THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

edqm

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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Survival Kit for national vigilance officers for the assessment SAR & SAE (tissues and cells) reportable during the EU annual exercise

1st European training course on Biovigilance for tissues and cells

September 2021

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

EUSTITE V&S TOOLS V2.1

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

SAEs - Criteria

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

Severity (SARs)

Non serious	Mild clinical/psychological consequences. No hospitalisation. No anticipated long term consequence/disability
Serious	- hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following ART with donor gametes or embryos.
Life-threatening	- major intervention to prevent death or - evidence of a life-threatening transmissible infection or - birth of a child with a life-threatening genetic disease following ART with donor gametes or embryos.
Death	Death

Report to CA

Imputability (SARs)

NA Not assessable	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes.
1. Unlikely	Evidence clearly in favour of attributing to other causes.
2. Possible	Evidence is indeterminate.
3. Likely, Probable	Evidence in favour of attributing to the tissues/cells.
4. Definite, Certain	Conclusive evidence beyond reaonable doubt for attributing to the tissues/cells

Impact (SARs and SAEs)

1	Rare	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 1 – Probability of recurrence

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage	Some applications postponed
2	Significant	Serious	Damage to system – services will be affected for short period	Many applications cancelled or postponed
3	Major	Life threatening	Major damage to system – significant time needed to repair	Significant no. of procedures cancelled - importation required to make-up short-fall
4	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled

Step 2– Consequences of Recurrence

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

Step 3 - Impact

This picture is illustrative, specific tables are in each different section of this presentation.

Contents

You are assessing a reported SAR (actual harm to a recipient/offspring)
- Non-reproductive T&C
- Reproductive T&C

You are assessing a reported SAR in donor (actual harm to a donor)

You are assessing a reported SAE (potential harm to a recipient/offspring /(system/supply/if reoccurs))
- Non-reproductive T&C
- Reproductive T&C

You are assessing a reported SAR

Non-reproductive T&C

Severity

NOT REPORTABLE TO EC	Insignificant	No harm to the recipient or living donor
	Non-serious:	Mild clinical consequences which do not necessitate hospitalization and/or result in long term disability or consequences for the recipient or living donor.
TO BE REPORTED TO EUROPEAN COMMISSION	**Serious**:	Adverse reaction resulted in: - hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity and/or - medical or surgical intervention to preclude permanent damage or impairment of a body function and/or - evidence of transmission of a serious communicable disease and/or - disabling or incapacitating conditions
	Life-threatening:	- The living donor or recipient required major intervention following procurement or the tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death and/or - There is evidence of transmission of a life-threatening communicable disease
	Fatal:	Death in a living donor or a T&C recipient

Imputability

NOT REPORTABLE TO EUROPEAN COMMISSION	Not assessable	When there is insufficient data for imputability assessment
	Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes
	Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)
TO BE REPORTED TO EUROPEAN COMMISSION	**Possible 1**	When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells, to the donation process, or to alternative causes
	Likely, Probable 2	When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)
	Definite, Certain 3	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)

Remember! When assessing imputability in the case of infections and malignancies....

Table 16.2. **Scale describing possible outcomes of an imputability investigation**

	Criteria adapted from EUSTITE-SoHO V&S [9, 10]	Criteria for infectious and malignant transmissions, adapted from the Disease Transmission Advisory Committee [11]
Not assessable	Insufficient data for imputability assessment	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing an adverse reaction to alternative causes	Suspected transmission and fulfilment of at least one of the following conditions: • clear evidence of an alternative cause • the appropriate diagnostic tests carried out have failed to document infection by the same pathogen in any recipient from the same donor • laboratory evidence that the recipient was infected with the same pathogen or had a tumour before the application of organs, tissues or cells
1. Possible	The evidence is indeterminate for attributing an adverse reaction to the quality/safety of tissues and cells, to the donation process or to alternative causes	Either • suspected transmission and • laboratory evidence of the pathogen or tumour in a single recipient or • data suggest a transmission but are not sufficient to confirm it
2. Probable	The evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues and cells (for recipients) or to the donation process (for donors)	Not only are the following two conditions met: • suspected transmission and • laboratory evidence of the pathogen or tumour in a recipient but also at least one of the following conditions is met: • laboratory evidence of the same pathogen or tumour in other recipients • laboratory evidence of the same pathogen or tumour in the donor If there is pre-transplant laboratory evidence, such evidence must indicate if the same recipient was negative for the pathogen involved before transplantation
3. Definite; certain	The evidence is conclusive beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues and cells (for recipients) or to the donation process (for donors)	All the following conditions are met: • suspected transmission • laboratory evidence of the pathogen or the tumour in a recipient • laboratory evidence of the same pathogen or tumour in other recipients (if multiple recipients) • laboratory evidence of the same pathogen or tumour in the donor If there is pre-transplant laboratory evidence, it should be noted that the same recipient was negative for the pathogen before transplantation

This table can be adapted to other tissues or cells and for MAR in order to take into account the specificities of each type of product.

4th edition of the TC Guide

https://freepub.edqm.eu/publications

Impact matrix

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

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Probability of recurrence

Assessing likelihood of occurrence/recurrence of SAR/E

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

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Consequences

Consequences of SAR/E should it reoccur

IMPACT DESCRIPTION		INDIVIDUAL	SYSTEM	OTC SUPPLY
0	**Insignificant**	Insignificant	No effect	Insignificant
1	**Minor**	Non serious	Minor damage	Some applications postponed
2	**Moderate**	Serious	Damage for short period	Many cancellations or postponements
3	**Major**	Life-threatening	Major damage to system – significant delay to repair	Significant cancellations - importation required
4	**Catastrophic/ extreme**	Fatal	System destroyed - need to rebuild	All allogenic applications cancelled

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Competent authority involvement

- **Green** — The TE, fertility clinic, etc. manages the corrective and preventive measures. The CA files the report and maintains vigilance.
- **Yellow** — Requires intervention between TE, fertility clinic, etc. and the CA. The CA may request an inspection than focuses on the SARE and corrective and preventive measures.
- **Red** — CA will generally designate representatives to participate in developing or approving the corrective and preventive action plan. Inspection, follow-up and written communication of health authorities in other countries where relevant.

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

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Next steps

Conclusions (validation and closure of case)

Effectiveness of corrective and preventive measures (reapplying of Impact matrix following the implementation?)

Notification to the other SoHO CA (TC, Blood, Organs)?

Communication with TE regarding reporting to other vigilance systems (pharmacovigilance, medical devices, patient safety)

Issuing notification on RATC?

Notification to the EU (SARE Exercise)?

Classification of SAR in the Common Approach (EU SARE exercise)

1. Transmitted infections
   - Bacterial infections
   - Viral infections (HBV, HCV, HIV, other)
   - Parasitical infections (malaria or other:
   - Fungal infections
   - Prion disease
   - Other transmitted infections
2. Transmitted malignant diseases
3. Other disease transmission
   - Immunological disease
   - Genetic disease
   - Other donor derived disease
4. Other SAR
   - Other SAR: Cardiovascular reactions
   - Other SAR: Pulmonary reactions
   - Other SAR: Renal complications
   - Other SAR: Neurological reactions
   - Other SAR: Toxicity (e.g. due to DMSO)
   - Other SAR: Immunological reactions including allergic reactions, graft versus host disease*, rejection, haemolytic reactions, or other immunological reactions)
   - Other SAR: Graft failure/delayed engraftment
   - Other SAR: Undue exposure to risk-intervention
   - Other SAR: Infusion related non-specific symptoms (including febrile reaction)
   - Other SAR: Reactions other than those listed above

* GvHD: to be reported if unexpectedly serious and/or linked to product preparation

You are assessing a reported SAR

Reproductive T&C

ART V&S Assessment Tools

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

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

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

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

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

Hospitalisation for observation should be considered as non-serious.

SAEs - Criteria

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

Severity (SARs)

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

SoHO V&S Deliverable 5 (ART)

Severity

NOT REPORTABLE TO EC	Insignificant	No harm to the recipient or living donor
	Non-serious:	Mild clinical / psychological consequences. No hospitalisation. No anticipated long term consequence/disability.
TO BE REPORTED TO EUROPEAN COMMISSION	**Serious**:	Adverse reaction resulted in: - 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 MAR with non-partner gametes or donated embryos.
	Life-threatening:	- major intervention to prevent death or - evidence of a life-threatening transmissible infection or - birth of a child with a life-threatening genetic disease following MAR with non-partner gametes or donated embryos.
	Fatal:	Death in a living donor or a T&C recipient

*Hospitalisation for observation (normally less than 24h) should be considered as Non-serious

Imputability

NOT REPORTABLE TO EUROPEAN COMMISSION	**Not assessable**	Insufficient data for imputability assessment
	0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the MAR process
	1. Unlikely	Evidence clearly in favour of attributing to other causes than the MAR process
TO BE REPORTED TO EUROPEAN COMMISSION	**2. Possible**	Evidence is indeterminate
	3. Likely	Evidence in favour of attributing to the MAR process
	4. Certain	Conclusive evidence beyond reasonable doubt for attributing to the MAR process

Impact matrix

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

SoHO V&S Deliverable 8

Probability of recurrence

Assessing likelihood of occurrence/recurrence of SAR/E

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

SoHO V&S Deliverable 8

Consequences

Consequences of SAR/E should it reoccur

IMPACT DESCRIPTION		INDIVIDUAL	SYSTEM	OTC SUPPLY
0	**Insignificant**	Insignificant	No effect	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 numbers of procedures cancelled	Partial loss of gametes/embryos for 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

SoHO V&S Deliverable 8

Competent authority involvement

- **Green** The TE, fertility clinic, etc. manages the corrective and preventive measures. The CA files the report and maintains “vigilance on the TE”.

- **Yellow** Requires intervention between TE, fertility clinic, etc. and the CA. The CA may request an inspection than focuses on the SARE and corrective and preventive measures.

- **Red** CA will generally designate representatives to participate in developing or approving the corrective and preventive action plan. Inspection, follow-up and written communication of health authorities in other countries where relevant.

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

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Next steps

Conclusions (validation and closure of case)

Effectiveness of corrective and preventive measures (reapplying of Impact matrix following the implementation?)

Notification to the other SoHO CA (TC, Blood, Organs)?

Communication with TE regarding reporting to other vigilance systems (pharmacovigilance, medical devices, patient safety)

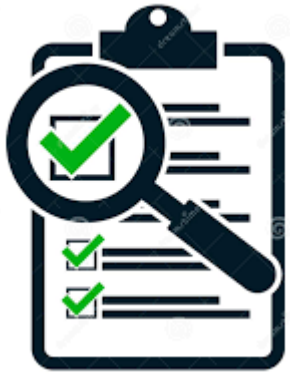
Issuing notification on RATC?

Notification to the EU (SARE Exercise)?

Classification of SAR in the Common Approach (EU SARE exercise)

1. Transmitted infections
   - Bacterial infections
   - Viral infections (HBV, HCV, HIV, other)
   - Parasitical infections (malaria or other:
   - Fungal infections
   - Prion disease
   - Other transmitted infections
2. Transmitted malignant diseases
3. Transmitted genetic conditions
4. Other SAR

You are assessing a reported SAR in donor



Common Approach

7. ANNUAL NOTIFICATION FOR SERIOUS ADVERSE REACTIONS IN DONORS

This reporting is MANDATORY for those reactions that impact on the safety and quality of the donated tissues or cells and NON-MANDATORY for those that have no impact on the donated substances.

It is noted that many Member State competent authorities collate information on donor adverse reactions not influencing the quality and safety of tissues and cells. It is acknowledged that some donor reactions should be reported to other vigilance systems (e.g. to pharmacovigilance systems), for example:

- Ovarian Hyper-Stimulation Syndrome (OHSS) as an exaggerated response to the use of ovulation induction medications
- Reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection.

Nevertheless, the Commission recognizes the value of these data in the context of tissue and cells regulation, and invites Member States to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells is included in the electronic report template. The declared data will not be calculated as part of the total number of SARs.

Severity

NOT REPORTABLE TO EC	Insignificant	No harm to the recipient or living donor
	Non-serious:	Mild clinical consequences which do not necessitate hospitalization and/or result in long term disability or consequences for the recipient or living donor.
TO BE REPORTED TO EUROPEAN COMMISSION	**Serious**:	Adverse reaction resulted in: - hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity and/or - medical or surgical intervention to preclude permanent damage or impairment of a body function and/or - evidence of transmission of a serious communicable disease and/or - disabling or incapacitating conditions
	Life-threatening:	- The living donor or recipient required major intervention following procurement or the tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death and/or - There is evidence of transmission of a life-threatening communicable disease
	Fatal:	Death in a living donor or a T&C recipient

Imputability

NOT REPORTABLE TO EUROPEAN COMMISSION	Not assessable	When there is insufficient data for imputability assessment
	Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes
	Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)
TO BE REPORTED TO EUROPEAN COMMISSION	**Possible 1**	When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells, to the donation process, or to alternative causes
	Likely, Probable 2	When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)
	Definite, Certain 3	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)

Impact matrix

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

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Probability of recurrence

Assessing likelihood of occurrence/recurrence of SAR/E

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

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Consequences

Consequences of SAR/E should it reoccur

IMPACT DESCRIPTION		INDIVIDUAL	SYSTEM	OTC SUPPLY
0	**Insignificant**	Insignificant	No effect	Insignificant
1	**Minor**	Non serious	Minor damage	Some applications postponed
2	**Significant**	Serious	Damage for short period	Many cancellations or postponements
3	**Major**	Life-threatening	Major damage to system – significant delay to repair	Significant cancellations - importation required
4	**Catastrophic/ extreme**	Fatal	System destroyed - need to rebuild	All allogenic applications cancelled

SoHO V&S Deliverable 8

Competent authority involvement

- **Green** The TE, fertility clinic, etc. manages the corrective and preventive measures. The CA files the report and maintains “vigilance on the TE”.

- **Yellow** Requires intervention between TE, fertility clinic, etc. and the CA. The CA may request an inspection than focuses on the SARE and corrective and preventive measures.

- **Red** CA will generally designate representatives to participate in developing or approving the corrective and preventive action plan. Inspection, follow-up and written communication of health authorities in other countries where relevant.

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

SoHO V&S Deliverable 8

Next steps

Conclusions (validation and closure of the case)

Effectiveness of corrective and preventive measures (reapplying of Impact matrix following the implementation?)

Notification to the other SoHO CA (TC, Blood, Organs)?

Communication with TE regarding reporting to other vigilance systems (pharmacovigilance, medical devices, patient safety)

Issuing notification on RATC?

Notification to the EU (SARE Exercise) mandatory (SAR affected Q&S of TC or SAE which leads to SAR in donor/voluntary (all other SAR in donors)?

Classification of SAR in donors the Common Approach (EU SARE exercise)

Non-reproductive

Haematopoietic Stem Cells /HPC:

1. Allergic reaction
2. Mechanical damage (from apheresis or bone marrow collection)
3. Thrombotic / embolic
4. Acute systemic toxicity during mobilization or collection
5. Infection
6. Autoimmune disease
7. Neurological disease
8. Musculoskeletal / joint affection
9. Psychiatric / psychogenic disorder
10. Reactions other than those listed above

Skin or cartilage harvest from living donors:

1. Bacterial infections
2. Bleeding
3. Reactions other than the above

Bone (allogeneic and autologous)

1. Bacterial infections (wound infection, dehiscence requiring incision and drainage)
2. Fractures
3. Surgical complications
4. Reactions other than the above

Vessels:

1. Bacterial infections
2. Bleeding
3. Reactions other than the above

Classification of SAR in donors the Common Approach (EU SARE exercise)

Reproductive

Oocytes:

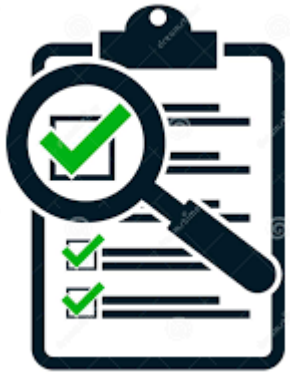
1. OHSS
2. Torsion of the ovary (leading to surgery with or without removal of fallopian tube and/or ovary)
3. Infection
4. Surgical complications
5. Reaction to anaesthetic
6. Reactions other than the above

Sperm (including MESA, PESE, TESE) and other reproductive tissues (ovarian or testicular tissue)

1. Infection
2. Surgical complications
3. Reaction to anaesthetic
4. Reactions other than the above

You are assessing a reported SAE

Non-reproductive T&C



Common Approach

To assess if adverse event is serious - severe and significant enough to notify it to the NCA

The following criteria should be applied to decide which adverse events are reportable to Competent Authorities and, subsequently, to the Commission for **Non-Reproductive T&C**:

(1) Inappropriate tissues/cells have been distributed for clinical use, even if not used;

(2) The event could have implications for other patients or donors because of shared practices, services, supplies or donors;

(3) The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;

(4) The event resulted in the loss of a significant quantity[5] of unmatched allogeneic tissues or cells.

Imputability

Not assessable	Insufficient data for imputabilit
0 Excluded	Conclusive evidenc to alternative causes.
1 Unlikely	to alternative causes
2 Possibl	ate.
3	early in favour of attribution to OTC.
4 L	Conclusive evidence beyond reasonable doubt for attribution to OTC

Because it is an event there is no need for assesment of the imputability

The impact matrix

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

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Likelihood of probability

Assessing likelihood of occurrence/recurrence of SAR/E

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

SoHO V&S Deliverable 8

Consequences

Consequences of SAR/E should it reoccur

IMPACT DESCRIPTION		INDIVIDUAL	SYSTEM	OTC SUPPLY
0	**Insignificant**	Insignificant	No effect	Insignificant
1	**Minor**	Non serious	Minor damage	Some applications postponed
2	**Significant**	Serious	Damage for short period	Many cancellations or postponements
3	**Major**	Life-threatening	Major damage to system – significant delay to repair	Significant cancellations-importation required
4	**Severe**	Fatal	System destroyed - need to rebuild	All allogenic applications cancelled

SoHO V&S Deliverable 8

Competent authority involvement

- **Green** — The TE, fertility clinic, etc. manages the corrective and preventive measures. The CA files the report and maintains vigilance.
- **Yellow** — Requires intervention between TE, fertility clinic, etc. and the CA. The CA may request an inspection than focuses on the SARE and corrective and preventive measures.
- **Red** — CA will generally designate representatives to participate in developing or approving the corrective and preventive action plan. Inspection, follow-up and written communication of health authorities in other countries where relevant.

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

SoHO V&S Deliverable 8

Next steps

Conclusions (validation and closure of case)

Effectiveness of corrective and preventive measures (reapplying of Impact matrix following the implementation?)

Notification to the other SoHO CA (TC, Blood, Organs)?

Communication with TE regarding reporting to other vigilance systems (pharmacovigilance, medical devices, patient safety)

Issuing notification on RATC?

Notification to the EU (SARE Exercise)?

Classification of SAE in the Common Approach (EU SARE exercise)

DESCRIPTION OF ACTIVITY STEPS

Transport
Transport is the transfer or conveying of tissues and cells from one place to another within one organization, between other sites or transport by third parties.

Donor selection
Donor selection or evaluation is performed in order to avoid performing a procurement procedure in a living donor with increased risk of complications and to avoid risk of transmission of infectious diseases or other adverse effects to the recipient and as far as possible to avoid risk of genetic abnormalities in the offspring.

Procurement
Procurement is the process by which tissues or cells are made available for banking or clinical use. This process includes evaluation, obtaining consent for donation, removal or collection of tissues or cells.

Testing
Testing is the mandatory or discretionary testing carried out by the tissue establishment during or after procurement or processing.

Processing
Processing covers all the operations involved in the preparation, manipulation, preservation and packaging, quality control and testing of tissues and cells intended for human application.

Storage
Storage is maintaining the product under appropriate controlled conditions until distribution by the tissue establishment. For organisations responsible for human application, storage is maintaining the product under appropriate controlled conditions until application.

Product selection (possible TE and ORHA activity step)
Means the selection of the appropriate product by a tissue establishment (TE) or organisation responsible for human application (ORHA) based on the recipient's needs. This occurs before issue.

Issue (possible TE and ORHA activity step)
Means the provision of tissues or cells by a tissue establishment or organisation responsible for transplantation, infusion, insemination or transfer, i.e. the process of linking the correctly selected product to the correct patient, and patient records and the labelling of that product, to maintain traceability. Issue does not include transportation and delivery, which should be reported in the relevant activity step.

Distribution
Distribution is the transportation and delivery of tissues and cells intended for human application. (Directive 2004/23/EC). Distribution is the act of delivery of tissues and cells to the other tissue establishments or the organizations responsible for human application. It does not include the issuing of tissues or cells for transplantation. SAE generated during issuing should be reported in the relevant activity step.

Other
Others refers to any other activity or parameter in the process that may affect quality and safety of tissues and cells or potentially harm the patient.

Classification of SAE in the Common Approach (EU SARE exercise)

SPECIFICATION OF SAEs

Tissues and cells defect
This should be understood as a defect in the quality or safety of the tissues and cells due to an inherent unpredictable safety or quality deficit, e.g. a defect due to an undiagnosed illness or genetic factor or an unknown exposure to a toxic agent.
For example: genetic condition discovered in a sperm donor, years after sperm donation.

Equipment failure
This should be understood as a defect in the quality or safety of the tissues or cells due to a fault in critical equipment used in procurement, processing, storage or distribution. For example: embryos lost due to incubator breakdown.

Materials
This should be understood as a defect/potential impact on the quality or safety of the tissues or cells due to defective materials used during procurement, processing, storage or distribution.
Examples: Contamination of a culture medium. Outdated cryoprotectant used during processing.

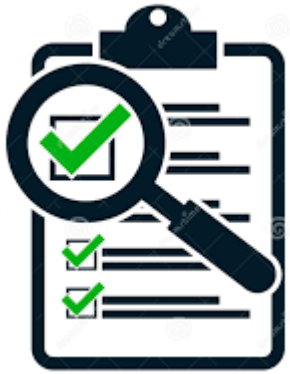
System failure (please specify)
This should be understood as a failure of the quality management system.
Training or education
Staffing, workload or skill-mix
Inadequate process, procedure or documentation
Other (please specify)

Human error (please specify)
This should be understood as a defect in the quality or safety of the tissues or cells due to an error by a member of personnel during procurement, processing, storage or distribution.
Incorrect decision or omission following the correct procedure
Following the wrong procedure
Other (please specify)
Examples : The following examples may be considered as human errors. However if root cause analysis reveals underlying causes such as inadequate staffing levels or staff not having been trained properly, they would be classified as system failure.
Embryos were mistakenly transferred into a Petri dish (unused) labelled for another couple. The error was detected (following distribution) but prior to embryo transfer.
Oocytes were fertilized with spermatozoa from the wrong person.

Other
This should be understood as a defect in the quality or safety of the tissues or cells due to any other cause during procurement, processing, storage or distribution.
For example: an air company/ Pilot refused to accept cells in liquid nitrogen on board.

You are assessing a reported SAE

Reproductive T&C



ART V&S Assessment Tools

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

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

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

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

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

Hospitalisation for observation should be considered as non-serious.

SAEs - Criteria

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

Severity (SARs)

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

SoHO V&S Deliverable 5 (ART)

Common Approach

To assess if adverse event is serious - severe and significant enough to notify it to the NCA

The following criteria should be applied to decide which adverse events are reportable to Competent Authorities and, subsequently, to the Commission for **Reproductive T&C**:

(1) Inappropriate gametes, embryos or germinal tissues have been released for clinical use, even if not used;

(2) The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors

(3) The event resulted in a mix-up of gametes or embryos

(4) The event resulted in a loss of traceability of gametes or embryos

(5) Contamination or cross contamination

(6) Accidental loss of gametes, embryos, germinal tissues (e.g. break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle.

Imputability

Not assessable	Insufficient data for imputabilit
0 Excluded	Conclusive evidenc to alternative causes.
1 Unlikely	to alternative causes
2 Possibl	ate.
3	early in favour of attribution to OTC.
4 L	Conclusive evidence beyond reasonable doubt for attribution to OTC

Because it is an event there is no need for assesment of the imputability

The impact matrix

Likelihood of recurrence Consequences	Rare 1	Unlikely 2	Possible 3	Likely 4	Certain / Almost certain 5
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Minor 1	1	2	3	4	5
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SoHO V&S Deliverable 8

Likelihood of probability

Assessing likelihood of occurrence/recurrence of SAR/E

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

SoHO V&S Deliverable 8

Consequences

Consequences of SAR/E should it reoccur

IMPACT DESCRIPTION		INDIVIDUAL	SYSTEM	OTC SUPPLY
0	**Insignificant**	Insignificant	No effect	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 numbers of procedures cancelled	Partial loss of gametes/embryos for 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

SoHO V&S Deliverable 8

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SARE-TC@edqm.eu

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
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Facebook: **@EDQMCouncilofEurope**