

SOHO V&S Guidance for Competent Authorities:



Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells

SOHO V&S GUIDANCE FOR COMPETENT AUTHORITIES:

COMMUNICATION AND INVESTIGATION OF SERIOUS ADVERSE EVENTS AND REACTIONS ASSOCIATED WITH HUMAN TISSUES AND CELLS



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Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)

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CHAPTER 1: INTRODUCTION AND BACKGROUND

BACKGROUND

Directive 2004/23/EC, and its associated Commission Directives 2006/17/EC and 2006/86/EC, require EU Member States (MS) to nominate Competent Authorities with responsibilities for the implementation of a series of regulatory activities in the field of human tissues and cells for transplantation and for assisted reproduction. A key function that must be put in place in each MS is a system for vigilance and surveillance (V&S) of these activities, with reporting and investigation of serious adverse events and reactions. Surveys conducted by the Public Health Directorate of the European Commission and presented to the Competent Authorities meetings indicate that many MS are establishing new Competent Authorities and most are developing new systems for V&S in this field. This was confirmed during the EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments) project (Fehily et al. 2007¹, 2008²). A review of tissue and cell V&S systems, conducted as part of the EUSTITE project in 2007, indicated that only two MS had well developed systems, namely France and UK; all the others were adapting related vigilance systems or developing new systems and procedures.

Vigilance in this field is complicated by the broad scope of application, the degree of importation from third countries and distribution between EU MS and the mixture of public and private sector service providers.

BUILDING ON THE WORK OF EUSTITE

EUSTITE was a three-year EU-funded project that was completed at the end of 2009. The project promoted standardisation of inspection and vigilance across the EU through the development of common inspection guidelines, vigilance tools³ and training for Competent Authority officials in these activities. The vigilance tools included:

- criteria for reporting Serious Adverse Events (SAEs)
- a severity grading system for Serious Adverse Reactions (SARs) with guidance on which level to report
- an imputability grading system for SARs
- an impact grading system (risk matrix including wider system implications) for SAEs and SARs.

The tools were tested during a one year pilot study involving 20 MS³. Over 300 reactions and events were reported to the pilot and evaluated using the tools. The tools were amended following the pilot and are currently in use in many MS. In its final recommendations, the project identified V&S as a field that needed considerably more work at an EU level. A number of areas were identified and formed the basis of a new project proposal, 'Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)' which was granted EU funding and was launched in March 2010.

SOHO V&S PROJECT OBJECTIVES

The project took forward the work of EUSTITE and addressed a number of areas that were identified as requiring wide consultation and discussion. This included working to develop a shared view of how serious adverse events and reactions associated with tissue and cell donation or human application are reported, evaluated and investigated. It aimed to address harmonisation of terminology and documentation and a consensus on how information should be exchanged between EU MS, the European Commission and third countries.

THE TEAM

SOHO V&S was coordinated by the Italian National Transplant Centre (CNT). It had a Steering Committee and a large number of collaborating partner organisations, including all of the major European professional societies in the field (see Appendix 1).

¹ Fehily D, Delvecchio C, Di Ciaccio P. et al. 2007 *The EUSTITE project: working towards harmonised implementation of European regulation of tissues and cells*. *Organs, Tissues & Cells*, Volume 10(1): 31-36.

² Fehily D, Kurz J, Hornez T. et al. 2008 *The development of EUSTITE guidelines for the inspection of tissue and cell procurement and tissue establishments in the European Union*. *Organs, Tissues & Cells*, Volume 3: 167-174.

³ Fehily D, Sullivan S, Noel L. et al. 2012 *Improving Vigilance and Surveillance for Tissues and Cells in the European Union: EUSTITE, SOHO V&S and Project NOTIFY*. *Organs, Tissues and Cells* vol. 15, no. 2:85-95.

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Steering Committee

National Transplant Centre, Italy (Project Co-ordinator)
Donor Action Foundation, Belgium
Irish Medicines Board, Ireland
National Transplant Organisation, Spain
Biomedicine Agency, France
French Agency for the Safety of Health Products, France
National Centre for Tissue and Cell Banking, Poland
Human Fertilisation and Embryology Authority, UK
Human Tissue Authority, UK
World Health Organisation, Switzerland.

The involvement of the World Health Organisation, and many collaborating partners from outside the EU, ensured that the guidance produced in this project reflected international needs and realities, in the context of global movement of human tissues and cells for human application. The Human Tissue Authority in the UK was responsible for dissemination of the project's outputs throughout its duration, including a final conference in the UK in 2013. The Donor Action Foundation acted as internal project evaluator and maintained contact with two external peer reviewers.

THE NOTIFY PROJECT

In September 2010, the SOHO V&S project joined forces with the World Health Organisation (WHO) and the Italian National Transplant Centre (CNT) to organise a major global initiative aimed at raising the profile of V&S of substances of human origin; the initiative was called Project NOTIFY. The scope of the project included organs, tissues and cells for transplantation and for assisted reproduction. Ten international expert groups worked collaboratively on a Google site where over 100 participants (regulators, clinicians, professional society representatives, scientific experts) inserted and reviewed documented cases of reactions and events across the scope of the substances under consideration, using published articles and vigilance system reports as their sources. Over 1,700 published references were inserted on the site. The cases were used as the basis for developing draft guidance on detection and confirmation of reactions and events, with an emphasis on the key role of the treating physician.

NOTIFY held a meeting of 113 invited experts from 36 countries that took place in Bologna from February 7th to 9th 2011. The participants represented regulatory and non-regulatory government agencies, professional societies and scientific and clinical specialities from all WHO regions. The meeting was made possible with funds raised by CNT together with those allocated within the SOHO V&S project for an international meeting on vigilance reporting and investigation. All associated partners of the SOHO V&S project and 26 of the 27 collaborating partners were represented in Bologna. The meeting explored the work already carried out on-line and agreed on priorities for the future development of global V&S for organs, tissues and cells. The didactic documents that had been drafted before the meeting were further developed since the meeting, taking into account the discussions held in Bologna and they have been published together with the meeting report⁴. Each document addresses a type of reaction or event, transmission of infection, transmission of malignancy etc., and provides guidance on detection and confirmation based on the experience demonstrated in the collection of cases in the database. As a leading partner in the Bologna initiative, the SOHO V&S project has used these documents in the development of this guidance.

WORK PACKAGE 7 AIMS AND OBJECTIVES

This document is the key deliverable of work package 7 (WP7) of the project. The objective of the deliverable is to provide guidance to EU Competent Authorities on the investigation and management of Serious Adverse Reactions and Events (SARE) associated with tissues and cells for transplantation and for assisted reproduction. The document summarises, and in some cases fully incorporates, work carried out in other project work packages, particularly WP4, WP5 and WP6. Figure 1.1 shows the relationship between WP7 and the other project work packages.

⁴ NOTIFY. *Exploring Vigilance Notification for Organs, Tissues and Cells*. Organs Tissues & Cells, 2011, November, 14, 3: Suppl.

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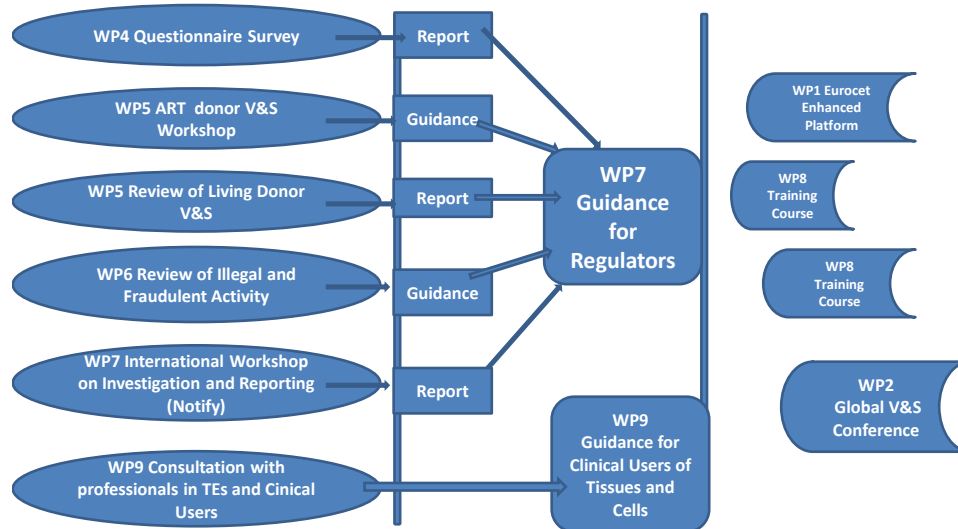


Figure 1.1 SOHO V&S Project outline (WP = work package)

The following organisations participated in the drafting of this document (the working group members are acknowledged individually at page 45):

National Transplant Centre, Italy
National Centre for Tissue and Cell Banking, Poland
Human Tissue Authority, UK
World Health Organisation, Switzerland
Biomedicine Agency, France
French Agency for the Safety of Health Products, France
TRIP, the Netherlands
Health Protection Agency, UK
Irish Medicines Board
Paul Ehrlich Institute, Germany

The team met on five occasions and worked by email. The work of the WP4, 5 and 6 was summarised and approved by the relevant WP leaders for inclusion in chapters 2, 4 and 9, respectively. Two of the meetings were also attended by a representative of Sanco (Directorate General Health and Consumer Protection of the European Commission). Chapters 3, 5, 6 were developed using, in particular, the outputs of NOTIFY. It was agreed with Sanco that the EU instructions and forms for annual SARE reporting and for Rapid Alert communications in the EU should be summarised in this guide, in chapters 7 and 8, respectively, so that this document provides a complete compendium of the current guidance for Competent Authorities for vigilance and surveillance in tissues and cells.

While developing the document, the working group was invited to make recommendations to Sanco for improvements to the Commission's Annual SARE reporting programme, both the reporting template and the associated guidance document. As foreseen in the project plan, this document was the subject of discussion at 3 'focus group' meetings of regulators and professionals, one each in the UK, Germany and Spain in February of 2012. These meetings served to improve the content before the document is opened to consultation with the EU Competent Authorities and other key stakeholders and experts.

Following the consultation, a final meeting of the working group agreed incorporations and changes before the final version is submitted to the EC.

CHAPTER 2: STATE OF THE ART – VIGILANCE FOR TISSUES AND CELLS IN THE EU

INTRODUCTION AND BACKGROUND

Work package 4 of the SOHO V&S project consisted of a survey regarding the Vigilance & Surveillance (V&S) systems for tissues and cells used in transplantation and in assisted reproduction in the European Union in the year 2010. The survey was conducted by the Spanish National Transplant organisation, as leader of that work package. This chapter provides a summary of the key findings.

SURVEY RESULTS

All EU Member States (MS) except two participated in the survey. Responses from 4 non-EU countries were also received. Three EU MS answered two questionnaires each, one for tissues and cells for transplantation and one for tissues and cells for ART. This reflected the fact that these countries have separate Competent Authorities for these sectors, while the majority of MS have a single Competent Authority regulating both fields.

All those that responded indicated that they have a V&S system in place. The number of EU MS with a V&S system in place for tissues and cells had increased from 15 countries (56%) in 2009 to 23 countries (96%) in 2010. The V&S systems have mostly been established during the last three years (Figure 2.1).

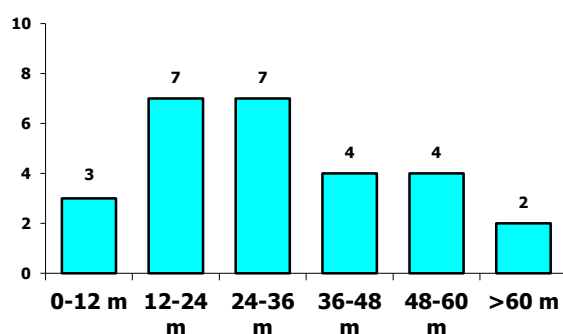


Figure 2.1: Length of time that EU V&S Systems for Tissues and Cells have been in place

The survey results describe the general characteristics of these V&S systems. They are mostly nationally organised systems (Figure 2.2), mostly based on the 2004 and 2006 EU Directives, usually with a common programme for reporting Serious Adverse Reactions and Events (SARE) for all types of tissues and cells, often overlapping with blood and drug vigilance and with multiple ways to send or receive SARE reports.

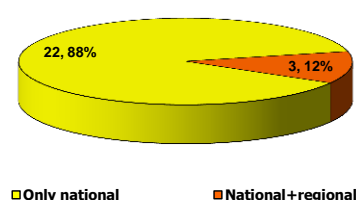


Figure 2.2: National versus regional organisation

The majority of national systems incorporate some or all of the vigilance tools developed in the EU-funded EUSTITE project. MS report annually to the European Commission, as required by the Directives, and half of them publish the results of their V&S programmes. Twelve of 24 respondents collaborate with scientific societies for vigilance activities. A majority disseminate to the field learning points that emerge in their vigilance programmes and half publish the results without centre identification. Seventeen of 25 responders report that they have national systems for issuing alerts when immediate action is required, often by using existing health safety networks and 70% have a procedure for disseminating information that is received via the European Commission Rapid Alert system (RATC).

The survey indicated a high level of involvement of Competent Authorities in SARE investigations (Figure 2.3) and most use experts to give them assistance.

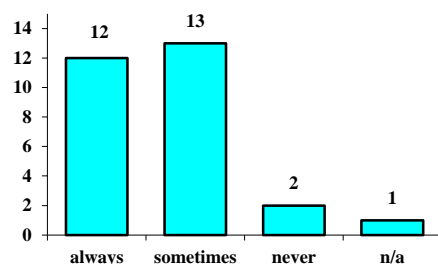


Figure 2.3: Degree of CA participation in SARE investigations

Nearly 80% are interested in the development of an international SARE investigation team that would be available to all MS for conducting particularly challenging investigations.

Sixty one percent of MS have dedicated vigilance officers and only 11 of 28 responders reporting that the vigilance officer role is combined with the inspector role although most report that there is interaction between vigilance officers and inspectors. Practically all countries are interested in having access to an EU training course on this topic. Sixty eight percent of MS have the requirement to report SARE in living donors, while nine countries have a registry of these donors. Finally, there do not appear to be significant differences between the programmes run by Competent Authorities which are specialised in ART and those which are not.

CONCLUSIONS

It can be concluded that vigilance systems for tissues and cells in the European Union are generally at an early stage of development. There is a need for guidance and training of Competent Authority personnel, particularly in investigation. Many MS require reporting of SARE that goes beyond the requirements of the Directives particularly in relation to donor reactions that do not influence the quality and safety of the procured tissues or cells.

The full survey report is available on the SOHO V&S Project website (www.sohovs.org)

CHAPTER 3: REPORTING SERIOUS ADVERSE REACTIONS AND EVENTS IN NON-REPRODUCTIVE TISSUES AND CELLS

INTRODUCTION AND BACKGROUND

The EUSTITE project explored the topic of Serious Adverse Reaction and Event (SARE) reporting in the EU and developed tools and guidance to support MS. These tools are reproduced in this chapter in the final version agreed following a one year EUSTITE pilot involving 20 EU Member States (MS). They have since been incorporated in European Commission guidance to MS for the completion of their annual SARE reports.

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

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

Directive 2006/86/EC makes it clear that the role of the TE does not preclude a PO or an ORHA from also directly notifying the CA if it so wishes.

RESPONSIBILITIES

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

The CA is responsible for establishing the national (or regional) framework for SARE reporting. The CA should provide TEs with clear instructions, forms and guidance on reporting of SARE in accordance with the national requirements. The vigilance programme should be incorporated within the CA's Quality System, with one or more standard operating procedures that describe the process for acknowledgment of reports received, retention of reports in the CA's archives, evaluation of SARE investigations, follow up on corrective and preventive actions at subsequent inspections, or sooner where considered necessary, and reporting annually to the European Commission on the reports they have received (see Chapter 8). The CA's vigilance officer(s) should be trained for this function.

The TE is responsible for providing clinical user entities, procurement organisations and critical third parties with clear instructions, forms and guidance on how to notify SARE in accordance with the national or local requirements. SARE reporting and management should be incorporated within the TE's Quality System, with one or more standard operating procedures that describe the process for acknowledgment of notifications, investigation, follow up on corrective and preventive actions and reporting to the CA. The procedures must include the management of SAE detected within the TE itself. The procedures should enable rapid action to be taken by all affected organisations to protect the safety of recipients. This may involve tissue and cell quarantine, recall and look-back in patients who have already had implicated tissues or cells applied. These actions may need to be taken by organisations other than the one that received the original notification. The following figure indicates a series of actions that might need to be taken in the case of a report of a suspected transmission from a deceased organ and tissue donor.

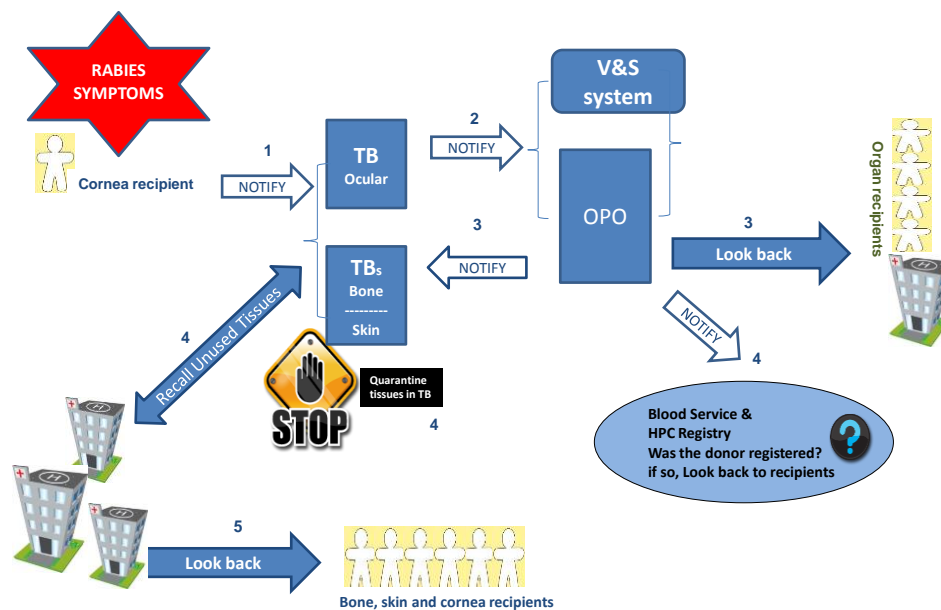


Figure 3.1: Actions in the case of suspected reaction in recipient of tissue from an organ and tissue donor (developed for the EDQM Council of Europe Guide for Safety and Quality of Tissues and Cells, 2013).

SERIOUS ADVERSE REACTION OR SERIOUS ADVERSE EVENT?

As the definitions for these two types of notification specify, an incident that has resulted in serious harm to a donor or recipient is reported as an SAR, while one which has posed a risk, but has not, or not yet, caused harm is reported as an SAE. It should be noted that only one report should be notified for each incident; even when an SAR is the result of an adverse event, from the moment where a recipient or donor has been harmed this takes precedence and the incident should be reported as an SAR. The only exception to this is where an adverse event results in a reaction in a donor and where that reaction does not fall within the mandatory reporting criteria (i.e. not caused by or resulting in a quality or safety defect in the tissues or cells donated)⁵. In this case, it is recommended that the event is reported as an SAE (mandatory) and the reaction is reported in the non-mandatory category of donor reactions if that is the procedure applied in that MS.

Although the minimum requirements described in Article 5 of Directive 2006/86/EC require ORHAs and POs to notify to TEs only **serious** adverse events and reactions, it is recommended here that all adverse events and reactions that are suspected of being related to the quality and safety of tissues or cells should be notified, by clinical users and organisations carrying out procurements from living donors, to TEs to allow trends in minor events and reactions to be monitored for continuous improvement purposes. TEs should then identify those **serious** adverse reactions that should be notified to CAs.

SERIOUS ADVERSE REACTION REPORTING

Serious Adverse Reaction (SAR) is defined in European legislation as follows:

‘Serious adverse reaction’ means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening,

⁵ An example would be where a peripheral blood stem cell donor, who should have been excluded from donation due to a known health risk, has a serious adverse reaction during apheresis; the cells are suitable for transplantation. In this case, the SAR can be reported as a non-mandatory reaction as there is no impact on the quality or safety of the cells but the SAE (the error in donor selection) must also be reported as it meets the criteria for mandatory reporting.

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disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity' (*Directive 2004/23/EC, Article 3(n)*)

A reaction can occur from transplantation to an unlimited time after transplantation. There must be a causal relation to the transplantation or other clinical application (see Imputability below).

It is noted in the same Directive, article 11, paragraph 1 that '*Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions **which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells.***'

For EU reporting, there is a requirement to report the following reactions:

- transmitted bacterial infection
- transmitted viral infection
- transmitted parasitical infection
- transmitted malignant diseases
- other transmitted diseases
- other adverse reaction.

Clinicians should look for symptoms or situations suggesting that any of the following reactions might have occurred in a tissue or cell recipient (**abbreviated descriptions in brackets**). Note that the list is not exhaustive.

- (a) Unexpected primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion) (**Infection from Donor**).
- (b) Transmitted infection (viral, bacterial, parasitic, fungal, prion) possibly due to contamination or cross-contamination by an infectious agent on the procured tissues, cells or associated materials from procurement to clinical application (**Infection from Tissue/cells**).
- (c) Hypersensitivity reactions, including allergy, anaphylactoid reactions or anaphylaxis. (**Hypersensitivity**)
- (d) Malignant disease possibly transferred by the tissue/cells (whatever the origin, donor or process) (**Malignancy**).
- (e) Unexpectedly delayed or absent engraftment, graft failure (including mechanical failure) (**Failure**)
- (f) Toxic effects from tissues and cells or associated materials (**Toxicity**)
- (g) Unexpected immunological reactions due to tissue/cell mismatch (**Mismatch**)
- (h) Aborted procedure involving unnecessary exposure to risk e.g. wrong tissue supplied, discovered after patient is anaesthetised and the surgical procedure has begun (**Undue Risk**)
- (i) Suspected transmission of genetic disease (**Genetic Abnormality**)
- (j) Suspected transmission of other (non-infectious) illness (**Other Transmission**)
- (k) Other (e.g. in the case of HPC transplantation, other reactions can also be observed, such as: unexpected or severe **GVHD** and some transfusion related reactions such as haemolytic reaction, **TRALI** (transfusion-related acute lung injury or **TACO** (transfusion-associated circular overload).

The role of the treating physician is critical to the detection of adverse reactions in recipients. The SOHO V&S project includes a dedicated work package that is developing guidance for units that apply human tissues and cells. This will be published separately from this document.

For the reporting of SAR in living donors see chapter 5.

ASSESSING SEVERITY OF SAR

SAR in recipients that are graded as 'serious', Life-threatening or Death should be reported to the CA.

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Severity	Comments
Nil	No harm, no risk, patient not informed as there was no risk of harm
Non-serious	Mild clinical/psychological consequences No hospitalization. No anticipated long term consequence/disability
Serious	Hospitalization or prolongation of hospitalization and/or Persistent or significant disability or incapacity Intervention to preclude permanent damage Evidence of a serious transmitted infection Birth of child with a serious genetic illness following ART with donor gametes or embryos
Life-threatening	Major intervention to prevent death Evidence of a life-threatening transmitted infection Birth of child with a life-threatening genetic illness following ART with donor gametes or embryos
Death	Death

PRELIMINARY ASSESSMENT OF IMPUTABILITY OF SAR

Imputability is defined as

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

SARs should be reported to the CA unless there is conclusive evidence for attributing them to alternative causes. Further guidance, including on root cause analysis, and an imputability tool are provided in Chapter 6 on Investigation. Grades allocated might change in the course of an investigation and should, where possible, be assigned at the point of initial notification to the CA and again at the completion of the reaction investigation. However, imputability assessment conducted prior to reporting to the CA should be considered preliminary and should not delay reporting. In particular, it is not advisable that a report is delayed until laboratory test results are received. The preliminary assessment is conducted only to avoid reporting those cases where imputability is concluded to be ‘Excluded’ (see Imputability scale in Chapter 6); reporting without an imputability assessment is better than reporting late.

SERIOUS ADVERSE EVENTS REPORTING

Serious Adverse Event (SAE) is defined in European legislation as follows:

‘serious adverse event’ means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity; (Directive 2004/23/EC, Article 3(m)).

For reporting to the European Commission, SAE are split in four categories:

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- Tissues and Cells defect (*this should be understood to mean an inherent defect in the tissues or cells, not caused during procurement, processing, storage or distribution*)
- Equipment failure
- Human error
- Other (*this category would include any type of Process Failure from procurement to clinical application*).

Adverse events can be detected at any stage in the process from donation to transplantation. Competent Authorities do not need to be informed about every deviation from an SOP within a TE. Directive 2006/86/EC clarifies that only ‘serious’ adverse events should be reported to the CA. Events with no obvious potential for harm (negligible impact) should be collected and followed up at hospital or TE level, as they may indicate defects in the quality of the service delivered. The CA does not normally capture these incidents unless multiple errors are reported. This may indicate a system failure. Directive 2004/23/EC defines SAE in terms of the potential to cause a SAR. Seriousness might relate to potential severity of an adverse reaction if the event had not been discovered or to the severity of an adverse reaction that might occur due to a repetition of the event in another place or time. Where an SAE arises from a single incident but has consequences for multiple products it should, nonetheless, be reported as one SAE.

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 CA, even if the event occurred only in one TE, when one or more of the following criteria applies:

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

*A ‘significant quantity’ should be considered as a quantity that will impact on patient treatment; thus it will be lower for those tissues or cells in short supply and higher for those in plentiful supply.

Thus, where the criteria listed above are met, the AE can be considered as posing a serious risk to patient health and in those circumstances it should be reported to the CA. Events that are commonly referred to as ‘near misses’ are included in the above categories.

TYPES OF EVENT

The following is a non-exhaustive list of different types of events that might be reported:

Event Description	Report to CA (yes/no)	Reporting Criterion
Bacterial contamination of tissues or cells distributed for transplantation	YES	1
Viral contamination of tissues or cells distributed for transplantation: retrospective analysis demonstrates viral contamination of tissues or cells, previously screened and found negative	YES	1
Evidence of contamination in a tissues subjected to a claimed sterilization process that is used in many TEs – no tissues distributed	YES	2
Incorrect tissue or cell type: a different type of tissue or cells is supplied by the TE than intended or requested	YES	1
An oocyte is fertilised with sperm from the male of the wrong couple	YES	3
A bone marrow donation for a specific patient is lost during delivery to the transplant hospital	YES	4
Bacterial growth is detected in an autologous cord blood collection; the cells are maintained in storage with the intention to treat the patient with antibiotics if the cells are ever used in future	NO Rates of contamination should be reviewed during inspection	N/A
An entire bank of heart valves is lost due to failure to refill the liquid nitrogen in a tank	YES	5
A cornea is discarded at the TE due to low cell count	NO No regulatory action	N/A

CHAPTER 4: REPORTING SERIOUS ADVERSE REACTIONS AND EVENTS IN ASSISTED REPRODUCTION

INTRODUCTION

Work package 5 of the SOHO V&S project developed guidance on vigilance reporting in the field of Assisted Reproduction Technology (ART). The full document is shown at Appendix 4. The following is a summary of the Recommendations developed in that document.

TERMINOLOGY

The following vocabulary is adapted to the ART context.

Donor

- i) **Partner donation**: in a couple, man and woman are considered donors to each other⁸.
- ii) **Non partner donation** means that the donor is another person apart from the couple.
- iii) **Surrogacy** means that a woman carries a pregnancy for another individual or couple (full or partial surrogacy).

Tissue establishment (TE)

TE applies to establishments performing ART activities: ART centres, ART laboratories, sperm banks, etc.

Direct use (Art. 1 of Dir. 2006/17/EC)

This term is not applicable to reproductive cells and tissues that are being processed, cultured, banked or stored.

Autologous

The terms 'autologous donors' and 'autologous use' apply in ART to cases of preservation of fertility. Procurement of oocytes and subsequent application in the same woman (*in-vitro* fertilisation (IVF) treatments) is an example of 'autologous donation'.

DEFINITIONS OF SAR AND SAE IN THE CONTEXT OF ART

To complement the European tissue and cell directives,

1. The definition of SAR should be extended to the offspring in the case of non-partner donation, only for cases of transmission of genetic diseases.
Hospitalisation for observation should be considered as non-serious⁶.
2. The definition of SAE should include the total loss of germinal tissues, gametes or embryos for one cycle.

⁶All participants but the Agence de la biomédecine (ABM) and the Irish Medicines Board (IMB) agree that hospitalisation, when for observation only, should be considered as 'non-serious' criterion. The reason is that for ART professionals, hospitalisation in ART is often for observation only, patients being discharged on the day after (if any medical treatment is required during hospitalisation then it should be classed as serious). The ABM considers that the usual definition of SAR and the one in Directive 2004/23/EC include 'hospitalisation' or 'prolongation of hospitalisation'. Moreover, hospitalisation is a usual criterion widely used to define SAR in all vigilance systems, e.g. pharmacovigilance, medical devices vigilance, etc. Therefore, it is not considered by ABM that it should be changed specifically for the purposes of ART vigilance and that if it is to be changed, a global review is necessary, both at the European Commission and the World Health Organisation levels. The Irish Medicines Board (IMB) considers that, while these reports concern non-mandatory reports, for consistency, the definition of SAR in Directive 2004/23/EC should apply. In this respect, reactions which result in or prolong hospitalisation are considered reportable by the IMB. This is also consistent with pharmacovigilance reporting.

Reporting of SARE

CRITERIA FOR REPORTING SAREs

In ART vigilance, deviations from Standard Operating Procedures in TEs, or other adverse events, which may influence the quality and safety of tissues and cells should result in SARE reporting to the CA when one or more of the following criteria apply:

- inappropriate gametes, embryos, germinal tissues have been released for clinical use, even if not used
- the event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors
- the event resulted in a mix-up of gamete or embryo
- the event resulted in a loss of traceability of gametes or embryos
- contamination or cross contamination
- accidental loss of gametes, embryos, germinal tissues (*e.g.* break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle.

LEVEL OF ASSESSMENT OF SARE: CENTRAL OR LOCAL?

Assessment tools should be used at both CA and health professional levels, but should not be mandatory for health professionals.

EQUIPMENT AND PRACTICES

SENSITIVITY OF GAMETES AND EMBRYOS, IMPACT OF CULTURE MEDIA AND EQUIPMENT

When SARE reporting criteria are met:

1. SAREs which are suspected to be linked to the culture media and equipment used in ART should be reported to the manufacturer and to ART vigilance to facilitate corrective and preventive measures, if appropriate, and to disseminate relevant information to other centers.
2. When the event is associated with a Medical Device, reporting is mandatory to the national CA for Medical Devices. Also the national CA for ART vigilance should be notified and coordination between these sectors should be organised.
3. If appropriate, an alert should be transmitted through the rapid alert system in cases of Medical Devices distributed nationally (via national rapid alert) or in several Member States (MS), (via the RATS system).

MIX-UPS

According to Directive 2006/86/EC, article 6 paragraph 2, misidentifications and mix-ups shall be reported as serious adverse events. However, the following recommendations can be added:

When SARE reporting criteria are met. Where a mismatching incident has occurred this should be reported as an SARE so that the cause can be investigated and the learning points shared in order to spread best practices across the sector.

1 All mix-up of gametes or embryos, whether partner or donor, should be reported as a SARE regardless at what stage the mix-up is detected. A full investigation should be initiated immediately after the mix-up is known. The causal factors should be noted and learning points shared.

2 All of the patients involved should be advised that the mix-up has occurred as soon as clinic staff becomes aware. Patients should be offered ad hoc counselling and support.

TRACEABILITY OF GAMETES AND EMBRYOS

When SARE reporting criteria are met; if a centre fails to trace gametes or embryos due to misrecording or

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loss of information, leading to the loss of gametes or embryos, this should be reported as a SAE to the CA.

COMPLICATIONS OF PROCUREMENT AND SEVERE OVARIAN HYPERSTIMULATION SYNDROME

1. All SARE related to procurement, as well as severe OHSS according to a definition adopted in all EU MS, should be reported to a CA⁷. These SARE should be notified to a specialist ART CA in countries where it exists.
2. A coordination between various systems of vigilance (e.g. medical device, pharmacovigilance, ART vigilance) should be organised both at the local level (TE) and at the national level (CAs)
3. Written information on major risks related to procurement should be available for patients and couples.

VIGILANCE IN RELATION TO THE TRANSMISSION OF GENETIC DISEASES BY ART WITH NON-PARTNER DONOR GAMETES

1. The birth of a child with a genetic disease following non-partner donation of gametes or embryos should be reported as a suspected **SAR**. It should be investigated as such so that further gametes, or embryos created from that donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
2. The diagnosis of a genetic disease in adults who have previously donated gametes or embryos to other couples should be reported as an **SAE** so that stored gametes, or stored embryos created from these donors' gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
3. Gamete/embryo non-partner donors and recipients should be asked at the time of donation whether they wish to be informed in the event that it is later established that the resulting progeny carries a gene or chromosomal abnormality that might be relevant to the donor's own health or to the health of their own children (already born or still to be born).

To facilitate the effectiveness of SARE reporting and investigation in these circumstances, the following is recommended:

4. Couples having ART treatment with non-partner donated gametes or embryos should be strongly advised to inform any doctors subsequently treating the resulting child(ren) of the donor origin. They should understand that, in the unlikely event that a child will manifest an inherited condition, informing the clinic could protect further families. Consideration could be given to the development of a carefully worded standard leaflet explaining these issues that could be provided to all couples. In the analogous situation of allogeneic cord blood banking, some banks provide the donor mother with a leaflet asking her to contact the bank in the unlikely event that the donor child manifests a genetic or other disease, so that the transmission of the disease by transplantation of the cord blood can be prevented.
5. Gamete and embryo non-partner donors should be strongly advised to inform the clinic where they donated, in the event that they are subsequently diagnosed with any genetic disease. In this case also, a standard information leaflet for donors might be considered.
6. Specialist genetic centres should always consider whether a child manifesting a genetic disease might have been conceived with non-partner donor gametes or embryos. This issue should be raised immediately and openly with the parents in the interests of other potential offspring and when parents acknowledge the involvement of a non-partner donor, they should be strongly urged to contact the ART centre. This issue should be included in the appropriate professional standards and guidance for specialist genetic centres.

⁷ The reporting of non-mandatory SAREs was the topic of much discussion in the development of this document. A consensus was reached as regards the necessity of reporting SAREs whose reporting is not required by the EUTCD (non-mandatory reporting). The CA to which it is reported depends on the organisation of the vigilance system in the MS.

TRIGGERING CONDITIONS FOR RAPID ALERTS AT NATIONAL AND INTERNATIONAL LEVELS

- Any SARE or information that could have immediate direct or indirect consequences in other centres in the country and/or other countries (*e.g.* media, equipment, etc.) should trigger a rapid alert and urgent communication between TEs and CAs at national (NRA) and/or EU/EEA (via RATC) levels. Their initial reporting is to the national CA.
- The rapid alerts system in ART should be coordinated by the national CA.
- The consultation process (TE—CA) will allow the CA to trigger a rapid alert.
- Different vigilance systems at European, international levels should be coordinated.

CROSS BORDER MANAGEMENT OF SARE

1. CAs should encourage health professionals to report SARE even when it is established to be related to ART cross border care.
2. In case of CBRC, the CA receiving the SARE notification should inform all other concerned CAs without any delay.
3. CAs should encourage TEs to provide patients with information about any adverse outcome. In particular, patients, couples and donors should be informed by health professionals to report adverse outcomes even in case of cross-border reproductive care.

GENERAL RECOMMENDATIONS

1. CAs should internally develop specific skills in ART including vigilance systems applied to ART,
2. Close cooperation between CAs and health professionals (*i.e.* professional societies) in the ART vigilance field should be strongly encouraged,
3. CAs should organise a coordination between ART vigilance systems and other vigilance systems (*e.g.* pharmacovigilance, medical devices vigilance),
4. TEs should advise ART health professionals about potential risks of SARE associated to ART treatment even in case of CBRC. CAs should support TEs in doing so.

CHAPTER 5: DONOR REACTION REPORTING (NON-ART)

INTRODUCTION

This chapter is an output of work package 5 of the SOHO V&S project (Deliverable 6). The objective of this deliverable was to conduct a detailed review of Serious Adverse Reactions and Events (SARE) reported to the EUSTITE pilot or collected by professional or other organisations where donors (non ART) were adversely affected by donation. The nature and seriousness of donor reactions are compared with the reporting requirements of the EU Directives and recommendations on donor reaction reporting developed. As a separate Deliverable was developed within this work package that provides guidance on vigilance in assisted reproduction, that field is not specifically covered in this report.

Project partners and other experts from within and outside the EU were consulted in the development of this report, in the interests of promoting global approaches to vigilance.

BACKGROUND

The EU legislative framework in relation to SAR reporting in living donors is reported in the following text. Requirements for ensuring the quality and safety of tissues and cells in the EU are set out in Directive 2004/23/EC⁸ and its implementing measures (Commission Directives 2006/17/EC⁹, 2006/86/EC¹⁰).

Directive 2004/23/EC defines a 'Serious Adverse Reaction' as

'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;'

Thus, donors are given equal importance to recipients in the definition. From this statement, it is interpreted that serious reactions in donors that are associated with the procurement should be reported.

However, in Article 11, paragraph 1, of the same Directive, it is stated that:

*'Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions **which may influence the quality and safety of tissues and cells and which may be attributed to the procurement**, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells.'*

The implication that Serious Adverse Reactions in donors should be reported **only** where there is an influence on the quality or safety of the procured tissues and cells is reiterated in Directive 2006/86/EC, Article 5 paragraph 1 (a) where it is stated that:

*'procurement organisations (must) have procedures in place to retain the records of tissues and cells procured and to notify tissue establishments without delay of any **serious adverse reactions in the living donor which may influence the quality and safety of tissues and cells**.'*

This approach of limiting adverse reaction reporting to cases where the safety and quality of the procured tissues and cells has been influenced by, and is consistent with, the Blood Directives (notably [Commission Directive 2005/61/EC](#)) but not entirely with the spirit of the introduction to Directive 2006/86/EC, where Recital 9 states:

⁸ Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004. Official Journal of the European Union. L102, 7.4.2004. p.48

⁹ Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Official Journal of the European Union. L38, 9.2.2006. p.40

¹⁰ Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. L294, 25.10.2006. p.32

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Serious adverse reactions may be detected during or following procurement in living donors or during or following human application. They should be reported to the associated tissue establishment for subsequent investigation and notification to the competent authority.

EUROPEAN COMMISSION GUIDANCE AND CURRENT PRACTICE

These texts have resulted in different practices in different MS, with some following the Directives very precisely and requiring donor reactions to be reported only where quality or safety of procured tissues has been influenced and others requiring, or at least accepting, reports of any donor reactions, regardless of whether tissue or cell quality or safety was impacted.

The survey carried out in WP4 of the SOHO V&S project included a question regarding reporting requirements for SAR in donors even where the quality and safety of the donated tissues or cells has not been affected. Twenty eight national regulators (Competent Authorities, CA) from 26 EU MS responded (in two cases there were different CAs for the ART field). Nineteen of the 28 CAs reported that they did require donor SAR reports even in these circumstances while nine reported that they did not. The types of donor reactions that most commonly required reporting were reactions associated with ovarian hyperstimulation in ART, with Granulocyte Colony-stimulating Factor treatment for peripheral blood stem cell collection and with reactions (i.e. calcium toxicity), also during peripheral blood stem cell collection.

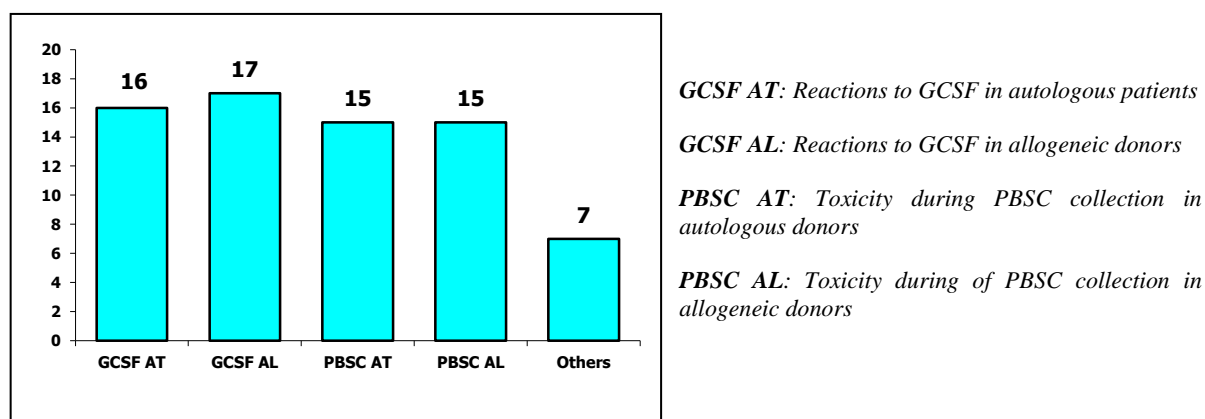


FIGURE 5.1: DONOR ADVERSE REACTIONS REQUIRING REPORTING IN EU MEMBER STATES¹¹

The 'other' types of donor reactions that required reporting were described in a general way as any reactions resulting in harm, additional medical intervention or hospitalization of a donor. The survey reported that in just under one third of the responding MS, registers of living donors are maintained to follow their health in the long term. In most cases, these are maintained at the centre level but a number of countries have national registries for haematopoietic stem cell donors. Some countries report that they are developing registries for reproductive cell donors.

This outcome reflects the fact that the European Commission has provided guidance to MS in 2009 and 2010 for the completion of their Annual Serious Adverse Reaction and Events Reports. In that guidance, referred to as the 'Common Approach document' it states that *'The Commission recognizes the value of this data [i.e. reports of donor reactions where the quality and safety of the tissues or cells were not affected], in the context of tissue and cells regulation, and invites Member States to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template. The declared figures won't be calculated as part of the total number of SARs'*.

This report aims to summarise the kinds of adverse reactions that most commonly occur in tissue and cell donors, to consider whether they meet the criterion of influencing tissue or cell quality and safety and to make recommendations on good practice regarding the reporting of these reactions in the EU.

¹¹ From the **SOHO V&S Survey of European Vigilance & Surveillance Systems Report** (Work Package 4) April 2011 – ART donor data removed (www.sohovs.org)

METHODOLOGY

THE NOTIFY PROJECT

For the purposes of this report, those cases that described adverse reactions in donors were extracted from the NOTIFY database for inclusion in this report. This document was then developed, as an analysis of those cases, with the inputs of the associated and collaborating partners shown in Appendix 1. No specific meetings were held to carry out the work, apart from the Bologna consensus meeting, all discussion being conducted by email.

TYPES OF TISSUE AND CELL LIVING DONORS

There are a number of different types of living donors of tissues and cells. They can broadly be categorised into autologous and allogeneic donors. The largest group is represented by living donors of haematopoietic stem cells: bone marrow, peripheral blood stem cells or cord blood. Allogeneic donors can be related to the recipient (this can also be referred to as 'directed donation') or unrelated to the recipient.

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

DONOR REACTIONS REPORTED VIA VIGILANCE SYSTEMS AND THE LITERATURE (NOTIFY)

BONE MARROW DONOR REACTIONS

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

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

PERIPHERAL BLOOD STEM CELL DONOR CASES

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

OTHER TISSUES – AUTOLOGOUS

The NOTIFY review of living tissue donor adverse reactions identified only cases associated with autologous musculoskeletal donation. They included fracture of the anterior superior iliac spine, persistent pain and sensory disturbance, persistent drainage, wound dehiscence, incision drainage, infections and long-term functional impairment in patients having autologous bone grafts removed from the iliac crest. Wound infection and pain have also been associated with the recovery of autologous rib and femoral head grafts and sensory loss and gait disturbance associated with tendon and tibia removal for autologous implantation.

DISCUSSION

Programmes of allogeneic tissue and cell transplantation rely entirely on the good will of donors and donor families; without them, there would be no transplantation. Living donor care and protection is of fundamental importance both from an ethical perspective and to ensure the continued willingness of society to donate for the benefit of others. Allogeneic living donors should be well informed of the risks they take when agreeing to donate and the collation of donor reactions provides concrete information on which this risk evaluation can be based. As the numbers of reactions are relatively low, the data are more valuable when consolidated from a wide geographic area. Considerable benefit might be accrued from clearly requiring this kind of reporting to Competent Authorities on an EU-wide basis, even where the safety or quality of the tissue or cells was not compromised by the adverse reaction.

As evident from the NOTIFY exercise, the group of allogeneic living donors, non-ART, that is exposed to the greatest risk is the HPC donor group, both bone marrow and peripheral blood stem cells. It is noted that the World Marrow Donors Association (WMDA) already collects, records and publishes all cases of serious adverse reactions in allogeneic, unrelated donors reported by its members; indeed almost all of the cases included in the NOTIFY collection were provided by this registry (Serious Events and Adverse Reactions, SEAR). Worldwide, unrelated bone marrow donor registries must participate in this vigilance programme, sending quarterly reports, to maintain their accreditation. The results are made publicly available.

In the light of this well-developed programme, the added value of reporting donor reactions to Competent Authorities in the EU, where they do not impact on the safety or quality of the donated cells, in unrelated HPC donors, might be questioned. The benefits of reporting these reactions to Competent Authorities would be to include also the related allogeneic donors (although this extension is already planned by WMDA) and the autologous donor reactions. It is clear that the latter cases, none of which were included in the NOTIFY collection, do not impact on willingness to donate but they could provide important information for safety improvements in allogeneic programmes.

Donors of tissues that are removed for therapeutic purposes, in some countries referred to as 'surgical residue', are not normally exposed to additional risk by agreeing to donate; no cases of harm to such donors were recorded in the NOTIFY process. Some reactions associated with tissue removal for autologous transplantation were recorded. As these tissues are not normally donated by living donors in the allogeneic setting (apart from the different circumstance of surgical residue), reactions in this setting do not impact the willingness of donors to donate and do not provide information for improving allogeneic donor safety. For these reasons, reactions associated with autologous tissue removal should be reported and managed within the hospital patient safety system and not necessarily reported to the tissue and cell vigilance system.

CONCLUSIONS AND RECOMMENDATIONS

In the allogeneic donor setting (related or unrelated) donor reactions should be reported, collated and the information made available publicly, either by the registries or by the CAs, regardless of the impact on the quality and safety of the donated cells. According to the global organisation World Bone Marrow Transplantation (WBMT), donors of bone marrow and peripheral blood stem cells should be followed up for at least 10 years, with check-ups at 1, 5 and 10 years, to ensure that long-term reactions such as haematologic and non-haematologic malignancy or autoimmune disease are detected and survival monitored. In general, duplicate reporting should be avoided. Thus, where a CA requests that these cases be reported, consideration should be given to CAs requesting a copy of the SEAR report rather than asking for a duplicate report with different documentation.

It is recommended that in any future revisions of the EU tissues and cells Directives consideration should be given to make the reporting of all donor reactions mandatory as already required in some MS, regardless of any impact on the quality or safety of the donation. Where a donor reaction is caused by a medical device or a drug, for example, for stimulating the release of stem cells to the peripheral blood, it should be reported, through a relevant vigilance system; in any case, the vigilance systems should communicate with each other to ensure that an overview of such reactions is maintained.

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In the autologous setting, reactions associated with tissue or cell removal should be reported to local patient safety programmes. Where these reactions may provide important learning for allogeneic programmes, they should be published or shared in another way with the professional community.

The bibliography related to the cases mentioned in this chapter is included in the NOTIFY Report¹²

¹² NOTIFY. *Exploring Vigilance Notification for Organs, Tissues and Cells*. *Organs Tissues & Cells*, 2011, November, 14, 3: Suppl.

CHAPTER 6: THE INVESTIGATION OF SERIOUS ADVERSE REACTIONS AND EVENTS

THE OBJECTIVE OF SARE INVESTIGATION

The aim of an SAR investigation is to establish imputability. Imputability is defined as

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

Imputability of an SAR may change in the course of the investigation, as evidence is gathered. In the case of SARs in recipients, evidence may relate to establishing a link between the condition in the recipient and a characteristic of the tissues or cells applied, or the identification of a similar condition in the donor. Alternatively, it may relate to the identification of other possible sources or causes for the condition in the recipient. The following scale for Imputability is included in the instructions for annual reporting to the European Commission.

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

The aim of an SAE investigation is to establish what caused the event. Wherever possible, root causes should be sought rather than superficial causes. Hence, rather than attributing an SAE only to ‘human error’, efforts should be made to understand any contributing factors or circumstances that exacerbated the risk of the error occurring.

WHO SHOULD INVESTIGATE A SUSPECTED SARE?

THE ROLE OF THE TISSUE ESTABLISHMENT

Directive 2006/86/EC recognises the central role of the TE in SARE reporting and investigation in most cases. The TE has, or has access to, all the relevant information regarding the donor, the procurement, the processing and storage records, the quality control results and the distribution records, including those for tissues or cells not directly involved in the SARE but implicated by it in some way. The TE should involve other parties, a Procurement Organisation, the clinical users, specialist laboratories and relevant experts etc., as necessary, and should take responsibility for initial reporting to the Competent Authority and subsequent reporting of the final investigation outcome. Each SARE investigation should be led by a named individual in the TE and should be fully documented. In the case of SARs, communication with the treating clinician or the clinician responsible for a living donor should generally be led by the nominated physician at the TE.

In general, tissues and cells that are linked in some way to a suspected SARE should be quarantined securely for the duration of the investigation. The TE should decide at which point the evidence justifies either destruction or recall of

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distributed tissues and cells, or look-back in other recipients. These decisions should be based on appropriate application of the 'precautionary principle'¹³ and should be fully documented.

Investigation reports should be filed together with the SARE documents and should be made available during inspections by the CA or its nominated inspection body.

TEs should provide training to relevant staff on how to conduct an investigation to establish imputability of an SAR or root cause of an SAE. The Responsible Person should ensure that procedures for reporting, investigation, recall and look-back, with standard template forms and decision algorithms should be included in the TE Quality System.

THE ROLE OF THE CLINICAL USER

For most types of well-established tissue and cell transplantation, detailed clinical outcome reporting by the clinical user to the TE is required only in those exceptional circumstances where there is a serious adverse reaction. Routine clinical follow-up and reporting of tissue and cell recipient clinical progress is required, however, for all highly matched life-saving transplants such as haematopoietic stem cell infusions or when novel tissue or cell processes have been applied or new types of tissues or cells are being transplanted. This routine clinical follow-up is not generally considered as part of vigilance.

Even when applying tissues and cells in well established procedures, clinical users play a critical role in being vigilant to unexpected or untoward outcomes. Adverse outcomes might result from many diverse factors associated with the surgical procedure or the patient's underlying condition and so clinicians might not consider the tissues or cells applied as a possible source of the outcome. TEs that supply tissues and cells should have implemented effective systems to advise clinical users of tissue and cells to always consider whether adverse outcomes might have been associated with the tissues or cells transplanted so that similar occurrences might be prevented. In the case of tissues and cells directly imported from a third country, the transplant centre is responsible for ensuring that associated reactions are also reported to the CA in the recipient's country and to the TE in the supplying country.

The SOHO V&S project is developing separate dedicated guidance for vigilance at the level of the clinical unit.

THE ROLE OF BIOVIGILANCE OFFICERS AND TRANSPLANT CO-ORDINATORS

In some MS, there are dedicated biovigilance officers in hospitals who have responsibility for coordinating vigilance activity for SARE associated with substances of human origin. These individuals should play a key coordinating role in the investigation of SARE at the hospital level, acting as a focal point for communication between the TE and the relevant hospital clinicians or laboratories. In some MS, hospital transplant coordinators fulfill a very similar role. Wherever an SARE is associated with a multi-organ and multi-tissue donor, the transplant coordinator service will be a key player in the investigation and follow up of a SAR that is suspected to be of donor origin.

THE ROLE OF THE COMPETENT AUTHORITY

The CA should review all initial SARE reports to evaluate the need for their participation in the investigation. In most cases, this should not be necessary and the CA should limit its involvement to review of the final SARE report and review of the full investigation report, if considered necessary. Where the impact of an SARE is likely to be broad and important, the CA is likely to participate in the investigation, possibly supporting it by providing access to government funded experts and/or laboratories. CAs should also accept direct reporting by clinical users.

Discussions in the WP7 working group of SOHO V&S concluded that the following criteria might be appropriate for deciding when the CA should participate in a specific SARE investigation:

1. there are implications for other MS or third countries
2. there are implications for public health in general
3. there are public perception issues that could damage donation
4. there are public perception issues that could damage the reputation of the health service in general
5. there is some evidence to suggest criminal or fraudulent activity (see chapter 8)
6. there is dispute regarding responsibility for investigation/follow up actions.

The EUSTITE project developed an Impact Assessment tool which may help CAs decide on whether they should participate actively in investigation or planning of follow up actions for individual SARE. In principle, the broader the

¹³ See European Commission Communication on the Precautionary Principle COM/2000/0001 final
http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=52000DC0001

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impact of a particular SARE, the more involved the CA should be. Certain SAR that have minor consequences for an individual donor or recipient might imply significant risk in a broad way, for example a donor SAR that receives wide public dissemination might discourage donation in general, putting patients at risk through an impact on supply of tissues or cells generally. These broader implications can be assessed using the EUSTITE impact assessment tool that evaluates both the system consequences and the probability of recurrence. The impact tool is shown at Appendix 2.

The CA may support TEs conducting investigations by referring them to appropriate specialist laboratories and experts that should provide technical support and advice for particular types of investigations being conducted by public or private TEs. See 'The Role of Others' below. The CA could compile and publish lists of laboratories with experts in particular types of infectious agents or malignancy, especially unusual or emerging agents or rare diseases for which scientific testing expertise is not easily identified. Such lists would be an important resource for improving the quality of investigations and might be made available via the Eurocet registry. Such advice structures could be shared between EU CAs (perhaps via the European Commission and ECDC) so that countries that might not have an expert laboratory for a particular agent (e.g. variant CJD, West Nile Virus) could avail of the services of an expert laboratory service in another MS.

A critical role of the CA is to review and evaluate the investigations conducted by TEs bearing in mind that the TE may, in some cases, have had a conflict of interest in the case. Independent technical experts may be asked to support the CA by reviewing investigations that have been carried out.

When conducting routine inspections, inspectors should review the investigations of SARE for completeness.

It is the role of the CA to complete an annual report to the European Commission following the instructions in the Commission's Common Approach document. The report must be completed online.

THE ROLE OF OTHERS

Any **third party** providing services to a TE or a PO could detect an SAE and could be involved in the investigation of an SAE or SAR. The role of these parties in detecting, reporting and investigating SARE should be described in the written agreement or contract that they hold with the TE or PO.

Scientific or medical experts, specialist scientific laboratories or institutes and scientific and professional societies can also play a crucial role in the investigation of an SAR or SAE, providing testing services, advice and interpretation, relevant data from other sources etc. Independent scientific or clinical input may also be required by a CA for the evaluation of an SARE investigation conducted by a TE. For these reasons, it is important for CAs to have well established working relations with leading government or independent experts and to have access to that expertise when necessary. CAs should have well established communication lines with **other vigilance systems** (medical device vigilance, pharmacovigilance etc.) when issues of concern are detected that might impact on the quality and safety of tissues or cells for transplantation. Duplicate reporting via two vigilance systems should be avoided but that would only be possible if there is effective communication between the two systems to ensure that investigations are conducted collaboratively when appropriate and that records show a link to a relevant incident investigation documented in another system. It is important that any lessons learnt and follow up actions are documented in both systems.

Where relevant, the CA should communicate **with other MS CAs** or with the European Commission to ensure that the impact of a particular SARE is investigated, managed and communicated appropriately. In circumstances where an SARE or a suspected SARE is associated with activity in more than one MS, consideration should be given to the establishment of a multi-MS investigation team utilizing, as necessary, the expert or laboratory services of one nominated MS to ensure the optimal outcome of the investigation.

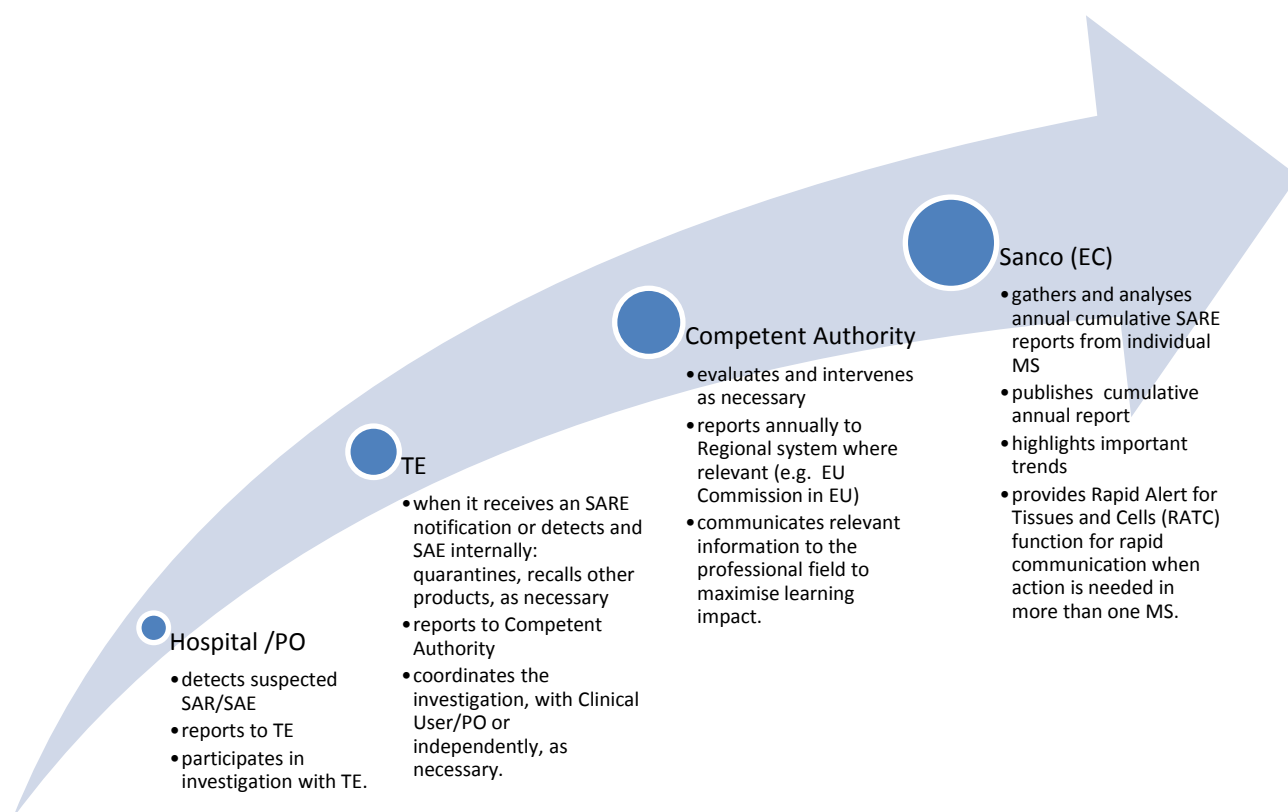


Figure 6.1: Responsibilities of different organisations for SARE reporting and investigation.

INVESTIGATION METHODOLOGY

Investigation methodology will depend on the type of suspected SAR or the SAE that has occurred. In either case, previous description of the SARE will provide important information for the investigation. The NOTIFY Library (www.notifylibrary.org) is a useful source of information regarding previous cases described, as well as the methodology followed for the assessment of imputability.

ESTABLISHING IMPUTABILITY FOR SARs INVOLVING POSSIBLE INFECTIOUS TRANSMISSIONS

As the guidance below indicates, investigations of this type rely heavily on the availability of archive samples of donor serum or cells. Although keeping such archives is not a minimum requirement in the EU Directives, CAs should encourage TEs and POs to follow this practice as an invaluable tool for the investigation of any subsequent suspected transmission.

SUSPECTED TRANSMISSION OF VIRAL, PARASITIC OR NON-CONVENTIONAL AGENTS (SUCH AS PRION) FROM AN ALLOGENEIC DONOR

For the investigation of suspected transmission of an infection from an allogeneic donor, the TE and the clinical unit that has detected the possible transmission should be involved, together with a reference laboratory with the established specialist expertise for that infection and preferably with experience of investigating similar transmission events. Infectious donations may arise either through a failure of the screening process, such as a failure to detect donor risks, or false negative donor screening test results, or through a failure to detect a "window period" infection. The investigation of a potential transmission is greatly facilitated by access to residual material used for initial testing though this may not be available. In the case of living donors a later sample from the donor may also be informative especially as it may demonstrate an evolution of markers compatible with an acute infection. Testing other recipients of materials from the same donor may be indicated but it must be borne in mind that the use of antibody tests alone to define infection is not optimal given the inherent immunosuppression that may be present in the other recipients. It is reasonable that a CA could expect that the following steps would normally be included in an investigation:

- a full review of the recipient's clinical symptoms, the test results which triggered the investigation, any further relevant test results and careful consideration of alternative risk factors (life-style risk, relevant

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medical history, exposure to other SOHO especially blood or plasma components/products) including exposure to possible nosocomial sources of infection

- if it is still considered possible that the tissue/cell donor may be the source of the infection
 - check/test other recipients of material from that donor preferably using antigen or genome based detection assays
 - review donor history for risk factors or other relevant information
 - if the donor is deceased and an autopsy has been performed, check whether there are findings of relevance to this suspected transmission
 - review the testing protocols for donor screening determining whether antibody alone, combined antigen and antibody, antigen alone or NAT testing was undertaken
 - perform additional testing as relevant on appropriate biological material from the donor should this be available.

If the suspected infectious agent is one of those viruses for which routine screening is mandated and NAT testing or antigen testing has not been performed on the donor sample prior to tissue/cell release, the most sensitive available assay should be performed on an archive sample from the donor should it be available for testing. Antibody-only testing for some of the blood borne infections carries the risk of the screening failing to detect an early infection present in the donor before seroconversion has occurred. Combined antigen and antibody tests mitigate this risk but do not entirely remove it and for most infections NAT testing remains the most sensitive way of detecting these early infections. NAT is usually the method of choice for investigating potentially infected donors. For living donors similar testing of a further sample from the donor should be considered using both serological and NAT tests. In particular if no donation sample is available seroconversion may still be demonstrated by retesting the living donor.

The CA should assist the TE in identifying a suitable reference laboratory to perform a range of reference tests on the recipient and other recipients of involved donations as well as on appropriate donor material as part of the investigation. This is particularly important in the case of new and emerging infections where many laboratories will neither be equipped to test with appropriate sensitivity or specificity nor will they have experience in the interpretation of their findings.

In the case of transmission of conventional infectious agents the CA might expect the TE on confirming imputability to have shown most or all of the following

- supportive epidemiology linking the donor and recipient in time and space
- identification of similar symptoms/syndrome in both donor and recipient(s)
- identification of the same agent in both donor and/or donor material and recipient(s)
- corroboration of identity of infections by genomics including phylogenetic analysis.

In the case of transmission of emerging, novel or unconventional agents confirming imputability may have to rest on

- supportive epidemiology linking the donor and recipient in time and space
- identification of similar symptoms/syndrome in both donor and recipient(s).

RESPONSE TO A POSSIBLE ALLOGRAFT-ASSOCIATED BACTERIAL OR FUNGAL TRANSMISSION

The clinician must be suspicious that transmission of bacterial or fungal infection may occur in association with tissue or cell implantation or infusion.

In the setting of unexpected graft dysfunction, local signs (e.g., erythema, oedema, pain) of infection or inflammation, fluid collections or bleeding, local samples must be obtained for microbiological analysis. These include Gram stain and culture, bacterial and fungal cultures, and, if appropriate, mycobacterial smears and cultures. Special assays may be indicated based on the nature of the graft or reaction. Complete blood counts and differential counts should also be obtained.

Signs of infection or inflammation (e.g. fever, rigors and tachycardia, leukocytosis, hypotension, confusion, pneumonia, meningismus) merit blood cultures, and sputum or cerebral spinal fluid cell counts, glucose and protein, microbiological cultures as appropriate from the site of infection.

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If a nosocomial infection has been excluded or deemed unlikely, the tissue or cells should be investigated as the potential source of infection. Bacterial or fungal contamination, either originating from the donor or from the process of procurement, processing or storage should be considered. As part of the investigation, any remaining samples of tissues or cells from the donor should be similarly tested. Detection of the same bacterial strain by approved techniques in the recipient's blood or the infection site and in other tissues or cells from the donor can provide confirmation of transmission.

If the donor is not identified as the source, then

- tissues or cells processed in the same processing area, before and after the implicated tissues or cells should be tested
- any reagent or additive batches used in the implicated procurement or preparation process should be tested.
- the environmental monitoring results on the day of processing should also be reviewed if the donor is excluded as the source of contamination.

ESTABLISHING IMPUTABILITY FOR SARS INVOLVING POSSIBLE MALIGNANCY TRANSMISSIONS

There are very few documented cases of transmission of malignancy in the field of tissues and cells. Quantitatively, the most relevant information is related to haematopoietic stem cell (HSC) transplantation. Malignancies transmitted through HSC are typically haematologic malignancies, which become clinically evident through tumour-specific symptoms (abnormal blood counts/differential) and in late stages.

In general, a history of malignancy is cause to exclude a potential tissue or cell donor. An exception is cornea transplantation because of its avascular nature. Reports compare the incidence of cancer in recipients of cornea coming from donors with malignancies with recipients of cornea from donors without malignancies, concluding no statistical or clinical evidence to suggest the transmission of cancer from donors with malignancies via corneal transplantation.

Transmission of haematological malignancies through cell transplantation has been reported in a number of well described cases.

Clinicians diagnosing a malignancy after transplantation that might be donor-transmitted should always consider other recipients from the same donor might be affected and should activate the corresponding mechanisms to alert the teams in charge of other potentially affected recipients. Donor transmitted malignancies should be suspected on the basis of clinical criteria. Clinicians should also take into consideration existing risk factors in the recipient's medical history. Even if imputability has not yet been determined, the suspicion of a transmitted malignancy should activate the alert, since preventive and therapeutic measures could be initiated for other recipients. Wherever possible, the investigation team should include an expert for the type of malignancy that is suspected to have been transmitted so that the most appropriate laboratory analysis methodologies will be made available. The following steps would normally be included in the investigation:

- full review of recipients clinical symptoms, test results and any alternative risk factors for the malignancy in the donor's medical history
- if it is considered possible that the tissue/cell donor is the source of the malignancy
 - check other recipients of SOHO from that donor
 - review donor history relevant information that might have been missed and, for living donors, check the donor's current health status
 - if the donor is deceased and an autopsy has since been performed, check whether there are results of relevance to this suspected transmission
 - perform histology on relevant biological material from the donor if possible.

Determination of the genetic identity of donor and recipient tumours can provide a high degree of confidence regarding imputability.

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

Additionally, previous description of the transmission is important. A correct assessment of a case involves the analysis of the literature in order to understand whether the same tumour type has been transmitted before by the

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type of tissues or cells. The NOTIFY Library (www.notifylibrary.org) provides important information regarding previous cases described, as well as the methodology followed for the assessment of imputability.

ESTABLISHING IMPUTABILITY FOR SARs INVOLVING POSSIBLE GENETIC TRANSMISSIONS

GENETIC TRANSMISSIONS BY HPC

Although volunteer donors of HPC are not screened for genetic diseases, it is assumed that donors with genetic diseases are deferred as this can be deduced from the medical history or from findings of the laboratory tests undertaken. Transmission of genetic diseases by cord blood units has a significantly higher risk than stem cells from peripheral or bone marrow donation since the disease might not be easily recognised at birth or even for some time later. Although public cord blood banks request that information on the health status of the newborn/donor be provided by the family even sometime after the donation and prior to the listing of the unit, it is possible that some genetic diseases will be missed as might not be manifested until much later in life.

Theoretically, all congenital diseases originating from bone marrow-derived cells are transmissible. Very few cases of genetic disease transmission through haematopoietic cells have been reported. Cyclic neutropenia and Gaucher's disease were transmitted via sibling HPC transplantation (Krance et al. 1982). According to the EU Directives on tissues and cells, genetic disease transmission by tissues and cells is considered as an adverse reaction and, as such, should be reported to the Competent Authority and investigated to confirm the transmission.

GENETIC TRANSMISSIONS BY GAMETES AND EMBRYOS

Conditions such as Severe Congenital Neutropenia (SCN), Hypertrophic Cardiomyopathy, Autosomal Dominant Cerebellar Ataxia (ADCA), Opitz Syndrome, Neurofibromatosis type 1 (NF 1), Autosomal recessive Polycystic Kidney Disease (ARPKD), Congenital adrenal hyperplasia (CAH), Fragile X syndrome and Phenylketonuria (PKU) have been reported in offspring originating from gamete donation. Although these events are not numerous, they show the need to consider the potential of genetic disease transmission using donor gametes. Gametes are the only cells that carry such genetic material which could potentially affect the recipient (offspring) with any genetic disease. Information should be shared with women/couples requesting this service/treatment, as any donor could be a potential carrier of a genetic disease.

One could argue that the number of children born with a genetic disease that are conceived through Assisted Reproduction Technology (ART) and gamete donation is probably larger than reported since couples are reluctant to reveal or share information regarding the method of conception and the use of a donor gametes.

Recommendations for investigation of genetic transmissions by gamete or embryo donation are addressed in Chapter 4.

ESTABLISHING IMPUTABILITY FOR SARs OF OTHER TYPES (E.G. GRAFT FAILURE, TOXICITY, ALLERGY, GENERAL MISMATCH)

There can also be adverse reactions in recipients of tissues or cells that are not associated with disease transmission. Examples would be:

- failed engraftment of a HPC infusion
- mechanical graft failure such as fracture of a transplanted long bone;
- toxic reactions such as DMSO toxicity in HPC recipients with symptoms that might be mild (e.g. hives, flushing, transient bradycardia) or severe¹⁴
- allergy, including life-threatening anaphylaxis
- general mismatch, such as an incorrectly sized heart valve or the left rather than the right meniscus being provided.

Some of these reactions may be due to avoidable errors during the process from recovery to clinical use. If the reason for an SAR such as a graft failure was:

- anticipated;

¹⁴ Cox M.A., Kastrup, J & Mikulas H (2012) *Historical Perspectives and the future of adverse reactions associated with haematopoietic stem cells cryopreserved with dimethyl sulfoxide*. Cell and Tissue Banking 13: 203-215.

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- known not to be the result of an adverse event, impacting on the quality and safety of the tissues and cells; and
- discussed between the patient and the clinician prior to clinical application,

then it will not require investigation. Examples might be known low cell counts or a poor HLA match for transplanted cells with no better option for the recipient.

If the SAR was not anticipated, there should be a full investigation to establish the cause of the failure. The investigation should map the process from donation to transplantation, paying special attention to any non-compliances with standard operating procedures. The investigation should include:

- review of the recipient patient's health condition and any risk factors
- review of quality control checks performed at all stages of the process including cell counts, where appropriate, and any other critical parameters
- repeat quality checks on stored samples, if available
- review of the storage and transportation conditions from the TE to the clinical user
- review of the storage and handling of the tissues and cells between receipt at the clinical unit and final transplantation.

A root cause analysis should be conducted to establish the cause of the process failure, where identified (see the following section on investigating SAEs).

INVESTIGATING SAEs

The investigation of SAEs essentially comprises a 'root cause analysis' process (RCA). RCA is a structured approach to identifying the factors that resulted in the nature, the magnitude, the location, and the timing of a harmful, or potentially harmful, outcome. RCAs should be conducted in a structured and objective way, to reveal all the influencing and causal factors that have led to an adverse event. The aim is to learn how to prevent similar incidents happening again. The approach should shift the focus away from individuals and on to the system.

There will usually be a coordinator and a team that carries out the investigation. Normally, the following steps should be included in the process:

1. **Gathering Data** – to include full details of what happened, as well as relevant policies and procedures.
2. **Mapping the Information** – possibly in timelines, flowcharts or a chronological narrative of the chain of events allowing the identification of any information gaps and showing contributing factors.
3. **Identification of the problem(s) that contributed to the occurrence** – this could require a review meeting with relevant personnel involved.
4. **Analysis of the contributing factors** with prioritisation.
5. **Identification and agreement on the root causes** – the fundamental contributory factors which, if resolved, will eradicate or have the most significant effect on reducing likelihood of recurrence
6. **Reporting.**

The implementation of corrective and preventive actions should be managed and monitored within the Quality Management System, with an action plan and audit and any relevant findings being fed back into the original investigation report.

It is easy to conclude that mistakes are caused by 'human error' but this error often has an underlying cause that must be identified and addressed if repetition of the error is to be avoided. The underlying causes might be understaffing, unduly long working hours, procedures that are not clear to staff, inadequate training or, indeed, true human error. To arrive at the 'root' cause, it is recommended that a structured approach be adopted. Relevant personnel should be trained in effective methods for conducting RCAs.

FIVE WHYS

One well established quick and simple method is to ask a series of 'why' questions, continuing until a satisfactory explanation for what has occurred is reached. See examples in the Annex to this chapter. As a problem becomes more complex, this tool may not be sufficient to allow identification of the root cause and a more sophisticated technique may be needed, such as the Ishikawa (or cause and effect method).

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CAUSE AND EFFECT ANALYSIS

Also known as the *Ishikawa Diagram* or the *Fishbone Diagram for Process Failure*, this method encourages the investigation to follow a structured process of identifying contributing factors and risks. The technique uses a diagram-based approach for thinking through all of the possible causes of a problem.

It can be summarised in the following steps and on the corresponding diagram below:

1. identification of the problem – the SAE (what has gone wrong?)
2. identification of the factors that could contribute to causing the problem (systems? equipment? personnel? external factors? etc.)
3. identify possible causes for each factor
4. analyse the diagram and decide on further actions to test the different potential causes (data analysis? survey? interview? research?).

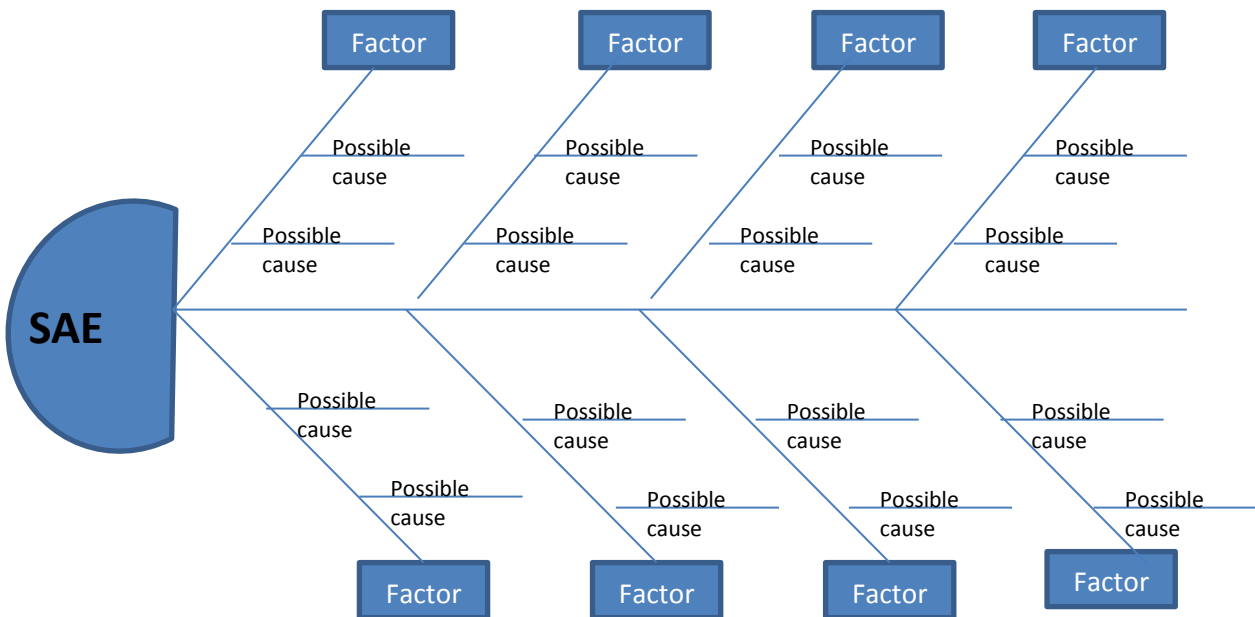


Figure 6.2: Fishbone diagram method for establishing root cause.

There are many other methods that might be applied to support the process of root cause analysis. The chosen method is not important; what is that the approach is structured, logical, thorough and well documented.

INTERNATIONAL INVESTIGATIONS

Where a particular SARE has implications or causes in more than one MS, consideration should be given to the establishment of a multi-MS investigation team. This suggestion was strongly supported by MS CAs in their responses to the SOHO V&S survey (see Chapter 2). Triggers for the establishment of an international investigation team might include the following:

- the incident is associated with activity in more than one MS (e.g. donation in one and processing and storage in another)
- the incident is associated with a risk that is well understood in one MS but newly emerging in another
- the incident involves distribution and affected recipients in multiple MS.

In general, the investigation should be coordinated by the MS where the SARE was detected.

ACTION ON THE BASIS OF THE PRECAUTIONARY PRINCIPLE

On certain occasions it will not be possible to confirm imputability but it will be appropriate, in any case, to take preventive measures on the basis of the Precautionary Principle. The European Commission Communication on the Precautionary Principle (2000) provides useful guidance. The following text is taken from that communication.

Where action is deemed necessary, measures based on the precautionary principle should be, inter alia:

- proportional to the chosen level of protection,*
- non-discriminatory in their application,*
- consistent with similar measures already taken,*
- based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis),*
- subject to review, in the light of new scientific data, and*
- capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment.*

Proportionality means tailoring measures to the chosen level of protection. Risk can rarely be reduced to zero, but incomplete risk assessments may greatly reduce the range of options open to risk managers. A total ban may not be a proportional response to a potential risk in all cases. However, in certain cases, it is the sole possible response to a given risk.

Non-discrimination means that comparable situations should not be treated differently, and that different situations should not be treated in the same way, unless there are objective grounds for doing so.

Consistency means that measures should be of comparable scope and nature to those already taken in equivalent areas in which all scientific data are available.

Examining costs and benefits entails comparing the overall cost to the Community of action and lack of action, in both the short and long term. This is not simply an economic cost-benefit analysis: its scope is much broader, and includes non-economic considerations, such as the efficacy of possible options and their acceptability to the public. In the conduct of such an examination, account should be taken of the general principle and the case law of the Court that the protection of health takes precedence over economic considerations.

Subject to review in the light of new scientific data, means measures based on the precautionary principle should be maintained so long as scientific information is incomplete or inconclusive, and the risk is still considered too high to be imposed on society, in view of chosen level of protection. Measures should be periodically reviewed in the light of scientific progress, and amended as necessary.

Assigning responsibility for producing scientific evidence is already a common consequence of these measures. Countries that impose a prior approval (marketing authorisation) requirement on products that they deem dangerous a priori reverse the burden of proving injury, by treating them as dangerous unless and until businesses do the scientific work necessary to demonstrate that they are safe.

Where there is no prior authorisation procedure, it may be up to the user or to public authorities to demonstrate the nature of a danger and the level of risk of a product or process. In such cases, a specific precautionary measure might be taken to place the burden of proof upon the producer, manufacturer or importer, but this cannot be made a general rule.

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ANNEX 1

'FIVE WHYS' EXAMPLES

WHY WAS THE WRONG VIROLOGY REPORT RECORDED?

Question	Answer
Why was the wrong virology report recorded?	It was a human error – the technician saw the reactive result but ticked the 'non-reactive' box on the results form.
Why did the technician make a mistake like this?	He was not used to manually recording results and was carrying out a number of tests simultaneously.
Why was he manually recording results if he was not used to doing that?	The automated testing system is used during the normal busy day but not at night when the number of tests required is too low to justify the cost.
Why was he not familiar with the night time procedure?	It was his first time working alone at night and he had not used the manual procedure for a number of years.
Why was he carrying out a procedure for which his competence had not been checked?	The person who normally worked at nights was ill.
Root Cause	The technician was carrying out a task for which he had not been adequately trained and supervised.

WHY WAS THE BONE PACKAGING TORN WHEN IT WAS RECEIVED IN THE OPERATING THEATRE?

Question	Answer
Why was the bone packaging torn when it was received in the operating theatre?	The cortical bone strut inside was sharp and tore the packaging material.
Why was material used for packaging that was susceptible to tearing by sharp bone?	It had always been used by the tissue bank for all their previous skeletal tissues.
Why had this problem not been seen when the packaging was validated?	The validation was carried out only for ground bone that does not have sharp points.
Why was the packaging material not validated for this new type of bone?	The validation already in place for ground bone was considered adequate.
Why was this new risk not identified as a reason for validation of the packaging for cortical struts?	No risk assessment was carried out when this new bone preparation process was introduced.
Root Cause	Lack of a risk assessment when a significant processing change was being introduced.

CHAPTER 7: VIGILANCE COMMUNICATION FOR TISSUES AND CELLS IN THE EUROPEAN UNION

INTRODUCTION

Communication is a critically important aspect of effective vigilance. Communication may be for the purposes of sharing the lessons learned from vigilance or for the purposes of ensuring rapid action to prevent harm to donors or recipients.

SHARING THE LESSONS LEARNED FROM SARE INVESTIGATIONS

TISSUE ESTABLISHMENTS AND CLINICAL USERS

Tissue Establishments and clinical users who have detected and investigated a specific SARE, should be encouraged to publish the results of their investigations in clinical and scientific journals where there are useful lessons that could prevent recurrence. Publication of adverse outcomes, even when they resulted from avoidable error, increases transparency and facilitates improvements in practice on a wide scale. The publication of sentinel events, such as the transmission of HIV to organ and tissue recipients by a donor in the seroconversion window period or the transmission of *Clostridium* infection to multiple tendon recipients by tissues for which the sterilization process had not been properly validated, has provided invaluable evidence for the need for practice improvements to increase safety.

COMPETENT AUTHORITIES FOR TISSUES AND CELLS

Competent Authorities (CA) should summarise the reports they receive and make this information available to the TE and clinical user community, e.g. on their website. The European consolidated annual reports received from the European Commission (EC) should be shared with the TEs. They should monitor trends so that evidence of increasing risk or improving practice can be highlighted. CA can use a number of communication tools to ensure that the maximum learning is achieved from the reports they receive. The following are important communication tools at a national level:

- National Information Notices – where a national trend is observed that highlights a need for change towards better practice (non-urgent) or provides useful information for the field;
- Annual Reports which should include a summary of the SARE reported during the year and any key consequences
- National Rapid Alerts (see below).

Where appropriate, CA should nominate independent experts to review vigilance investigations and to support the development of recommendations for endorsement by the CA.

Where particular SARE have implications for, or involve, other vigilance systems, the CA should communicate with the relevant regulator to ensure information sharing and avoid duplication of activity. This might occur where organs, equipment, ancillary products, medicines, medical devices are implicated or affected.

EUROPEAN COMMISSION

When urgent action is required in two or more MS, the EC's RATC system should be used to ensure appropriate responses (see below).

The EC should analyse and report the data received in the annual reports from MS so that trends in risk and safety improvements across the EU can be seen in MS. The reports should provide enough detail to allow TEs and CAs to take preventive action on the basis of what has been reported elsewhere and should provide activity denominators so that the accumulated data gives an EU estimate of risk.

THE NOTIFY LIBRARY OF ADVERSE EVENTS AND REACTIONS FOR ORGANS, TISSUES AND CELLS (WHO)

One of the major outputs of NOTIFY (see Chapter 1) was the development of a website where the database of adverse events and reactions collected by the participating international experts is made available to the public. The site (www.notifylibrary.org) is hosted by the Italian National Transplant Centre on behalf of WHO and it contains over 1,700 bibliographic references, together with guidance notes on alerting symptoms and methods of confirmation, by type of reaction. New cases are reviewed by experts for inclusion in the searchable database. This communication instrument aims to improve the sharing of lessons learned from vigilance, on a global scale.

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RAPID ACTION TO PREVENT HARM TO DONORS OR RECIPIENTS

NATIONAL RAPID ALERTS FOR TISSUES AND CELLS (NRATC)

Each CA should have a procedure for the issue of National Rapid Alerts for Tissues and Cells (NRATC) – where a risk is identified that requires immediate action but has no implications outside the MS. Appropriate contact lists should be maintained for communication to key stakeholders when urgent corrective or preventive action is required.

EU RAPID ALERTS FOR TISSUES AND CELLS (RATC)

The EU Rapid Alert Tissues Cells (RATC) system ensures the secure transmission of information between CA of the EU and the European Economic Area (EEA) and the EC when urgent remedial or precautionary action is needed due to a serious public health threat. The procedure is supported by an electronic communication tool hosted within the secure area of the EC's internet platform. The system is live since February 2013. All EU CA have nominated individuals who have access to this platform where they can launch a RA, respond to a RA launched by another MS, notify further MS of a RA if they consider it necessary and contribute to the final reports of individual RAs as appropriate. This rapid exchange of information allows all the MS to verify immediately whether they are affected by a problem initially raised by a MS or the EC, and for which a precautionary/corrective measure should be implemented.

The types of threats that should be communicated using this network include:

- quality and/or safety defects of specific tissues/cells intended for human application
- illegal and fraudulent activities in the field of tissues and cells intended for human application
- development of rapid/significant epidemiological situations (e.g. disease outbreaks) which may have cross-border implications in the field of tissues and cells intended for human application
- notifications (recalls, preventive measures, advice, etc.) from other related healthcare sectors (e.g. medical devices, blood and blood products, medicinal products, organs) with potential consequences on the quality and safety of tissues and cells intended for human application.

Only alerts requiring immediate/urgent consideration or follow up measures in two or more MS should be recorded in the system. The system should not be used for the exchange of less urgent information or for alerts requiring consideration only at national level. To be encoded in the RATC system, an alert should fulfill the following criteria:

- coverage/extent: in two or more MS;
- risk: a known risk to patients, or potential patients
- severity: issues (quality and safety defects, illegal and fraudulent activities, notifications from other sectors, outbreaks of communicable diseases) of a serious or potentially serious nature
- public health implications: wider public health implications.

All users of the RATC system are responsible to ensure business continuity, therefore each CA should have at least one back-up for the main user of the RATC system. Each CA should have a written procedure for the issue, receipt and handling of notifications of defective products, batch recalls and other rapid alerts. As host, the EC services also have several operators to ensure permanent operability of the system.

Where the EC receives a request from a third country or third party (ECDC/WHO etc.) to issue an alert on its behalf, it disseminates the information provided via the RATC platform. This dissemination by the EC does not imply any assumption of responsibility for the information transmitted, which remains with the notifying body.

All exchanges of information within the RATC system are strictly confidential and must not be disclosed outside the secured network, e.g. to patients, other tissue establishments than those involved in the alert, manufacturers, media, third persons or the public.

Where an issuing or receiving CA has a working relationship with an independent organisation for evaluating and acting on information received it must ensure confidentiality is maintained at all times, and that the provisions of Directive 95/45/EC as implemented at national level are respected concerning the processing of personal data. A disclaimer highlighting the users' responsibility when filling out the content of an alert or attaching documents is included in the RATC system.

The EC also ensures the proper functioning of the system and prepares and regularly updates the standard operating procedures and guidelines concerning the management of RATC by the EC and the MS, therefore the classification of the alerts as described below may be updated/revised as appropriate.

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RAPID ALERTS RELATED TO QUALITY AND/OR SAFETY DEFECTS (QSD)

Definition: Rapid alerts related to quality and/or safety defects of specific tissues/cells intended for human application (QSD) should be understood as alerts requiring field corrective actions, e.g. recall, quarantine, discard of the concerned human tissues/cells potentially impacting patient safety in other MS.

The CA of the MS in which the QSD was reported should issue the RATC notification to the MS and the EC.

Examples:

- recall of products because of inappropriate sterilisation
- recall/quarantine of products because the donor was diagnosed/suspected at a later stage of having had a malignant/infectious disease.

RAPID ALERTS RELATED TO ILLEGAL AND FRAUDULENT ACTIVITIES IN THE FIELD OF TISSUES AND CELLS INTENDED FOR HUMAN APPLICATION (IFA)

Definition: IFA are defined as alerts used to notify MS and the EC of the possible presence in the distribution network of tissues or cells resulting from illegal and fraudulent activities in the procurement, testing, processing, packaging, distribution, labelling, import/export or promotion of human tissues or cells.

The CA of the MS in which the fraud was first detected should issue the RATC notification to the MS and the EC.

Example:

- detection of a counterfeit authorisation certificate for the processing and storage of a particular type of tissues or cells.

EPIDEMIOLOGICAL NOTICES (EN)

Definition: EN are rapid alerts related to the development of significant epidemiological situations (e.g. disease outbreaks) which may have cross-border implications in the field of tissues and cells intended for human application.

A disease outbreak is defined by WHO (http://www.who.int/topics/disease_outbreaks/en/) as:

- The occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season. An outbreak may occur in a restricted geographical area, or may extend over several countries. It may last for a few days or weeks, or for several years.

or

- A single case of a communicable disease long absent from a population, or caused by an agent (e.g. bacterium or virus) not previously recognised in that community or area, or the emergence of a previously unknown disease, may also constitute an outbreak and should be reported and investigated.

The CA of the MS in which the disease outbreak was first reported should issue the RATC notification to the MS and EC. Such alerts should be regularly updated by the initiator regarding the progress of the situation (e.g. number of suspected cases, affected patients, deceased patients, preventive/corrective measures implemented/foreseen, recommendations, etc.) until the outbreak/EA is closed.

From the point of view of the follow-up of an EA, they can be classified in:

- EN requiring preventive actions – should be sent to all MS
- EN requiring corrective actions – can be sent to all MS (for both information and corrective measures as appropriate) or only to the affected MS (following inquiries or based on information received from ECDC or other international bodies).

Examples

- West Nile Virus alert in Italy, Greece and Romania
- Q fever alert in the Netherlands.

INFORMATION NOTICES (IN)

Definition: IN are formal notifications by a CA regarding the field corrective actions initiated and performed by other healthcare sectors (e.g. medical devices, blood and blood products, medicinal products, organs) which are of significance to the tissues & cells sector.

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Example:

- notifications from a medical device manufacturer regarding the recall of unused products because of errors in manufacturing.

INQUIRIES

Inquiries should be seen as a rapid means of bilateral communication between the CAs of two MS related to any type of alert (QSD, IFA, EA, IN) to be used in particular situations, e.g.:

- the need to substantiate/confirm information related to a potential rapid alert before the official submission in the RATC system
- any other situation which is deemed appropriate for such an alert.

At a later stage, an inquiry can be either closed or converted into another type of alert (QSD, IFA, EA).

Where relevant, after consultation with the coordinating CA, the EC should inform its counterparts outside the EU of the alert, where the information has direct and/or immediate implications for their health services. Examples of when regulators outside of the EU should be informed include SARE involving tissues or cells imported from or exported to that country, SARs involving new or emerging infectious diseases with potential global spread, or SAEs due to a defect in a commonly used device or piece of equipment. This should be performed by sending a summary of the information.

VIGILANCE COMMUNICATION AND THE GENERAL PUBLIC

The general public is entitled to be informed about the risks associated with donation, transplantation and assisted reproduction and the quality of the services provided should be open to scrutiny. Consolidated vigilance reports provide a unique and important parameter for allowing potential donors and recipients to evaluate risk and should be communicated in a comprehensible and easily accessible manner. However, CAs and professionals in the field should manage communication with the media, as far as possible, so that rare negative outcomes are not presented in a sensational manner, without the required information relating to numbers of procedures carried out and numbers of tissues or cells transplanted with positive results. This balance is essential to ensuring the continued support of the public for donation of tissues and cells. CAs for tissues and cells should limit communication with the media to personnel who are specifically responsible and trained for that activity.

CHAPTER 8: ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS TO THE EUROPEAN COMMISSION

LEGISLATIVE REQUIREMENTS

According to Article 7.1 of Directive 2006/86/EC Member States (MS) shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events received by the competent authorities for tissues and cells. The Commission shall submit to the competent authorities of MS a summary of the reports received. The competent authority shall make this report available to tissue establishments. An annex to that Directive provides the minimum data that should be included in the annual reports for SARs and SAEs.

THE COMMON APPROACH DOCUMENT

The European Commission has developed an electronic reporting tool to facilitate the submission of SARE annual reports by CAs. This tool is supported by a guidance document which specifies how each field in the report is to be filled. The guidance document is referred to as the Common Approach Document.

Annual reports must include numbers and types of SAR and SAE for each tissue and cell types but also, where available, total numbers of tissues and cells distributed, numbers of recipients for each type of tissue or cell and numbers of tissues or cells processed. These activity data provide denominators to allow SARE frequency to be estimated. Not all MS can currently provide all of the requested data but each year the reporting is more complete.

For the purposes of the Annual Report, the following units should be provided for tissues and cells distributed or processed:

One (1) unit equals to:

Skeletal Tissues: One individually packaged graft (e.g. one femoral head, one unit of demineralised bone, one container of bone chips, one femoral strut, one osteochondral allograft, one individually packaged tendon or part of a tendon)

Haematopoietic Stem Cells: One single bag or container of cells

Ocular Tissues: One individually packaged or contained graft (e.g. one cornea, one piece of sclera)

Cardiovascular Tissues: One individually packaged or contained graft (e.g. one valve, one package containing one or more lengths of vessel)

Skin: One container of skin, regardless of the area of skin it contains

Amniotic Membrane One container of tissue, regardless of the area of tissue it contains.

Sperm: One individual straw, the contents of which will be used together in one laboratory process or clinical application

Embryo: One individual embryo

Oocyte: one individual oocyte.

The total number of recipients for one type tissues and cells (number of recipients affected) should be understood to mean the total number of patients who had at least one unit of tissues or cells applied during the year concerned in a given country, regardless of whether they had a reaction or not. In the context of ART, this means the number of patients who have been inseminated with sperm or have had an embryo transfer.

The number of tissues and cells distributed should be understood as 'the total number transported or delivered to a clinical unit, even if the clinical unit is in the same building or the same floor'. The number should not include tissues or cells sent to another TE for distribution or tissues or cells that were subsequently returned to the distributing TE.

The total number of tissues or cells processed includes all of those prepared at Tes, whether distributed or not.

The Common Approach document specifies that SARs should be included in the Annual Report only when their investigation has been completed; only when they are serious (see Severity scale in Chapter 3 for Non-ART tissues and cells and in Appendix 4 for ART) and only when imputability is possible, likely or certain (see Severity scale in Chapter 3 for Non-ART tissues and cells and in Appendix 4 for ART).

SARs are categorised in two main groups in the Annual Report:

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A. Disease transmission:

- bacterial infections
- viral infections
- parasitic infections
- malignant disease
- other disease transmission (e.g. prion, immunological and genetic disease transmissions).

B. Other Adverse Reactions: for non-reproductive tissues and cells these could include allergic reactions, cardiovascular reactions, pulmonary reactions, renal complications, neurological reactions, toxicity or any other type of adverse outcome in a recipient. For reproductive tissues and cells there is no drop-down list but a field for free text entry.

It is noted that many CA collate information on donor adverse reactions not influencing the quality and safety of tissues and cells. These reactions fall outside the scope of the tissues and cells Directives (see Chapter 5) and should be reported elsewhere as appropriate (e.g. to pharmacovigilance systems). They include:

- Ovarian Hyper-Stimulation Syndrome (OHSS) in oocyte donors (partner or non-partner)
- reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection
- reactions which result in harm to the donor (i.e. cardiac or neurological episodes).

Although these reactions fall outside the scope of the legislation, the EC recognises the value of these data in the context of tissue and cells regulation, and invites MS to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template. The declared data are not calculated as part of the total number of SARs.

SAEs are to be included in the Annual Report only when the following criteria apply:

Non-ART tissues and cells:

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

Reproductive T&C:

1. inappropriate gametes, embryos or germinal tissues have been released for clinical use, even if not used
2. the event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors
3. the event resulted in a mix-up of gametes or embryos
4. the event resulted in a loss of traceability of gametes or embryos
5. the event resulted in contamination or cross contamination of gametes or embryos
6. accidental loss of gametes, embryos, germinal tissues (e.g. break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle.

In line with Annex V, part B of Directive 2006/86/EC, SAEs must be categorised as follows:

1) Tissues and cells defect

This should be understood as a defect in the quality or safety of the tissues and cells due to an inherent unpredictable safety or quality deficit, e.g. a defect due to an undiagnosed illness or genetic factor or an unknown exposure to a toxic agent.

Examples:

- Sporadic CJD diagnosed and reported in a living femoral head donor several years after procurement.
- Significant loss (80%) of stem cells in an allogeneic bone marrow graft following freezing/thawing (viability and CD34+ measured). Graft infused (no other option).
- Genetic condition discovered in a sperm donor years after he donated sperm.

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2) **Equipment failure**

This should be understood as a defect in the quality or safety of the tissues or cells due to a fault in critical equipment used in procurement, processing, storage or distribution.

Examples:

- 150 heart valves thawed due to simultaneous failure of liquid nitrogen automatic filling system and alarm system.
- Embryos lost due to incubator breakdown.

3) **Human error**

This should be understood as a defect in the quality or safety of the tissues or cells due to an error by a member of personnel during procurement, processing, storage or distribution.

Examples:

- Cardiac valve distributed for surgery; mis-sized rendering it unusable.
- Embryos were mistakenly transferred into a Petri dish (unused) labeled for another couple. The error was detected (following distribution) but prior to embryo transfer.
- A frozen femoral head is held by a courier company for 72 hours in a holding depot rather than being delivered immediately (Courier company used by many TEs in the country).

4) **Other:** this should be understood as a defect in the quality or safety of the tissues or cells due to any other cause during procurement, processing, storage or distribution.

Example:

- Air company/Pilot refused to accept cells in liquid nitrogen on board.

ANNUAL REPORT FEEDBACK TO STAKEHOLDERS

Up to 2011, the SARE annual reporting exercise has been carried out and has revealed valuable data regarding adverse reactions and events reported. However, the process has been challenged by different interpretations of terms and by an unavailability of denominator data (numbers of tissue or cells distributed or number of recipients) in many MS. For this reason, the aggregated data has been presented by the Commission to CA meetings but not disseminated beyond CAs as it was not considered to be adequately robust. The guidance revision in 2012 was more extensive and from 2012 onwards (2011 data) the aggregated summary of the MS reports will disseminated, beyond CAs, in summary form. Once those reports are received by CAs, they should be shared with professionals in the field to increase knowledge and to promote participation in reporting generally.

CHAPTER 9: ILLEGAL AND FRAUDULENT ACTIVITY – SUMMARY OF WP6 RECOMMENDATIONS

INTRODUCTION AND BACKGROUND

Work package 6 of the SOHO V&S project developed recommendations and tools for Competent Authorities to support the detection and investigation of illegal and fraudulent activity in tissue and cell procurement and banking. The full guidance document has been provided to EU Competent Authorities for Tissues and Cells. This chapter summarises the conclusions.

Combating trafficking in human organs and tissues is challenging. In a 1998 report on human tissue transplantation crime,¹⁵ its authors stated that *'illegality arising from the transplantation of human tissue exists primarily because of an international shortage of donors able to provide tissue suitable for use in recipients'*. A report on organ trafficking from the United Nations Economic and Social Council¹⁶ indicated that *'some Member States do not have the resources and capacity to respond adequately to the problem ..., because awareness, law enforcement resources, judicial expertise and cooperation between national and international law enforcement agencies are insufficient or lacking. Effective law enforcement efforts and international cooperation are necessary'*.

OBJECTIVES

Work package 6 has as its primary aim the preparation of a guidance document that outlines the key issues related to suspected IFA in the area of tissues and cells. Drawing upon the experience and findings both within the European Union and in third countries, the document aims to assist Competent Authorities in detecting/identifying, investigating, managing and communicating such activity.

METHODOLOGY

In order to meet the objectives of WP6, its working group (AFSSAPS, CNT, HTA, IMB, KCBTiK) assessed the level of IFA across the Member States (MS) and the experiences and approaches of the Competent Authorities in this field. A questionnaire was prepared and submitted to EU competent authorities for tissues and cells as well as to several other partners. The scope of the questionnaire was that of Directive 2004/23/EC on tissues and cells used in transplantation and assisted reproduction. It addressed the legislation in place at individual MS level, the requirements in place at the level of the CA in relation to suspected IFA of tissues and cells, and any experience with IFA in this area.

The questionnaire results were analysed by the group and a series of principles and tools for detection and investigation were developed. The group also drew on its experience and on information and advice from enforcement expertise in other related fields. The draft guidance was circulated to EU Competent Authorities for comment before finalisation.

IFA QUESTIONNAIRE RESULTS

The WP6 survey questionnaire on IFA elicited 30 responses from 22 EU MS, three European non-EU countries and one non-European country.¹⁷ In addition, responses were received from two non-European countries¹⁸ on a modified WP6 questionnaire that had been sent to participants attending the September 2010 meeting in Paris of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S).

The analysis of the questionnaire responses regarding the situation in the EU and in third countries led the WP6 members to agree that there is significant diversity throughout the EU with respect to the management of suspected IFA in the context of tissues and cells. They noted that although inspectors and enforcement officers have identified authority, there is a lack of specific training dealing with how to identify and handle cases of suspected IFA related to T&C. Although the majority of reported IFAs occurred during the procurement phase they could take place at any

¹⁵ No.87 *Human tissue transplantation crime*. Elizabeth King and Russell G. Smith. B. Trends & issues in crime and criminal justice. May 1998.

¹⁶ *Preventing, combating and punishing trafficking in human organs*. Report of the Secretary-General: United Nations Economic and Social Council. 21 February 2006. CN.15/2006/10.

¹⁷ Belgium, Cyprus, Czech Republic, Denmark, Germany, Estonia, Spain, Finland, France, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Sweden, United Kingdom. Croatia, Iceland, Liechtenstein, USA.

¹⁸ Australia, Singapore

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stage, including during processing and distribution. Competent Authorities noted that the apparent lack of standard operating procedures (SOPs) for the management of IFAs within a CA's quality management system made it difficult to handle such alleged cases when they arose. In addition, the WP6 Members identified the need for definitions of the terms 'illegal' and 'fraudulent'. The issues raised in the questionnaire responses formed the basis of discussions in the working group and provided the outline for the development of guidance on how to detect IFA.

RECOMMENDATIONS

The following recommendations aim to assist Competent Authorities in developing and implementing SOP's in their quality management system or updating National/Regional legislation or regulation regarding IFA :

1. A *risk-based* inspection programme, which prioritises inspections of establishments with the greatest risk, may help competent authorities to identify IFA.
2. Competent Authorities should draw up specific SOPs for dealing with suspected IFA in their Quality System.
3. A specific training programme on the identification and management of suspected IFA should be developed for inspectors and enforcement officers and be integrated by CAs into national training programmes. Inspectors/enforcement officers should be trained in the relevant law, procedure and the proportionate use of powers conferred upon them.
4. The Competent Authority should ensure that only appropriately trained individuals communicate with the media regarding specific IFA cases or IFA in tissues and cells in general. Inspectors or enforcement officers should not communicate with, or be interviewed by, the media regarding a case that is under investigation or prosecution.
5. The severity of a suspected illegal or fraudulent activity should be assessed by a series of criticality criteria ranging from the risk to quality and safety to the extent of international involvement.
6. The Competent Authority must take into account the result of any ongoing risk assessment and risk management and the elements of a specific case, such as the danger to public health and the extent and severity of the infringement, when considering the course of action.
7. The Competent Authority should also be aware of the legal jurisdiction in which the tissue establishment is located in order to avoid delays and increase the likelihood of a successful prosecution by proceeding in compliance with the correct legal procedures for that jurisdiction.
8. In order to combat the threat of IFA, a coordinated effort of a diverse group of stakeholders will be required. To be effective, national, regional as well as international efforts need to be strengthened. Medical and paramedical services need to be made aware of these issues and law enforcement agencies should to be engaged.
9. The CA should collaborate with other law enforcement and regulatory bodies to bring joint prosecutions in order to avoid any disqualification of the IFA case. For coordination of the management of the suspected IFA, clearly defined roles and adequate resources should be established.
10. Co-operation should be established between regulatory authorities especially with respect to the detection of alleged IFA linked to the import and export of tissues and cells and to distribution between European Union MS.
11. Collaboration with the European Commission, the Council of Europe, WHO as well as national and international law enforcement agencies, such as Interpol and Europol, are indispensable where IFA is detected or suspected at an international level or with the potential to have international consequences.
12. A single contact point should be established in each CA to facilitate the exchange of information about IFA cases.
13. A systematic procedure should be implemented to assist the Competent Authority in determining whether to submit a suspected CFA to the Court. This procedure should evaluate the strength of evidence and the severity and impact to public health of the case under consideration. These procedures, in conformity with the jurisdictional process, should facilitate a successful legal outcome. In some jurisdictions, when an alleged criminal case has been dismissed by the court, the regulatory (administrative) sanctions previously imposed by the Competent Authority might also be overturned.

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14. Competent Authorities need to recognise the potential negative impact of suspected IFA not only on the availability and safety of tissues and cells but also on public confidence and willingness to donate.

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ACKNOWLEDGEMENTS

SOHO V&S WORK PACKAGE 7 WORKING GROUP

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The following individuals attended focus group meetings in the UK, Germany and Spain to provide in-depth comments on a draft version of this document.

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American Association of Tissue Banks

Danish Medicines Agency

World Marrow Donors Association

Agenzia Italiana del Farmaco

Centro Nazionale per i Trapianti

Donor Action Foundation

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Executive Agency of Transplantation (EAT)

Centro operativo adempimenti legge 40/registro nazionale PMA (PMA)

World Health Organisation (WHO)

Danish Medicines Agency (DMA)

Inspectie voor de Gezondheidszorg Toezichtende Geneesmiddelen en Medische Technologie (IGZ)

Federal Ministry of Health (Austria)

United States Food and Drug Administration (FDA)

Blood Safety Surveillance and Health Care Acquired Infections Division, Centre for Communicable Disease and Infection Control, Public Health Agency of Canada (PHAC)

Tissue and Cell Inspectorate Cyprus (Cyprus)

Slovenia-transplant (Slovenia)

Transfusion Reactions in Patients (TRIP)

Office of Blood, Organ and other Tissue Safety, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (CDC)

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European Association of Tissue Banks (EATB)

American Association of Tissue Banks (AATB)

European Society for Human Reproduction and Embryology (ESHRE)

European Eye Banking Association (EEBA)

European Society for Bone Marrow Transplantation (EBMT)

UK Public Health Agency (PHA)

International Haemovigilance Network (IHN)

Ministry of Health, Malta (Malta)

American Association of Blood Banks

World Marrow Donor Association

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APPENDIX 2: EUSTITE IMPACT ASSESSMENT TOOL

The Impact Assessment tool assists practitioners and regulators in planning their response to a given adverse reaction or event, taking into account broad consequences, beyond the individual patient affected or potentially affected. The assessment should be based on available data, past experience and scientific expertise.

STEP 1: ASSESSING LIKELIHOOD OF OCCURRENCE/RECURRENCE OF SARE

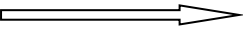

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to happen again
3	Possible	May occur occasionally
4	Likely	Expected to happen again but not persistent
5	Probable	Expected to happen again on many occasions

STEP 2: ASSESSING IMPACT /CONSEQUENCES OF A SARE SHOULD IT RECUR

Impact Level		On individual(s)		On System		On Tissue/Cell Supply
0	Insignificant	Nil	OR	No affect	OR	Insignificant
1	Minor	Non-serious	OR	Minor damage	OR	Some applications postponed
2	Moderate	Serious	OR	Damage for short period	OR	Many cancellations or postponements
3	Major	Life-threatening	OR	Major damage to system - significant delay to repair	OR	Significant cancellations - importation required
4	Catastrophic/extreme	Death	OR	System destroyed - need to rebuild	OR	All allogeneic applications cancelled

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STEP 3: APPLYING THE IMPACT MATRIX

Likelihood of recurrence 	1 Rare	2 Unlikely	3 Possible	4 Likely	5 Certain /Almost Certain
Impact of recurrence 					
0 Insignificant	0	0	0	0	0
1 Minor	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Major	3	6	9	12	15
4 Catastrophic /Extreme	4	8	12	16	20

Step 4:

The response of a tissue or cell bank or a health authority to a specific SAE/SAR should be proportionate to the potential impact as assessed by the matrix described.

White: The tissue or cell bank to manage the corrective and preventive actions and the health authority to file the report and keep a 'watching brief'.

Pale grey: Requires interaction between the tissue or cell bank and the health authority which may request an inspection that focuses on the SAE/SAR and corrective and preventive actions to be followed up, including evidence of effective recall, where necessary. Written communication to professionals working in the field might be appropriate.

Dark grey: Health authority will generally designate representatives to participate in developing or approving the corrective and preventive action plan, possibly a task force to address broader implications. Inspection, follow up and written communication as previously and possibly notification of health authorities in other countries where relevant.

The effectiveness of the response can be assessed by re-applying the impact matrix following the implementation of the corrective and preventive actions. The impact can be reduced by:

- reducing the probability of recurrence through preventive measures
- increasing the detectability of the risk, or
- reducing the severity of the consequences, if it should recur.

APPENDIX 3: GLOSSARY OF TERMS AND ABBREVIATIONS

GLOSSARY

2PN: 2 pronucleus stage (2 PN): A two-pronuclear zygote (2PN); stage after the sperm has entered the ovum but in which the female and male pronuclei have not yet fused.

Advanced Therapy Medicinal Products (ATMPs): A medicinal product which is either a gene therapy medicinal product, a somatic cell therapy medicinal product, a tissue engineered product, or a combined advanced therapy medicinal product (which are ATMPs incorporating cells and medical devices/active, implantable medical devices).

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

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

Apheresis: Medical technique in which peripheral blood of a donor or patient is passed through an apparatus that separates out one particular constituent.

Assisted reproductive technology: Methods used to achieve pregnancy by artificial or partially artificial means. This includes, but is not limited to, in vitro fertilisation, intra-cytoplasm sperm injection, cryopreservation and intrauterine insemination.

Audit: Documented review of procedures, records, personnel functions, equipment, materials, facilities, and/or vendors in order to evaluate adherence to written SOPs, standards, or government laws and regulations, conducted by professional peers, internal quality system auditors or certification body auditors.

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

Batch: A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogenous.

Best practice: A method or technique that has consistently shown results superior to those achieved with other means, and that is used as a benchmark.

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

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

Complications of procurement: Complications associated with the procurement of reproductive tissues or cells such as haemorrhage, infection, etc.

Cord blood bank: A specific type of tissue establishment where haematopoietic progenitor cells collected from the placental and umbilical cord blood vessels are processed, cryopreserved and/or stored. It may also be responsible for procurement, testing or distribution.

Critical: Potentially having an effect on the quality and/or safety of or having direct contact with the cells and tissues.

Cross border reproductive care (CBRC): Refers to the movement of patients within the EU Member States or to neighbouring non EU-countries to seek ART treatment outside their country of residence.

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

Deviation: Departure from an approved instruction or established standard.

Direct use: Any procedure where cells are donated and used without any banking. This term is not applicable to reproductive cells and tissues that are being processed, cultured, banked or stored.

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

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

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

Embryo: Pre-implantation, reproductive tissue resulting from the combination of oocyte and sperm.

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

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Final Product: Any tissue or cell preparation intended to be transplanted or administered after the final release step.

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

Gamete: Mature human germ cell, whether oocyte or sperm.

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

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

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

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.

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

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

Incident reporting (Adverse event reporting, serious/critical incident reporting): A system in a health care organisation for collecting, reporting and documenting adverse occurrences impacting on patients that is inconsistent with planned care. *e.g.* medication errors, equipment failures, violations.

In vitro fertilisation: A procedure by which an embryo is created in a laboratory using male and female gametes.

Medicinal product: Any substance or combination of substances presented as having properties for treating or preventing disease in human beings, or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Mix-up: In the context of ART, is a serious adverse event (SAE) resulting from an error in the attribution of gametes or embryos that can occur at any stage of the laboratory or clinical process of assisted reproduction.

Non-conformity: Refusal or failure to conform to accepted standards, conventions, rules, or laws.

Non-conventional infectious agents: A distinctive, transmissible agent that, although having some properties in common with viruses, does not fit the classic definition of a virus.

Non-partner donation: In the context of ART, means that the donor is another person apart from the couple.

Partner donation: Donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship.

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

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

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

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

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

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

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

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

Recovery or Retrieval: See Procurement.

Reproductive cells: Means cells intended to be used for the purpose of assisted reproduction.

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

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

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

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

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

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

Surrogacy: A woman carries a pregnancy for another individual or couple (surrogacy can be full or partial).

Surveillance: The systematic on-going collection, collation and analysis of data for public health purposes and the timely dissemination of this information for assessment and public health response as necessary.

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 or assisted reproduction.

Third country: Any country that is not a Member State of the European Union.

Third party: Any organisation that provides a service to a procurement organisation or a tissue establishment on the basis of a contract or written agreement.

Tissue: An aggregate of cells joined together by, for example, connective structures and performing a particular function.

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

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

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

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

Trafficking: The recruitment, transport, transfer, harbouring or receipt of living or deceased persons or their cells, tissues or organs, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving to or receiving by, a third party of payments or benefits to achieve the transfer of control over the potential donor, for the purpose of exploitation by the removal of cells, tissues and organs for transplantation.

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

Validation: Establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

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

ABBREVIATIONS

2PN	2 pronucleus stage
ADCA	Autosomal dominant cerebellar ataxia
AE	Adverse Event
AMH	Anti-Mullerian hormone
ART	Assisted reproductive technologies
ATMP	Advanced Therapy Medicinal Product
CA	Competent authority (authorities)
CE	Conformité Européenne or European Conformity marking
DVT	Deep vein thrombosis
ECDC	European Centre for Disease Control
EUROCET	European Registry for Organs, Tissues and Cells
EUSTITE	European Union Standards and Training in the Inspection of Tissue Establishments (EU-funded project)
GIFT	Gamete Intra-fallopian Transfer
GnRH	Gonadotropin-releasing hormone
GVHD	Graft versus Host Disease
hCG	Human chorionic gonadotropin
HFEA	Human Fertilisation and Embryology Authority (UK)
HIV	Human immunodeficiency virus
HPC	Haematopoietic Progenitor Cell
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In-vitro fertilization
LH	Luteinizing hormone
MS	Member State(s)
NA	Not assessable
NAT	Nucleic acid Amplification Techniques
NRA	National rapid alert
OPO	Organ Procurement Organisation
ORHA	Organisations responsible for human application of tissues and cells
PBSC	Peripheral Blood Stem Cell
PGD	Preimplantation genetic diagnosis
PO	Procurement organisation

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RATC	Rapid alert tissues cells (EU system)
RCA	Root cause analysis
SAE	Serious adverse event
SAR	Serious adverse reaction
SARE	Combination of SAE and SAR
SNC	Severe congenital neutropenia
SOHO	Substances of Human Origin
SOP	Standard Operating Procedure
TACO	Transfusion related circular overload
TE	Tissue establishment
TRALI	Transfusion related acute lung injury
V&S	Vigilance and surveillance

APPENDIX 4: DELIVERABLE 5 - VIGILANCE IN ART - FULL TEXT

1. INTRODUCTION

This guidance provides recommendations and tools for vigilance and surveillance in the field of assisted reproductive technologies (ART), in the framework of:

- Directive 2004/23/EC¹⁹ of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells,
- Directive 2006/17/EC²⁰ of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells,
- Directive 2006/86/EC²¹ of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

This guidance includes Serious Adverse Reactions and Events (SARE) reporting tools adapted to the field of ART, a proposed list of items that National reporting forms should contain, a classification and examples of SARE in the field of ART and a glossary.

2. BACKGROUND

This guidance was developed in the framework of the European Union funded project 'Vigilance and Surveillance of Substances of Human Origin' (SOHO V&S project²²) which followed on from the vigilance pilot of the EUSTITE project²³.

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 tissues and cells for human application, were developed as part of the EUSTITE project. These tools were tested during a pilot scheme involving Competent Authorities from Member States across the European Economic Area (EEA).

At the completion of the project, it was highlighted that further work should be performed to adapt these tools in the field of ART, given its specificities compared to other tissues and cells. Several recommendations²⁴ were drawn from the Pilot and some specifically addressed the field of Assisted Reproductive Technologies:

- V&S tools as designed by the EUSTITE project should be reviewed and adapted more specifically for the field of assisted reproduction.
- The issue of vigilance in donors needed to be addressed. The directive requires the reporting of SARs 'which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any Serious Adverse Reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells'. Yet, SARs occur in donors without any influence on the quality and safety of tissues and cells (*e.g.* intraperitoneal infection after aspiration).
- Common definitions for SARE and common tissue and cell nomenclature had to be agreed.
- A standardised EU template for the reporting of SARE to the CAs would facilitate the comparison of the data.

¹⁹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF>

²⁰ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF>

²¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF>

²² www.sohovs.org

²³ European Union Standards and Training for the Inspection of Tissue Establishments, www.eustite.org

²⁴ EUSTITE deliverable 11

Consequently, Work Package 5 of the SOHO project was specifically dedicated to vigilance and surveillance in Assisted Reproductive Technologies. It aimed at:

- Identifying the specific issues related to V&S;
- Adapting the EUSTITE tools to the field of vigilance and surveillance of assisted reproduction;
- Drawing recommendations for the reporting of Serious Adverse Reactions and Events, with the final aim of developing a Guidance on Vigilance and Surveillance in Assisted Reproductive Technologies in the European Union.

3. METHODOLOGY

An Exploratory Workshop was held in June 2010 and was followed by a series of three working group meetings from October 2010 to March 2011 to draft the guidance.

The SOHO exploratory workshop followed on from the vigilance pilot of the EUSTITE project and aimed at identifying the specific issues relating to V&S in Assisted Reproduction, by applying the tools and recommendations developed during the EUSTITE project to ART cases. Specific SARE issues and relevant literature in the ART field were reviewed and feedback was gathered from the EUSTITE project on the reporting and evaluation of SARE in this field.

The first drafting meeting allowed for more detailed discussion on the specific issues of ART and a first adaptation of the vigilance reporting tools for ART was proposed. Then all participants agreed to contribute to the writing of the discussion papers and prepared them individually or in groups, each one focusing on a given ART specificity or on the ART tools.

The discussion papers were written according to a common template. They were presented and commented on during the second and third drafting meetings. Special attention was given to limit the scope to vigilance and surveillance, while following good practices within quality systems. For each ART characteristic, recommendations were drawn up and discussed during the last drafting meeting.

The exploratory workshop was attended by both Health Professionals and Competent Authorities, with significant representation from the major professional society in the field in Europe, ESHRE (the European Society for Human Reproduction and Embryology) and a smaller group attended the drafting meetings in order to facilitate the drafting work.

Decisions on the recommendations were reached by consensus. A consensus was reached among all the participants for all the recommendations but one. There was a lack of consensus on the meaning of 'hospitalisation' as used in the SARs severity grading tool (see Chapter 7.1).

Another work package (WP 4²⁵) of the SOHO V&S project gathered detailed information on the vigilance systems in place in the Member States (MS) for tissues and cells and for Assisted Reproduction. Part of the information collected in WP 4 was used in this document.

4. SCOPE

This guidance covers:

- Terminology and definitions used in the Tissues and Cells (T&C) directives as understood in the context of ART;
- Reporting recommendations for SARs and SAEs related to ART;
- Reporting and assessment tools adapted to ART vigilance.

Good practices and management of quality in ART are outside the scope of this guidance.

This guidance is addressed to competent authorities (CAs) for vigilance and surveillance (V&S) in ART or to T&C CAs in charge of ART in countries where no CA specifically dedicated to ART exists⁷.

²⁵ Vigilance and Surveillance of Substances of Human Origin, Survey of European Vigilance & Surveillance Systems (SOHO V&S, Work Package 4)

5. CHARACTERISTICS OF ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

Specific characteristics of ART on which the attention should be focused in terms of vigilance were identified in order to highlight SARE that might occur. Examples of ART SARE collected during the EUSTITE Pilot project are given in Annex 4.

Reproductive cells or embryos are different from other cells (*e.g.* stem cells, chondrocytes) in the following ways:

- Oocytes and embryos are available in very limited numbers;
- Reproductive cells are particularly sensitive to external factors (culture media, laboratory equipment, pollutants, etc.);
- Any defect may have an impact not only on the recipient of the cells but also on one or more other individuals (*e.g.* twins);
- Adverse outcomes are generally associated with a loss of gametes or embryos, and subsequent loss of chance of pregnancy, rather than with failure to cure an illness or disability or with the transmission of an infectious or malignant disease.

The specific aspects of ART detailed in this guidance are:

- Sensitivity of gametes and embryos, impact of culture media and equipment;
- Traceability;
- Mix-ups;
- Complications of procurement;
- Cross-border management of SARE.

IMPORTANT: in this Guidance, the term 'embryo' includes the zygote (a 2-pronucleus stage, 2PN) although it is acknowledged that some MS differentiate, from a legal perspective, between zygotes and embryos.

5.1. ART VIGILANCE

5.1.1. Overview of ART vigilance systems in the EU

A survey was carried out in July 2010 as part of Work Package 4⁷ (WP4) of the SOHO V&S project. It was completed by 32 countries, including the 27 MS, and aimed at gathering detailed information on systems in place for V&S in the fields of tissues and cells for transplant and for ART vigilance.

ART vigilance in the EU can be considered generally as a “new” regulatory activity. The WP 4 survey showed that, although more than 80% of the MS have a system in place for ART vigilance, their system is quite recent (average of 3 years).

5.1.2. Reporting to vigilance programmes

An efficient vigilance system relies on the involvement of all stakeholders. Reporting should be promoted and can be encouraged by systems that are non-punitive, open, transparent and disconnected from inspection. In return, CAs should provide regular feedback to stakeholders, contributing to practice improvement by sharing and learning. Finally, there is a need for coordination with other vigilance systems in place.

⁷ Vigilance and Surveillance of Substances of Human Origin, Survey of European Vigilance & Surveillance Systems (Work Package 4).

5.2. TERMINOLOGY

5.2.1. Assisted reproductive technologies (ART)

Assisted Reproductive Technologies (ART) can be defined as all treatments including handling of human gametes (oocytes and sperm), embryos and reproductive tissues to establish a pregnancy or to preserve fertility for the future – often called MAR (Medically Assisted Reproduction). It also includes the cryopreservation of gametes, embryos or germinal tissues for preservation of fertility.

5.2.2. Vocabulary

During the EUSTITE project²³, it was acknowledged that the vocabulary should be adapted to the field of ART since the terms used in Directive 2004/23/EC are more appropriate for other tissues and cells. In this regard, the European Society of Human Reproduction and Embryology (ESHRE) published a position paper²⁶.

As far as ART is concerned, the terminology used in the Directive should be understood as follows:

Donor

In the Directive the term ‘donor’ means ‘every human source whether living or deceased, of human cells or tissues’.

In the ART context, it covers three different situations:

- i) **Partner donation** in the Directive means ‘the donation of reproductive cells between a man and a woman who declare to have an intimate physical relationship’.

In the ART context, in a couple, man and woman are considered donors to each other⁸.

- ii) **Non-partner donation** means that the donor is another person apart from the couple.

- iii) **Surrogacy** (not defined in the Directive) means a woman who carries a pregnancy for another individual or couple (full or partial surrogacy).

Tissue establishment (TE)

The definition in article 8 of the Directive 2004/23/EC applies: ‘tissue establishment’ means ‘a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;’

In the field of ART, TE applies to establishments performing ART activities, *e.g.* ART centres, ART laboratories, sperm banks, etc.

Direct use (Art. 1 of the Directive 2006/17/EC)

In the Directive, the term is defined as ‘any procedure where cells are donated and used without any banking’.

This term is not applicable to reproductive cells and tissues that are being processed, cultured, banked or stored²⁷⁸.

Autologous

²⁶ ESHRE Position paper on the EU Tissues and Cells Directive EC/2004/23, November 2007.

The terms ‘autologous donors’ and ‘autologous use’ in the Directives apply in ART to cases of preservation of fertility. Procurement of oocytes and subsequent application in the same woman (*in-vitro* fertilisation (IVF) treatments) is an example of ‘autologous donation’.

In addition to the vocabulary used in the Directive, ‘*patient*’ in this guidance relates to individuals or couples seeking treatment for infertility. It includes healthy women with an infertile male partner or without a male partner⁹.

5.2.3. Definitions of Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs)

Serious Adverse Reactions and Events (SARE) are defined in article 3 of the Directive 2004/23/EC. However, the definition of SAE does not include all Serious Events in ART that should be collected at national level and should be extended to misidentifications, mix-ups and total loss of germinal tissues, gametes and embryos for one cycle. As stated in article 6.2 (Directive 2006/86/EC), any type of gamete or embryo misidentification or mix-up shall be considered to be a Serious Adverse Event.

Likewise, the definition of SAR should be extended to the offspring in the case of non-partner donation, only for the cases of transmission of genetic diseases (for further information, see chapter 5.4.2).

Recommendations

According to the Directive 2004/23/EC:

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

‘Serious Adverse Event’ means ‘any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patient or which might result in, or prolong, hospitalisation or morbidity.’ The Directive 2006/86/EC stipulates that in the case of Assisted Reproduction, any type of gamete or embryo misidentification or mix-up shall be considered to be a serious adverse event.

To complement the Directive 2004/23/EC,

1. The definition of SAR should be extended to the offspring in the case of non-partner donation, only for cases of transmission of genetic diseases.

Hospitalisation for observation should be considered as non-serious²⁸.

2. The definition of SAE should include the total loss of germinal tissues, gametes or embryos for one cycle.

5.2.4. Nomenclature of biological products

Definitions/interpretations of terms used in Annex V, part A of Directive 2006/86/EC were proposed by the European Commission to ensure a common approach to data reporting in the CAs’ annual vigilance report to the Commission (for

⁹ Janssens P.M.W. Editorial Commentary: Rules and regulations in reproductive medicine: sensible requirements that should start with evidence, *Hum Reprod*, vol 25, 2010; 12:3055-3057.

²⁸ All participants but the Agence de la biomédecine (ABM) and the Irish Medicines Board (IMB) agree that hospitalisation, when for observation only, should be considered as ‘non-serious’. The reason is that for ART professionals, hospitalisation in ART is often for observation only, patients being discharged on the day after (if any medical treatment is required during hospitalisation then it should be classed as serious). The ABM considers that the usual definition of SAR and the one in the Directive include ‘hospitalisation’ or ‘prolongation of hospitalisation’. Moreover, hospitalisation is a usual criterion widely used to define SAR in all vigilance systems, e.g. pharmacovigilance, medical devices vigilance, etc. Therefore, it is not considered by ABM that it should be changed specifically for the purposes of ART vigilance and that if it is to be changed, a global review is necessary both at the European Commission and the World Health Organisation levels. The Irish Medicines Board (IMB) considers that, while these reports concern non-mandatory reports, for consistency, the definition of SAR in the Directive should apply. In this respect, reactions which result in or prolong hospitalisation are considered reportable by the IMB. This is also consistent with pharmacovigilance reporting.

further information see '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 (2009)').

The following description list is proposed:

- Sperm
- Oocyte
- Embryo²⁹ (for this purpose, embryo refers to any fertilised oocyte which has begun to divide, therefore blastocyst is included)
- Other Reproductive tissues and cells (*e.g.* ovarian or testicular tissue).

5.3. EQUIPMENT AND PRACTICES

5.3.1. Sensitivity of gametes and embryos, impact of culture media and equipment

Gametes and embryos present specific features with respect to their sensitivity to *in vitro* culture conditions attempting to mimic the *in vivo* environment. The handling and culturing of human embryos *in vitro* require standards to ensure safety and quality criteria are met prior to release. Moreover, handling and incubation of gametes and embryos in ART procedures have to be performed with caution in order to minimise the effect of a compromised environment.

The following factors related to environment are of primary importance with respect to gametes and embryo development:

- Temperature
- pH
- Osmolarity
- Exposure to air-borne toxic agents

• *Effects of temperature on gamete and embryo viability and quality during handling and incubation*

Temperature is a critical factor for gametes and embryos; particularly oocytes are extremely sensitive to an inappropriate temperature. Even mild cooling affects the oocyte micro tubular spindle, cortical microfilaments and the polar microtubule-organising centres. It is well demonstrated in humans as well as in animals that these alterations are temperature and time dependent and often irreversible after re-warming, risking aneuploidy of the resulting embryo^{30,31,32,33}.

In addition, temperature shifts can affect transmembrane transport and intracellular metabolic processes in gametes and embryos.

• *Effects of temperature on gamete and embryo viability and quality during freezing*

Freezing can have a negative impact on gamete and embryo survival. Sperm is less impacted by temperature fluctuations during cryopreservation due to a low cytoplasmic content and the high number of male gametes.

However, this is not the case for embryos and especially not for oocytes. Cooling can disrupt the oocyte's meiotic spindle and the formation of ice crystals and high osmotic pressure can severely damage the cell structure of the oocyte and the embryo's blastomeres. In order to reduce these risks, the method used for freezing requires accurate decrease of temperature and is related to cryoprotectant concentrations, according to the current state of the art.

²⁹ Some MS differentiate, from a legal perspective, between zygotes and embryos.

³⁰ Pickering SJ, Braude PR, Johnson MH, Cant A, Currie J. Transient cooling to room temperature can cause irreversible disruption of the meiotic spindle in the human oocyte. *Fertil Steril*, 1990, 54: 102-108.

³¹ Almeida PA, Bolton VN. The effect of temperature fluctuations on the cytoskeletal organization and chromosomal constitution of the human oocyte. *Zygote*, 1995; 3:357-365.

³² Wang WH, Meng L, Hackett RJ, Odenbourg R, Keefe DL. Limited recovery of meiotic spindles in living human oocytes after cooling-rewarming observed using polarized light microscopy. *Hum Reprod*, 2001; 16:2374-2378.

³³ Suzuki H, Kumai T, Matsuzaki M; Effect of Temperature Decline on the Cytoskeletal Organization of the Porcine Oocyte; *JMOR*, 2007; 24(3):107-113

Once frozen, adequate storage in liquid nitrogen does not have a detrimental affect on the quality of oocytes or embryos.

- *Effect of culture media pH on gamete and embryo viability and quality*

Handling, fertilization and culture of gametes and embryos take place in specific (culture) media, which require use of a special atmosphere enriched in carbon dioxide (usually 5-6% CO₂ according to the media manufacturer specifications related to the composition of media including bicarbonate buffer). However, there are certain problems with sustaining and monitoring the CO₂ gas concentration:

1. The indication on the incubators is rarely precise and the actual concentrations are often lower or higher;
2. During the openings of the incubator door, gas is lost and the internal environment of the incubator is affected; several minutes are required to recover the previous gas balance, depending on the type of incubator;
3. During handling, oocytes and embryos are subjected to normal air gas concentrations outside the incubators that very rapidly modify the pH even under mineral oil; it is well established that bicarbonate buffer reaches equilibrium rather slowly when back in the incubator³⁴.

All these factors may influence the pH of the medium and may have a deleterious impact on both the normal fertilization and embryo development^{35,36,37}. This phenomenon is well known in ART centres which therefore perform periodic monitoring of pH in the media and CO₂ levels in the incubators. Some recommend the use of a Time Lapse camera system in the incubators, which could reduce this risk.

- *Effect of culture media osmolarity on gamete and embryo viability and quality*

All media support gamete and embryo viability and development at certain osmotic ranges (usually 270 – 285 mOsm/L). Maintaining osmolarity in media requires air saturated with water vapor. Water loss from the media can lead to an increase in medium osmolarity and interfere with gamete viability and embryo development (through internal cell dehydration or osmotic shock). It has been found in animal models that early stage embryos are more tolerant to osmotic changes than blastocysts, as these are more likely to arrest at higher osmotic pressure³⁸.

Increased osmolarity can occur:

1. During preparation of culture dishes and medium handling ;
2. While handling gametes and embryos in open systems *i.e.* in medium not under oil.

In conclusion, maintaining normal osmolarity is important and can be achieved by minimising evaporation during processes (rapid dish handling, using oil whenever possible) and incubation using high relative humidity incubators when culturing in open systems.

- *Exposure to air-borne toxic agents*

Incubated cells are largely unprotected and are therefore likely to be more sensitive to certain compounds than complex organisms.

Air pollutant compounds can be potentially toxic for cultured cells, including gametes and embryos. They can be:

- Volatile organic compounds (VOC) produced by industry
- Small inorganic molecules (N₂O, SO₂, CO)
- Substances from building materials (such as aldehydes and acrolein)
- Released by pesticides or aerosols containing butane or isobutane as propellant

³⁴ Blake DA, Forsberg AS, Hillensjö T, Wikland M (1999) The practicalities of sequential blastocyst culture. Presented at ART, Science and Fiction, the Second International Alpha Congress, Copenhagen(Denmark).

³⁵ Lane M, Bavister BD. Regulation of intracellular pH in bovine oocytes and cleavage stage embryos. Mol. Reprod. Dev. 1999;54:396–401.

³⁶ Phillips KP et al. Intracellular pH regulation in human preimplantation embryos. Hum Reprod. 2000; 15(4):896-904.

³⁷ Swain J. Back to Basics: pH for the ARTisan (importance of pH and buffer selection in IVF); J Clin Embryol, 2010; 13(2): 9-25.

³⁸ McKiernan SH and Bavister BD. Environmental variables influencing in vitro development of hamster 2-cell embryos to the blastocyst stage. Biol Reprod, 1990; 43(3): 404-413.

- Liquids such as floor waxes that contain heavy metals.

They can originate from inside the laboratory (compressed CO₂, sterile plastic ware made of polystyrene, devices that off-gas compounds, etc.) or come from outside air (paints and glues, anaesthetic gas, refrigerants from the air conditioning, cleaning agents, aromatic compounds, etc.).

There has been no valuable toxicological evaluation of air and its effects on fertilisation and development outcomes after ART although in one case report, the blastocyst rate significantly dropped at the time of installation of floor tiles³⁹.

There is limited conclusive information on a possible impairment of embryo development due to increased VOC concentration.

Information on the detrimental effect of aldehydes on pregnancy outcome is available. Mouse embryo development is inversely correlated with the concentration of acrolein (both compounds come from new construction sites and road resurfacing)⁴⁰.

When air pollutant testing is performed⁴¹, data obtained should be monitored and corrective measures taken if necessary. However, fluctuations in air quality only, have to be registered: there is no need to report them as SAE since it cannot be confirmed that air quality alone is the cause for decrease or failure in fertilisation.

However, knowledge of which agents might be toxic and of the threshold level at which they demonstrate toxicity impacting on fertilisation and embryo development is lacking. Additionally, it is also difficult to differentiate between normal fluctuations related to other parameters and a real toxic effect of compounds in the background air.

Any problem detected with compressed CO₂, plastic hardware or devices that off-gas potentially toxic compounds should result in a formal notification of a serious adverse event if there is a potential consequence for other TE (see also 6.2).

Impact of medical devices on gamete and embryo viability and quality

A large spectrum of medical devices is available for ART.

In the early nineties the Dutch society of Clinical Embryologists stated that ‘all devices which directly or indirectly make contact with biological material should be considered as medical devices’⁴².

However IVF media do not strictly comply with the medical device definition given that the intended use for a medical device is defined for human beings (reference Article 1(2)a) of Directive 93/42/EEC, as amended) and not for biological material as reproductive cells.

In May 2008, the Medical Device Expert Group’s classification and borderline working group came to the determination on the regulation of IVF media products, that they can be classified as medical devices⁴³. The consensus agreement indicates that the IVF products used in ART may be qualified and regulated as medical devices provided that they meet the definition of a medical device, as laid out in Directive 93/42/EEC, taking into consideration the principal intended purpose of the product⁴⁴.

According to the Directive 2006/86/EC, critical reagents and materials must meet documented requirements and specifications and, when applicable, the requirements of the Directive 93/42/EEC on medical devices and Directive 98/79/EC on *in-vitro* diagnostic medical devices.

³⁹ Cohen J, Gilligan A, Esposito W, Schimmel T, Dale B. Ambient air and its potential effects on conception in vitro. *Hum Reprod.* 1997;12(8):1742-9.

⁴⁰ Hall J, Gilligan A, Schimmel T, Cecchi M, Cohen J. The origin, effects and control of air pollution in laboratories used for human embryo culture. *Hum reprod* 1998; 13 Suppl 4:146-55.

⁴¹ Differences may be observed between EU countries: there is no consensus whether air quality control is part of the quality control system in ART laboratories or not.

⁴² AMM Wetzels, PMM Kastrop. Dutch technical specification (NTA 8070) on devices for assisted reproductive technologies. *Reproductive Biomedicine Online* (2010) 21, 252-258.

⁴³ Theresa Jeary. Classification of IVF media under the MDD. *Regulatory Rapporteur*, May 2010, 9 – 11.

⁴⁴ Medical Device Directive (MDD), “Manual on Borderline and Classification in the Community. Regulatory Framework for Medical Devices Version 1.8 (01-2011), 4.3. In-Vitro Fertilisation (IVF) and Assisted Reproductive Technologies (ART) products”.

The revised Guidelines on a Medical Devices Vigilance System (MEDDEV 2.12-1 rev 6)⁴⁵ have not taken into consideration that medical devices in ART procedures do not act directly on the patients, but rather on reproductive cells. Suggestions to include IVF/ART devices in the MEDDEV is proposed and is based on the assumption that most incidents with IVF/ART devices will indirectly affect the woman as a consequence of inappropriate treatment on *e.g.* the reproductive cells with an IVF/ART device. Even if medical devices used in ART do not act directly on the patient, critical material and equipment might potentially have an impact on the fertilisation process and embryo development *in vitro*. It is known that initiatives to change the MEDDEV 2.12-1 revision 6 to include IVF/ART devices are currently ongoing.

Impact of the culture media

Many different culture media are used in ART, during culture and processing (flushing, sperm preparation, denudation, freezing, thawing, etc.). The aim is that the media should mimic *in vivo* conditions, for maintenance of the physiological homeostasis required to support and promote fertilisation and *in vitro* development and to minimise cellular damage during processes. Since media are in direct contact with gametes and embryos they are considered as critical materials. They are composed of a mixture of physiological inorganic salts, energy sources, amino acids and proteins. A wide range of different formulations is available.

The composition, validation and maintenance of culture media are crucial factors for a laboratory in order to achieve adequate success rates in ART and should reflect the best available conditions of quality and safety. Even if it is recommended to test culture media for human embryo development *in vitro* on adequate animal models, to date there is no test available in animals that would be sensitive enough to allow extrapolation to human oocytes and embryos. Moreover, data regarding the optimal composition of culture media according to the different stages of embryo development (*i.e.* for energy substrates, growth factors, cytokines, proteins and other compounds) are still in progress.

As a consequence, the final testing of new media can, so far, only be done in the actual ART situation. The general viewpoint is that the current formulations of media can still be improved for consistency, reproducibility, safety and efficacy.

Another concern is that in a few laboratories media are still prepared locally. This could be avoided by a mandatory CE mark or as a minimum met by a requirement that media prepared locally are validated to be at least as safe and suitable as equivalent CE marked media.

- *Impact of the equipment*

Critical equipment can be defined on the basis of their characteristics as devices, *e.g.* direct contact with gametes and embryos (pipettes, tubes, dishes, etc.) or invasive instrumentation (*e.g.* intracytoplasmic sperm injection needles).

Due to the high sensitivity of human oocytes and embryos, defective equipment (such as incubators and freezers and associated computing systems/software) might have a deleterious impact leading to a total loss of gametes or embryos. Different types of adverse events could occur resulting from random break down of equipment or insidious damage to equipment. Both have to be detected as soon as possible.

A defect in critical equipment might involve gametes and embryos of several couples and could lead to a lack of or delayed or inappropriate ART outcome and finally a loss of chance of pregnancy.

Examples of reportable SAEs

- Non conformity of culture medium

In 2010, a Danish ART centre noticed a white precipitate in a bottle of culture medium. In parallel, unexpected low development of embryos was reported by a Cypriot centre using the same culture medium batch number. Following these reports the manufacturer's investigations confirmed a contamination of the medium by a fungus and the

⁴⁵ Guidelines on a medical devices vigilance system (MEDDEV 2.12-1 rev 6) including IVF/ART devices.

manufacturer recalled the affected product, which had been distributed to several EU MS. A rapid alert was triggered through all EU MS via the European Commission's RATC (Rapid Alert for Tissues and Cells) system.

- Environmental contamination

During inopportune disinfection of premises close to the IVF laboratory during ART processing, the spread of toxic substances in the air into the laboratory led to an arrest of embryo development affecting 5 couples.

- Equipment breakdown

In February 2008, several reports of SAE to the ART vigilance system linked to a breakdown of embryos freezers and led to a loss of embryos in some of them. Further to investigation, in collaboration with the manufacturer, a joint action with the medical device vigilance officers concluded that the cause was a change in the fabrication of some of the freezers' gas valves (the freezers were replaced by the manufacturer).

- For further examples see *Annex 4*: examples 16, 22, 27 to 29 and 31.

Recommendations

When SAE reporting criteria are met (see 7.1 Assessment tools):

1. SAEs which are suspected to be linked to the culture media and equipment used in ART should be reported to the manufacturer and to ART vigilance to facilitate corrective and preventive measures, if appropriate, and to disseminate relevant information to other centres.
2. When the event is associated with a medical device, reporting is mandatory to the national CA for Medical Devices. Also the national CA for ART vigilance should be notified and coordination between these sectors should be organized.
3. If appropriate, an alert should be transmitted through the rapid alert system in cases of medical devices distributed nationally (via a national rapid alert) or in several Member States (via the RATC system) (see Chapter 6 Reporting of SARE).

5.3.2. Organisation

5.3.2.1. *Vigilance in relation to the mix up of gametes and embryos in ART*

Mix-ups are a rare occurrence. However, consequences can be distressing for all concerned. The frequency of mix-ups occurring is not known, but it is suggested that 1:50,000 to 1:100,000 may occur. In a well regulated clinic with appropriate quality systems, the risk should be extremely low.

According to the Directive 2006/86/EC, article 6.2, misidentifications and mix-ups shall be reported as Serious Adverse Events.

A mix-up is a SAE resulting from an error in the attribution of gametes or embryos that can occur at any stage of the laboratory or of the clinical process of assisted reproduction (*e.g.* gamete collection, insemination, embryo transfer, freezing).

The reporting of mix-ups, regardless of whether they result in a live birth or not, is relevant to ART vigilance reporting and, consequently, is included in the scope of the Directive 2006/86/EC.

Additionally, misidentification due to a patient's voluntary action is also to be reported to ART vigilance but is considered a fraudulent activity. Another work package of the SOHO project addresses this issue specifically (WP 6).

The consequences of mix-ups are diverse. Mix-ups during ART may or may not involve gametes and embryos that subsequently give rise to the birth of a baby. However the effects on the patients involved and the reputation of assisted

reproduction may be severe, regardless of the clinical result. Adverse publicity is often associated with such events and it can have a detrimental impact on ART at a national level and even internationally.

Risk factors

- Multiple processing steps – oocyte retrieval, sperm collection, fertilisation, embryo culture and transfer – involve transferring gametes and embryos from one dish to another and transferring embryos from dishes into a catheter for embryo transfer. Misidentification and/or mismatching of gametes and embryos may occur at any stage of ART;
- Many people involved (the couple, biologists, technicians, clinicians, operating theatre staff, surgeons, administrative staff, etc.);
- Work overload of the staff;
- Poor witnessing processes;
- Inadequate organisation of the TE, *e.g.* lack of/or a poor quality management system, including standard operating procedures, lack of an audit system and/or poorly trained staff.

Issues

Consequences for the patients

- Lack of traceability:
 - Errors in sample labelling resulting in the repeat of sample collection (*e.g.* sperm collection),
 - Loss of gametes or embryos (*e.g.* loss of oocytes when follicular liquid has not been labelled);
- Loss of chance of procreation:
 - Cancellation of transfer if the error is discovered during the process;
- Unintended additional risk: transmission of a genetic disease, transmission from an infected person to an uninfected non-partner (theoretical risk), etc.;
- Psychological impact: *e.g.* for a patient having to use an emergency contraceptive treatment to prevent a pregnancy establishing;
- Recognition of a possible mix-up may not occur until after birth of a baby (*e.g.* skin colour or inconsistent blood group). A chance also exists that a mix-up will occur and not be detected at birth;
- Selected donated gametes no longer meet the needs of couple or individual using ART (*e.g.* physical characteristics that match their own). A mix-up can occur at the step of selection of the compatible donor. However, phenotypic criteria are of low level of evidence and there are specific criteria to perform genotypic tests;
- Ethical and legal issues arise should a baby be born as a result of a mix-up.

Consequences on the ART clinics and their staff

- Negative psychological impact on staff involved;
- Possible damage to the professionals' reputation and personnel resources;
- Trust in the ART process and the clinic will be reduced;
- Legal action may be taken by patients, with possible reporting to professional organisations.

Mismatching incidents result from checking errors occurring at different points in healthcare processes, including laboratory testing⁴⁶. In the context of an IVF laboratory, the key matching processes relate to:

- Matching the correct patient eggs to the correct sperm (i.e. the patient's partner or intended donor) prior to fertilization;
- Matching the correct embryos to the correct patient prior to embryo transfer.

⁴⁶ Plebani M and Carraro, Mistakes in a stat laboratory: types and frequency. Clin Chem. 1997 Aug; 43(8 Pt 1):1348-51.

There have been a small number of publicised cases^{47,48,49,50,51,52} of mix ups in assisted conception. These have included cases where the wrong sperm has been used to inseminate a woman and cases where the embryos of one couple have been used in the treatment of another couple.

Discussion

The rare occurrence of mix-ups is a demonstration that most ART clinics have good quality management systems and effective vigilance systems in place.

Vigilance gives the opportunity to learn from errors. Simple and effective tools for reducing *a priori* risks of mix-ups do exist and should be considered (*e.g.* active identification of the donors and recipients: active contemporaneous double witnessing⁵³, bar coding, etc.).

Vigilance and reporting can also raise awareness among ART health professionals and ensure clinics review their adherence to risk and quality standards.

Reporting and monitoring mix-ups will ensure that regulatory action can be taken, should a greater number of mix-ups arise in a particular clinic.

Vigilance is complementary to but does not substitute for an effective internal quality control system and for adequate training of new staff before they start handling gametes or embryos in the laboratory. If there is poor compliance with or insufficient quality systems in place, then mix-ups may either occur more frequently or not be detected early enough to allow preventive action.

However, despite having effective quality systems in place and good vigilance systems, human error cannot be totally avoided.

All mismatching incidents which have involved:

- Inseminating a woman with sperm from the non intended partner or donor,
- Fertilising eggs with sperm from the non intended partner or donor,
- Transferring embryos *e.g.* intended for one couple into another woman or transfer of a sick embryo after preimplantation genetic diagnosis (PGD),

should be reported as a Serious Adverse Event.

Examples

For examples of mix-up refer to *Annex 4*; examples 14 and 18.

Recommendations

According to the Directive 2006/86/EC article 6.2, misidentifications and mix-ups shall be reported as Serious Adverse Events. However, the following recommendations can be added:

⁴⁷ Dr Kirsty Horsey, IVF mistake was 'labelling error'. Progress Educational Trust, 09 November 2002. www.ivf.net/ivf/ivf-mistake-was-labelling-error-o107.html

⁴⁸ Dr Kirsty Horsey, IVF error discovered after 13 years, Progress Educational Trust, 22 August 2003 . www.ivf.net/ivf/ivf-error-discovered-after-13-years-o194.html

⁴⁹ US woman receives \$1m compensation for IVF error, 09 August 2004. www.bionews.org.uk/page_12063.asp

⁵⁰ Fertility watchdog investigates serious IVF mix-ups at London hospital. BioNews, 3 May 2009. <http://www.bionews.org.uk>

⁵¹ HFEA rebuked by medical risk expert. BioNews, http://www.bionews.org.uk/page_13792.asp

⁵² Canadian fertility doctor sued over sperm mix-up claims. BioNews, 20 Sep 2010. http://www.bionews.org.uk/page_70931.asp

⁵³ Reducing risk in the IVF laboratory: implementation of a double witnessing system. Clinical Risk Volume 10. No. 5 Pp. 176-180.

When SAE reporting criteria are met (see 7.1 Assessment tools), where a mismatching incident has occurred, this should be reported as an SAE so that the cause can be investigated and the learning points shared in order to spread best practices across the sector.

1. All mix-up of gametes or embryos, whether partner or donor, should be reported as a SAE regardless at what stage the mix-up is detected. A full investigation should be initiated immediately after the mix-up is known. The causal factors should be noted and learning points shared.
2. The ART clinic should ensure that all of the patients involved are advised that the mix-up has occurred as soon as clinic staff become aware. Affected patients should be offered *ad-hoc* counselling and support.

5.3.2.2. *Vigilance in relation to the traceability of gametes and embryos during processing*

Directive 2004/23/EC, article 8, requires that all tissues and cells procured, processed, stored or distributed be traced from the donor to the recipient and vice versa. This traceability should also apply to all relevant data relating to products and material coming into contact with these tissues and cells. Traceability is defined in article 2 of the Directive 2006/86/EC (see the Directive for full definition).

Traceability means the ability:

- (a) to identify and locate gametes and embryos during any step from procurement to use for human application or disposal,
- (b) to identify the donor and recipient of particular gametes or embryos, and
- (c) to identify and locate all relevant data relating to products and materials coming into contact with particular gametes or embryos and which can affect their quality or safety.

Issues regarding gametes and embryos

In vitro fertilisation involves the creation of embryos outside the body. In most cycles of IVF, more embryos develop than are used in one cycle of treatment. The embryos not used in a fresh IVF cycle are often cryopreserved and stored so that the patient may have further treatment cycles without the need of stimulatory drugs. The cryopreserved embryos are stored in storage vessels (dewars) containing embryos from many patients. In addition, the TE may also store cryopreserved gametes for patients and donors in the same storage vessel. Tissue establishments are expected to record the physical location of these cryopreserved gametes and embryos in the storage vessel.

Centres are required to record the location of these cryopreserved gametes and embryos.

These issues raise the following question: if a centre has recorded the wrong location of stored gametes or embryos for a particular patient, should this be reported as a Serious Adverse Event?

Discussion

In most cases, this would be due to a simple typographical error which would be classed as a near miss because the right gametes/embryos would be located quickly. It should be captured within the quality management system, at the TE, for internal review. In these cases, centres would not be expected to report the incident as a SAE to the CA.

However, if a centre fails to locate cryopreserved gametes or embryos, this should be reported as a SAE.

If the failure to record the location of gametes or embryos results in a complete search of the dewars and as a result of this search the viability of embryos or gametes were compromised, *e.g.* thawed or straw were damaged, this should be reported as a SAE to the CA.

Issues regarding data related to products and material

ART centres are required to identify and locate all relevant data relating to products and materials coming into contact with particular gametes or embryos which can affect their quality or safety.

The question arises as to whether the failure to record information about products and material, that have come into contact with particular gametes or embryos, which can affect their quality or safety or the health of a patient, should be reported as a SAE to the CA.

Discussion

If a centre fails to record information about events that may affect the quality and safety of gametes *e.g.* media used for embryos' culture or the make and batch number of catheter used to transfer embryos, then this in itself should not be reported as a SAE but documented via the quality system for review, as part of the inspection process.

In the event that a manufacturer or a CA informs fertility centres that a particular culture media or catheter, dish etc., had had a toxic affect on embryos or had caused an adverse effect on the patient (*e.g.* number of patients had had an adverse reaction to a particular make of catheter) and that a centre cannot trace which patients had received treatment with embryos cultured or transferred with the defective media/equipment, then this should be reported as a SAE, since the centre had clearly not complied with traceability requirements and this may have serious consequences for the safety of patients. Therefore, if a centre fails to trace gametes, embryos or patients which have come into contact with products or materials which could affect their quality and safety then this should be reported as a SAE to the CA.

Recommendations

When SAE reporting criteria are met (see 7.1 Assessment tools), if a centre fails to trace gametes or embryos due to misrecording or loss of information, leading to the loss of gametes or embryos, this should be reported as a SAE to the CA.

5.3.3. Cross-border management of SARE

Cross border reproductive care (CBRC) refers to the movement of patients within the EU MS or to neighbouring non EU-countries, seeking ART treatment outside their country of residence. It is well known that patients from different EU MS travel abroad to access fertility treatment. This phenomenon has been increasing during the last 10 years and is now common. Cross border care is a phenomenon with a number of challenges for patients, practitioners and policy makers, regarding quality of care and information requirements for patients. However there are limited available data to estimate the scale of this practice, except for a small number of studies, including an ESHRE study that compiled data from six countries⁵⁴.

The motivations for travelling abroad have been studied among selected European countries and on a larger scale. According to various surveys performed, these motivations vary from one country to another and include:

- Legal restrictions: infertility treatment required not legally authorised in the country (*e.g.* IVF with donor gametes, IVF in post-menopausal women, insemination of single women, preimplantation genetic diagnosis (PGD));
- Long waiting times in the country of residence for a specific method due to egg/sperm shortage, scarcity of donors and insufficient activity of authorized centres;
- Unavailability of a specific service due to the lack of expertise or technical facilities or search for better standard of care and expertise;
- Search for better success rates including opportunity to have more embryos replaced than recommended in the country of residence;
- Cost of treatment lower (particularly when not reimbursed in the country of residence);
- Financial compensation for donors not allowed in the country of residence.

⁵⁴ Shenfield et al 'Cross border reproductive care in six European countries' Hum Reprod 2010 Vol. 25(6) 1361-1368

Directive 2011/24/EC clarifies patient's rights to access safe and good quality treatment across EU borders⁵⁵. However, the reimbursement of health care provided abroad by the health insurance of a given country depends on the legal framework and the financial rules of this country.

Arrangements may exist between clinics or practitioners from different countries for recommending clinics abroad. However, most patients do not seek referral from a physician and select treatment and a clinic on their own. There is a wide range of information on all types of treatment methods available on the internet through patient associations, social networks or directly on the clinics' websites. Since all procedures are detailed on the websites in several European languages, selecting a clinic is an easy process. Furthermore, specific information on travelling and accommodation may also be given directly by the clinic. A few clinics propose appropriate counselling for recipients.

Although medical advertising is prohibited in many EU countries, various marketing methods are observed. Quality is usually highlighted, providing unverifiable, attractive success rates, emphasizing treatment safety standards referring to the European Directives, and giving reassurance on selection, compensation and screening of the donors, as well as on the conditions of their recruitment.

Since cross border reproductive care is a very attractive and developing market, there may be a lack of transparency and success rates may be exaggerated.

Issues

Patients may receive a treatment, leave the country and return to their country of residence. This may also happen for gamete donors travelling abroad for donation. Complications may occur after the treatment such as severe Ovarian hyperstimulation syndrome, ovarian abscess, haemoperitoneum, life-threatening multiple pregnancy, etc.

A number of SARE such as infection of the donor or of the recipient, gamete or embryo mix-up, wrong PGD data, etc. may become apparent once the patients have returned to their country of residence. Many patients may be hesitant to share information about having received ART abroad (*i.e.* treatment with donor gametes) or simply may not associate the SARE with the treatment they received.

According to the European Directives, such SARE are under the responsibilities of the TE offering the service, to investigate and inform the local CA^{19,20,21}.

In this situation where different countries are involved, the risk is that neither the treating ART centre and its corresponding CA nor the CA in the country of origin will be informed of the occurrence of the SARE.

When CAs are informed, they should ensure that the relevant stakeholders are – in turn – informed and that the information is complete and not overlapping.

Discussion

Patients must be informed by the ART centre abroad about the risks of ART in order to be able to recognise SARE as associated with ART and to inform the ART centre as well as the physician at home if a suspected SARE should occur.

If hesitant to reveal that they had ART abroad once back home, patients should be reassured that medical confidentiality applies.

SARE must be reported through the national system of ART vigilance in the country where the treatment occurred. However, if it is first reported at home by an individual physician to the national CA through the national ART vigilance system in place, the CAs of both countries involved should exchange data in order to avoid double reporting for the same SARE and ensure that appropriate investigations are performed and corrective measures are taken.

⁵⁵ Directive 2011/24/EU of 9 March 2011 on the application of patients' rights in cross-border healthcare.

Recommendations

1. CAs should encourage health professionals to report a SARE even when it is established to be related to ART cross border care.
2. In the case of CBRC, the CA receiving the SARE notification should inform the other CAs involved without any delay.
3. CAs should encourage TEs to provide patients with information regarding possible adverse outcome. In particular, patients, couples and donors should be encouraged by health professionals to report adverse outcomes even in the context of cross border reproductive care.

5.4. SAFETY ISSUES

5.4.1. Complications of stimulation and of procurement

5.4.1.1. Severe ovarian hyperstimulation syndrome (OHSS)

Severe Ovarian hyperstimulation syndrome (OHSS) is one of the most serious iatrogenic disorders resulting from ovarian stimulation during assisted reproductive technology (ART) whenever the patient is either an egg donor or a woman attempting IVF for herself. It occurs usually during the luteal phase or during early pregnancy. According to the different classifications, OHSS may be mild, moderate, or severe. The clinical impact of the syndrome depends on the variety of symptoms. It can be accompanied by severe morbidity. Exceptionally, severe OHSS may lead to death due to thromboembolism, renal failure or respiratory distress syndrome. In the literature, its incidence ranges from 0.2 to 5 % after ovarian hyperstimulation for IVF, but remains difficult to assess due to the different classifications used. There is a need for consensus regarding OHSS classification.

The current concern is not to determine the best treatment of an existing OHSS but is focused on determining the best methods of prevention, since there is no completely curative therapy.

Cancellation of the cycle is the only method that totally avoids the risk of OHSS but the heavy psychological and financial burden for the patient, the donor and the society should be taken into account. Other strategies can be proposed once the oocyte retrieval has been performed, in order to limit the impact of the syndrome: luteal support, additional medical interventions (albumin administration, dopamine agonist administration), laboratory rescue, and Single Embryo Transfer (SET) or cancellation of any fresh embryo transfer associated with cryopreservation. The occurrence of a pregnancy usually worsens the severity of the syndrome.

Administration of progesterone is clearly associated with a lower risk of hyperstimulation as compared to patients receiving luteal phase support with both progesterone and human chorionic gonadotropin (hCG). Indeed, the administration of hCG for luteal support is associated with an increase in the occurrence of OHSS. Further studies are needed to evaluate the interest of recombinant luteinizing hormone (LH). Cryopreservation of embryos and cancelling the transfer of fresh embryos seem to be the most efficient alternative in some cases. In most studies the rate of pregnancy after frozen embryo transfers is as high as when using fresh embryos. The triggering of ovulation with Gonadotropin-releasing hormone (GnRH) agonists could even be more effective but only in patients treated by GnRH antagonists. Nevertheless, pregnancy rates appear to be reduced following the latter option.

Ideally, patients at risk⁵⁶ should be identified prior to the ovarian stimulation. Then, the safest protocol should be selected and finally the strategy for luteal phase and embryo transfer should be adapted, requiring an effective surveillance. Further studies are needed regarding the dopamine agonists and GnRH agonists, the triggering of ovulation with GnRH agonists and the cryopreservation at the 2 PN stage or later. Cycle cancellations should not be the only available method to guarantee complete avoidance of OHSS.

⁵⁶ Polycystic ovarian syndrome, increase in the level of AMH concentration, before treatment, young patients, low body mass index (BMI), history of OHSS, LH/FSH > 2, ultrasound visualisation of an ovary with ≥ 12 antral follicles 2-8 mm in diameter.

Data from ART vigilance show that severe OHSS are reported through this system by the professionals.

Article 11(1) of the Directive 2004/23/EC defines the type of serious adverse reactions and events (SARE) that are reportable. Reportable SARE are those ‘which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells’. The legal interpretation of these definitions is that there is no mandated requirement to report events or reactions in living donors which do not influence the quality and safety of the tissues or cells. Similarly, reactions in recipients which are not linked to the quality and safety of the tissues or cells applied are not reportable under this legal framework.

However, many MS CAs currently receive information on donor adverse reactions not influencing the quality and safety of tissues and cells. Reactions such as OHSS or other reactions result in harm to the donor or to the recipient (e.g.: haemoperitoneum, etc.). In this regard, the survey carried out as part of the WP 4 SOHO V&S project showed that:

- 19 (68%) CAs required reporting SARs in donors even if the quality and safety of the tissues or cells have not been affected,
- Among the CAs, 10 reported OHSS in non-partner oocyte donor and 13 reported OHSS in partner oocyte donors.

Some of the adverse reactions should be reported to the pharmacovigilance system when appropriate (serious or unexpected). The European Commission recognised the value of these data in the context of tissue and cells regulation and invited MS to include donor reactions reported to the CA on a voluntary basis in the annual report⁵⁷. Therefore, an additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template.

Issues

Ovarian stimulation is an intended step in the ART treatment process. However, in some cases, ovarian hyperstimulation may lead to adverse reactions ranging from mild to severe. So far, not all OHSS may be prevented. Severe OHSS should be considered as a SAR and notified to a vigilance system (ART vigilance, pharmacovigilance). In France, an OHSS classification has been developed⁵⁸ after a consensus was reached with professional societies (see details below).

Severe OHSS:

- **Grade A** : severe clinical signs without severe modification of the laboratory parameters
 - vomiting, diarrhoea, oliguria
 - respiratory signs (dyspnoea)
 - clinical ascites with important abdominal distension
 - hydrothorax
 - ultrasound examination : large ovaries and ascites
 - non severe modification in the laboratory parameters
- **Grade B**: aggravation of the clinical signs and severe modification of the laboratory parameters
 - very rapid weight gain (> 2 kg in 24 h)
 - severe dyspnoea and oliguria
 - increase in blood creatinine level (> 100 µmol/L) and hepatic dysfunction (liver enzymes * 3 normal values)
- **Grade C** : organ failure
 - acute respiratory distress syndrome

⁵⁷ European Commission. 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 (2009)

⁵⁸ Adapted from B. Rizk and M. Aboulghar, eds. Classification, pathophysiology and management of ovarian hyperstimulation syndrome. Second ed. A textbook of In-Vitro Fertilization and Assisted Reproduction. 131-55. P. Brindsen, Editor (1999).

- renal insufficiency

Complications of OHSS:

- Thrombosis,
- Adnexa torsion

This classification is generally similar to the Royal College of Obstetricians and Gynaecologists' one⁵⁹ and to the Ovarian Hyperstimulation syndrome (OHSS) Guidelines⁶⁰.

Most of the OHSS reports fall in the scope of ART vigilance system. Experience of the two most experienced countries in ART vigilance showed that very few OHSS were actually captured by the pharmacovigilance system. Further data on the role of these practices and of the different drugs and protocols used for the stimulation should be collected.

Severe OHSS can occur both in the oocyte non-partner donors and in women having IVF for themselves (partner donor). Given that pregnancy is in itself a risk factor for OHSS, most severe cases are usually observed at early pregnancy stage in women who had IVF for themselves.

5.4.1.2. Complications of procurement

The complications of the procurement are not explicitly included in the scope of the Directive since the Directive does not regulate clinical care (*e.g.* couples having clinical treatment for ART). Moreover, these complications are not linked to any quality or safety concerns of tissues and cells.

Other complications such as hemorrhage, infection, etc., are associated with the procurement and are related to the invasive nature of the procedure.

5.4.1.3. Examples

For examples of complications of procurement see *Annex 4* examples 1 to 5 and 7 to 12,

For examples of OHSS see *Annex 4* example 13.

Recommendations

1. All SARE related to procurement, as well as severe OHSS according to a definition adopted in all EU MS, should be reported to a CA⁶¹. These SARE should be notified to a specialist ART CA in countries where it exists.
2. A coordination between various systems of vigilance (*e.g.* medical device, pharmacovigilance, ART vigilance) should be organised both at the local (TE) and at the national levels (CA).
3. Written information on major risks related to procurement should be available for donors, patients and couples.

⁵⁹ Royal College of Obstetricians and Gynaecologists; Guideline N°5: The management of ovarian hyperstimulation syndrome, September 2006.

⁶⁰ Delvigne A. and Serge Rozenberg Human Reprod Update, 9 (1) : 77-96, 2003 Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS).

⁶¹ The reporting of non-mandatory SAREs was the topic of much discussion in the development of this document. A consensus was reached as regards the necessity of reporting SAREs whose reporting is not required by Directive 2004/23/EC (non-mandatory reporting). The CA to which it is reported depends on the organisation of the vigilance system in the MS.

5.4.2. Vigilance in relation to the Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Issues

The use of donated gametes implies the potential risk of genetic disease transmission to the offspring. Although it is a rare occurrence, given the screening of the donors for various genetic diseases, the consequences can be devastating for the families involved. A number of documented cases of genetic transmissions to offspring, created with gametes donated by non-partner donors, can be found in the medical literature and in the popular media. They include conditions such as Severe Congenital Neutropenia (SCN)⁶², Hypertrophic Cardiomyopathy^{63,64}, Autosomal Dominant Cerebellar Ataxia (ADCA)⁶⁵ and Opitz Syndrome⁶⁶, Neurofibromatosis type 1 (NF 1)⁶⁷, Autosomal recessive Polycystic Kidney Disease (ARPKD)³⁸, Congenital adrenal hyperplasia (CAH)³⁸ and Phenylketonuria (PKU)³⁸.

It is neither cost effective nor possible to require testing of gamete donors for all known genetic conditions that might theoretically be transmitted. In some cases, there is no test yet available but even where tests are available, the likelihood of transmission from an asymptomatic healthy donor is very low and the tests are usually very costly. Normal reproduction also carries the risk that a child will inherit a genetic illness from one or both of its parents and it is not considered reasonable to conduct extensive genetic testing before a healthy couple has a child. Although, in some instances, pre-conception screening is undertaken where the donor population concerned has a high prevalence of a genetic condition *e.g.* Beta Thalassemia in the Mediterranean population.

This raises the questions:

- i) should the transmission of a genetic illness from a gamete donor be considered as a SAR?
- ii) should there be systems for the reporting of such transmissions to CAs for Tissues and Cells in the EU?

There are also circumstances where the diagnosis of a genetic defect in a child born of a gamete or embryo donor might have important implications for the health of the donor. For example, in France, one woman in 350 carries the pre-mutation for Fragile X Syndrome (FXS). Children with FXS are usually diagnosed at around 5 to 6 years of age in the context of an aetiological diagnosis of a severe mental retardation. A woman with the pre-mutation has a 5% chance of developing a serious neurodegenerative disorder when she reaches 40 years of age.

- iii) If a child born of a gamete donor is diagnosed with a genetic condition, should the donor and recipients be contacted and informed in case there may be consequences for him/her or for his/her own offspring?

Discussion

Supply of gametes

In most of the cases reported, it would have been very difficult, or impossible, to have identified the risk in advance of the initial donation, therefore it might be argued that these tragic occurrences will inevitably happen on rare occasions. It is very important to note, however, that in many of the cases reported where the sperm donor was the source of the genetic defect, the sperm bank continued to supply sperm from that donor, without knowing about, or without taking account of, a genetic transmission that had occurred. The result was multiple children affected by the same genetic defect.

For example, in a case of SCN transmitted by a sperm donor, 5 children were born with the defect⁶². Another donor transmitted Hypertrophic Cardiomyopathy to 9 children⁶⁴. In the early years of ART, a single donor, whose sperm was used to create 42 children, was shown to carry the gene for Opitz Syndrome, with a 50:50 chance of inheritance⁶⁶. The

⁶² Roxanne Khamsi, Children with Gene Disorder Share Sperm Donor Dad 23 May 2006 <http://www.newscientist.com/article/dn9208-children-with-gene-disorder-share-sperm-donor-dad.html> - accessed on December 22nd 2010.

⁶³ Nine Children inherit high risk heart disease from sperm donor. <http://ushealths.net/2010/10/9-children-inherit-high-risk-heart-disease-from-sperm-donor/> - accessed on December 22nd 2010.

⁶⁴ Maron BJ et al. (2009) Implications of Hypertrophic Cardiomyopathy transmitted by sperm donation. JAMA, Vol 302: (15) 1681-1684.

⁶⁵ D O E Gebhardt (2002) Sperm donor suffers years later from inherited disease. J Med Ethics;28:213-214.

⁶⁶ Sperm donor children may have fatal gene. Sunday Times 23 September 2001. Lois Rogers. <http://www.mindfully.org/Health/Sperm-Donor-Fatal.htm> - accessed on December 22nd. 2010.

⁶⁷ Reported to the Vigilance System for Tissues and Cells at the Danish Medicines Agency.

first affected child was conceived just before the Human Fertilisation and Embryology Authority (HFEA) was created in 1991 in the UK; the regulator subsequently introduced the limit of 10 offspring created from one donor.

Importance of vigilance

These cases of multiple affected offspring highlight the value of vigilance reporting of genetic transmissions of disease by donors of reproductive cells in the context of ART. In some cases the condition is diagnosed immediately after birth or early in the life of the child; a SAR report could prevent further use of the sperm and the birth of further children with the same condition. In some cases, the condition manifests itself only years after puberty so a SAR report will be too late to prevent further use of the sperm. For example, sperm from a donor with ADCA was used for the conception of 18 children in 13 women⁶⁵. Half of the children would have inherited the gene but it would not have been detected in the offspring until after puberty. In this case, the donor himself was the first to manifest the condition and an immediate serious adverse event report might have prevented further use of the sperm.

Challenges

One of the challenges of notification, either by the families of affected children or by donors, is the secrecy that often surrounds gamete donation and the use of ART to conceive. Genetic conditions are usually diagnosed in children in specialist units and may never be communicated to the sperm bank or to the clinic where an oocyte donation was performed. This is complicated by the degree to which couples travel to other countries for ART, usually due to restrictive laws in their own country. There is no international registry of gamete donors.

Examples

For examples of suspected transmission of genetic diseases see *Annex 4*: examples 19, 21, 25 and 26.

Recommendations

7. The birth of a child with a genetic disease following non-partner donation of gametes or embryos should be reported as a suspected **SAR**. It should be investigated as such so that further gametes, or embryos created from that donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
8. The diagnosis of a genetic disease in adults who have previously donated gametes or embryos to other couples should be reported as a **SAE** so that stored gametes, or stored embryos created from these donors' gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
9. Gamete/embryo non-partner donors and recipients should be asked at the time of donation whether they wish to be informed in the event that it is later established that the resulting progeny carries a gene or chromosomal abnormality that might be relevant to the donor's own health or to the health of their own children (already born or still to be born).

To facilitate the effectiveness of SARE reporting and investigation in these circumstances, the following is recommended:

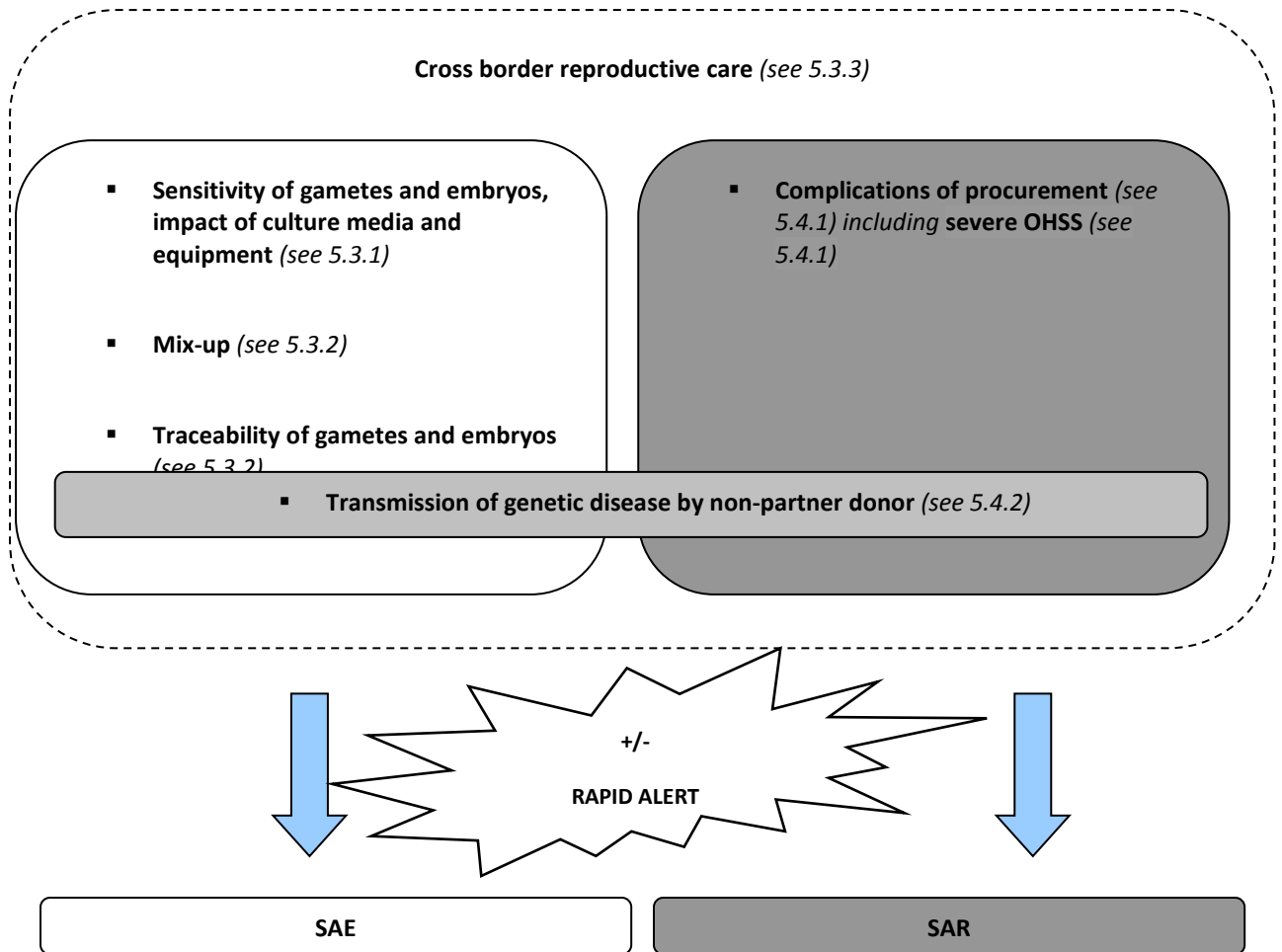
10. Couples having ART treatment with non-partner donated gametes or embryos should be strongly advised to inform any doctors subsequently treating the resulting child(ren) of the donor origin. They should understand that, in the unlikely event that a child will manifest an inherited condition, informing the clinic could protect further families. Consideration could be given to the development of a carefully worded standard leaflet explaining these issues that could be provided to all couples. In the analogous situation of allogeneic cord blood banking, some banks provide the donor mother with a leaflet asking her to contact the bank in the unlikely event that the donor child manifests a genetic or other disease, so that the transmission of the disease by transplantation of the cord blood can be prevented.
11. Gamete and embryo non-partner donors should be strongly advised to inform the clinic where they donated, in the event that they are subsequently diagnosed with any genetic disease. In this case also, a standard information leaflet for donors might be considered.
12. Specialist genetic centres should always consider whether a child manifesting a genetic disease might have been conceived with non-partner donor gametes or embryos. This issue should be raised immediately and openly with the parents in the interests of other potential offspring and when parents acknowledge the involvement of a non-partner donor, they should be strongly urged to contact the ART centre. This issue should be included in the appropriate professional standards and guidance for specialist genetic centres.

6. REPORTING OF SARE

6.1. GENERAL REQUIREMENTS

The notification requirements for SARE are set out in article 11 of the Directive 2004/23/EC and in articles 5 (SARs) and 6 (SAEs) of the Directive 2006/86/EC. However, the European Commission accepts annual reports including donor reactions reported by MS even when they do not influence the quality and safety of tissues and cells. The results of the SOHO WP 4 survey also showed that these reactions were reported although they were not in the scope of the directive.

Directive 2004/23/EC requires that all SARE be notified to the CA, but some MS went further since their legislation requires that non-Serious Adverse Events or Reactions also be reported.



6.1.1. Criteria for reporting SAEs

In ART vigilance, deviations from Standard Operating Procedures in TEs, or other adverse events, which may influence the quality and safety of tissues and cells should result in SAE reporting to the CA when one or more of the following criteria apply:

- inappropriate gametes, embryos, germinal tissues have been released for clinical use, even if not used;
- the event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors;
- the event resulted in a mix-up of gamete or embryo;
- the event resulted in a loss of traceability of gametes or embryos;
- contamination or cross contamination;
- accidental loss of gametes, embryos, germinal tissues (e.g. break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle.

6.1.2. Responsibilities

The directives describe how SARE should be reported within the MS and with tissues and cells originating from another MS or imported from a third country.

All persons or procurement organisations (PO) or organisations responsible for human application (ORHA) performing assisted reproduction shall report to the supplying tissue establishments for investigation and notification to the

competent authority (CA). However, the directives make it clear that the role of the TE does not preclude a PO or an ORHA from also directly notifying the CA.

6.1.3. Reporting timeframes

Articles 5 and 6 of the Directive 2006/86/EC describe the reporting scheme and stipulate that MS shall ensure that PO, OHRA and TE have procedures in place to notify any SAR (art. 5) or SAE (art. 6) *without delay*.

However, MSs may have a defined mandatory reporting timeframe in their legislation²⁵.

6.1.4. Reporting forms

The minimum reporting requirements are set out in Annexes III and IV of the Directive 2006/86/EC. Parts A of the Annexes are for rapid⁶⁸ notification for suspected SARs or SAEs, Parts B are for conclusions of SARs or SAEs investigations.

In addition to these forms, an extended list of minimal items that should be included in a national form was developed during this WP 5 work package of the SOHO V&S project (for further details, see *Annex 3*).

6.1.5. Level of assessment of SARE: central or local?

SAE assessment exercises performed by both professionals and CAs during the SOHO WP 5 Exploratory Workshop showed that the use of the assessment tools (see 8.1) at a central (by CAs) or local (by TEs) levels would give different results.

Recommendation

Assessment tools should be used at both CA and health professional levels, but should not be mandatory for health professionals.

6.2. TRIGGERING CONDITIONS FOR RAPID ALERTS AT NATIONAL AND INTERNATIONAL LEVELS

The purpose of this chapter is to identify specific ART conditions or events generating potential areas of risk, where *indirect* or *direct* harm could result for patients, that should trigger a rapid alert at national and/or international levels.

Identifying and reporting such ART-specific SARE aims:

- a. To prevent or reduce harm to all patients (and children-to-be)
- b. To make ART professionals aware of potential areas of risk
- c. To make national and international ART stakeholders aware of potential public health risks
- d. To facilitate appropriate and rapid preventive/corrective actions.

6.2.1. Existing “communication networks”

Rapid alerts result in urgent notifications by or through the CA in a MS to alert organisations about a potential threat. This may be triggered by information received from another regulator, the European Commission, an ORHA, TE, PO or industry.

Rapid alerts are coordinated by the CA of the MS when issued nationally, or in collaboration with another CA, the European Commission and/or the World Health Organisation when issued across the EU or globally.

Different ways to disseminate an alert using communication networks are already in place to ensure the safety of tissues and cells and to inform stakeholders:

- At the national level: national rapid alerts (NRA) managed by each MS
- At the EU level: the Rapid Alert Tissues Cells (RATC) System⁶⁹ for tissues and cells

⁶⁸ ‘Without delay’, according to Directive 2006/86/EC.

- Outside the EU: alerts managed principally by the European Commission.

6.2.2. Conditions for triggering a rapid alert

ART treatments are medical interventions. As such, risks that are present in the practice of medicine apply to ART practice, too. In some situations, potential risks arising from ART should imply a rapid dissemination of information to all stakeholders, depending on the nature and the potential consequences of the risks.

In general, the final aims of rapid alerts are:

- Communication to ART professionals via the CA,
- Implementation of preventive/corrective measures.

Since rapid alerts imply rapid and widespread communication and potentially extensive actions, they should only be issued in exceptional circumstances, *i.e.* those alerts whose urgency and seriousness cannot allow any delay in transmission and follow-up. Each of the following conditions must be satisfied for issuing of rapid alerts:

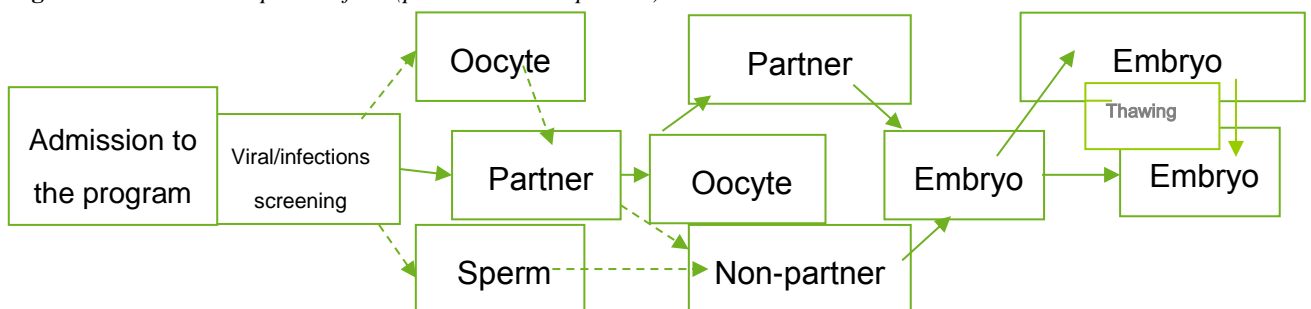
- The Quality/Safety of the tissues/cells concerned is of a serious or potentially serious nature;
- Several patients are or may be affected;
- The risk has wider public health implications;
- Rapid intervention is needed: preventive or corrective measures, therefore urgent communication.

All the previous conditions should be verified before the rapid alert is triggered. Thus, a rapid alert should not be issued for the transmission of information related to a SARE that does not fulfil the above-mentioned conditions (*e.g.* an adverse event with impact limited to a single patient). Moreover, it is not to be used for advising other CAs of single incidents, unless those incidents have a clear implication for public health in other countries.

6.2.3. Examples in ART practice

The ART process includes several processing steps, teams (laboratory technicians, nurses, physicians) and facilities (laboratory, clinics, etc.). In order to identify potential areas of risk, an example of 'process flow' of IVF treatment is presented in *Figure 1*. Both partner and non-partner donations are included.

Figure 1. IVF treatment process flow (partner and non-partner).



Events that require triggering a rapid alert at the national, European or international levels may apply to:

- Material or equipment used in ART that may be distributed in several TEs⁷⁰ in a country/several countries,
- Donors, patients or individuals (*e.g.* in cases of cross-border reproductive care) that could travel abroad for ART treatment,
- Gametes that could be distributed in several TEs in a country/several countries (*e.g.* sperm banks distributing worldwide) for infertility treatment,
- Environmental factor that may impact ART practices or patients (*e.g.* epidemic or pollutant),
- Suspicion or evidence of fraud or counterfeit, depending on the nature and on the potential consequences.

⁶⁹ Rapid Alert Tissues Cells (RATC) System for Human Tissues and Cells, Working Party on Rapid Alerts for Human Tissues and Cells (RATC), June 2010, rev2.

⁷⁰ See definition of a TE applying to ART in the glossary.

The proposed list below focuses on specific stages such as: procurement, testing, processing, storage, distribution and clinical follow-up. It shows, by use of some **examples**, the levels at which a rapid alert triggering event can occur in the specific context of ART practice:

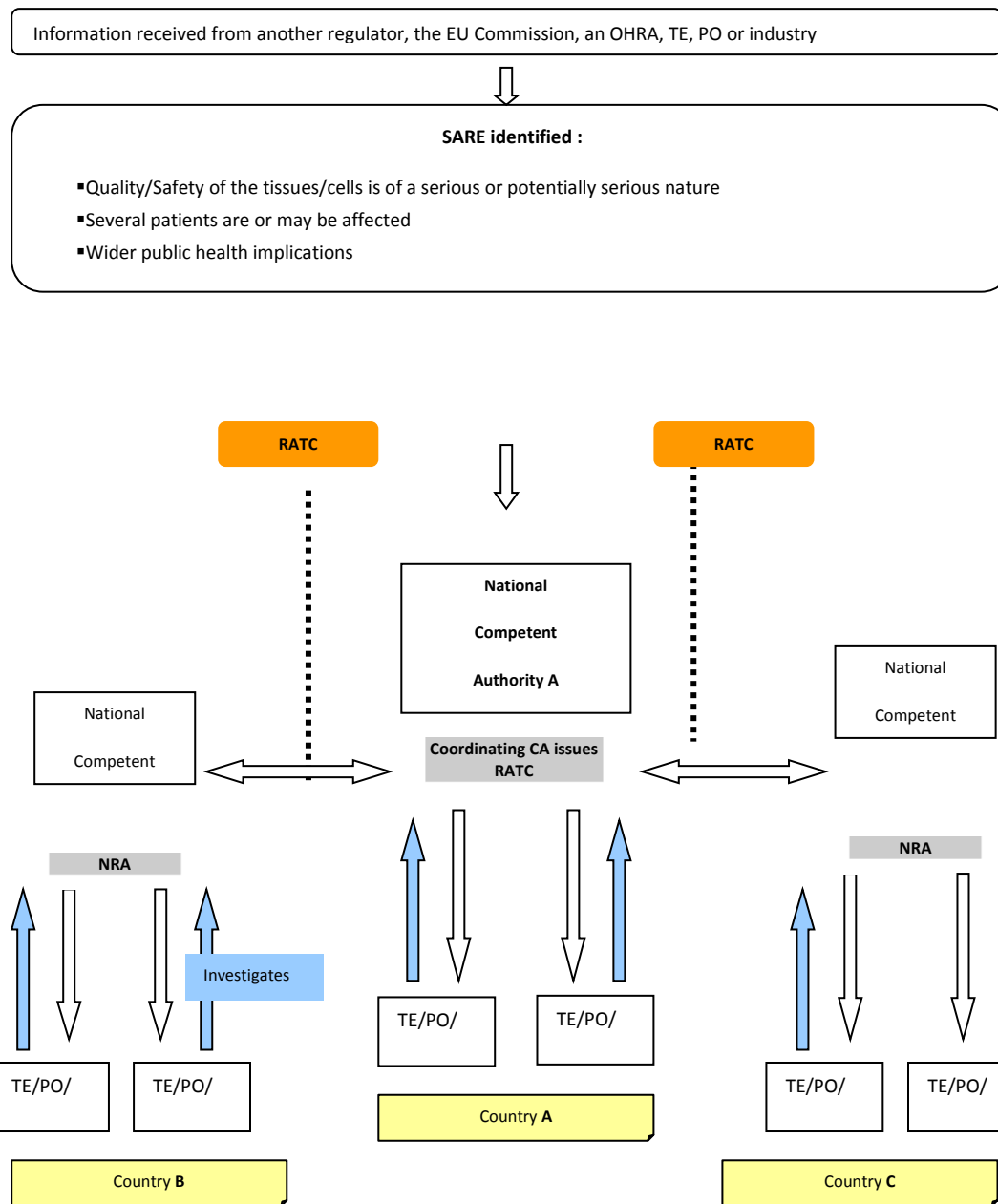
Stage	Examples of Risk	NRA/RATC	Comments
Procurement (Oocyte collection)	<ul style="list-style-type: none"> ▪Complication post-oocyte collection due to medical device failure (e.g. failure of needles for the same batch number) 	<p>If at least 1 patient impacted in several centers</p> <p>or</p> <p>if several patients in 1 TE</p> <p>⇒ National: NRA if material distributed in the country only</p> <p>⇒ EU/EEA: via RATC⁷¹ if distributed in several MS</p> <p>⇒ International: rapid alert if distributed outside the EU/EEA</p>	<p>⇒ Coordination with other vigilance systems (medical devices,...) in any case</p>
Processing and distribution (all laboratory procedures involving manipulation of gametes, embryos or reproductive tissues to include embryo transfer)	<ul style="list-style-type: none"> ▪Mix-up of gametes or embryos 	<p>⇒ National: NRA if gametes, embryo or tissues distributed in the country only (safety issues, ethical issue, societal issue through media)</p> <p>⇒ EU/EEA: via RATC⁷¹ if distributed in several MS</p> <p>⇒ International: rapid alert if distributed outside the EU/EEA</p>	<p>Misidentification of gametes involving ≥ 2 couples shall also trigger a rapid alert</p>
	<ul style="list-style-type: none"> ▪Loss of gametes, embryos or reproductive tissue 	<p>Only if related to equipment failure</p> <p>⇒ National: NRA if equipment distributed in the country only</p> <p>⇒ EU/EEA: via RATC if distributed in several MS</p> <p>⇒ International: rapid alert if distributed outside the EU/EEA</p>	<p>⇒ Coordination with other vigilance systems (medical devices or other) in any case</p>
Storage	<ul style="list-style-type: none"> ▪Laboratory materials (culture media) or culture equipment failure/ recall⁷¹ ▪Loss of reproductive material (gametes, embryos or cryopreserved tissue) due to failure of storage tank, container, freezer, IT software, ...) 	<p>⇒ National: NRA if materials or equipment distributed in the country only</p> <p>⇒ EU/EEA: via RATC⁷¹ if materials or equipment distributed in several MS</p> <p>⇒ International: rapid alert if</p>	<p>⇒ Coordination with other vigilance systems (medical devices,...) in any case</p>

⁷¹ This procedure is NOT applicable for human or veterinary medicinal, blood components or medical devices. However, where precautionary/corrective action taken is relevant, an exchange of information should be ensured with the national and European regulatory authorities responsible for these sectors.

	If no loss, significant cumulative evidence of non-conformity of material or equipment	<i>distributed outside the EU/EEA</i>
	<ul style="list-style-type: none"> ▪ Proven cross-contamination of cryo-stored reproductive material 	<p>⇒ <i>National: NRA if gametes, embryo or tissues distributed in the country only</i></p> <p>⇒ <i>EU/EEA: via RATC if distributed in several MS</i></p> <p>⇒ <i>International: rapid alert if distributed outside the EU/EEA</i></p>
Clinical follow-up	<ul style="list-style-type: none"> ▪ Proven infection of male or female partner resulting from ART process 	Rapid alert if new hazard (e.g. new type or unexpected infection or pollutant) or several patients concerned
	<ul style="list-style-type: none"> ▪ Preventable death or with potential public health implications 	<p>If several patients in 1 TE (cluster)</p> <p>If ≥ 1 patient in several TEs in the country (same pattern)</p> <p>⇒ <i>National: NRA</i></p>
	<ul style="list-style-type: none"> ▪ Genetic abnormality in donor diagnosed after gamete distribution or genetic disease diagnosed in offspring issued from donor ART. 	<p>If donor gives to > 1 patient in the country</p> <p>⇒ <i>National: NRA</i></p> <p>If donor's gametes distributed in several MS</p> <p>⇒ <i>EU/EEA via RATC</i></p> <p>⇒ <i>International: rapid alert if outside the EU/EEA</i></p>

The process of identifying and reporting an event that should form part of a national or an European alert is depicted in *Figure 2*.

Figure 2. Process flow for EU/EEA rapid alerts in ART



* ART v, T&C, medical devices, etc.

Recommendations

Any SARE or information that could have immediate direct or indirect consequences in other centres in the country and/or other countries (e.g. media, equipment, etc.) should trigger a rapid alert and urgent communication between TEs and CAs at national (NRA) and/or EU/EEA (via RATC) levels. Their initial reporting is to the national CA.

- The rapid alerts system in ART should be coordinated by the national CA.
- The consultation process (TE—CA) will allow the CA to trigger a rapid alert.
- Different vigilance systems at European, international levels should be coordinated.

Limitations

One important caveat of ART practice is that SARE occurring during or after ART therapy are not always immediately identifiable. Their delayed occurrence makes it difficult to realise a problem exists. As such, regular reporting draws practitioner’s attention to the possibility of such an occurrence and helps create systems that will reduce the incidence of SARE occurring in the first instance.

7. ART-SPECIFIC REPORTING TOOLS

7.1. ASSESSMENT TOOLS

The tools developed during the EUSTITE project for the vigilance and surveillance of tissues and cells have been adapted to ART practice and to issues specific to the field. Some remarks have also been added in order to facilitate the use of the tools, to clarify steps in the reporting or to explain some of the terms used.

Directive 2004/23/EC requires that all serious adverse events or reactions be notified to CAs. However, the legislation in some countries requires that also non-serious events or reactions be reported to the CA.

SAR Severity Grading

At least all adverse reactions graded as ‘Serious’, ‘Life-threatening’ or ‘Fatal’ should be reported to the CA. It is further recommended that adverse reactions in donors, even if graded as ‘non-serious’ should be monitored on a national or regional basis.

S A R	1. Non serious	Mild clinical/psychological consequences. No hospitalisation. No anticipated long term consequence/disability.
	2. Serious	<ul style="list-style-type: none"> - hospitalisation* or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following ART with non-partner gametes or donated embryos.
	3. Life-threatening	<ul style="list-style-type: none"> - major intervention to prevent death or - evidence of a life-threatening transmissible infection or - birth of a child with a life-threatening genetic disease following ART with non-partner gametes or donated embryos.
	4. Fatal	Death

* Hospitalisation for observation should be considered as non-serious¹⁰

¹⁰ All participants but the Agence de la biomédecine (ABM) and the Irish Medicines Board (IMB) agree that hospitalisation, when for observation only, should be considered as ‘non-serious’ criterion. The reason is that for ART professionals, hospitalisation in ART is often for observation only, patients being

SAR Imputability Grading

At least all Severe (serious, life-threatening or fatal) Adverse Reactions shall be graded in terms of imputability. Grades allocated might change in the course of an investigation and should generally be assigned at the point of initial notification and again at the completion of the reaction investigation.

Not assessable	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the ART process
1. Unlikely	Evidence clearly in favour of attributing to other causes than the ART process
2. Possible	Evidence is indeterminate
3. Likely	Evidence in favour of attributing to the ART process
4. Certain	Conclusive evidence beyond reasonable doubt for attributing to the ART process

SAR/SAE Impact Assessment

The Impact Assessment tool assists practitioners and regulators in planning their response to a given adverse reaction or event, taking into account broad consequences, beyond the individual patient affected or potentially affected.

- *Step 1 - Assessing probability of recurrence of SARE*

Recurrence assessment should be done with and without consideration of control measures.

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

discharged on the day after (if any medical treatment is required during hospitalisation then it should be classed as serious). The ABM considers that the usual definition of SAR and the one in Directive 2004/23/EC include 'hospitalisation' or 'prolongation of hospitalisation'. Moreover, hospitalisation is a usual criterion widely used to define SAR in all vigilance systems, e.g. pharmacovigilance, medical devices vigilance, etc. Therefore, it is not considered by ABM that it should be changed specifically for the purposes of ART vigilance and that if it is to be changed, a global review is necessary both at the European Commission and the World Health Organisation levels. The Irish Medicines Board (IMB) considers that, while these reports concern non-mandatory reports, for consistency, the definition of SAR in Directive 2004/23/EC should apply. In this respect, reactions which result in or prolong hospitalisation are considered reportable by the IMB. This is also consistent with pharmacovigilance reporting.

- Step 2 - Assessing impact/consequences of SARE should it recur

	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on ART service provision	Impact on availability of 'reproductive cells'
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage or some procedures postponed	Partial* loss of gametes/embryos for one couple
2	Significant	Serious	Damage to system – services will be affected for short period Many procedures cancelled or postponed	Partial loss of gametes/ embryos for some couples or total** loss for one couple
3	Major	Life- threatening	Major damage to system – significant time needed to repair Significant number of procedures cancelled	Partial loss of gametes/ embryos for all couples or total loss for few couples
4	Severe	Fatal	System destroyed – need to rebuild All procedures cancelled	Total loss of gametes/ embryos for all couples

**Partial loss*: loss of embryos, gametes without disappearance of the chance of procreation for one cycle.

***Total loss*: loss of embryos, gametes with disappearance of the chance of procreation for one cycle or final loss for the couple.

- Step 3 - Applying the impact matrix

Recurrence probability → Consequences ↓	Almost impossible	Unlikely	Possible	Likely	Almost certain
	1	2	3	4	5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15
Severe 4	4	8	12	16	20

- Step 4

The response of a tissue or cell bank or a health authority to a specific SAE/SAR should reflect the potential impact assessed by the impact matrix.

GREEN: The TE (*i.e.* ART centre, sperm bank, ART laboratory, etc.) manages the corrective and preventive actions and the CA files the report and keeps a 'watching brief'.

YELLOW: Requires interaction between the TE (*i.e.* ART centre, sperm bank, ART laboratory, etc.) and the CA which may request an inspection that focuses on the SAE/SAR and corrective and preventive actions to be followed up, including evidence of effective recall, where necessary. Written communication to professionals working in the field might be appropriate.

RED: CA will generally designate representatives to participate in developing or approving the corrective and preventive action plan, possibly a task force to address broader implications. Inspection, follow-up and written communication and possibly notification of health authorities in other countries where relevant.

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
- Increasing the detectability of the risk, or
- Reducing the severity of the consequences, should it recur.

7.2. ART VIGILANCE REPORTING FORMS

TEs (i.e. ART Centres, sperm banks, ART laboratories, etc.) in the context of this guidance are obliged to communicate to the CA without delay relevant information about suspected serious adverse reactions and events as referred to in part A and B of annex III and IV of 2006/86/EC. While the minimum reporting requirements are set out within the legislative framework, the SOHO V&S working group recognised the need to develop and broaden the scope of information required in the national reporting forms to support the analysis of ART case reports submitted.

A proposition for minimal items that should be entailed in National reporting forms is detailed in *Annex 3*.

8. GENERAL RECOMMENDATIONS

In addition to the recommendations related to specific characteristics of ART, broader ones apply, highlighting the role that CAs should play:

1. CAs should internally develop specific skills in ART including vigilance systems applied to ART,
2. Close cooperation between CAs and Health Professionals (*i.e.* professional societies) in the ART vigilance field should be strongly encouraged,
3. CAs should organize a coordination between ART Vigilance Systems and other vigilance systems (*e.g.* Pharmacovigilance, Medical Devices Vigilance),
4. TEs should advise ART Health Professionals about potential risks of SARE associated with ART treatment even in the case of CBRC. CAs should support TEs in doing this.

9. SUMMARY OF RECOMMENDATIONS AND ASSESSMENT TOOLS

TERMINOLOGY

Vocabulary in the context of ART

Donor

- i) Partner donation: in a couple, man and woman are considered donors to each other⁸.
- ii) Non-partner donation means that the donor is another person apart from the couple.
- iii) Surrogacy means a woman who carries a pregnancy for another individual or couple (full or partial surrogacy).

Tissue establishment (TE)

TE applies to establishments performing ART activities: ART centres, ART laboratories, sperm banks, etc.

Direct use (Art. 1 of Dir. 2006/17/EC)

This term is not applicable to reproductive cells and tissues that are being processed, cultured, banked or stored⁸.

Autologous

The terms ‘autologous donors’ and ‘autologous use’ apply in ART to cases of preservation of fertility. Procurement of oocytes and subsequent application in the same woman (in-vitro fertilisation (IVF) treatments) is an example of

‘autologous donation’.

Definitions of SAR and SAE in the context of ART

To complement the Directive 2004/23/EC,

1. The definition of SAR should be extended to the offspring in the case of non-partner donation, only for cases of transmission of genetic diseases.

Hospitalisation for observation should be considered as non-serious⁷².

2. The definition of SAE should include the total loss of germinal tissues, gametes or embryos for one cycle.

EQUIPMENT AND PRACTISES

Sensitivity of gametes and embryos, impact of culture media and equipment

When SAE reporting criteria are met (see 7.1 Assessment tools):

1. SAEs which are suspected to be linked to the culture media and equipment used in ART should be reported to the manufacturer and to ART vigilance to facilitate corrective and preventive measures, if appropriate, and to disseminate relevant information to other centres.
2. When the event is associated with a Medical Device, reporting is mandatory to the national CA for Medical Devices. Also the national CA for ART vigilance should be notified and coordination between these sectors should be organised.
3. If appropriate, an alert should be transmitted through the rapid alert system in cases of Medical Devices distributed nationally (via national rapid alert) or in several Member States (via the RATC system) (see Chapter 6 Reporting of SARE).

Organisation

Mix-ups

According to the Directive 2006/86/EC, article 6.2, misidentifications and mix-ups shall be reported as Serious Adverse Events. However, the following recommendations can be added:

when SAE reporting criteria are met (see 7.1 assessment tools), where a mismatching incident has occurred this should be reported as an SAE so that the cause can be investigated and the learning points shared in order to spread best practices

⁷² All participants but the Agence de la biomédecine (ABM) and the Irish Medicines Board (IMB) agree that hospitalisation, when for observation only, should be considered as ‘non-serious’ criterion. The reason is that for ART professionals, hospitalisation in ART is often for observation only, patients being discharged on the day after (if any medical treatment is required during hospitalisation then it should be classed as serious). The ABM considers that the usual definition of SAR and the one in Directive 2004/23/EC include ‘hospitalisation’ or ‘prolongation of hospitalisation’. Moreover, hospitalisation is a usual criterion widely used to define SAR in all vigilance systems, e.g. pharmacovigilance, medical devices vigilance, etc. Therefore, it is not considered by ABM that it should be changed specifically for the purposes of ART vigilance and that if it is to be changed, a global review is necessary both at the European Commission and the World Health Organisation levels. The Irish Medicines Board (IMB) considers that, while these reports concern non-mandatory reports, for consistency, the definition of SAR in Directive 2004/23/EC should apply. In this respect, reactions which result in or prolong hospitalisation are considered reportable by the IMB. This is also consistent with pharmacovigilance reporting.

across the sector.

1. All mix-up of gametes or embryos, whether partner or donor, should be reported as a SAE regardless at what stage the mix-up is detected. A full investigation should be initiated immediately after the mix-up is known. The causal factors should be noted and learning points shared.
2. The ART clinic should ensure that all of the patients involved are advised that the mix-up has occurred as soon as clinic staff becomes aware. Affected patients should be offered ad hoc counselling and support.

Traceability of gametes and embryos

When SAE reporting criteria are met (see 7.1 assessment tools), if a centre fails to trace gametes or embryos due to misrecording or loss of information, leading to the loss of gametes or embryos, this should be reported as a SAE to the CA.

Cross border management of SARE

4. CAs should encourage health professionals to report SARE even when it is established to be related to ART cross border care.
5. In the case of CBRC, the CA receiving the SARE notification should inform the other CAs involved without any delay.
6. CAs should encourage TEs to provide patients with information regarding possible adverse outcome. In particular, patients, couples and donors should be encouraged by health professionals to report adverse outcomes even in the context of cross border reproductive care.

SAFETY ISSUES

Complications of procurement and severe ovarian hyperstimulation syndrome

1. All SARE related to procurement, as well as severe OHSS according to a definition adopted in all EU MS, should be reported to a CA⁷³. These SARE should be notified to a specialist ART CA in countries where it exists.
2. A coordination between various systems of vigilance (*e.g.* medical device, pharmacovigilance, ART vigilance) should be organised both at the local (TE) and at the national levels (CAs).
3. Written information on major risks related to procurement should be available for donors, patients and couples.

Vigilance in relation to the Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

13. The birth of a child with a genetic disease following non-partner donation of gametes or embryos should be reported as a suspected **SAR**. It should be investigated as such so that further gametes, or embryos created from that donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
14. The diagnosis of a genetic disease in adults who have previously donated gametes or embryos to other couples should be reported as an **SAE** so that stored gametes, or stored embryos created from these donors' gametes, are not used without confirmation that they do not carry the gene(s) or chromosomal abnormality.
15. Gamete/embryo non-partner donors and recipients should be asked at the time of donation whether they wish to be informed in the event that it is later established that the resulting progeny carries a gene or chromosomal abnormality that might be relevant to the donor's own health or to the health of their own children (already born or still to be born).

⁷³ The reporting of non-mandatory SAREs was the topic of much discussion in the development of this document. A consensus was reached as regards the necessity of reporting SAREs whose reporting is not required by Directive 2004/23/EC (non-mandatory reporting). The CA to which it is reported depends on the organisation of the vigilance system in the MS.

To facilitate the effectiveness of SARE reporting and investigation in these circumstances, the following is recommended:

16. Couples having ART treatment with non-partner donated gametes or embryos should be strongly advised to inform any doctors subsequently treating the resulting child(ren) of the donor origin. They should understand that, in the unlikely event that a child will manifest an inherited condition, informing the clinic could protect further families. Consideration could be given to the development of a carefully worded standard leaflet explaining these issues that could be provided to all couples. In the analogous situation of allogeneic cord blood banking, some banks provide the donor mother with a leaflet asking her to contact the bank in the unlikely event that the donor child manifests a genetic or other disease, so that the transmission of the disease by transplantation of the cord blood can be prevented.
17. Gamete and embryo non-partner donors should be strongly advised to inform the clinic where they donated, in the event that they are subsequently diagnosed with any genetic disease. In this case also, a standard information leaflet for donors might be considered.
18. Specialist genetic centres should always consider whether a child manifesting a genetic disease might have been conceived with non-partner donor gametes or embryos. This issue should be raised immediately and openly with the parents in the interests of other potential offspring and when parents acknowledge the involvement of a non-partner donor, they should be strongly urged to contact the ART centre. This issue should be included in the appropriate professional standards and guidance for specialist genetic centres.

REPORTING OF SARE

Criteria for reporting SAEs

In ART vigilance, deviations from Standard Operating Procedures in TEs, or other adverse events, which may influence the quality and safety of tissues and cells should result in SAE reporting to the CA when one or more of the following criteria apply:

- Inappropriate gametes, embryos, germinal tissues have been released for clinical use, even if not used;
- The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors;
- The event resulted in a mix-up of gamete or embryo;
- The event resulted in a loss of traceability of gametes or embryos;
- Contamination or cross contamination;
- Accidental loss of gametes, embryos, germinal tissues (*e.g.* break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle.

Level of assessment of SARE: central or local?

Assessment tools should be used at both CA and Health Professional levels, but should not be mandatory for Health Professionals.

Triggering conditions for rapid alerts at national and international levels

Any SARE or information that could have immediate direct or indirect consequences in other centres in the country and/or other countries (*e.g.* media, equipment, etc.) should trigger a rapid alert and urgent communication between TEs and CAs at national (National Rapid Alert) and/or EU/EEA (via RATC) levels. Their initial reporting is to the national CA.

- The rapid alerts system in ART should be coordinated by the national CA.
- The consultation process (TE—CA) will allow the CA to trigger a rapid alert.
- Different vigilance systems at European, international levels should be coordinated.

GENERAL RECOMMENDATIONS

1. CAs should internally develop specific skills in ART including vigilance systems applied to ART,
2. Close cooperation between CAs and health professionals (*i.e.* professional societies) in the ART vigilance field should be strongly encouraged,
3. CAs should organize a coordination between ART vigilance systems and other vigilance systems (*e.g.* pharmacovigilance, medical devices vigilance),
4. TEs should advise ART health professionals about potential risks of SARE associated to ART treatment even in case of CBRC. CAs should support TEs in doing so.

ASSESSMENT TOOLS

For the assessment tools refer to the next two pages.

ART VIGILANCE PROPOSED REPORTING FORM

Refer to *Annex 3*.

ASSESSMENT TOOLS

ART V&S Assessment Tools

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

In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered to be a serious adverse event.

In addition, the definition of SAE should include the total loss of germinal tissues, gametes or embryos for one cycle.

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

The definition of SAR should be extended to the offspring in the case of non-partner donation, only for cases of transmission of genetic diseases;

Hospitalisation for observation should be considered as non-serious.

SAEs - Criteria

CRITERIA FOR REPORTING SAEs
Inappropriate gametes, embryos, germinal tissues have been released for clinical use, even if not used
The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors
The event resulted in a mix-up of gametes or embryos
The event resulted in a loss of traceability of gametes or embryos
Contamination or cross contamination
Accidental loss of gametes, embryos, germinal tissues (e.g. break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle

Severity (SARs)

Non serious	Mild clinical/psychological consequences. No hospitalisation. No anticipated long term consequence/disability.
Serious	<ul style="list-style-type: none"> - hospitalisation* or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following ART with non-partner gametes or donated embryos.
Life-threatening	<ul style="list-style-type: none"> - major intervention to prevent death or - evidence of a life-threatening transmissible infection or - birth of a child with a life-threatening genetic disease following ART with non-partner gametes or donated embryos.
Fatal	Death

*Hospitalisation for observation should be considered as non-serious

Imputability (SARs)

NA	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the ART process
1. Unlikely	Evidence clearly in favour of attributing to other causes than the ART process
2. Possible	Evidence is indeterminate
3. Likely,	Evidence in favour of attributing to the ART process
4. Certain	Conclusive evidence beyond reasonable doubt for attributing to the ART process

Impact (SARs and SAEs)

Step 1- Probability of recurrence

Step 2 – Consequences

Step 3 - Impact

The impact tool could be used also by the centres, but it should be optional

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

Recurrence assessment should be done with and without control measures

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on ART service provision	Impact on availability of 'reproductive cells'
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage or some procedures postponed	Partial* loss of gametes/embryos for one couple
2	Significant	Serious	Damage to system – services will be affected for short period Many procedures cancelled or postponed	Partial loss of gametes/embryos for some couples or total loss for one couple
3	Major	Life threatening	Major damage to system – significant time needed to repair Significant no. of procedures cancelled	Partial loss of gametes/embryos for all couples or total loss for few couples
4	Severe	Fatal	System destroyed – need to rebuild All procedures cancelled	Total** loss of gametes/embryos for all couples

**Partial loss*: loss of embryos, gametes without disappearance of the chance of procreation for one cycle.

***Total loss*: loss of embryos, gametes with disappearance of the chance of procreation for one cycle or final loss for the couple.

Recurrence → probability Consequences ↓	Almost impossible	Unlikely	Possible	Likely	Almost certain
	1	2	3	4	5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15
Severe 4	4	8	12	16	20

ANNEX 1. GLOSSARY

Autologous use: means cells or tissues removed from and applied in the same person. In ART, the terms ‘autologous donors’ and ‘autologous use’ apply to cases of preservation of fertility. Procurement of oocytes and subsequent application in the same woman (which happens in all forms of IVF-treatments) is an example of ‘autologous donation’.

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

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

Complications of procurement: complications associated with the procurement of reproductive tissues or cells such as haemorrhage, infection, etc.

Cross border reproductive care (CBRC): refers to the movement of patients within the EU Member States or to neighbouring non EU- countries to seek ART treatment outside their country of residence.

Direct use: *any procedure where cells are donated and used without any banking².* This term is not applicable to reproductive cells and tissues that are being processed, cultured, banked or stored⁷.

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

Donation: *donating human tissues or cells intended for human applications.*

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. Includes errors, preventable adverse events and hazards.

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

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

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 tissue or cell or to ART process.

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 organisations for collecting, reporting and documenting adverse occurrences impacting on patients that is inconsistent with planned care. *E.g.* Medication errors, equipment failures, violations. The culture of the organisation 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 means that the effectiveness of incident reporting can be limited.

Mix-up: is a serious adverse event (SAE) resulting from an error in the attribution of gametes or embryos that can occur at any stage of the laboratory or clinical process of assisted reproduction.

Non-partner donation: means that the donor is another person apart from the couple.

Partner donation: *means the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship.*

Patient: in ART, relates to individuals or couples seeking treatment. It includes healthy women with infertile male partner or without male partner.

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.

2PN: 2 pronucleus stage (2 PN): a two-pronuclear zygote (2PN); stage after the sperm has entered the ovum but in which the female and male pronucleus have not yet fused.

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, cells or embryos are applied.

Reproductive cells: means all tissues and cells intended to be used for the purpose of assisted reproduction.

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 patient or which might result in, or prolong, hospitalisation or morbidity. Directive 2006/86/EC says that in the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered to be a serious adverse event.

In addition, the definition of SAE should include the total loss of germinal tissues, gametes or embryos for one cycle.

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.

The definition of SAR should be extended to the offspring in the case of non-partner donation, only for cases of transmission of genetic diseases.

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

Storage: maintaining the tissues and cells under appropriate controlled conditions until distribution.

Surrogacy: a woman carries a pregnancy for another individual or couple (surrogacy can be full or partial).

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.

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.

In the field of ART, TE applies to establishments performing ART activities: ART centres, ART laboratories, sperm banks, etc.

Tissue: An aggregate of cells joined together by, for example, connective structures which perform the same particular function, e.g. ovarian tissue.

Traceability: the ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue

establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells.

ANNEX 2. ABBREVIATIONS

ADCA	Autosomal dominant cerebellar ataxia
AMH	Anti-Mullerian hormone
ART	Assisted reproductive technologies
CA	Competent authority
EUROCET	European Registry for Organs, Tissues and Cells
EUSTITE	European Union Standards and Training in the Inspection of Tissue Establishments
GIFT	Gamete Intra-fallopian Transfer
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
HFEA	Human Fertilisation and Embryology Authority (UK)
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In-vitro fertilization
LH	Luteinizing hormone
NRA	National rapid alert
PGD	Preimplantation genetic diagnosis
2PN	2 pronucleus stage
RATC	Rapid alert tissues cells
SAE	Serious adverse event
SAR	Serious adverse reaction
SARE	Combination of SAE and SAR
SNC	Severe congenital neutropenia
SOHO	Substances of Human Origin
TE	Tissue establishment
V&S	Vigilance and surveillance

ANNEX 3. ART VIGILANCE PROPOSED REPORTING FORMS

Initial Notification ART *(minimal items that a national form should contain)*

• Name of Reporting Establishment	(Include centre number if relevant nationally).
• Name of Reporting Person	(To include contact details).
• Report Identification number(s)	A system is required to link information back to this case to ensure that the SAR/SAE may be fully traceable in the future. This may for example consist of a case number assigned by the CA in addition to a unique identifying number assigned at the reporting site.
• SAR/SAE	Indication if considered to be a suspected serious adverse reaction or a suspected serious adverse event.
• Dates	Information surrounding relevant dates if known <i>i.e.</i> reporting date, date of procurement, date of human application, date of occurrence of SARE. (It would be useful to know the date of observation if different).
• Place	Place of occurrence of SARE if different from reporting establishment. Place of procurement (if relevant) Place of human application (if relevant).
• Type of ART procedure	IUI , IVF, ICSI, GIFT, gamete collection or procurement, etc. Some information specific to ART: <i>i.e.</i> is the incident involving, partner?/non-partner (donation)?/autologous (autopreservation)?/not applicable.
• if SAR	<ul style="list-style-type: none"> • Type of suspected adverse reaction. This is inclusive of such reactions as immunological mismatch, malignancy which can occur during a cryopreserved ovarian tissue graft due to reintroduced malignant cells etc.. • Subject of the suspected adverse reaction <i>i.e.</i> involving Donor non-partner/Donor partner /Recipient (woman) /Baby/Child (only in cases of genetic disease transmission involving non-partner donor)/Other <ul style="list-style-type: none"> - Infection transmission (viral, bacterial, other) <i>please specify</i> - If donor reaction <i>please specify (e.g. OHSS)</i> - Other <i>(please specify)</i>
• if SAE	<ul style="list-style-type: none"> - A brief description of the event is required. • Stage at which the event occurred:

Procurement/Collection, Testing/Transport/Processing (including cryopreservation and thawing)/Storage/Distribution (including import and export)/Materials/Other (*please specify*)

- Specification

Tissue and cells defect/Equipment failure/Human error /misidentification/mix-up/Other (*please specify*)

• Impacts on donor, recipient, couple	Impact or harm to donor, recipient or couple. It is important to identify the impact on the chance of procreation for the patient/couple involved (for one cycle). Indicate if this incident resulted in a possible/partial/total, loss of chance of procreation for the patient /couple involved.
• Reproductive tissue or cells implicated/affected	Indicate the type of reproductive tissues or cells involved. - Oocytes/Semen/Embryos/Reproductive tissue(s) – <i>specify (e.g. ovarian or testicular tissue)/Other – (specify).</i> - It is important to list the fate of any other implicated tissues and cells (if known) and provide detail of any damage or loss. In this regard it would be useful to include details of the gametes or embryos unique identification number on the form (if in place).
• Details of other sites or vigilance systems notified.	It is essential to know which organisations have been notified. Appropriate communication between supplying and receiving tissue establishments and other organisations or other vigilance systems may be required, <i>e.g.</i> medical device in the case of culture media. Include details of implicated medicinal products, equipment, materials etc. if applicable. CAs may need to communicate amongst themselves and/or to the European Commission.
• Reporting Criteria	It is recommended that the ART reporting criteria be included in the form <i>i.e.</i> <ul style="list-style-type: none">▪ Inappropriate gametes, embryos, germinal tissues have been released for clinical use, even if not used▪ The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors▪ The event resulted in a mix-up of gametes or embryos▪ The event resulted in a loss of traceability of gametes or embryos▪ Contamination or cross contamination▪ Accidental loss of gametes, embryos, germinal tissues (<i>e.g.</i> break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle.

Initial Notification - additional useful information

- **Communication**

It is useful to know if the recipient /donor are aware of the incident. In some cases this may be required.

- **Initial assessment (severity, imputability, impact assessment)**

It is recommended that the ART tools for evaluating and grading of SARE should be included in the form.

Conclusion form for SAR (minimal items that a national form should contain)

- **Conclusion**

- Confirmation of the serious adverse reaction or details of any change in classification

- **Clinical outcome**

- Complete recovery

- Minor sequelae/reduced chances of procreation

- Serious sequelae/total loss of chance of procreation

- Death

- Unknown.

- **Recommendations**

- Describe any general recommendations for preventive and corrective actions resulting from this SAR and add any other comments

- Does it have implication for other patients or centres?

Conclusion form for SAE (minimal items that a national form should contain)

- **Conclusion**

- Confirmation of the type of serious adverse event and details of any change in classification

- Final Consequences for this event

- Root cause analysis

- Corrective measures, description of any general recommendations for preventative and corrective actions resulting from this SAE.

- Does it have implication for other patients or centres?

ANNEX 4. EXAMPLES

The examples below are taken from the EUSTITE Pilot Report of June 2010. Please note that the lists below are not exhaustive.

Examples of reported SARs

Infection – Tissue and Cells
1. Reproductive Cells. Communicable disease or infectious event: Pelvipерitonitis ten days post artificial insemination. Peritoneal fluid +ve to <i>Escherichia coli</i> . Pt. Has history of ovarian endometrial surgery.
2. Ovarian abscess 20 days post oocyte retrieval. No difficulties during puncture. Patient very thin. <i>Clostridium sp.</i> identified.
3. Embryo. Pelvipерitonitis one month after intrauterine implantation of two embryos. Patient has history of endometriosis. Treatment by antibiotic and rehydration. Oocytes retrieval was managed with antibiotics. Late spontaneous abortion at 14 weeks of amenorrhoea (twin pregnancy)
4. Drainage of ovarian abscess 10 days post oocyte retrieval. The left ovary was difficult to reach during the puncture.
5. 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.
6. Twin pregnancy complicated by threatened premature delivery (20 weeks amenorrhea). Delivery at 21 weeks of twins (stillborn). Before oocyte retrieval, patient 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.
7. Pelvipерitonitis 13 days post oocyte retrieval. Origin unknown without any germ detected.
8. Utero-adnexal 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.
9. Ovarian abscess after artificial insemination
10. 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.

OTHER
11. Oocyte retrieval one and half months previously. Patient is pregnant. Suspicion of jugular thrombosis. Neck oedema, discomfort, no risk factor. Hospitalisation.
12. Menorrhagia 17 days post transfer. Small metallic fragment observed in blood. Fragment corresponded to part of transfer catheter. Patient had ectopic pregnant.
13. 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.

Examples of reported SAEs by stage of occurrence

Processing
14*. Embryo - Failure of witnessing process - embryo from Couple A injected for a second time with Sperm of couple B. Patient A lost 1 potentially fertilised egg. Patient B - lost 10 of 16 potentially fertilised eggs.
15. Total loss of two embryos from patient during the manipulation of the culture dish. The patient requires a new cycle of IVF.
16. 2 incubators were disconnected from the power source during 20 hours (T27°C instead of 37°C) Destruction of embryos. Total loss of chance for 5 couples.
17. 10 oocytes were fertilised by ICSI. No embryos/oocytes in dish during scheduled check after 2 days.
18*. Sperm. Woman inseminated with wrong partner sperm due to mix-up
Procurement
19. 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%.
20. Embryo. Contamination of culture media by <i>E. coli</i> . Analysis requested for straws and vaginal sampling.
21. Sperm. Existing donor discovered own father had malignant hypothermia.

Storage
22. Tank containing bone, semen, amniotic membrane - liquid nitrogen ran out - all tissues and cells thawed
23. 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 the hospital completely frozen whereas the medium should not be frozen. The ovary cannot now be stored.
24. 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.

* These examples are also referred to in "Human error" below

Examples of reported SAEs by classification

Tissue and cell defect
25. Sperm Donor later developed bowel disease. (Colitis ulcers). A child from this donor has around a 4-16% chance of inheriting this medical condition.
26. After donation, a sperm donor discovered his father had congenital malignant hyperthermia.
Equipment Failure refers to breakdown or problems with any piece of equipment used in the procurement, processing, testing, storage or distribution of tissue and cells.
27. Loss of three oocytes from five due to use of a pipette with known production error.
28. Loss or fracture of straws: Occurrence of a break of a high-security straw containing frozen sperm HIV infected.
29. Power failure resulting in shut down of the incubator and possible loss of 13 embryos and 5 microinjected oocytes.
Other – this category is used when defect is of unconfirmed origin
30. Contamination of culture dishes of four couples by <i>Acinetobacter lwoffii</i> . All embryos failed to progress.
31. 2 incubators were disconnected from the power source during 20 hours (T270C instead of 37°C) Destruction of embryos. Loss of pregnancy possibility for 5 couples.
Human error
14*. 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.
32. A technician inadvertently knocked over Petri dish containing embryos whilst trying to take another dish from the incubator.
18*. Woman inseminated with wrong partner sperm due to mix-up at clinic

*These examples are also referred to in "Processing" in the previous table

ANNEX 5. DISTRIBUTION LIST

Competent authorities for tissues, cells and ART:

A list of competent authorities per country is available on the EUROCET website: <http://www.eurocet.org>

