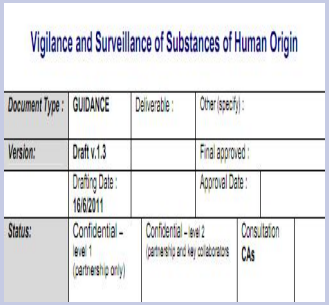
Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies



Vigilance and Surveillance of Substances of Human Origin

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European Union (Work Package 5)

EU Second Programme of Community Action in the Field of Health
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Recommendations and tools for the vigilance and surveillance in the field of assisted reproductive technologies (ART)

Salvo Reina (2011)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

framework of the European Union funded project 19
Vigilance and Surveillance of Substances of Human Origin
(SOHO V&S project, 20 www.sohovs.org)

Directive 2004/23/EC
of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of **human tissues and cells (EUTCD)**

Directive 2006/17/EC
of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

Directive 2006/86/EC
of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells !

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project 21
European Union Standards and Training for the Inspection of Tissue Establishments (www.eustite.org)

Competent authorities from Member States across the European Economic Area (EEA)

- 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

- 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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project 21
European Union Standards and Training for the
Inspection of Tissue Establishments (www.eustite.org)

Work Package 5 of the SOHO project was specifically dedicated to the 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 to assisted reproduction,

• making 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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project
European Union Standards and Training for the
Inspection of Tissue Establishments (www.eustite.org)

METHODOLOGY

- The exploratory workshop was attended by both health professionals and competent authorities,

- Smaller group attended the drafting meetings in order to facilitate the drafting work.

- Decisions on the recommendations were made by consensus.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project
European Union Standards and Training for the Inspection of Tissue Establishments (www.eustite.org)

RESULTS & SCOPE

- 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 tools adapted to ART vigilance.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project
European Union Standards and Training for the
Inspection of Tissue Establishments (www.eustite.org)

CHARACTERISTICS OF ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

Reproductive cells or embryos are different from other cells in that

- oocytes and embryos are in **limited number**

- reproductive cells are particularly **sensitive to external factors** (culture media, laboratory equipment, pollutants, etc.).

- any defect may have a **diffuse 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 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 disease.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project
European Union Standards and Training for the
Inspection of Tissue Establishments (www.eustite.org)

CHARACTERISTICS OF ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

Reproductive cells or embryos are different from other cells in that
The following aspects of ART need to be addressed and outlined :

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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

ART VIGILANCE

Overview of ART vigilance system in the EU

SOHO V&S project was completed by 32 countries including 27 Member States (MS) and aimed at gathering detailed information on systems in place for the 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 (V&S systems in place for an average of 3 years).

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

ART VIGILANCE

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****, which helps improving practices and sharing learning points.*

Finally, there is a need for coordination with other vigilance systems in place.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Assisted Reproductive Technologies (ART) can be defined as

1) **all treatments** that include 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).

2) It also includes the cryopreservation of gametes, embryos or germinal tissues for preservation of fertility.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Vocabulary

EUSTITE project vocabulary should be adapted to the field of ART.

It was pointed out that the terms used in the EUTCD are more appropriate for other tissues and cells than for ART.

In November 2007, the European Society of Human Reproduction and Embryology (ESHRE) published a position paper 7 on the EU Tissues and cells Directive 2004/23/EC.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Vocabulary - terminology used in the European Tissues and Cells Directive (EUTCD) should be understood as in the following example :

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:

1) **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 other 7

.

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

3) **Surrogacy** (not defined in the Directive) means that a woman carries a pregnancy for another individual or couple (surrogacy can be full or partial).

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Vocabulary - terminology used in the European Tissues and Cells Directive (EUTCD) should be understood as in the following example :

Tissue establishment (TE)

The definition in article 8 of Directive 2004/23/EC applies and 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** should be understood e.g. as ART centres, sperm banks, etc.*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Vocabulary - terminology used in the European Tissues and Cells Directive (EUTCD) should be understood as in the following example :

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

In the Directive, it means

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

.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Vocabulary - terminology used in the European Tissues and Cells Directive (EUTCD) should be understood as in the following example :

Autologous

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 (which happens in **all forms of 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 infertile male partner or without male partner

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Serious Adverse Reactions (SARs)

1. According to the **EUTCD** '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'.

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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

Definitions of serious adverse events (SAEs)

2. According to the EUTCD ‘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.’

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.

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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EUSTITE project

TERMINOLOGY

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 reporting data in the annual report by the CAs (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 is proposed: **a) Sperm , b) Oocyte**

Note : 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).

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

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 that attempts to **reproduce the accurate in vivo environment**.

The handling and the culture of human embryos in vitro requires standards which need to be met to ensure their safety and quality prior to release. Caution has to be taken during handling and incubation of gametes and embryos in ART procedures 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**
- **Air transmitted exposure of toxic agents**

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

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

Gametes and embryos don't have the same sensitivity to inappropriate temperature!

Oocytes are extremely sensitive to it. Even mild cooling affects the oocyte micro tubular spindle, cortical microfilaments and the polar microtubule-organising centres.

It is well demonstrated in animals as well as in humans that these alterations are temperature and time dependent and often irreversible after re-warming, risking aneuploidy of the resulting embryo.

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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

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

Freezing can have a negative impact on gametes and embryos' survival. The impact of temperature's fluctuations during cryopreservation on sperm is less worrying due to the high number of male gametes and their reduced amount of cytoplasm.

This is not the case for embryos and especially 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 current state of art.

Once frozen, adequate storage in liquid nitrogen doesn't affect the quality of oocytes or embryos.

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

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 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 correct 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; it takes typically several minutes to recover the designated gas balance, depending on the type of incubator;
3. While 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 incubator .

All these factors may influence the actual medium pH and have a deleterious impact on the normal fertilization and embryo development. This phenomenon is well known in ART centres and periodic monitoring of actual pH in the media and CO2 levels in the incubators are performed.

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

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 (**270 –285** mOsm/L). Maintaining osmolarity in media requires saturated air with water vapour. 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 pressure

Increased osmolarity can occur:

1. During preparation of culture dishes and medium handling ;
2. During 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 (dish preparation (quick handling), using oil whenever possible) and incubation using high relative humidity incubators when culturing in open systems.

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

Air transmitted exposure of toxic agents

Incubated cells are largely unprotected and it is likely that cells grown in vitro are 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:

1. - **Volatile organic compounds (VOC) produced by industry**
2. - **Small inorganic molecules (N2O, SO2, CO)**
3. - **Substances from building materials (such as aldehydes and acrolein)**
4. - **Released by pesticides or aerosols containing butane or isobutane as propellant**
5. - **Liquids as floor waxes that contain heavy metals.**

They can be originated **inside of 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.).

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

Air transmitted exposure of toxic agents

There has been no valuable toxicological evaluation of air and its effects on fertilisation an development outcomes after ART. In a case report, the blastocyst rate significantly dropped at the time of installation of floor tiles. There is **limited conclusive information available** on a possible impairment of embryo development due to increased VOC concentration. There is information on the **detrimental effect of aldehydes** on pregnancy outcome. Mouse embryos development is inversely correlated with the concentration of acrolein

.

When air pollutant testing is performed , data obtained should be monitored and corrective measures taken if necessary. Fluctuations in air quality only, have to be registered: **there is no need to report them as SAE**. **It cannot be determined that air quality the cause for decrease or failure in fertilisation.**

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

Any problem detected in compressed CO2 or plastic hardware or device that off-gas potentially toxic compounds should result in a rapid alert if there is a potential consequence for other TE.

Most of the cases will only affect the TE concerned and should not result i rapid alerts.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

Impact of medical devices on gamete and embryo viability and quality

A large spectrum of medical devices is available for ART. As defined by the Dutch society of Clinical Embryologists and by the EU medical device directive, 'all devices which directly or indirectly make contact with biological material should be considered as medical devices'

The devices used in ART that meet the definition of a medical device may be qualified and regulated as medical devices, as laid out in Directive 93/42/EEC, taking into consideration the principal intended purpose of the product

According to the EUTCD 2006/86, critical reagents and materials must meet documented requirements and specifications and when applicable the requirements of 93/42/EEC and 98/79/EC Directives

In the revised Guidelines on a Medical Devices Vigilance System (MEDDEV 2.12-1 rev 6) **it has not been taken into consideration that medical devices in ART procedures do not act directly on the patients, but rather on reproductive cells**.

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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

Impact of the culture media (p. 1)

Many different culture media are used in ART, during culture and processes (flushing, sperm preparation, denudation, freezing and thawing, etc.). The media intend to provide the appropriate physical and chemical conditions for imitating the in vivo condition, for maintenance of the physiological homeostasis required to support and promote fertilisation and in vitro development. They also intend to minimise cellular damage during the processes. As they are in direct contact with gametes and embryos they are considered as **critical material**.

They are composed of a mixture of physiological inorganic salts, energy sources, amino acids and proteins, and 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 sensitive enough for the results to be extrapolated to human oocytes and embryos**.

Collection of knowledge about the optimal composition of culture media according to the different stages of embryo development (for energy substrates, growth factors, cytokines, proteins and other compounds) is still in progress.

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

Impact of the culture media (p. 2)

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.

However, it must be noticed that the extensive quality testing compliance with the level for a **CE mark does not necessarily take enough into account the ART** features and it cannot be excluded that this might inhibit the development of appropriate media.

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

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) 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 may occur. It could be a rough break down of equipment as well as an insidious deleterious process. Both have to be detected as soon as possible.

The defect of such **critical equipment might involve gametes and embryos** of several couples and leads to a lack of, delayed or inappropriate ART outcome and finally a **loss of chance of pregnancy**.

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

Practical examples of reportable SAEs : HOW IT WOULD SOUND LIKE ?

Non conformity of culture medium

In 2010, a Danish ART centre noticed a white precipitate in a bottle of culture medium. In addition, 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 manufacturer recalled the affected product distributed in several EU MS. A rapid alert was triggered through all EUMS.

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

EQUIPMENT AND PRACTICES

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

Practical examples of reportable SAEs : HOW IT WOULD SOUND LIKE ?

Non conformity of Environmental contamination

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

Serious Adverse Reactions and Events (SARE)

EQUIPMENT AND PRACTICES

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

Practical examples of reportable SAEs : HOW IT WOULD SOUND LIKE ?

Non conformity of Equipment breakdown

In February 2008, several reports of SAEs linked to a breakdown of embryos freezers led to a loss of embryos for some of them. Further to investigation in collaboration with the manufacturer, a joint action with the medical device vigilance officers evidenced that the cause was a change in the fabrication of the gas valve of some freezers. All the freezers concerned have been replaced by the manufacturer.

EQUIPMENT AND PRACTICES

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

Recommendations

When SAE reporting criteria are met (see 8.1 assessment tools):

1. SAEs which are suspected to be linked to the **culture media** and equipment used in ART should be **reported to ART vigilance** in order to spread information, to inform the manufacturers and to decide corrective and preventive measures if appropriate.

2. When the event is associated with a **medical device**, reporting is mandatory to the CA for Medical Devices, but also the **CA for ART vigilance** should be notified and **coordination between these vigilance systems should be developed.**

3. If appropriate, an alert should be transmitted through the rapid alert system in cases of medical devices distributed **nationally or in several Member States** (cf. Chapter 7 Reporting of SARE).

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

Organisation

Organisation

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**. However it is suggested that 1:50,000 to 1:100,000 may occur. In a well regulated clinic the risk should be extremely low.

Misidentifications and mix-ups, according to the Directive 2006/86/EC, article 6 paragraph 2, shall be reported as serious adverse events. **A 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 of the clinical process of assisted reproduction (e.g. gamete collection, insemination, embryo transfer, freezing). The reporting of mix-ups regardless of whether it results in a live birth or not, is relevant to ART vigilance reporting and, consequently, is included in the scope of the EUTCD 2006/86/EC.

Misidentification due to a patient's voluntary action is also to be reported to ART vigilance but is **related to a fraudulent activity**. SOHO project addresses specifically (WP 6).

The consequences of mix-ups are diverse. Mix-ups of gametes and embryos during ART may or may not result in the birth of a baby. However the effects on the patients involved and the reputation of assisted reproduction may be severe regardless of the result. Advers publicity often occurs, which has a **detrimental impact on ART often at a national level an even internationally**.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

Organisation

Risk factors

Many processing steps – egg collection, sperm preparation, fertilisation, embryo culture and transfer – involve moving 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.

1. Numerous people are involved (the couple, biologists, technicians, clinicians, operating theatre staff, surgeons, administrative staff, etc.)
2. Work overload of the staff
3. Poor witnessing processes
4. 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.

Serious Adverse Reactions and Events (SARE)

Organisation

Consequences for the patients

- Lack of traceability:
  Errors in samples labeling 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 labeled)
- 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: for example 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 small 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.

Serious Adverse Reactions and Events (SARE)

Organisation

Consequences on the ART clinics and their staff

1. Morale of staff involved will be harmed with possible damage to professional reputation

2. Trust in the ART process and the clinic will be reduced

3. Legal action may be taken by patients with possible reporting to professional organisation.

Mismatching incidents result from checking errors that occur at different points in healthcare processes including laboratory testing (Plebani, 1997). 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 partners or intended donors) prior to fertilisation and*
- *to matching the correct embryos to the correct patient prior to embryo transfer.*

There have been a few number of publicised cases 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 (see Annex 7 References).

Serious Adverse Reactions and Events (SARE)

Organisation

Answers

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, effective and proactive tools for reducing the risk of mix-ups do exist and should be considered (e.g. active contemporaneous double witnessing, bar coding, etc.).

Vigilance and reporting can also **raise awareness among ART health professionals** and ensure clinics look at their adherence to risk and quality standards. Reporting and monitoring mix-ups will ensure that should a greater number of mix-ups arise in a clinic that regulatory action can be taken.

Vigilance is **complementary to but does not substitute for an effective internal quality management system**. If there is poor compliance with or insufficient quality systems in place then mix-ups either may occur more frequently or may not be detected early enough.

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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

Organisation

All mismatching incidents which have involved:

1. *inseminating a woman with sperm from the non intended partner or donor*
2. *fertilising eggs with sperm from the non intended partner or donor*
3. *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.

Recommendations

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 SAE reporting criteria are met (see 8.1 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. 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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

Organisation

Vigilance in relation to the traceability of processing gametes and embryos

The EUTCD (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 (defined in article 2 of Directive 2006/86/EC).

“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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

Organisation

Vigilance in relation to the traceability of processing gametes and embryos

Issues involving gametes and embryos

In vitro fertilisation involves the creation of embryos outside the body.

In most cycles of IVF more embryos develop than 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.

Centres also store cryopreserved gametes for patients and donors.

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

This raises the 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?

Serious Adverse Reactions and Events (SARE)

Organisation

Vigilance in relation to the traceability of processing gametes and embryos

Answers

*In the majority of cases this would be due to a **simple typographical** error which would be classed as a near miss because the gametes / embryos would be located quickly.*

*It should also 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 Competent Authority.*

*If a centre fails to be able to locate cryopreserved gametes or embryos this should be **reported as an 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 an SAE to the CA.

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

Organisation

Vigilance in relation to the traceability of processing gametes and embryos

Issues involving data related to products and material

ART centres are expected 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 has come into contact with particular gametes or embryos, which can affect their quality or safety or can affect the health of a patient should be reported as an SAE to the CA.*

Answers

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

Say a manufacturer or a CA issued an alert to fertility centres informing them that a particular culture media or catheter, dish etc had had a toxic affect on embryos or had caused an effect on the patient (e.g. number of patients had had an adverse reaction to a particular make of catheter) and a centre cannot trace which patients had received treatment with embryos cultured or transferred with the defective media / equipment; this should be reported as a SAE because 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**.*

Serious Adverse Reactions and Events (SARE)

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

*Cross border reproductive care (**CBRC**) refers to the movement of patients within the EU MS or to neighbouring non EU-countries to seek ART treatment outside their home country.*

*The movement of patients within the EU MS to seek medical treatment, referred to as 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. It is well known that **patients from different EU MS travel abroad to look for fertility treatment**.*

This phenomenon has been increasing for the last 10 years and is now well entrenched.

However there are no available data to estimate the phenomenon, except for a few studies including an ESHRE study that compiled data from six countries

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

The motivations for travelling abroad have been studied among selected European countries and on a larger scale. Motivations, vary from a country to another:

- *legal restrictions: infertility method treatment not legally authorised in the country (e.g.: IVF with donor, IVF in post-menopausal women, insemination of single women, preimplantation genetic diagnosis (PGD),*
- ***waiting-time** duration for a specific method due to eggs/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 experts,*
- *search for **better success** rates including opportunity to have more embryos replaced than recommended in the home country,*
- ***cost of treatment** (when not reimbursed in the home country), financial compensation for donors.*

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

*The principle of the free movement of patients across EU in order to obtain health care set up by an EU directive is admitted. 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. Moreover a new version clarifies patient's rights to access safe and good quality treatment across EU borders*

*Arrangements may exist between clinics or practitioners from different countries in recommending clinics abroad. However most of the **patients do not seek referral** from a physician and select treatment and clinic by themselves. A wide range of information on all types of methods of treatment is accessible on the web through **patient associations, social networks** or directly by the websites of clinics. This makes the selection of the clinic and of the treatment particularly easy for patients, since all procedures are detailed on the websites in several European languages. Specific information on travel and accommodation may also be given by the clinic. A few clinics propose **appropriate counselling for recipients**.*

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

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

Since cross-border reproductive care is a very attractive and developing market, it is not possible to get reliable information from the clinics themselves.

Lack of transparency and exaggerated success rates may be frequent.

Patients may have treatment and later leave the country in which the service was offered and return to their place of residence. The same situation may 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, infection, etc. may emerge once the **patients have returned to their home country**. Many patients may be **unwilling to share information** about having performed ART abroad (i.e. treatment with donor gametes) or simply do not associate SARE with the treatment they received.*

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

According to the EUTCD, cross-border SARE are within the responsibilities of the TE offering the service to investigate and inform the local CA

.

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 any such SARE.

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

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

Answers

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 unwilling to reveal that they had ART abroad once back home, patients should be reassured that medical secrecy 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.*

Organisation
Cross-border management of SAREs

Cross-border management of SAREs

Recommendations

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 CRBC, the CA receiving the SARE notification should inform all other CAs concerned without any delay.

3. CAs should encourage TEs to promote 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.

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

*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 represents 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** and 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 it remains difficult to assess because of the different classifications used.*

There is a need for a consensus regarding the OHSS classification.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

*The current concern is not to determine the best treatment of an existing OHSS. It aims at determining the **way of prevention** given there is no completely curative therapy for OHSS. **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 oocyte retrieval has been performed in order to limit the impact of the syndrome: luteal support, additional medical interventions (albumin administration, dopamine agonist), 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 HCG. Indeed the administration of HCG for luteal support is associated with an increase in the occurrence of OHSS.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Cryopreservation of embryos and cancelling the transfer of fresh embryos seem to be the most efficient alternative in some cases, and in most studies the ***rate of pregnancy after frozen embryo transfers is as high as when using fresh embryos****.*

Even more effective could be the triggering of ovulation with GnRH agonists but only in patients treated by GnRH antagonists. Nevertheless, pregnancy rates appear to be reduced following the latter option. Actually, at risk patients 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.

Data from ART vigilance show that severe OHSS are reported through this system by the professionals. There is a need for further studies to evaluate the interest of recombinant LH*.*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

The article 11of the EUTCD describes 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 coverage of these definitions means 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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Many Member State 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.). The survey carried out as part of the WP 4 SOHO V&S project showed that:

- *19 (68%) MS required reporting SARs in donors even if the quality and safety of the tissues or cells have not been affected,*
- *Among the countries, 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.*

*The European Commission recognised the value of these data in the context of tissue and cells regulation and **invited Member States to submit donor reactions reported to the CA on a voluntary basis in the annual report**.*

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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Issues

Ovarian stimulation is an intended step which is fully part of the ART treatment.

However, in some cases, ovarian hyperstimulation may lead to adverse reactions that could range from mild to severe. So far, not all OHSS may be prevented.

Severe OHSS should be considered as an SAR and notified to a vigilance system (ART vigilance, pharmacovigilance).

In France, an OHSS classification has been developed after a consensus work with professional societies (see next …).

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

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 under the liver***
  - ***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) / hepatic dysfunction (liver enzymes * 3 normal values)***
- ***Grade C : organ failure***
  - ***acute respiratory distress syndrome***
  - ***renal insufficiency***
  - ***other complications : thrombosis, adnexa torsion***

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Most of the OHSS reports fall in the scope of ART vigilance system. Experience in 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 the 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 who perform IVF for themselves (partner donor). Given that ***pregnancy is in itself a risk factor for OHSS****, most severe cases usually are observed in women who perform IVF for themselves at early pregnancy stage.*

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

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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Complications of procurement and Severe Ovarian Hyperstimulation Syndrome

Recommendations

1. *All SARE related to procurement, as well as severe OHSS according to a definition adopted in all EU Member States, should be reported to a CA. These SARE should be **notified to a specialist ART CA** in countries where it is in place.*

2. *Written information on major risks related to procurement should be **available for patients and couples**.*

3. *A coordination between various **systems of vigilance** (e.g.: medical device, pharmacovigilance, ART vigilance) should be in place both at the **local level (TE) and at the national level (CAs)***

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission 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, 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**), Hypertrophic Cardiomyopathy, Autosomal Dominant , Cerebellar Ataxia (**ADCA**) and Opitz Syndrome, Neurofibromatosis type 1 (**NF 1**), Autosomal recessive Polycystic Kidney Disease (**ARPKD**), Congenital adrenal hyperplasia (**CAH**) and Phenylketonuria (**PKU**)*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes

Issues

*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 population concerned has a higher than usual risk of having a genetic condition e.g. Beta Thalassaemia in Mediterranean population

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes

Questions eraising from cost-benefit genetic incidence prediction in ART

i) should the transmission of a genetic illness from a gamete donor be considered as an 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?

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes

Answers
Supply of gametes

Given that 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, 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 defect
Another donor transmitted Hypertrophic Cardiomyopathy to 9 children

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 inheritance
The first affected child was conceived just before the HFEA was created in 1991 in the UK; the regulator restricted to 10 the number of offspring from one donor.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes

Importance of vigilance

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; an 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 an 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 women 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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes

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.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes Recommendations

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).

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

Transmission of Genetic Diseases by ART with Non-partner Donor Gametes

Vigilance on theTransmission of Genetic Diseases by ART with Non-partner Donor Gametes Recommendations

To facilitate the effectiveness of SARE reporting and investigation in these circumstances, 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**.*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES
REPORTING OF SARE

General requirements

The notification requirements for SAREs are set out in article 11 of EUTCD and in articles 5 (SARs) and article 6 (SAEs) of directive 2006/86/EC. However, the European Commission accepts annual reports including donors' reactions reported by member states 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****.*

The EUTCD requires that all SARs be notified to the CA, but in some Member States, the legislation requires that ***non-serious adverse events or reactions also be reported as well****.*

In addition to the ***minimum reporting requirements*** *set out in Annexes III and IV of 2006/86/EC, an extended list of minimal items that should be included in a national form has been developed and is available in Annex 4.*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

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.*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES
REPORTING OF SARE

Responsibilities

The directives describe how SARE should be reported within the Member States (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 tissue establishment (TE) does not preclude a PO or an ORHA from also directly notifying the CA.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Level of assessment of SARE: central or local?

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

Recommendation

An assessment using the assessment tools should be made at both CA and professional levels, but should not be mandatory.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

*The purpose of this chapter is to identify potential areas of risk, where **indirect or direct harm could result**, with the final aim of identifying SAREs that will trigger a rapid alert at national and/or international levels.*

The purpose of identifying and reporting such ART-specific SAREs is four fold:

a. to reduce harm to patients and child-to-be
b. to alert other practitioners of potential areas of risk
c. to make national and international ART stakeholders aware of potential public health implications
d. to take appropriate preventive/corrective actions.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

Consequences on other patients / donors / individuals / TEs

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

Rapid alerts are co-ordinated 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 ssued across the EU or globally.

Rapid alerts should only be issued in exceptional circumstances, i.e. those alerts whose urgency and seriousness cannot permit any delay in transmission and follow up.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels
Consequences on other patients / donors / individuals / TEs

Each of the following criteria must be satisfied for issuing of ***rapid alerts*** *within a member state, or across*

Member States:

- ***SAE/SAR of a serious or potentially serious nature***
- ***Potential risk to other individuals or other TEs***
- ***Wider public health implications,***
- ***Rapid intervention needed: preventive or corrective measures, urgent communication.***

The system should not be used for the transmission of less urgent information (e.g. single event occurring at the national level). It is not to be used for advising other CA's of single incidents, unless those incidents have a clear implication for public health in other countries.

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

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

International alerts

Reasons for triggering a rapid alert at the international level are that:

- *material or equipment can be commercialised and distributed in several countries,*
- *donors, patients or individuals (e.g. in cases of cross-border reproductive care,...) can travel abroad for ART treatment,*
- *gametes can be distributed in several countries (e.g. sperm banks distributing worldwide) for infertility treatment.*

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES
REPORTING OF SARE

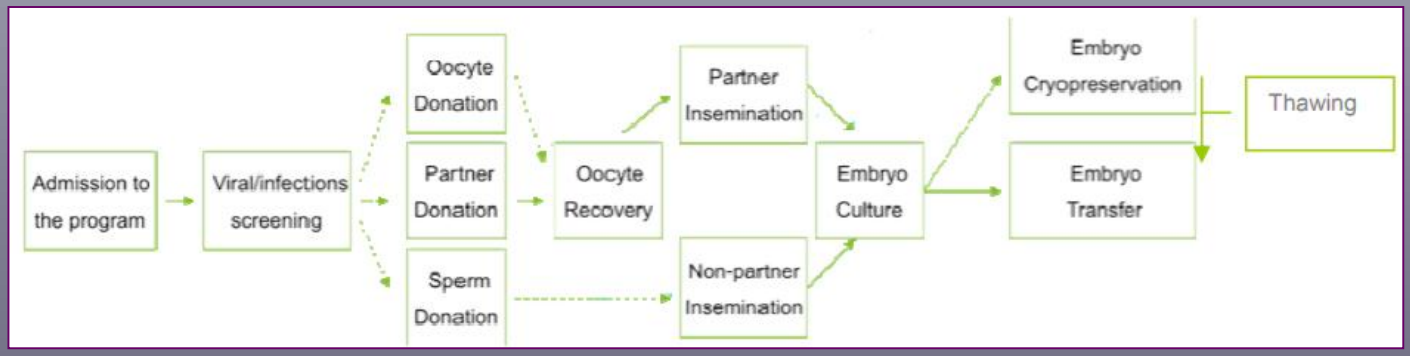
Triggering conditions for rapid alerts at national and international levels

Triggering conditions

ART treatments are medical interventions. As such, risks that are present in the practice of medicine translate to ART practice, too. Yet, not all SARE occurring in ART practice imply a rapid dissemination of information at national or international level.

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 the Figure.

Both partner and non-partner donations are included.



Serious Adverse Reactions and Events (SARE)

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Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES
REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

Triggering conditions

The proposed list of rapid alerts focuses on specific stages such as: screening, procurement, testing, processing, storage, distribution and clinical follow up.

Stage	Examples of Risk	Comments
Procurement (Oocyte collection)	**Complication post-oocyte collection due to medical device failure** (e.g. failure of needles for the same batch number)	If >1 patient impacted in several centers or if several patients in 1 TE 1) National rapid alert if material distributed in the country only 2) International rapid alert if distributed in several MSs 3) Coordination with other vigilances (medical devices, ...) in all cases
Processing and distribution (all laboratory Procedures involving manipulation of gametes, embryos or reproductive tissues to include embryo transfer)	> Mix-up of gametes or embryos > Loss of gametes, embryos or reproductive tissue	> National rapid alert if gametes, embryo or tissues distributed in the country only (safety issues, ethical issue, media coverage) > International rapid alert only if distributed in several Member States (N.B: misidentification of gametes involving ≥ 2 couples shall also trigger a rapid alert) **Only if related to equipment failure** National rapid alert if equipment distributed in the country only International rapid alert if distributed in several Member States Coordination with other vigilances (medical devices, ...) in all cases

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Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES
REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

Triggering conditions

The proposed list of rapid alerts focuses on specific stages such as: screening, procurement, testing, processing, storage, distribution and clinical follow up.

Stage	Examples of Risk	Comments
Storage	Laboratory materials (culture media) or culture equipment failure/ recall Loss of reproductive material (gametes,embryos or cryopreserved tissue) due to failure of storage tank, container, freezer, IT software, …) If no loss, significant cumulative evidence of non-conformity of material or Equipment	National rapid alert if materials or equipment distributed in the country only International rapid alert if materials or equipment distributed in several Member States Coordination with other vigilances (medical devices, ...) in all cases
	Proven cross-contamination of cryo-stored reproductive Material	> National rapid alert if gametes, embryo or tissues distributed in the country only > International rapid alert if distributed in several Member States

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

Triggering conditions

The proposed list of rapid alerts focuses on specific stages such as: screening, procurement, testing, processing, storage, distribution and clinical follow up.

Stage	Examples of Risk	Comments
Clinical follow-up	Proven infection of male or female partner resulting from ART process Preventable death or with potential public health implications Genetic abnormality in donor diagnosed after gamete distribution or genetic disease diagnosed in offspring issued from donor ART.	Rapid alert if new hazard (i.e. new type or unexpected infection) or several patients concerned If several patients in 1 TE (cluster) - If ≥ 1 patient in several TEs in the country (same pattern) National rapid alert - If donor gives to > 1 patient in the country National rapid alert - If donor's gametes distributed in several member states International rapid alert

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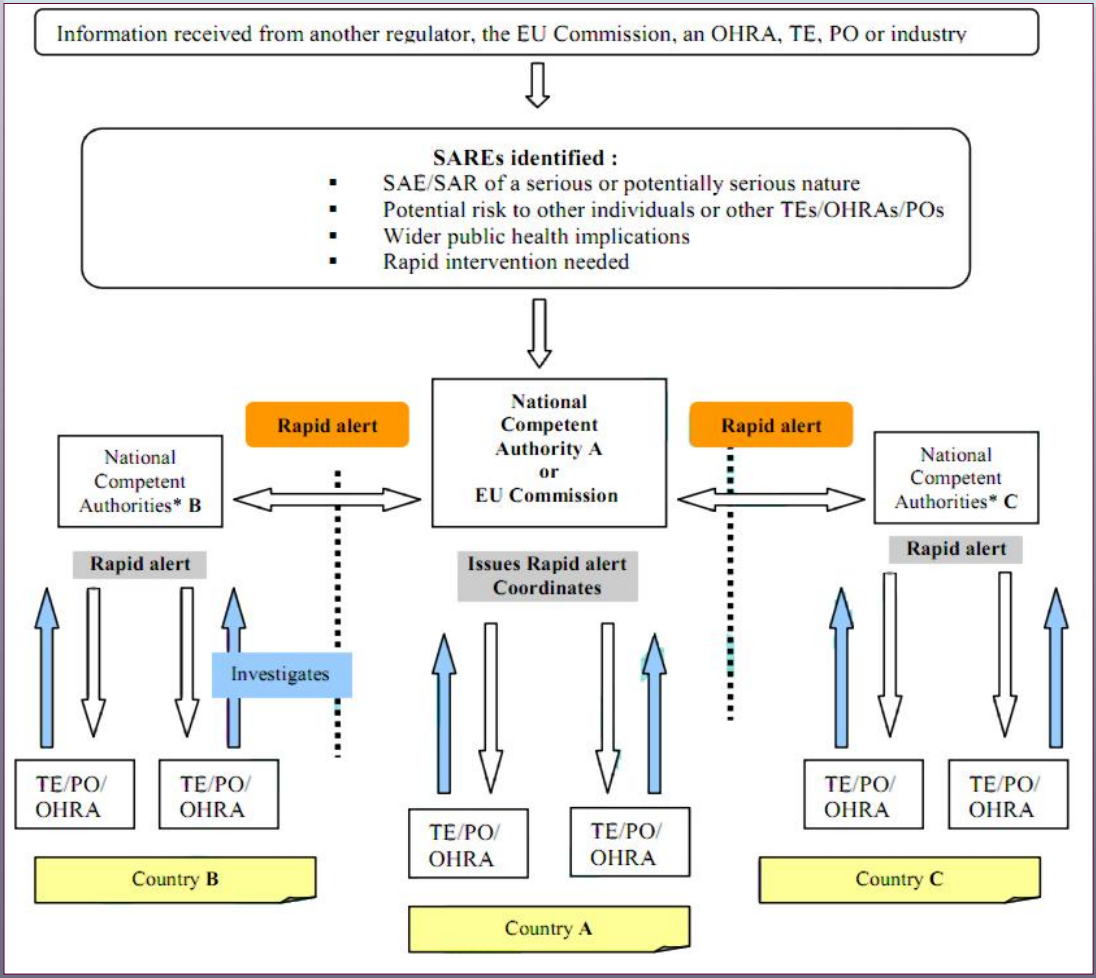
Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

REPORTING OF SARE

Triggering conditions for rapid alerts at national and international levels

The process of identifying and reporting an event that should form part of a national or an international alert



Recommendations

Any SARE or information that could have immediate direct or indirect consequences in other centres in the country and/or other countries (eg media, equipment, etc.) should trigger a rapid alert and urgent communication between units and Competent Authorities at national and/or European 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.

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Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

ART-SPECIFIC REPORTING TOOLS

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.

EUTCD requires that all serious adverse events or reactions be notified to CAs. However, the legislation in some countries require that non-serious be reported to the CA as well.

Serious Adverse Reactions and Events (SARE)

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

ART-SPECIFIC REPORTING TOOLS

Assessment tools

SAR Severity Grading

It is proposed that at least all adverse reactions that are 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.

1. Non serious	Mild clinical / psychological consequences. No hospitalisation. No anticipated long term consequence/disability.
2. Serious	- 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	- 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-serious

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Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

ART-SPECIFIC REPORTING TOOLS

Assessment tools

SAR Imputability Grading

It is proposed that at least all severe adverse reactions are 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

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES

ART-SPECIFIC REPORTING TOOLS

Assessment tools

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 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

SAFETY ISSUES
ART-SPECIFIC REPORTING TOOLS

Assessment tools

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

LEV	Impact	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 some couples or total loss 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 couple.

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SAFETY ISSUES
ART-SPECIFIC REPORTING TOOLS

Assessment tools

Step 3 - Applying the impact matrix

Recurrence probability → / Consequences ↓	Almost impossible 1	Unlikely 2	Possible 3	Likely 4	Almost certain 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

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SAFETY ISSUES
ART-SPECIFIC REPORTING TOOLS

Assessment tools

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.*

GREEN ***The tissue establishment (TE) (i.e. ART centre, sperm bank, laboratory…) to manage the corrective and preventive actions and the competent authority (CA) to file the report and keep a 'watching brief'.***

YELLOW: ***Requires interaction between the TE (i.e. ART centre, sperm bank, laboratory…) 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 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 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.***

Guidance

Vigilance & Surveillance in Assisted Reproductive Technologies

SAFETY ISSUES
GENERAL RECOMMENDATIONS

In addition to the recommendations related to a specific aspect of ART, the following ones apply more generally, highlighting the role 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 co-ordination 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 Cross-border reproductive care (CBRC).

CAs should support TEs in doing so !

Serious Adverse Reactions and Events (SARE)