlikely’ there is still the possibility that the tissues or cells were indeed the cause of the reaction; this might not become apparent unless large numbers of cases are reported or supplementary evidence to link the tissues or cells to the reaction emerges. It was concluded that, ‘excluded’ and ‘unlikely’ should not be combined in the same imputability score. In the EUSTITE Final Recommendations (Deliverable 11), this has been changed; the Imputability definitions is amended to N/A, 0 – excluded, 1 – unlikely, 2 - possible, 3 - likely/ probable, 4 – definite/certain.

### 7.9 Investigations

Not all CAs included findings of investigations in their reports to the pilot. Therefore few changes in practice, technique or protocols, following lessons learned from particular SARE, were reported to the pilot scheme. This may have been because training in vigilance and surveillance is necessary in some countries together with training in the different investigative methods that might be applied. Feedback improved slightly towards the end of the pilot although few CAs gave feedback to the co-ordinator of any changes in classification or scoring of incidents post investigation. Reporting SARE will not by itself improve safety or quality. Consistent and proportionate investigation, follow up and feedback must take place. Normal inspection techniques are not necessarily sufficient in a serious incident investigation (sentinel event) or if unlawful activity is suspected. It is likely that the SARE reported to the pilot were investigated thoroughly at TE/clinician level but there was not a lot of evidence that the CA was receiving detailed feedback on these investigations.



### 7.10 Timescales

Timescales varied between events being detected and being reported to the CA, some being reported many months after the event. The Directive requires reporting “without delay”. A delay in reporting may have an impact where there are immediate lessons to be learned for other TEs and CAs or when there is risk of disease transmission. Failure to report expeditiously may exacerbate risk to other recipients by delaying the possible recall of infected or damaged tissue and cells especially if there may be further tissue and cells already in circulation. If there is a suspicion that disease transmission may have occurred because of transplanted tissue and cells then the precautionary principle should apply. An in-depth investigation of an SAR or SAE can sometimes take a considerable period of time to be completed and therefore notification should not rely on a completed investigation. Timescales for reporting of SARE should be clarified, at least at a national level.

### 7.11 Classification SAEs

Fifty percent of SAE were classified as *human error*. Human error is a very blunt tool – more information is necessary to allow understanding of the cause of the human error. Focused training on the analysis of human



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related factors may be necessary for those conducting investigations. The classification of SAEs, in general, is likely to require more refined definition in any future version of the tools. Many of the SAEs reported are likely to have a variety of contributory factors which would only become apparent after thorough investigation.

### 7.12 Infection from Donor/Infection from Tissues and Cells

It was not always clear whether SARs classified as infection involved infection arising from the donor or from contaminated tissues and cells. This may be because the definition needs to be clarified or because it is not always clear where the infection originated.

### 7.13 Reporting Rates

There was evidence of varying reporting rates in the pilot. Some countries reported no SARE throughout the year and others very few, while still others had high reporting rates. At present there is insufficient data from some countries regarding the volume and type of tissues and cells applied clinically to facilitate the estimation of the frequency of SARE. However, both the Council of Europe Transplant Newsletter and the Eurocet database ([www.eurocet.org](http://www.eurocet.org)) are making progress and allowed some estimates to be made using the pilot results. Further development of these instruments will be important for improving knowledge about adverse incident rates in this field.



### 7.14 Hypersensitivity

There were 34 reported SARs related to Peripheral Blood Stem Cells that included a variety of symptoms: hypertensive crisis, hypotension, nausea, vomiting and chest pain; all these cases related to probable DMSO toxicity. All but 12 cases were removed from the analysis during filtering due to the reported non-serious nature of the reactions. In Q1 and Q2 one country reported 21 SARs of type *Hypersensitivity* with a severity grading of Non Serious or Insignificant all linked to DMSO. During Q3 and Q4 the same country reported 12 cases and graded them as Serious (10) and Non Serious (2). Again, all were linked to DMSO. No other country reported any DMSO SAR. A published review of DMSO-related reactions in haematopoietic stem cell recipients (Windrum *et al.*, 2005) suggests that such reactions occur in approximately 1 in 70 transplants. Although a large proportion of these could be expected to be non-serious, the statistic, nonetheless, suggests that there are likely to be many more serious reactions of this type that are not being reported to CAs. Imputability of DMSO related hypersensitivity reactions is not always clear. In France, a national inquiry was conducted some years ago which concluded that the high number of granulocytes and dead cells were responsible for some of the SAR occurring after HSC grafting. France made recommendations for 1) washing the cells after thawing or 2) ensuring infusion of HSC with a high number of granulocytes.

### 7.15 Toxicity Reactions in Donors

There were 14 SARs in Peripheral Blood Stem Cell donors that were reported and classified as *Toxicity* associated with hypocalcaemia during apheresis. The severity grading for these 14 donor reactions was ‘non serious’ or ‘insignificant’ and the impact grading ranged from 0 to <3 and they were removed from the Pilot analysis during filtering as they did not meet the criteria for reporting SARs as defined in the EU Directives. Review of the pilot results stimulated discussion regarding the assessment of severity in altruistic donors versus recipients undergoing treatment for their own benefit. It was concluded that the threshold for reporting any reaction in a donor should be lower so that even minor risks can be trended and potential donors can be properly informed of these risks prior to giving consent.



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### 7.16 Reproductive Cells and ART - Complications of Procurement



During Q1 it became apparent that a number of reported cases did not precisely meet the requirements of the EUSTITE criteria and the EU Directives. Many of these cases involved reproductive cells. In their evaluation feedback at the end of the pilot, concern was expressed by some participant CAs that certain incidents involving ART did not belong in the pilot or were difficult to fit in the definitions provided. Examples: haemorrhage post oocyte collection or adnexal torsion post oocyte collection. It was considered by several CAs that these were donor reactions and that there is no requirement in the Directive to report this type of incident if it did not impact on the safety and quality of the tissues/cells procured. Many of the incidents concerned were serious and it was considered that they would be a source of learning for those countries still setting up their systems, especially in ART.

A decision was taken to create, for the duration of the pilot, an extra category *complications of procurement*, in which those ART cases that did not fit the other reaction types, and for which reporting was not mandatory according to the Directive, would be placed. This category was removed at the filtering stage at the end of the pilot to ensure that the final analysis was performed on those SARE that met the EU reporting criteria. ART incidents were reported by a number of countries but none by some countries who are known to have a considerable number of ART clinics. Both ART specialist CAs advised that they had difficulty in applying the definitions to ART cases. One specialist ART CA advised “*the definitions of SARs and SAEs are very patient focused and exclude most of the incidents reported in ART, which predominantly involve gametes and embryos rather than patients. With each report I found it quite difficult to apply the definitions and looking at the summaries am not clear how some of the incidents other members have reported fit the definitions*”. The other specialist ART CA reported many more patient focused SARE and also those involving gametes and embryos but they also had difficulty in being sure what should be reported. The nomenclature used in ART, especially involving donors and recipients is somewhat different to that used in other tissue and cell applications which suggests that in the final toolkit there should be clearer definitions and examples of which incidents involving ART tissue and cells are reportable. More consideration should be given to the definition and reporting of ART SARE.

A new project has since been funded by the European Commission (Vigilance and Surveillance of Substances of Human Origin, SOHO V&S) which has a specific work package that will address the issues and develop appropriate guidance for ART vigilance and for donor reactions in general.

### 7.17 Ovarian Hyper-stimulation Syndrome (OHSS)

A comparatively high number of serious OHSS cases were reported during Q1 as secondary information from one of the specialist ART CAs. Some CAs considered that as these reactions are a direct consequence of treatment with the relevant medicinal product, they should be managed as pharmacovigilance reports. Others, however, felt that they should be included in any ART vigilance programme. The pharmacovigilance regulator in the UK was contacted to know whether they could provide information on the number of cases reported to them. Between 01 January 2006 and 30<sup>th</sup> December 2008 – 9 cases of OHSS were reported to pharmacovigilance in the UK, one of which was a death from multi-organ failure. In contrast, during the one year period of the Pilot, 101 cases of OHSS were reported from the CA in the UK. In total, 194 cases of OHSS were reported during the Pilot. Even this is clearly a small percentage of those cases that occurred during the year, given that the European Society for Human Reproduction and Embryology (ESHRE) publications indicate that the rate of OHSS is 1.2% with over 3,000 cases occurring in Europe in 2005 (Nyboe Andersen A. *et al.* 2009). From the limited information available, it appears that cases of OHSS are not routinely being reported through the pharmacovigilance systems in place, possibly because of the expected nature of the effects and are often not reported to the CA for tissues and cells, as

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this is not an EU Directive requirement. This requires clarification from other countries so that appropriate risks can be calculated and patients undergoing treatment notified of the degree of risk, in addition to any regulatory/communication measures needed in respect of the medicinal products concerned. This impacts particularly on donors donating oocytes where regulation of ART is still not established at the national level. EU CAs for tissues and cells will need to decide whether they wish to have an overview of this type of donor/patient adverse reaction and whether the data collected and published by the professional community is adequate.

### 7.18 Donor Reactions other than OHSS

The issue of donor reactions in general caused some concern during the Pilot and needs to be addressed and decisions taken regarding non-mandatory reporting. It was sometimes found difficult by some CAs to use the tool appropriately in these cases. One of the aims of the pilot was to consider the needs of donors and advocate for them. Transplantation relies on donors and the risk of public concern impacting on donation is great if serious reactions occur to donors and there is insufficient investigation or response. In recognition of the importance of vigilance of donor reactions and the protection of donors, the European Commission informed CAs for tissues and cells during 2009 that it welcomes the inclusion of non mandatory donor related SARs in the Member State Annual Report to the Commission on a voluntary basis, even where the quality or safety of the procured cells was not adversely affected (*Common Approach for Definition of Reportable Serious Adverse Events and Reactions as laid down in the Tissues and Cells Directive 2004/23/EC and Commission Directive 2006/86/EC, Version 1.0, European Commission, July 2009*). This would include those reports which should be reported to the pharmacovigilance system where appropriate, i.e. OHSS and GCSF reactions.



### 7.19 Unlawful Activity

Reports received involving unlawful activity including: cord blood being procured on unlicensed premises, procurement of cornea without adequate consent and evidence that the “head employer” of a procurement organisation did not understand the Directives. The investigation of unlawful activity can be different from that of other types of SARE and requires special training for inspectors/investigators. The reports also demonstrate that specialist training is required by senior professionals taking on the role of Responsible Person e.g. an understanding of the requirements of the Directives and other legal imperatives. The new project that has since been funded by the European Commission (Vigilance and Surveillance of Substances of Human Origin, SOHO V&S) has a specific work package that will develop guidance for CAs on illegal and fraudulent activity and another work package that will provide investigation training.

## 8.0 APPLICABILITY OF THE TOOLS - EVALUATION BY THE PARTICIPATING VIGILANCE OFFICERS

In order to evaluate the pilot program, a questionnaire was sent to the vigilance officers in each CA by the project partner responsible for Evaluation (Agence de la Biomedicine) in order to obtain their feedback regarding the applicability, relevance and ease of use of the tools. The following organisations responded by sending completed questionnaires:

- Agence de la Biomédecine (France)
- Agence Française de Sécurité Sanitaire des Produits de Santé (France)
- Autoridade para os Serviços de Sangue e Transplantação (Portugal)
- Centro Nazionale Trapianti (Italy)

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- Danish Medicines Agency (Denmark)
- Dutch National Hemovigilance Office (The Netherlands)
- Hellenic Cord Blood Bank (Greece)
- Human Fertilisation and Embryology Authority (United-Kingdom)
- Human Tissue Authority (United Kingdom)
- Irish Medicines Board (Ireland)
- Ministry of Health (Republic Of Lithuania)
- Ministry of Health and Social Welfare (Croatia)
- Organización Nacional de Trasplantes (Spain)
- Paul Ehrlich Institute (Germany)
- Slovenija Transplant (Slovenia)
- State Agency of Medicines (Estonia)
- Unit Transplant – Inspectorate (Switzerland)
- University Hospital of Bratislava (Slovak republic)

After 12 months using the tools, the overall appreciation of the toolkit in its present format was mainly positive. Most vigilance officers considered it as good (6 answers/18) or very good (10 answers/18), but two considered it was average (ABM and ONT). The toolkit was considered as easy or very easy to apply (12 answer/18), but 5 gave a score of OK, and one officer considered it was difficult to apply (ABM). Most vigilance officers agreed or strongly agreed that the tools enabled the definition and classification of SARE effectively (15 answers / 18), 1 person had no opinion (Greece) and the two CA specialised in ART V&S (ABM and HFEA) disagreed.



Most officers agreed or strongly agreed that a pan European reporting system would improve quality and patient safety (16 answers/18), but 2 disagreed (AFSSAPS and Estonia). Interestingly, most officers thought that some or all of the tools would be incorporated to their national systems (16 answers/18), although 2 vigilance officers considered that this will not be the case (HFEA and ONT). It is interesting to compare this result to the opinions of the evaluation committee concerning the tools: several members thought that the tools would be difficult to apply in all countries, but it seems that a majority of vigilance officers were convinced by this system. In countries where no system is in place, the officers considered that all of the tool kit should be implemented. In countries with their own V&S system, the imputability scale and impact matrix were considered as interesting to incorporate. The HTA officer would even recommend a full incorporation of the tools, although the system would have to be adapted to their approach.

The tool kit defines 4 criteria for the reporting of SAEs, which were considered as logical and easy to apply, except by the AFSSAPS. The scale for describing the severity of a reaction was considered as easy to apply by all correspondents. The scale for describing the imputability of a reaction was estimated as logical and easy to use, except by the ABM which considered that it was difficult to apply to the field of ART.

The toolkit was considered as helpful by all/most correspondents for:

- classifying SARs and SAEs (all correspondents except ABM);
- understanding imputability scores for SARs (all correspondents except ABM and HFEA);
- understanding impact of SARs and SAEs (all correspondents except ABM);
- understanding and grading the severity of SARs (all correspondents).

The impact assessment tool was considered as useful or very useful to help decision making following some or all SARE by all the officers.

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Regarding quarterly reports sent by the co-ordinator, most of the officers agreed or strongly agreed that they were sufficiently informative (17 answers /18). Finally, the V&S website forum was rarely consulted by the officers: 6 persons never accessed to it and 10 persons accessed 1 to 3 times during the program.

A significant comment was submitted by the ABM and the HFEA, who considered that the tools were very patient-focused and therefore exclude most of the incidents reported in ART. This comment is consistent with the conclusions of the EUSTITE internal Evaluation Committee that evaluated the tools before the pilot programme.

Other comments that were submitted included:

- The tool system has only been tested at the CA level. It has to be tested in TE, ORHA and PO (by local biovigilance contacts). So it's too early to confirm the effectiveness of the system.
- The consequences score (in the Impact tool) is unclear (too close to severity grading) and should be more targeted on public health and on the broader system.
- The Reporting Triggers (SAR Classifications) as included in the tools document have provided clarity on the type of SARs/SAEs which should be reported to the CAs and have been of great benefit. In the interest of clarity it would be useful if the triggers used in the Pilot reports, reflected those listed in the vigilance and surveillance tools, i.e. complications of procurement is not listed in the SAR triggers.
- The Grading Tools are very useful in terms of defining a grading system and an appropriate response. However we have noted a variation in scoring from CAs for events which on the surface appear to be similar highlighting that the tool is subjective and open to interpretation. We consider that ongoing guidance and training would be useful in this regard. In some cases it is difficult to predict the probability of recurrence.
- Responsibilities / Information Flow/ Rapid Alerts: the Tools document has provided some very useful guidance in terms of reporting responsibilities and information flow. In practical terms the reporting responsibilities for tissues and cells are proving very complex and we consider that this is an area which would warrant further attention particularly in relation to cross border reporting and rapid alert notifications.
- Nomenclature: An issue identified in the course of the pilot regarding varied nomenclature used was addressed by reclassification using a list generated by EUSTITE. As suggested there should be a firm agreement in this regard. It might be appropriate to utilise the list generated in the Common Approach Document (European Commission guidance document to CAs for completion of their Annual SARE Reports, issued in 2009). In this event the reports generated should be consistent i.e. if using high level headings, Cord Blood should be in the Haematopoietic Stem Cells category and Amniotic Membrane should be captured in the Other category etc.
- The interpretation of the legal scope for SARE reporting to the Commission is one of the challenges faced by the CAs. The original thinking was that the pilot was to apply the tools to mandatory SARE as defined in the legislation and as per guidance in the Tools document. However, the Pilot reports appeared to include many non-mandatory cases which on review of the cumulative data do not appear to be attributable to/or did not influence the quality and safety of the tissues and cells, i.e. complications of procurement, ectopic pregnancy etc.
- While not specific to the Pilot project, some other comments in relation to vigilance reporting have been noted during the course of the project. With regard to SAEs, it is often difficult to select the stage where a deviation has occurred. Similarly SAE specifications can be unclear although the common approach document has provided some guidance in this regard.





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The evaluation report concluded that the pilot program showed that the tools designed by the EUSTITE project to classify SARE and to support decision-making were fully applicable. Even in countries with a system in place, the toolkit could be adapted to the existing process. The tools were mainly considered as easy to apply, logical and helpful. Most of the participating CAs considered that they should be partly or completely incorporated to their national system. However, as stated by the two CAs specialised in the field, the tools do not seem to be adequately adapted to the field of embryology and assisted reproduction. A different and more adapted toolkit may need to be designed to take into account the specificities of this field.

## 9.0 RECOMMENDATIONS AND FUTURE WORK

- 9.1** The EUSTITE V&S tools should be modified and resubmitted to the EC to take account of a number of enhancements that were proposed during the pilot and the discussion of its results:
- Separate the terms *excluded* from *unlikely* in the Imputability tool;
  - In the criteria for SAE reporting, clarify where mix-ups in ART should be included, or add a new criterion for this;
  - In the descriptions of the SAR severity grades, add the transmission of genetic illness following ART with donor gametes or embryos;
  - In the impact assessment tool, reverse the order of numbering, simplify the terms and change the colours to the commonly used red, yellow and green.
- 9.2** The EUSTITE V&S tools should be reviewed and adapted more specifically for the field of Assisted Reproduction. A work package dedicated to vigilance in this field is included in a follow-up project, SOHOV&S (Vigilance and Surveillance of Substances of Human Origin) which has been funded by the European Commission and which starts in March 2010 and runs for 3 years. This project will take this important work forward.
- 9.3** The issue of vigilance in donors of tissues and cells needs to be addressed specifically. Consideration should be given to developing a different severity grading scale for donors with the requirement that **any** adverse reaction be reported to a central registry. This is essential to the providing the protection and advocacy that donors should be given. The European Directives require reporting of adverse reactions only where they have impacted on safety and quality of the tissues and cells donated. Despite this, the Commission has welcomed the inclusion of donor reactions in the Member States annual vigilance reports (see reference at 7.18). A work package in the SOHO V&S project will address donor vigilance and develop a report and recommendations for the EU.
- 9.4** EU-wide guidance and training should be provided for CA vigilance officers and inspectors in the investigation of SARE, including where there is suspicion of illegal or fraudulent activity. Training courses on SARE investigation are included in the SOHO V&S project to address this requirement.
- 9.5** There is a need to progress without delay towards agreeing common definitions for SARE and common tissue and cell nomenclature. Common coding to support traceability, which is essential to effective vigilance, is also a priority and will allow comparison and sharing of information and data in a more meaningful way. The Common Approach guidance document issued by the European Commission to CAs in 2009, which incorporated a number of EUSTITE V&S tools, made progress in proposing product and reaction categories.

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- 9.6** Although this pilot was limited, in terms of direct involvement, to the CAs for tissues and cells, it is acknowledged that vigilance requires the active participation of all stakeholders to ensure the identification of reactions and events, their correct investigation and reporting with appropriate follow-up information sharing and corrective actions. Systems that are non-punitive, open and transparent and that provide regular feedback to stakeholders will encourage participation and add value to the information reported. The new project, SOHO V&S includes a work package that will develop guidelines for clinical users to promote vigilance at the critical level of the patient.
- 9.7** The pilot results showed evidence of significant under-reporting of SARE. This is likely to be largely due to the fact that most vigilance systems in the EU are newly established. It will take time for tissue establishments and, particularly for clinicians using tissues and cells, to engage in vigilance systems and to report as required. The professional societies will play an essential role in ensuring an adequate engagement of clinicians. The SOHO V&S project will take both of these issues forward with a work package dedicated to informing clinicians of their responsibilities for traceability and for reporting and investigation of SARE. The guidance produced will provide them with supportive tools. The major professional societies in the field of tissues and cells (ESHRE, EATB, EBMT, EEBA and WMDA) are all collaborating partners in this new project.
- 9.8** Consideration should be given to the use of unique identifiers for SARE to avoid double counting.
- 9.9** Development of a standardised EU template for the reporting of SARE to the CA, including initial and final conclusions of the investigation, would facilitate comparison of data. As systems become more mature, consideration should be given to developing such a form.
- 9.10** The further development of the EURO CET instrument ([www.eurocet.org](http://www.eurocet.org)) will facilitate the application of denominators to the EU-wide SARE reports collated by the European Commission.
- 9.11** The global circulation of tissues and cells and the complex interactions between tissues and cells and other regulated products such as medicines and medical devices means that there is a need for effective communication and discussion between the different regulatory sectors on an international basis. The WHO should play a central role in facilitating this network and in developing global approaches. The WHO Guiding Principles for Transplantation provide a mandate for this work and the WHO has already used the EUSTITE V&S tools to develop a version which was presented to a Global Consultation on the Regulation of Tissues and Cells in February 2010. It was agreed that this document will be the basis for a WHO Aide Memoire on Vigilance and Surveillance in the field. The SOHO V&S project has recruited a number of international organisations (including FDA, CDC and Health Canada) as collaborating partners in recognition of the need for this global approach; the WHO will continue to play a key role in the new project, ensuring that the global nature of tissue and cell circulation is reflected by a global approach to vigilance and surveillance.

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## 10.0 REFERENCES



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## ACKNOWLEDGEMENTS

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## Glossary

**Active Failures:** unsafe acts (errors of omission and commission and violations) committed by those at the “sharp end” of the system (clinicians, scientists, surgeons, anaesthetists, nurses, etc.). They are the people at the human-system interface whose actions can, and do, have immediate adverse consequences for patients.

**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.

**Allogeneic use:** cells or tissue removed from one person and applied to another

**Autologous use:** cells or tissue removed from one person and applied in same person

**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.

**Contributory factor (Causal Factor)**

A circumstance, action or influence which is thought to have played a part in the origin or development of an incident or to increase the risk of an incident e.g. a situational factor or latent failure,

**Distribution:** transportation and delivery of tissues or cells intended for human application

**Donation:** donating human tissues or cells intended for human application

**Donor:** every human source, whether living or deceased, of human cells or tissues

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

**Event:** Any occurrence or deviation from usual medical care that causes an injury to the patient or poses a risk of harm to the tissue and cell or transplant system. Includes errors, preventable adverse events, and hazards.

**Harm:** Temporary or permanent impairment of structure or function of the body and/or any deleterious effect arising from that, together with any adverse impact on the systems and process involved in donation and transplantation leading to possible reputational damage and a reduction in tissue and cell supply.

**Hazard:** a **circumstance, agent** or action with the potential to cause harm.

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

**Human error**

A term used to classify one category of potential causes for adverse occurrences impacting on patient care or outcomes.

**Impact matrix:** A feature of the Impact Assessment Tool in which the risk is assessed in terms of its potential consequences in the current situation and the probability of recurrence; it includes the actual or potential effects on the system, including impact on public opinion and tissue or cell supply.

**Imputability:** 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

**Incident reporting (Adverse event reporting, serious/critical incident reporting)**

A system in many health care organizations for collecting, reporting and documenting adverse Occurrences impacting on patients that are inconsistent with planned care. E.g. Medication errors, equipment failures, violations. The culture of the organization including fear of punitive action, non-involvement of clinicians in the system, a lack of understanding of the purpose of reporting or a failure to recognise an incident the effectiveness of incident reporting can be limited.



**ISBT:** International Society for Blood Transfusion

**Latent Failure:** A defect in the design, organization, training or maintenance in a system that lead to operator errors and whose effects are typically delayed or lay dormant in the system for a considerable period of time

**Near miss:** an error or deviation from standard procedures or policies that is discovered before application of the tissues/cells that could have led to an adverse reaction in a recipient. **Nomenclature** A set of specialized terms that facilitate precise communication by eliminating ambiguity.

**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) a health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells.

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**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 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 or a piece of equipment that is 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 the Vigilance and Surveillance Tool.

**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 of 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.

**System** A set of interdependent elements including people, processes and equipment interacting to achieve a common goal.



**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.

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## Annex 1

### Summary of EUSTITE Vigilance Tools as Applied in the Pilot

## Extracts from:

### Tools for Vigilance and Surveillance of Human Tissues and Cells

(EUSTITE Project Deliverable 10 Submitted to the European Commission

21.05.08, full version available at [www.eustite.org](http://www.eustite.org))

## Vigilance and Surveillance Medical Advisory Committee



### Extracts included in this summary:

<b>6.0</b>	<b>The Tool Box</b>
	<b>6.1 The Severity Grading Tool</b>
	<b>6.2 The Imputability Assessment Tool</b>
	<b>6.3 The Impact Assessment Tool</b>

### Definitions (from Directive 2004/23/EC)

**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.

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## 6.0 The Tool Box

### Criteria for Reporting SAEs to the Competent Authority

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.**



### Tools for Evaluating SAE/R

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.

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## 6.1 The Severity Grading Tool

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

**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: <ul style="list-style-type: none"> <li>- hospitalisation or prolongation of hospitalisation and/or</li> <li>- persistent or significant disability or incapacity or</li> <li>- medical or surgical intervention to preclude permanent damage or impairment of a body function or</li> <li>- there is evidence of a serious transmissible infection</li> </ul>
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

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## 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:

<b>Imputability level</b>		<b>Explanation</b>
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.

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### 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 SARs, 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.



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 SARE 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 SARE 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



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### STEP 2 (Consequences):

Again, taking account of the conditions and current controls in place and their adequacy, how critical are the consequences of this SARE? 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
<b>Severe 4</b>	Death	System destroyed – need to rebuild	All allogeneic applications cancelled
<b>Major 3</b>	Life-threatening	Major damage to system – significant time needed to repair	Significant number of procedures cancelled; importation required to make up shortfall
<b>Significant 2</b>	Serious	Damage to system; services will be affected for a short period	Many applications cancelled or postponed
<b>Minor 1</b>	Non-serious	Minor damage to system	Some applications postponed
<b>Insignificant 0</b>	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	Likely	Possible	Unlikely	Rare
	5	4	3	2	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


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#### Step 4: Response



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

 An SARE 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 SARE 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 SARE related inspection should focus on the subject of the SARE. 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 SARE.

 An SARE 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 SARE 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 SARE, 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.

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## Annex 2: Invitation to Participate and Reporting Forms

# Vigilance and Surveillance Pilot Scheme

## Invitation to Participate and Instructions to Participants



### 1.0 Introduction

This document describes the plan for the implementation of a pilot scheme for the reporting and management of adverse events and reactions related to tissues and cells in the EU. The pilot is an activity within the EUSTITE Project, co-funded by the European Commission ([www.eustite.org](http://www.eustite.org)). All European Union (EU) Member State (MS) Competent Authorities (CA) are invited to participate in this pilot for the one year period of July 2008 to June 2009.

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. The project is being carried out by a consortium of organisations from 10 MS 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 for tissues and cells for transplantation (including haematopoietic progenitor cells) or for assisted reproduction, both with and without experience to date. The WHO provides an essential link from the project to global developments in tissue and cell regulation and surveillance.

As part of the project, an epidemiologist contracted to the WHO conducted a review of existing systems in Europe and North America; **a report is available on the EUSTITE website**. Two meetings of the Vigilance and Surveillance Medical Advisory Committee of the EUSTITE project (see membership at Annex 4) have taken place. The first meeting, held in Madrid in March 2007, identified several key principles that should be addressed in a vigilance system for tissues and cells. The second meeting took place in Rome in July 2007. At this meeting systems for classification and reporting of Serious Adverse Reactions (SARs) and Serious Adverse Events (SAEs) were discussed with the aim of developing a model for reporting and investigating incidents associated with the quality and safety of tissues and cells. This meeting included a number of global invitees.

The recommendations that emerged from these meetings, and from the review of existing systems referred to above, have provided the basis of a document incorporating guidance and tools. **This document is available on the EUSTITE website**. The Vigilance and Surveillance Pilot will test these tools and guidance for a one year period. 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 clinical application in the EU.

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**Pilot SARE Reporting Forms**  
**Quarterly Reporting form for Events**

Competent Authority		Report Period (From – To)	
Total number of SAE reports submitted to CA in the period		Total number of SAE reports fulfilling Eustite Tools and Guidance Criteria	0

CA reference Number	Date of SAE	Date reported to CA	Type of Tissue/cell involved	Short Description of event	Stage at which event occurred*	Specification <sup>^</sup>	Impact grading	Description of investigation	Status of investigation (Completed/pending)

\***Stage at which event occurred:** Procurement, Testing, Transport, Processing, Storage, Distribution, Materials, Other (Specify)

<sup>^</sup>**Specification:** Tissue/cells defect, Equipment failure, Human error, Other (specify)

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## Quarterly Reporting form for Reactions

Competent Authority		Report Period (From – To)	
Total number of SAR reports submitted to CA in the period	0	Total number of SAR reports fulfilling legislative requirements	0

### Please complete a box for every SAR report received in the period

CA reference Number		Type of SAR (see below*)				Short Description of SAR			
Date of SAR detection	Date reported to CA	Type of Tissue/cell involved	Donor or recipient affected (D/R)	Severity grading	Imputability grading	Impact grading	Clinical Outcome (as Directive 2006/86/EC) please tick	Corrective actions taken by reporting establishment	Status of investigation (Completed/pending)
							complete recovery minor sequelae serious sequelae death		
CA response, actions and comments									

\*Type of SAR: Infection - Donor, Infection –Tissue/cells, Hypersensitivity, Malignancy, Failure, Toxicity, Mis-match, Undue Risk, Genetic Abnormality, Other Transmission, Other



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### Annex 3



#### Table of SARs reported to Pilot according to Type of SAR (after filtration)

Type of SAR	Severity	Imputability NA: non assessable 0: excluded/unlikely 1: possible 2: probable 3: certain	Impact
<b>Infection - donor</b>			
Case 1: Blood cultures from bone marrow donor showed infection with <i>Staph. epidermidis</i> post donation. Thought to have resulted from bone marrow aspiration from pt's own skin. Treated with antibiotics. Donation sample tested positive for same strain of <i>Staph. epidermidis</i> but not transmitted to recipient.	Serious	1	3
Case 2: Skull flaps. Audit of sterility of stored (unwanted, unimplanted) bone flaps was undertaken which showed colonisation of the bone with bacteria in 13 out of 37 "sterile" bone flaps. The bone flaps that had been autoclaved and stored longest were more likely to be colonised than those that had been stored a shorter time. A subsequent audit of all patients who have had cranioplasties over the last ten years showed a higher incidence of autoclaved bone flap infections compared with other cranioplasties - 29% compared with 10% for titanium.	Serious	2	0
Case 3: Cornea. Keratitis after treatment. Re-transplantation necessary. Examination of explanted cornea showed Acanthamoeba cysts. Keratitis also after second treatment. Donor asymptomatic. Second cornea from same donor transplanted in second MS also transmitted Acanthamoeba.	Serious	3	2
<b>Infection – Tissue and Cells</b>			
Case 1: Post infusion of stem cells recipient had fever of 39C. <i>Propionibacterium acnes</i> on bone marrow product.	Serious	2	6
Case 2: Reproductive Cells. Communicable disease or infectious event: Pelviperitonitis ten days post artificial insemination. Peritoneal fluid +ve to <i>Escherichia coli</i> . Pt. Has history of ovarian endometrial surgery.	Serious	1	4
Case 3: Femoral Head Grafts <i>Enterococcus sp.</i> and later <i>Staphylococcus sp.</i> and <i>Streptococcus sp.</i> cultured from wound.	Serious	1	4
Case 4: Ovarian abscess 20 days post oocyte retrieval. No difficulties during puncture. Patient very thin. <i>Clostridium sp.</i> identified.	Serious	1	6
Case 5: Autologous CD34-positive stem cells. Toxoplasma sepsis with ADS at day +69 after autologous stem cell transplantation	Death	0	4
Case 6: Cornea imported from another EU state with microbiological control negative. One day later eye infection: <i>Pseudomonas aeruginosa</i> . Antibiotics commenced. Control taken on day of transplant from cornea, <i>Pseudomonas aeruginosa</i> growth.	Lifethreatening	3	9
Case 7: Cornea. Infectious cornea abscess occurring 2/12 post cornea graft	Serious	1	4
Case 8: Embryo. Pelviperitonitis one month after intrauterine implantation of two embryos. Patient has history of endometriosis.	Serious	1	6





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Treatment by antibiotic and rehydration. Oocytes retrieval was managed with antibiotics. Late spontaneous abortion at 14 weeks of amenorrhoea (twin pregnancy)			
Case 9: Cultivated autologous donor skin cells. Lymph node inflammation in the groin on side with leg ulcer and redness about the ulcer. (Ulcer covered with a skin graft of autologous skin cells) Resolution after 7 days with local antibiotic application.	Serious	2	6
Case 10: PBSC. Infection with <i>Staph. aureus</i> with abscess in previously operated shoulder in 2005 with use of osteosynthetic material.	Serious	1	6
Case 11: Drainage of ovarian abscess 10 days post oocyte retrieval. The left ovary was difficult to reach during the puncture.	Serious	2	6
Case 12: Abdomino-pelvic pain 48 hours after oocyte retrieval. Biological inflammatory syndrome. Intravenous antibiotics. No transfer. Freezing of embryos. Patient's health status improved within 4 days.	Serious	1	6
Case 13: Twin pregnancy complicated by threatened premature delivery (20 weeks amenorrhoea). Delivery at 21 weeks of twins (stillborn). Before oocyte retrieval, pt. had an endometrioma. Patient had already had two operations. The endometrioma had been left and the puncture was treated with antibiotics. At about 2/40 of pregnancy, cyst was bigger. The operation established diagnosis of ovarian abscess that probably sparked off the very early delivery. The endometrioma would probably not have been infected without the puncture.	Serious	2	4
Case 14: Pelviperitonitis 13 days post oocyte retrieval. Origin unknown without any germ detected.	Serious	2	6
Case 15: Utero-adenexal infection after oocyte retrieval. Context=severe endometriosis. The puncture was done according to surgical sepsis regulations. The patient had a betadine suppository and 2 enemas the night before. She had vaginal disinfection just before the puncture. The patient was hospitalised for 7 days.	Serious	2	4
Case 16: Ovarian abscess after artificial insemination.	Serious	2	6
Case 17: Amnion. Transmitted bacterial infection. Swabs taken from patient's eye for identification of infectious source.	Serious	0	3
Case 18: Subsequent to oocyte collection patient reported symptoms of infection. She attended local emergency department where she was admitted and treated with intravenous fluids and antibiotics.	Serious	3	6
Case 19: Patient received bone transplant – culture showed positive result for <i>Enterococcus faecium</i>	Serious	2	4
<b>Hypersensitivity</b>			
Case 1: Haematopoietic stem cells. Recipient fell into coma (Glasgow 5) during autologous HSC infusion (total remission in 30 mins), medical imaging normal. Continuation of infusion in ITU.	Lifethreatening	2	9
Case 2: Allogeneic PBSC. Cardiopulmonary arrest 15 mins after transplantation.	Lifethreatening	1	6
Case 3: Cord Blood. Cutaneous rash appeared 12 hours after cord blood infusion (probably due to the degranulation of the cells: viability control of the J+1 sample showed 74% of mortality). A new cord blood graft was ordered urgently.	Serious	2	6
Case 4: PBSC. Transitory respiratory insufficiency, hypertensive	Serious	2	12

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crisis, chills, fever.			
Case 5: Patient reacted – bone marrow from family member. To ITU but recovered quickly. Suspected reaction to DMSO cryoprotectant – unsubstantiated.	Life-threatening	1	9
Case 6: Stem Cells. Significant allergic reaction. Nasal congestion, puffy face/eyes, total body urticaria, dry mouth and cough.	Serious	2	6
Case 7: PBSC. Suspected reaction to DMSO: nausea, vomiting, high BP.	Serious	2	4
Case 8: PBSC. Suspected reaction to DMSO: high BP.	Serious	2	4
Case 9: PBSC. Suspected reaction to DMSO: attenuation, chest pain.	Serious	2	8
Case 10: PBSC. Suspected reaction to DMSO: low BP.	Serious	2	4
Case 11: PBSC. Suspected reaction to DMSO: high BP.	Serious	2	4
Case 12: PBSC. Suspected reaction to DMSO: sickness	Serious	2	4
Case 13: PBSC. Suspected reaction to DMSO: sickness, vomiting.	Serious	2	4
Case 14: Donor became unwell during apheresis, chest tightness and nausea. Presumed allergic reaction ?calcium. Patient admitted overnight. Given hydrocortison and nebulised salbutamol. Discharged following day.	Serious	3	6
Case 15: PBSC. Suspected reaction to DMSO chest pain.	Serious	2	8
Case 16: PBSC. Suspected reaction to DMSO, sickness, vomiting, high BP.	Serious	2	4
Case 17: PBSC. Suspected reaction to DMSO, chest pain.	Serious	2	8
Case 18: PBSC. Hypotension, vomiting, fever, chills.	Serious	2	12
<b>Failure of grafts</b>			
Case 1: Corneal epithelial healing delayed after 15 days. Abnormal corneal thickness. Stromal scarring could be due to viral infection. Re-transplantation necessary.	Serious	2	4
Case 2: Cornea. Primary endothelial decompensation and corneal epithelial healing delayed, possibly due to low temperature in container during airplane transport.	Serious	3	6
Case 3: PBSC. A recipient with myelofibrosis disease grafted (Non Ablative Conditioning) with imported allogeneic HSC cells, haematological graft failure after 35 days. Administered graft was fresh and specifications correct. No manipulation before infusion. Graft failure because of the non-myeloblastic conditioning.	Serious	1	8
Case 4. Bone (Human Spongiose chips). Oedema of right half of face, 38.7C fever, chills, asthenia, general fainting and iterative headache. Presence of febricula 1 day post transplantation (filling right maxillary). Decreased oedema few days after treatment but persistent headache and asthenia 15 days post-graft.	Serious	1	4
Case 5: Haematological recovery delayed following Autologous Peripheral Haematopoietic stem cells and bone marrow transplantation for Hodgkin's disease in 2nd relapse.	Serious	NA	4
Case 6: Cornea graft failure	Serious	1	4
Case 7: Very poor quality of an imported allogeneic bone marrow product (88.10E8 TNC versus 209. 10E8 prescribed). Graft rejected by clinician and 2 placental blood units (PBU) have been recruited for the treatment. Haematological recovered on 22nd day, nevertheless recipient developed Grade II of GVH disease (grade 3)(+CNV reactivation)	Serious	3	6
Case 8: Graft failure: A recipient with myelofibrosis disease grafted	Serious	0	6

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(Non Ablative conditioning) with imported allogenic peripheral stem cells, haematological recovery on day 10 but with good chimerism recipient. However, patient relapsed, case of graft failure. Good quality of product at thawing.			
Case 9: Partial epileptic fit occurred 1 hour after end of graft infusion. Two generalised tonic-clonic crises occurred next morning.	Serious	1	8
Case 10: HSC. Graft failure after 43 days. The administered graft (allogeneic imported HSC from bone marrow) was fresh and specifications were correct. (HLA phenotype ok, results of quality control before injection CD34+, CNT, viability and CFU-GM ok). (No manipulation before infusion)	Serious	1	8
Case 11. Severe chest pain during stem cell collection; collection abandoned. In patient overnight observation. 12 hour troponin negative, serial ECGs normal. Medical team reviewed confirmed non-cardiac, likely muscular skeletal chest pain. Discharged home well next day.	Serious	1	2
<b>Mismatch</b>			
Case 1: Stem Cells. Cryopreserved bone marrow. Haemolysis, hypertension, vomiting & seizure immediately post transplant. Subarachnoid haemorrhage diagnosed. Donor and recipient were siblings of same blood group. Full neurological recovery reported. Later fungal infection developed (trichosporan species) source unknown and renal impairment. 15 days post transplant recipient died as a result of multi-organ failure.	Death	2	12
<b>Other</b>			
Case 1: Autologous PBSC. Neurological – long epileptic seizure.	Life-threatening	3	9
Case 2: Bone Marrow. Sibling bone marrow allograft. Post infusion of cells patient had chest deterioration leading to pulmonary haemorrhage and further respiratory compromise. Respiratory failure then cardio respiratory arrest followed 16 hours post infusion.	Death	1	12
Case 3: Oocyte retrieval one and half months previously. Patient is pregnant. Suspicion of jugular thrombosis. Neck oedema, discomfort, no risk factor. Hospitalisation.	Life-threatening	2	6
Case 4: PBSC. Dyspnoea after 400ml of Tx. Saturation 86%. Pulmonary crepitation. Volume overload? Spontaneous recovery after O <sub>2</sub> administered.	Serious	2	6
Case 5: PBSC allogeneic. Serious dyspnoea 45 mins after transplantation. Possible TRALI.	Life-threatening	1	6
Case 6: Very poor quality of imported allogeneic bone marrow product (viability and CD34+ are low). Haematological recovery delayed.	Serious	3	4
Case 7: Skin cells. Thrombosis in left leg after donating a skin ellipse from the abdomen for the manufacturing of a skin graft with autologous cells.	Serious	0	4
Case 8: Autologous bone marrow. Arrhythmia	Serious	1	9
Case 9: Cardiac decompensation. Autologous bone marrow cells.	Serious	0	4
Case 10: Autologous bone marrow cells. Nonspecific symptoms in thorax & epigastrium	Serious	0	2
Case 11: PBSC. Thoracic angina-like symptoms.	Serious	0	2
Case 12: PBSC. <i>Clostridium difficile</i> -associated enterocolitis with	Serious	0	2



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diarrhoea.			
Case 13: PBSC. Unstable angina pectorus, ileus, lung oedema, pneumonia.	Serious	0	4
Case 14: Menorrhagia 17 days post transfer. Small metallic fragment observed in blood. Fragment corresponded to part of transfer catheter. Patient had ectopic pregnant.	Serious	2	4
Case 15: Autologous PBSC. Hypotension, tachycardia, decreased awareness during Tx of 1st bag. After adrenalin IV: spasms in abdomen & chest, nausea & vomiting. Symptoms disappeared after several hours. Possibly a reaction to DMSO. Engraftment after 28 days.	Serious	3	8
Case 16: Ovarian hyper-stimulation and phlebitis 2 weeks after oocyte retrieval despite a preventive treatment the day of the triggering of ovulation and an anticoagulant treatment when clinical signs of OHSS appeared. Interruption of the pregnancy detected by ultrasonography and aspiration planned.	Life-threatening	2	6
Case 17: HSC. Cerebral Thrombosis	Serious	2	4
Case 18: Autologous bone marrow cells. Worsening of ulcerative colitis.	Serious	0	4
<b>Toxicity</b>			
Case 1: Haematopoietic stem cells. Neurological symptoms with convulsions, loss of consciousness, fall in BP.	Serious	3	6

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#### Annex 4: Examples of reported SAEs by stage of occurrence:

<b>Processing</b>
Case 1: Embryo - Failure of witnessing process - embryo from Couple A injected for a second time with Sperm of couple B. Pt. A lost 1 potentially fertilised egg. Pt. B - lost 10 of 16 potentially fertilised eggs.
Case 2: Total loss of two embryos from patient during the manipulation of the culture dish. The patient requires a new cycle of IVF.
Case 3: Cornea was prepared much thinner than requested and not usable for transplantation
Case 4: 2 incubators were disconnected from the power source during 20 hours (T27 <sup>0</sup> C instead of 37 <sup>0</sup> C) Destruction of embryos. Total loss of chance for 5 couples.
Case 5: Decontaminated Achilles tendons were issued as irradiated Achilles tendons to a hospital
Case 6: 10 oocytes were fertilised by ICSI. No embryos/oocytes in dish during scheduled check after 2 days.
Case 5: Sperm. Woman inseminated with wrong partner sperm due to mix-up.
<b>Procurement</b>
Case 1: Cornea - Inability to access sterile laboratory environment to use tissue due to absence of the Head Employer of the eye bank.
Case 2: PBSC allogeneic. On 2nd day of apheresis slightly increased number of B cells. Turned out to be Hairy Cell Leukaemia Variant
Case 3: Cornea. Autopsy showed donor had multiple myeloma. Report came after release of cornea.
Case 4: Sperm. Baby from donor developed hydrocephalus (unknown location). Genetic cause cannot be ruled out. The risk of transmission of hydrocephalus from this donor is estimated to be around 1%.
Case 5: Embryo. Contamination of culture media by <i>E. coli</i> . Analysis requested for straws and vaginal sampling.
Case 6: Cord Blood collected on unlicensed premises without appropriate agreements in place - lack of control over procurement.
Case 7: Cornea. Lymphoma found in donor by pathology after cornea had been transplanted.
Case 8: Cardiac Valve. Valve thawed for implant was unusable due to a tear at the sinus.
Case 9: Inadequate cornea procurement with inadequate reconstruction.
Case 10: Ocular Tissue. Donor not tested for MAT although donor history showed residence in malarial area.
Case 11: Sperm. Existing donor discovered own father had malignant hypothermia.
<b>Storage</b>
Case 1: Tank containing bone, semen, amniotic membrane - liquid nitrogen ran out - all tissues and cells thawed.
Case 2: Amniotic Membrane. Loss of significant quantity of amniotic membrane due to improper monitoring/storage.
Case 3: Femoral Heads. Electrical power supply to storage freezer switched off by contractors. Some material disposed of.
Case 4: Ovarian Tissue. A piece of ovary removed for fertility preservation. The tube was placed in a box containing dry ice instead of crushed ice. The content of the tube (medium + ovary) arrived at

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the hospital completely frozen whereas the medium should not be frozen. The ovary cannot now be stored.

Case 5: Sperm. Cryopreservation of sperm (12 straws stored) and use of fresh sperm for ICSI outside a specific viral risk circuit in a patient with Hepatitis B surface antigen positive. The serology hepatitis B was considered as negative due to an error in the reading of the laboratory results. Risk of transmission to patients who had gametes stored in the same container plus patients that had an attempt the same day.

### Distribution

Case 1: Cornea. 2 deswelling medias from same batch contaminated with *Pseudomonas aeruginosa*.

Case 2: Bone. Freezer bag of massive bone had rupture line at thawing stage.

Case 3: Cornea. Surgeon returned cornea to eye bank as cornea appeared hazy with numerous stromal folds suggesting oedema and poor endothelial function.

Case 4: PBSC. PBSC procured in European country and transported to transplant centre in another MS. Due to adverse weather conditions plane (and cells) were delayed Patient failed to engraft.

Case 5: Femoral Heads. Tissue being held in quarantine due to failure of data loggers monitoring the temperature at the retrieval hospital. 3 donations were released for transplant in error.

Case 6: PBSC accidentally transported on dry ice instead of ice packs resulting in reduced cell viability

Case 7: Amniotic Membrane. Error discovered at transplantation site with 3 different expiry dates on the leaflet.

### Testing

Case 1: Cornea. Weak positive serological test result for HBsAg in donor. Previously negative in another lab.

Case 2: PBSC. Collection facility staff completed a product handling form and failed to notice that microbiology results were incomplete. Transcribed results as negative for HCV.

Case 3: Cornea. Positive microbiological control on the deswelling medium of the cornea. (*Staphylococcus haemolyticus*) reported by graft establishment.

### Transport



Case 1: Corneas x 2 transported to eye bank but information not communicated in time so corneas kept longer before being received into eye bank.

Case 2: Cord Blood. Seven units of cord blood lost during transit to private cord blood bank because flight diverted and material lost for eight days in system by courier. Cells discarded upon receipt at TE.

Case 3: PBSC. Cells X-rayed during transport despite courier protestations.



Case 1: PBSC showed severe clumping on infusion led to patient being monitored for any engraftment problems.





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### Annex 5: Examples of SAE by classification.

<p><b>Tissue and cell defect</b> describes issues with the quality of or existing damage to the tissue and cells to be transplanted.</p> <p>Case 1: PBSC showed severe clumping on infusion.</p> <p>Case 2: PBSC. On 2nd day of apheresis slightly increased number of B cells. Turned out to be Hairy Cell Leukaemia Variant.</p> <p>Case 3: Autopsy showed donor had M. Kahler (multiple myeloma). Report came after release of cornea.</p> <p>Case 4: Sperm Donor later developed bowel disease. (Colitis ulcers). A child from this donor has around a 4-16% chance of inheriting this medical condition.</p> <p>Case 5: Irreversible clotting of PBSC harvest procured for patient who had been myoblated.</p> <p>Case 6: Surgeon returned cornea to eye bank as cornea appeared hazy with numerous stromal folds suggesting oedema and poor endothelial function.</p> <p>Case 7: PBSC procured in another MS and transported to transplant centre elsewhere in Europe. Due to adverse weather conditions plane (and cells) were delayed. Patient failed to engraft.</p> <p>Case 8: Lymphoma found in donor by pathology after cornea had been transplanted.</p> <p>Case 9: Mycelial filaments discovered during direct microscopic exam. Just before graft. (<i>Epicoccum sp.</i>)</p> <p>Case 10: Cardiac valve thawed for implant was unusable due to a tear at the sinus.</p> <p>Case 11: After donation, a sperm donor discovered his father had congenital malignant hyperthermia.</p>
<p><b>Equipment Failure</b> refers to breakdown or problems with any piece of equipment used in the procurement, processing, testing, storage or distribution of tissue and cells.</p> <p>Case 1: Ruptured line in freezer bag during thawing. Placental blood.</p> <p>Case 2: Loss of three oocytes from five due to use of a pipette with known production error.</p> <p>Case 3: Loss or fracture of straws: Occurrence of a break of a high-security straw containing HIV frozen sperm.</p> <p>Case 4: False negative serology (syphilis) for cornea, heart valves and musculo-skeletal tissue. (Equipment incorrect)</p> <p>Case 5: Power failure resulting in shut down of the incubator and possible loss of 13 embryos and 5 microinjected oocytes.</p>
<p><b>Other</b> – this category is used when defect is of unconfirmed origin</p> <p>Case 1: Late fungi growth on last culture. Corneas already transplanted.</p> <p>Case 2: Contamination of culture dishes of four couples by <i>Acinetobacter lwolffii</i>. All embryos failed to progress.</p> <p>Case 3: Cord blood – illegal activity; collected on unlicensed premises without appropriate agreements in place – lack of control over procurement.</p> <p>Case 4: PBSC. Bacterial contamination anaerobic organism.</p> <p>Case 5: 2 incubators were disconnected from the power source during 20 hours (T27<sup>0</sup>C instead of 37<sup>0</sup>C) Destruction of embryos. Loss of pregnancy possibility for 5 couples.</p> <p>Case 6: Numerous blood clots in 2 BMP bags and bags were swollen</p> <p>Case 7: Packing found to be damaged - sterility of bone may have been compromised.</p> <p>Case 8: Ocular tissue. Ocular donor not tested for MAT though had been resident in malaria area.</p>



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<b>Human Error</b>
Case 1: Expired collection kit used to collect cells for private cord blood bank. Cells discarded upon receipt at TE.
Case 2: Failure of witnessing process - embryo from Couple A injected for a second time with Sperm of couple B. Pt. A lost 1 potentially fertilised egg. Pt. B - lost 10 of 16 potentially fertilised eggs.
Case 3: Loss of traceability and breach of good practice. Evidence of a diluted PVP vial contaminated by sperm due to a technical error. Impact on two microinjection procedures.
Case 4: Cryogenic storage bag of PBSC dropped on unpacking from a correctly packed dry shipper causing two bags to fracture. Contents of one bag rendered unusable for transplant (one of 14 bags).
Case 5: PBSC accidentally transported on dry ice instead of ice packs resulting in reduced cell viability.
Case 6: LN <sub>2</sub> storage vessel temperature above -130 <sup>0</sup> C for 15 mins while staff carried out work. Guidelines state that PBSC should be stored below -130 <sup>0</sup> C.
Case 7: A technician inadvertently knocked over petri dish containing embryos whilst trying to take another dish from the incubator.
Case 8: Procurement of cornea without adequate consent.
Case 9: Woman inseminated with wrong partner sperm due to mix-up at clinic
Case 10: Multi-organ plus eye donor. To clarify cause of multi-organ failure many test were required shortly before procurement, among them HSV-1 DNA on spinal fluid. No information about this test was given to the Eye Bank before the results were available: results were positive. Corneas were still in culture and could therefore be discarded.
Case 11: 2 decontaminated Achilles tendons were issues as irradiated Achilles tendons to a hospital.

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### Annex 6: Examples of SAE Impact Grading

Impact	Detail
12	The failure to pass on to the eye bank information about positive results for <i>Herpes simplex</i> Virus-1 DNA in spinal fluid from a multi-organ plus cornea donor. Corneas remained in culture and were therefore discarded.
12	Late fungi growth on last culture. Corneas already transplanted.
9	After having donated sperm, donor discovered his father had congenital malignant hyperthermia.
9	Day after ICSI of one oocyte, technician dropped the cell culture dish containing the injected oocyte.
0	Electrical power supply to storage freezer switched off by contractors. Some femoral head material had to be disposed of.
0	Stored bags of autologous blood stem cells burst in nitrogen tank.

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### Annex 7: Participant Competent Authority Contacts

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