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Guidance
on Vigilance & Surveillance in Assisted Reproductive Technologies
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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/EC¹ 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/EC² 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/EC³ 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 project⁴) which followed on from the vigilance pilot of the EUSTITE project⁵.

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 recommendations⁶ 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.

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.

¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF>

² <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF>

³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF>

⁴ www.sohovs.org

⁵ European Union Standards and Training for the Inspection of Tissue Establishments, www.eustite.org

⁶ EUSTITE deliverable 11

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 4⁷) 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.

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 SAREs that might occur. Examples of ART SAREs 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.

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

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 SAREs.

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.

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 project⁵, 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 paper⁸.

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.

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

⁸ ESHRE Position paper on the EU Tissues and Cells Directive EC/2004/23, November 2007.

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 stored⁸.

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 (*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.

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.

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-serious¹⁰.

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 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
- Embryo¹¹ (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^{12,13,14,15}.

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'. 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.

¹¹ Some MS differentiate, from a legal perspective, between zygotes and embryos.

¹² 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.

¹³ 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.

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.

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 incubator¹⁶.

All these factors may influence the pH of the medium and may have a deleterious impact on both the normal fertilization and embryo development^{17,18,19}. 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 pressure²⁰.

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*

¹⁴ 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.

¹⁵ Suzuki H, Kumai T, Matsuzaki M; Effect of Temperature Decline on the Cytoskeletal Organization of the Porcine Oocyte; *JMOR*, 2007; 24(3):107-113

¹⁶ 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).

¹⁷ Lane M, Bavister BD. Regulation of intracellular pH in bovine oocytes and cleavage stage embryos. *Mol. Reprod. Dev.* 1999;54:396–401.

¹⁸ Phillips KP et al. Intracellular pH regulation in human preimplantation embryos. *Hum Reprod.* 2000; 15(4):896-904.

¹⁹ 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.

²⁰ 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.

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
- 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 tiles²¹.

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)²².

When air pollutant testing is performed²³, 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’²⁴.

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 devices²⁵. 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 product²⁶.

²¹ 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.

²² 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.

²³ 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.

²⁴ AMM Wetzels, PMM Kastrop. Dutch technical specification (NTA 8070) on devices for assisted reproductive technologies. *Reproductive Biomedicine Online* (2010) 21, 252-258.

²⁵ Theresa Jeary. Classification of IVF media under the MDD. *Regulatory Rapporteur*, May 2010, 9 – 11.

²⁶ 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”.

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.

The revised Guidelines on a Medical Devices Vigilance System (MEDDEV 2.12-1 rev 6)²⁷ 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.

²⁷ Guidelines on a medical devices vigilance system (MEDDEV 2.12-1 rev 6) including IVF/ART devices.

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 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 testing²⁸. 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.

There have been a small number of publicised cases^{29,30,31,32,33,34} 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.

²⁸ Plebani M and Carraro, Mistakes in a stat laboratory: types and frequency. Clin Chem. 1997 Aug; 43(8 Pt 1):1348-51.

²⁹ 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

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 witnessing³⁵, 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:

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.

³⁰ 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

³¹ US woman receives \$1m compensation for IVF error, 09 August 2004. www.bionews.org.uk/page_12063.asp

³² Fertility watchdog investigates serious IVF mix-ups at London hospital. BioNews, 3 May 2009. <http://www.bionews.org.uk>

³³ HFEA rebuked by medical risk expert. BioNews, http://www.bionews.org.uk/page_13792.asp

³⁴ Canadian fertility doctor sued over sperm mix-up claims. BioNews, 20 Sep 2010. http://www.bionews.org.uk/page_70931.asp

³⁵ Reducing risk in the IVF laboratory: implementation of a double witnessing system. Clinical Risk Volume 10. No. 5 Pp. 176-180.

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 SAREs

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 countries³⁶.

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.

Directive 2011/24/EC clarifies patient's rights to access safe and good quality treatment across EU borders³⁷. 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

³⁶ Shenfield et al 'Cross border reproductive care in six European countries' Hum Reprod 2010 Vol. 25(6) 1361-1368

³⁷ Directive 2011/24/EU of 9 March 2011 on the application of patients' rights in cross-border healthcare.

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^{1,2,3}.

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.

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 risk³⁸ 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.

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 report³⁹. 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 developed⁴⁰ after a consensus was reached with professional societies (see details below).

³⁸ 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.

³⁹ 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)

⁴⁰ 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).

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
 - renal insufficiency

Complications of OHSS:

- Thrombosis,
- Adnexa torsion

This classification is generally similar to the Royal College of Obstetricians and Gynaecologists' one⁴¹ and to the Ovarian Hyperstimulation syndrome (OHSS) Guidelines⁴².

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.

⁴¹ Royal College of Obstetricians and Gynaecologists; Guideline N°5: The management of ovarian hyperstimulation syndrome, September 2006.

⁴² Delvigne A. and Serge Rozenberg Human Reprod Update, 9 (1) : 77-96, 2003 Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS).

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 CA⁴³. 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.

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)⁴⁴, Hypertrophic Cardiomyopathy^{45,46}, Autosomal Dominant Cerebellar Ataxia (ADCA)⁴⁷ and Opitz Syndrome⁴⁸, Neurofibromatosis type 1 (NF 1)⁴⁹, 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 Thalassaemia 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

⁴³ 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.

⁴⁴ 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.

⁴⁵ Nine Children inherit high risk heart disease from sperm donor. <http://ushealth.net/2010/10/9-children-inherit-high-risk-heart-disease-from-sperm-donor/> - accessed on December 22nd 2010.

⁴⁶ Maron BJ et al. (2009) Implications of Hypertrophic Cardiomyopathy transmitted by sperm donation. JAMA, Vol 302: (15) 1681-1684.

⁴⁷ D O E Gebhardt (2002) Sperm donor suffers years later from inherited disease. J Med Ethics;28:213-214.

⁴⁸ 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.

⁴⁹ Reported to the Vigilance System for Tissues and Cells at the Danish Medicines Agency.

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 defect⁴⁴. Another donor transmitted Hypertrophic Cardiomyopathy to 9 children⁴⁶. 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 inheritance⁴⁸. The 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 women⁴⁷. 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

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 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.
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.

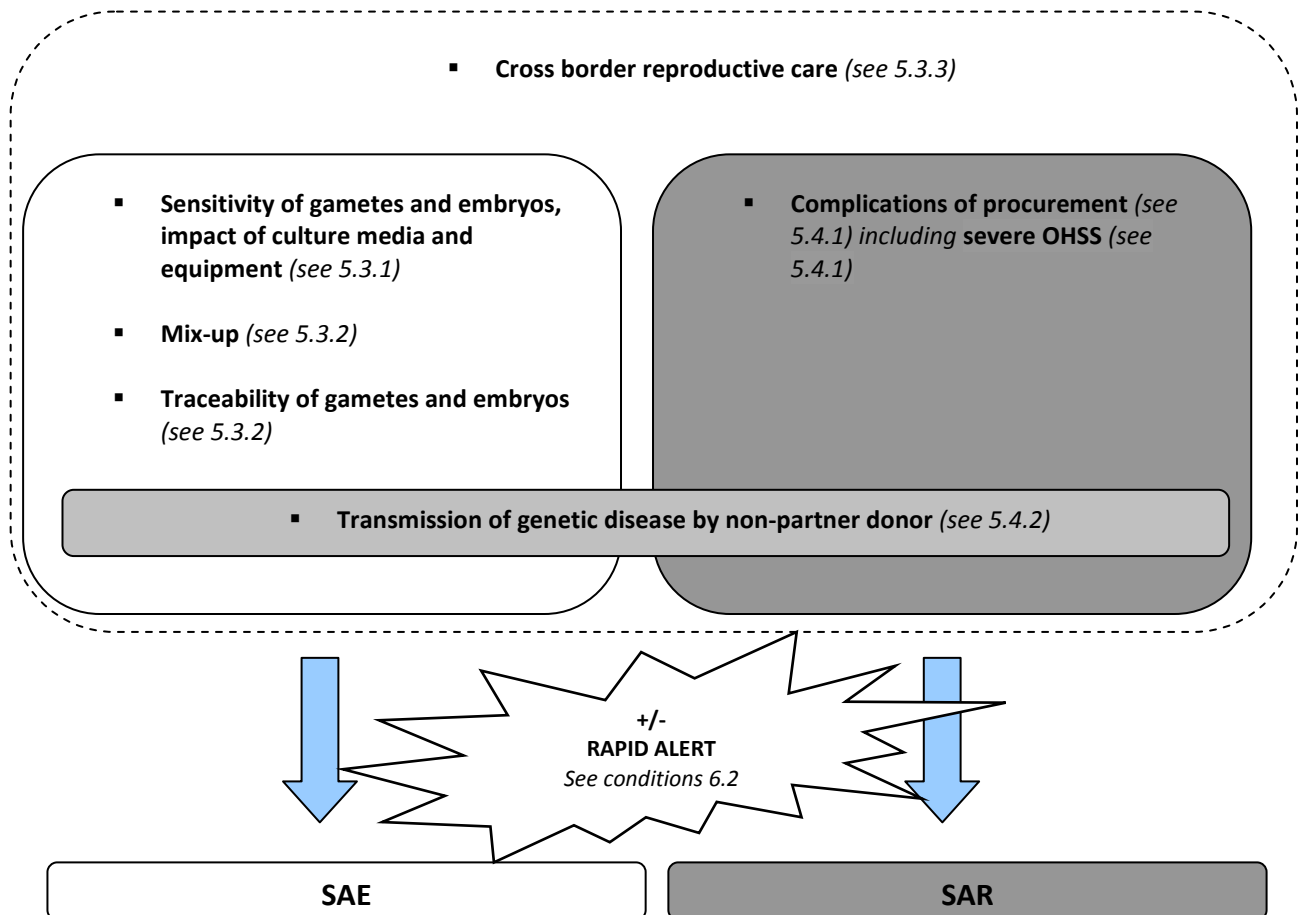
6. Specialist genetic centres should always consider whether a child manifesting a genetic disease might have been conceived with non-partner donor gametes or embryos. This issue should be raised immediately and openly with the parents in the interests of other potential offspring and when parents acknowledge 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.

6. REPORTING OF SAREs

6.1. GENERAL REQUIREMENTS

The notification requirements for SAREs 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 SAREs 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 legislation⁷.

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 rapid⁵⁰ 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 SAREs aims:

⁵⁰ 'Without delay', according to Directive 2006/86/EC.

- 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 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 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) System⁵¹ for tissues and cells
- 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.

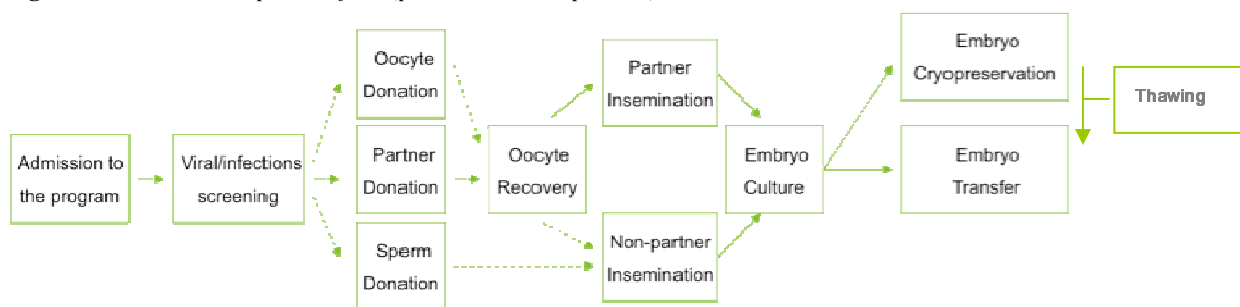
All the previous conditions should be verified before the rapid alert is triggered. Thus, a rapid alert should not be issued for the transmission of information related to a SARE that does not fulfil the above-mentioned conditions (*e.g.* an adverse event with impact limited to a single patient). Moreover, 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.

⁵¹ 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.

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 TEs⁵² 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.

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) 	If at least 1 patient impacted in several centers or if several patients in 1 TE ⇒ National: NRA if material distributed in the country only ⇒ EU/EEA: via RATC ⁵³ if distributed in several MS ⇒ International: rapid alert if distributed outside the EU/EEA	⇒ Coordination with other vigilance systems (medical devices,...) in any case
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 ▪ Loss of gametes, embryos or reproductive tissue 	⇒ National: NRA if gametes, embryo or tissues distributed in the country only (safety issues, ethical issue, societal issue through media) ⇒ EU/EEA: via RATC ⁵³ if distributed in several MS ⇒ International: rapid alert if distributed outside the EU/EEA Only if related to equipment failure ⇒ National: NRA if equipment distributed in the country only ⇒ EU/EEA: via RATC if distributed in several MS ⇒ International: rapid alert if distributed outside the EU/EEA	Misidentification of gametes involving ≥ 2 couples shall also trigger a rapid alert ⇒ Coordination with other vigilance systems (medical devices or other) in any case

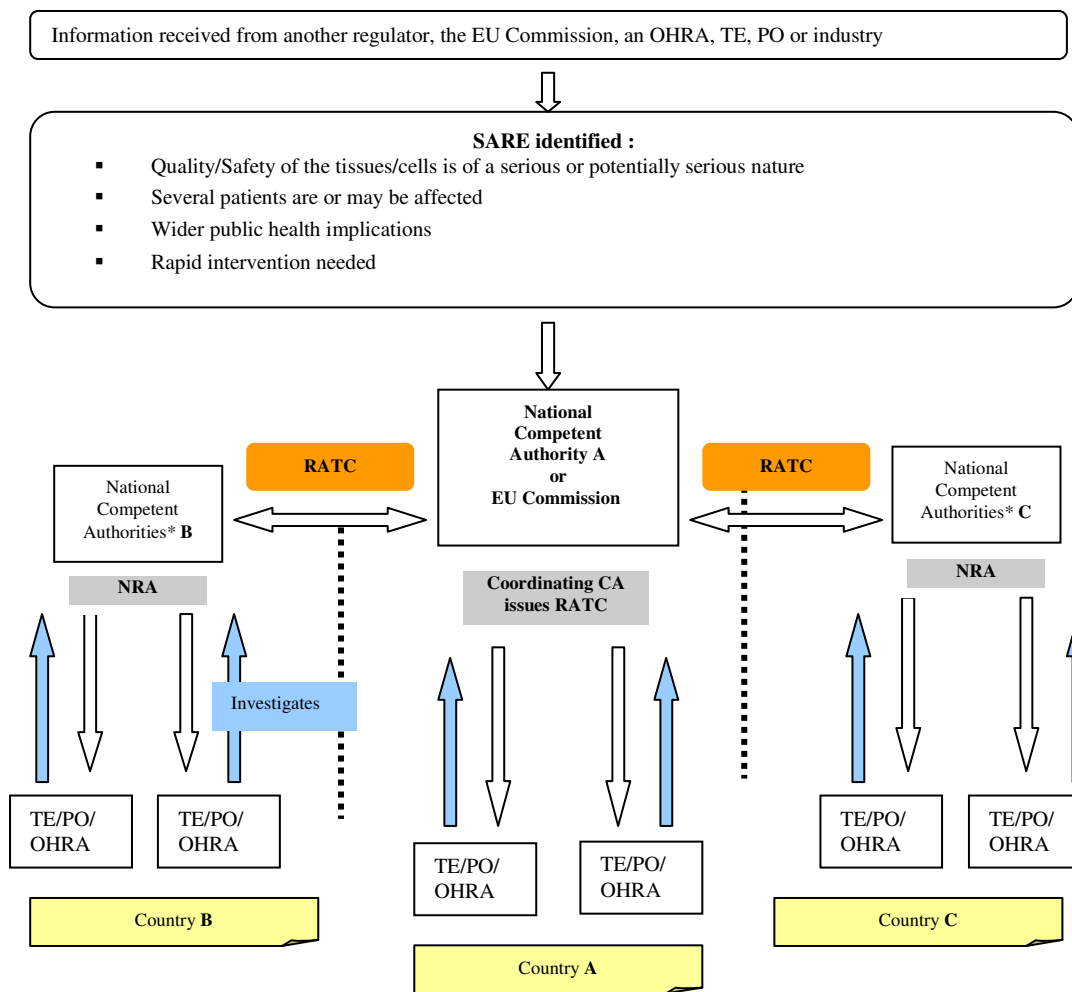
⁵² See definition of a TE applying to ART in the glossary.

⁵³ 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.

Storage	<ul style="list-style-type: none"> ▪ Laboratory materials (culture media) or culture equipment failure/ recall⁵³ ▪ Loss of reproductive material (gametes, embryos or cryopreserved tissue) due to failure of storage tank, container, freezer, IT software, ...) <p>If no loss, significant cumulative evidence of non-conformity of material or equipment</p>	<p>⇒ <i>National: NRA if materials or equipment distributed in the country only</i></p> <p>⇒ <i>EU/EEA: via RATC⁵³ if materials or equipment distributed in several MS</i></p> <p>⇒ <i>International: rapid alert if distributed outside the EU/EEA</i></p>	<p>⇒ <i>Coordination with other vigilance systems (medical devices,...) in any case</i></p>
	<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 	<p>Rapid alert if new hazard (e.g. new type or unexpected infection or pollutant) or several patients concerned</p>	
	<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

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

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 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.

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

- *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	Almost	Unlikely	Possible	Likely	Almost certain
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probability → Consequences ↓	impossible 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 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 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-serious⁵⁴.

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).

⁵⁴ 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.

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 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

1. CAs should encourage health professionals to report 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.

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 CA⁵⁵. These SAREs 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

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

⁵⁵ 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.

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.

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 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 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

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.

ART V&S Assessment Tools

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

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

Step 2 – Consequences

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.

Step 3 - Impact

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

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 SAR/E. (It would be useful to know the date of observation if different).
• Place	Place of occurrence of SAR/E 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	<p>- A brief description of the event is required.</p> <ul style="list-style-type: none"> • Stage at which the event occurred: Procurement / Collection, Testing / Transport / Processing (including cryopreservation and thawing) / Storage / Distribution (including import and export) / Materials / Other (<i>please specify</i>) • Specification Tissue and cells defect / Equipment failure / Human error / misidentification / mix-up / Other (<i>please specify</i>)
• 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.
<ul style="list-style-type: none"> • Reproductive tissue or cells implicated / affected 	<p>Indicate the type of reproductive tissues or cells involved.</p> <ul style="list-style-type: none"> - 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).
<ul style="list-style-type: none"> • Details of other sites or vigilance systems notified. 	<p>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.</p>
<ul style="list-style-type: none"> • Reporting Criteria 	<p>It is recommended that the ART reporting criteria be included in the form <i>i.e.</i></p> <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 SAREs 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: Pelviperitonitis 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. Pelviperitonitis 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. Pelviperitonitis 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>