Cells and tissues vigilance
- Principles for notification -

Symposium February 2024

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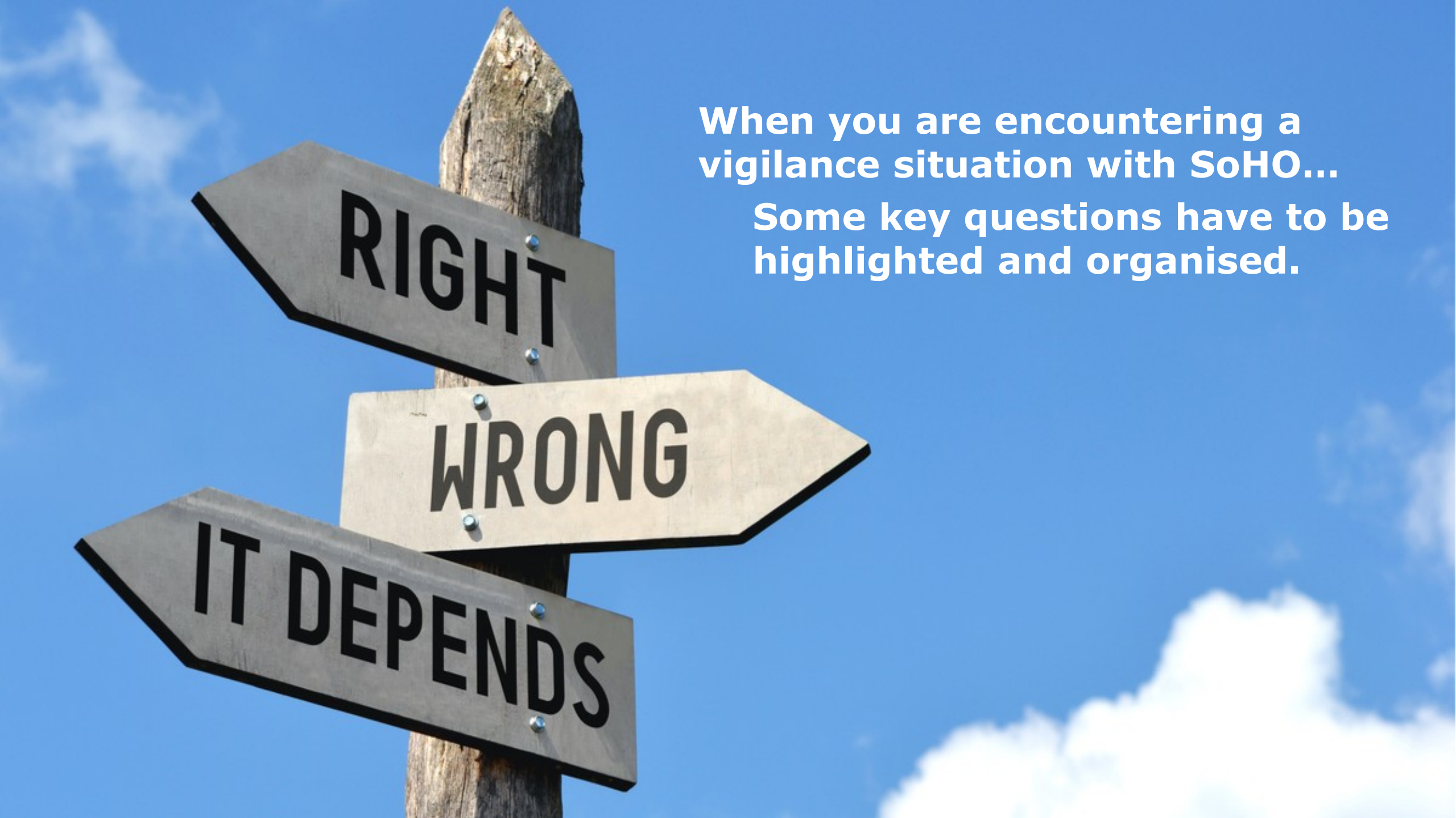


When you are encountering a vigilance situation with SoHO…

Some key questions have to be highlighted and organised.

Principles for notification

Detection

- What are we dealing with?
- What is the nature of the encountered situation?
- How serious is it?

Assessment

What is the likelihood that a SARE is related to a safety or quality defect in the tissue or cell or to the tissue or cell donation process?

Direct Actions

What are the first useful initiatives to manage the situation and/or to limit the impact?

Assess the likelihood of recurrence after CAPA

How to ensure the robustness of the CAPA plan?

Build CAPA Plan

How to mitigate the risk , the impact and the consequences?

Investigation

How to refine the management of the encountered situation with key elements?

Principles for notification

Reporting serious adverse incidents and reactions presents important learning opportunities that can help everyone involved to improve their processes and achieve rigorous safety and quality standards.

The SARE model canvas is a document that allows you to describe your biovigilance management approach, in complete simplicity according to the common steps of a vigilance approach. For a given situation, it allows you to represent on a single page, through a canvas, all of the essential stages of biovigilance management. Once completed, you will be able to manage your priorities by showing at a glance what you need, the steps to take and identify areas of progress for quality processes in terms of biovigilance.

Detection

Assessment

Direct Actions

Investigation

Build CAPA Plan

Assess the likelihood of recurrence after CAPA

Principles for notification

Reporting serious adverse incidents and reactions presents important learning opportunities that can help everyone involved to improve their processes and achieve rigorous safety and quality standards.

The SARE model canvas is a document that allows you to describe your biovigilance management approach, in complete simplicity according to the common steps of a vigilance approach. For a given situation, it allows you to represent on a single page, through a canvas, all of the essential stages of biovigilance management. Once completed, you will be able to manage your priorities by showing at a glance what you need, the steps to take and identify areas of progress for quality processes in terms of biovigilance.

Art.3 §1 RD « SARE »

Detection

- Definition SAR/E
  - (+) Criteria repro/non repro for SAE
    Or
  - (+) Severity for SAR

Assessment

- Imputability SAR
- Likelihood of occurrence/ recurrence

Direct Actions

- Precautionary measures
- Reporting to FAMHP (1/2)

Investigation

- Description of the linked activity
- Root cause analysis
- Specification SAR/SAE
- Evaluation of the impact/consequence
- Reporting to FAMHP (2/2)

Build CAPA Plan

Assess the likelihood of recurrence after CAPA

Principles for notification– SARE model canvas

Situation encountered: provide a sufficient description including the key dates and the most objective elements of the situation encountered (What? When? where? Whom? Why? How many?) - bullet points or text format according to your preferred mode of content.

Detection

.....Description.....
.....Description.....
.....Description.....

Assessment

.....Description.....
.....Description.....
.....Description.....

Direct Actions

.....Description.....
.....Description.....
.....Description.....

Assess the likelihood of recurrence after CAPA

.....Description.....
....Description.....
.....Description.....

Build CAPA Plan

.....Description.....
.....Description.....
.....Description.....

Investigation

.....Description.....
.....Description.....
.....Description.....

SARE Model Canvas: window 1 (a)

In this step, it is necessary to be able to identify the seriousness of the problem encountered. In other words: what is the underlying problem? is it serious enough to require notification? Start by remembering you the legal principle/definition (and no need to know it by heart, just know the principle).

Detection:

- **Definition**
  - (+) Criteria repro/non repro pour SAE
  - (+) Severity for SAR

SAR = Serious Adverse Reaction = "RIG" or "EOB"

SAE = Serious Adverse Event = "IIG" or "EOV"

Important keywords: likelihood of a damage (SAE), unpredictability of a damage that is occurred (SAR)

(offsprings, recipients, donors)

SARE Model Canvas: window 1 (a)

In this step, it is necessary to be able to identify the seriousness of the problem encountered. In other words: what is the underlying problem? is it serious enough to require notification? Start by remembering you the legal principle/definition (and no need to know it by heart, just know the principle).

Detection:

- **Definition**
  - (+) Criteria repro/non repro pour SAE
  - (+) Severity for SAR

MAR: special emphasis on genetic disease carrier state in donors

- The diagnosis of a genetic disease in adults who have previously donated gametes or embryos to other couples **should be assimilated and reported as an SAE** so that stored gametes, or stored embryos created from these donor's gametes, are not used without confirmation that they do not carry the gene(s) or chromosom abnormality
- The **birth of a child with a genetic disease following non-partner donation** of gametes or embryos **should be assimilated and reported as a (suspected) SAR**

  (Any remaining stored 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.)

SARE Model Canvas: window 1 (b) - replacement T&C + HSC

Remembering the legal principles/definition can be complicated in certain situations (SAE). When in doubt, refer to common sense criteria that may affect an individual.

Detection:

- Definition
- **Criteria repro/non repro for SAE**
- Severity for SAR

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 of unmatched allogeneic tissues or cells.	☐

1 = Quality defect of HBM that could affect an individual

2 = Quality defect in your system that could affect an individual (material, equipment, subcontractor…)

3 = Quality defect in OTC supply that could affect an individual

SARE Model Canvas: window 1 (b) - MAR

Remembering the legal principles/definition can be complicated in certain situations (SAE). When in doubt, refer to common sense criteria that may affect an individual

Detection:

- Definition
- **Criteria repro/non repro pour SAE**
- Severity for SAR

1. Inappropriate gametes, embryos or germinal tissues have been distributed for clinical use, even if not used	☐	1 = Quality defect of HBM that could affect an individual
2. Contamination or cross contamination	☐	
3. The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors	☐	2 = Quality defect in your system that could affect an individual (material, equipment, traceability, QMS,subcontractor…)
4. The event resulted in a mix up of gametes or embryos	☐	
5. The event resulted in loss of the traceability of gametes or embryos	☐	
6. Accidental loss of gametes, embryos or germinal tissues (e.g break down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle	☐	3 = Quality defect in OTC supply that could affect an individual

SARE Model Canvas: window 1 (c) - replacement T&C + HSC

An adverse reaction is unexpected, it is information that you receive in a somewhat “raw” way. After having taken the first medical initiatives or after having carried out the first medical consultations or coordination with those who communicated the information, please use these specifications to evaluate the situation and see if you will need to ensure notification to the FAMHP.

Detection:

- Definition
- Criteria repro/non repro pour SAE
- **Severity for SAR**

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.
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

SARE Model Canvas: window 1 (c) - MAR

An adverse reaction is unexpected, it is information that you receive in a somewhat “raw” way. After having taken the first medical initiatives or after having carried out the first medical consultations or coordination with those who communicated the information, please use these criteria to evaluate the situation and see if you will need to ensure notification to the FAMHP.

Detection:

- Definition
- Criteria repro/non repro pour SAE
- **Severity for SAR**

Insignificant	No harm to the recipient or living donor
Non-serious:	Mild clinical / psychological consequences. No hospitalisation. No anticipated long term consequence/disability.
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

SARE Model Canvas: window 2 (a) - replacement T&C + HSC

In this step, you must ask yourself the question of the extent of your problem because this will condition all your direct actions to take.
Imputability is an assessment of the likelihood that a reaction is related to a safety or quality defect in the tissue or cell or to the tissue or cell donation process. Only reactions that are reasonably considered to have been caused by the tissues or cells applied and linked to the quality and safety of the tissues and cells, or the procurement process in the case of a donor, should be reported to the FAMHP. Remark: imputability = an evolving concept during the SARE's management (before vs after investigation).

Assessment

- **Imputability SAR**
- Likelihood of occurrence/recurrence

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)
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)

SARE Model Canvas: window 2 (a) - MAR

In this step, you must ask yourself the question of the extent of your problem because this will condition all your direct actions to take.
Imputability is an assessment of the likelihood that a reaction is related to a safety or quality defect in the tissue or cell or to the tissue or cell donation process. Only reactions that are reasonably considered to have been caused by the tissues or cells applied and linked to the quality and safety of the tissues and cells, or the procurement process in the case of a donor, should be reported to the FAMHP. Remark: imputability = an evolving concept during the SARE's management (before vs after investigation).

Assessment

- **Imputability SAR**
- Likelihood of occurrence/recurrence

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
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

SARE Model Canvas: window 2 (b) - All

In this step, you must ask yourself the question of the extent of your problem because this will condition all your direct actions to take.
→ We have a serious problem, for a patient or for a product. To what extent is there a risk that the situation will grow and affect more products or more patients?
→ + without any capa plan or mitigation measures, does this event or reaction reoccure? + how far does it impact your system/process/supply?

Assessment

- Imputability SAR
- **Likelihood (of occurrence/recurrence)**

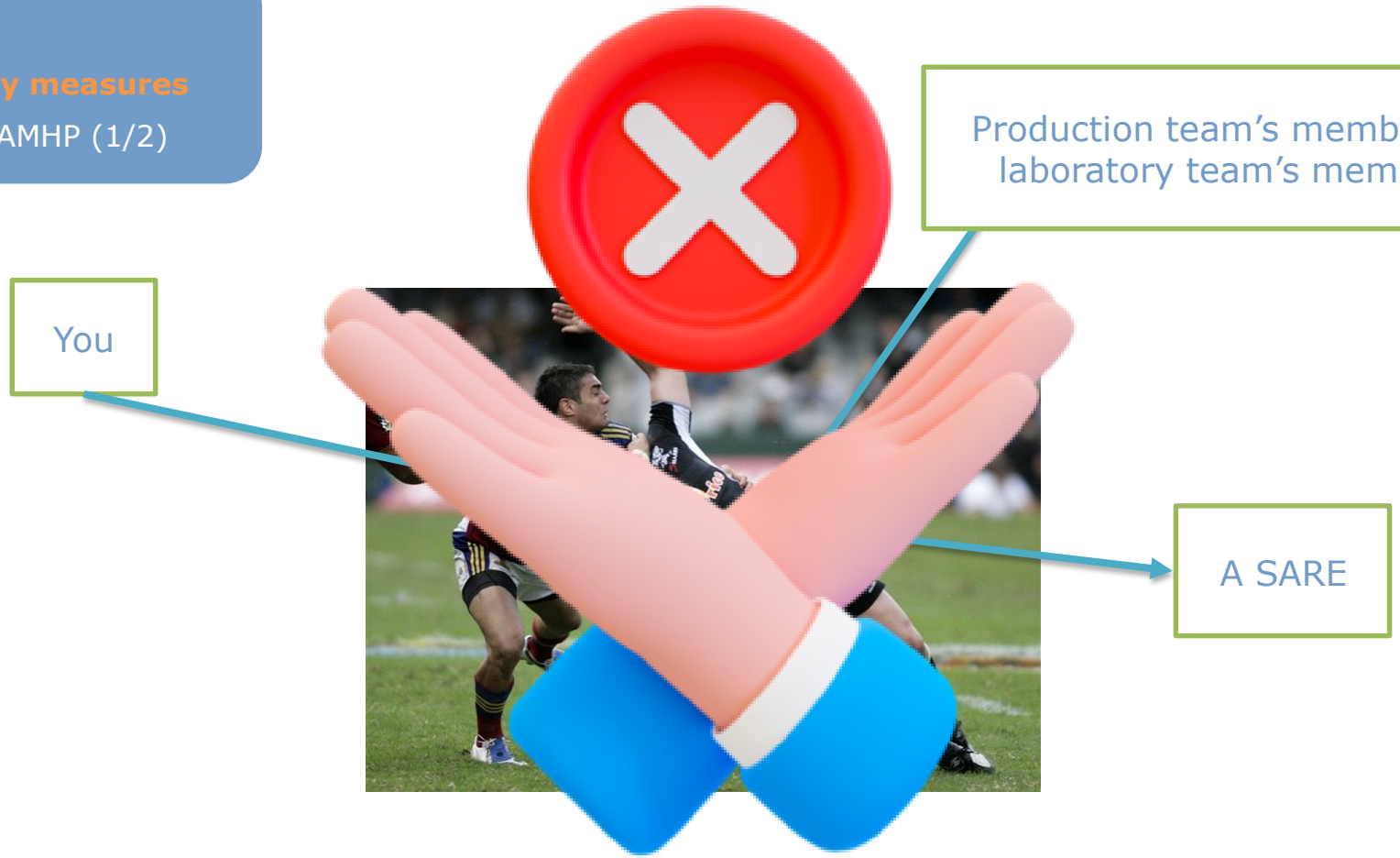
1	**Almost impossible**	Difficult to believe it could occur again.
2	**Unlikely**	Not expected to occur again.
3	**Possible**	May occur occasionally.
4	**Likely**	Probable to occur again but not persistent.
5	**Almost certain**	Likely to occur again on many occasions.

SARE Model Canvas: window 3 (a) - All

This step is the logical continuation of the previous window and consists of asking the key questions in terms of initiatives.
→ What do you do immediately to limit the impact of the situation so that the situation encountered does not escalate?

Direct Actions:

- **Precautionary measures**
- Reporting to FAMHP (1/2)



SARE Model Canvas: window 3 (a) - All

This step is the logical continuation of the previous window and consists of asking the key questions in terms of precautionary initiatives.
→ Part of a problem-solving approach.
→ To limit the impact so that the situation encountered does not escalate in terms of public health.

Direct Actions:

- **Precautionary measures**
- Reporting of notification

Part of the problem solving approach

- Immediate cessation of use + therapeutic alternative, technical alternative, alternative in terms of means (culture media, devices, equipment)
- Need additional tests? (if "yes", ask it) Need patient 's monitoring results? (If "Yes " ask it) → objective: obtain key information
- Are there any consequences for current or future procedures (=manipulations/operations)?
- Are there any consequences for supply continuity to your end users?

Additional Precautionary measures

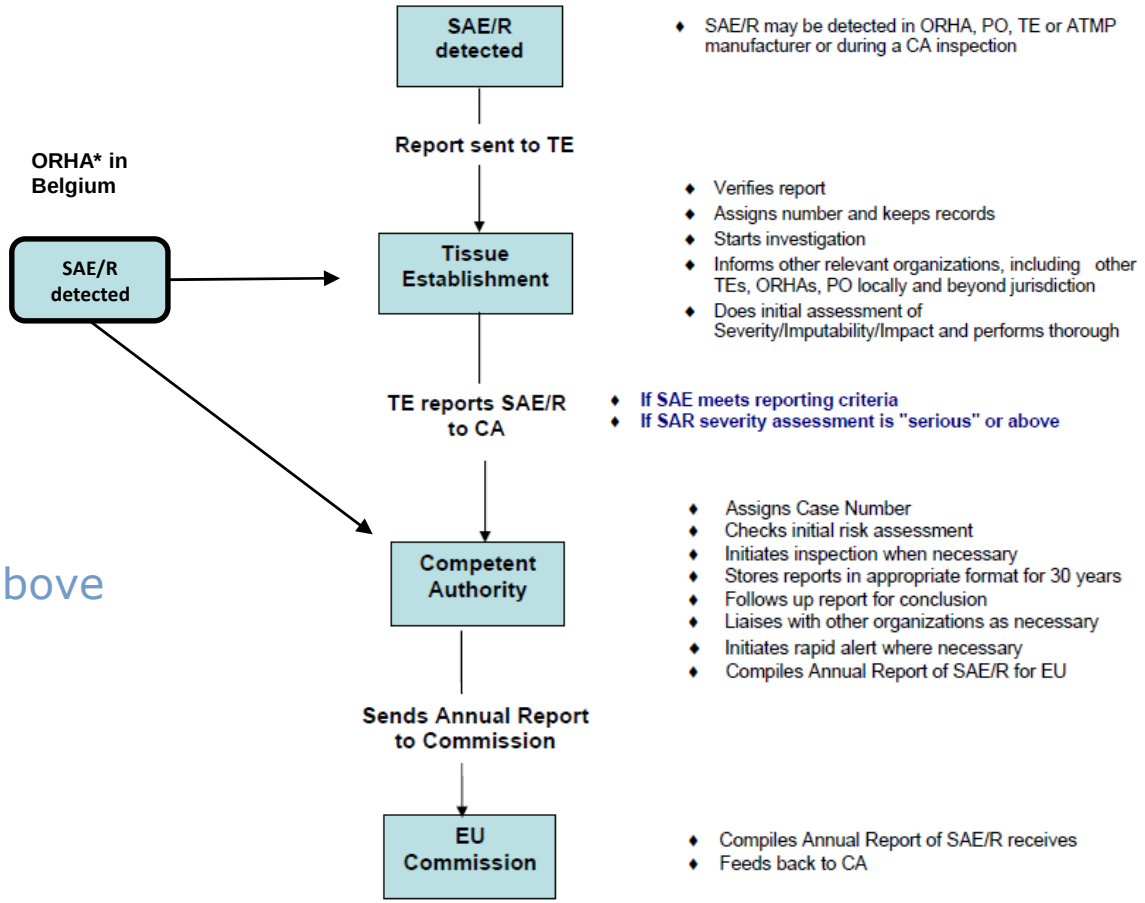
- Need to inform the end users/third parties/patients? Quid supply continuity?
- Need to activate the recall procedure? To quarantine? Lookback? Reconciliation?
- Need to communicate with other TE? Other EU NCA (organs, materio-, pharmacovigilance)?

SARE Model Canvas: window 3 (b) - All

Don't forget: timing is essential → question of credibility, insurance, legal and vigilance at the national level.

Direct Actions:

- Precautionary measures
- **Reporting to FAMHP (1/2)**



- IF SAE meets definition and reporting criteria
- If SAR severity assessment is « serious » or above
- In two times: (I) after detection (II) after investigation

Extracted and adapted from European Union Standards and Training for the Inspection of Tissue Establishments - Submitted to the European Commission 21.05.08*

SARE Model Canvas: window 3 (b) - All

Don't forget: timing is essential → question of credibility, insurance, legal and vigilance at the national level.

Direct Actions:

- Precautionary measures
- **Reporting to FAMHP (1/2)**

- ❑ Reporting to a competent authority is a legal obligation that must be a continuation of a collaborative approach.
- ❑ Quality communication between all stakeholders is essential for rapid action when necessary, for the improvement of the system itself but also for greater public transparency.

SARE Model Canvas: window 4 (a) - All

→ Start by describing the situation encountered without forgetting to specify the activity during which this situation takes place
→ Nb: can also be described in the previous window

Investigation
- **Description of the linked activity**
- Root cause analysis
- Specification SAR/SAE
- Evaluation of the impact/consequence
- Reporting to FAMHP (2/2)

A sufficient explanation + specify the time/operation during which the incident took place (this involves identifying the stage during which the problem occurred (SAE) or the stage identified as being that during which the source problem may be linked to the SAR.

Examples – operations:

Transport, donor selection, procurement, testing, processing, storage, product selection, issue, distribution …

SARE Model Canvas: window 4 (b) - All

Tip: call the most competent people to move forward on this central and collaborative point.

Investigation
- Description of the linked activity
- **Root cause analysis**
- Specification SAR/SAE
- Evaluation of the impact/consequence
- Reporting to FAMHP (2/2)

→ Do not reinvent anything, use the management tools for your deviations:

- 5 Whys
- The Ishikawa Fishbone Diagram (IFD)
- Failure Mode and Effects Analysis (FMEA)
- …

SARE Model Canvas: window 4 (c) – SAR replacement T&C + HSC

Investigation
- Description of the linked activity
- Root cause analysis
- **Specification SAR/SAE**
- Evaluation of the impact/consequence
- Reporting to FAMHP (2/2)

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

SARE Model Canvas: window 4 (c) – SAR MAR

Investigation
- Description of the linked activity
- Root cause analysis
- **Specification SAR/SAE**
- Evaluation of the impact/consequence
- Reporting to FAMHP (2/2)

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

SARE Model Canvas: window 4 (c) – SAE all

Investigation
- Description of the linked activity
- Root cause analysis
- **Specification SAR/SAE**
- Evaluation of the impact/consequence
- Reporting to FAMHP (2/2)

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.

SARE Model Canvas: window 4 (d) – replacement T&C + HSC

Aim: such matrix is shared in order to assist 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.

Investigation
- Description of the linked activity
- Root cause analysis
- Specification SAR/SAE
- **Evaluation of the impact/consequence**
- Reporting to FAMHP (2/2)

3 perspectives of your interest

Assign a score between 0 and 4 and consider mitigating this score once appreciated

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

SARE Model Canvas: window 4 (d) – MAR

Aim: such matrix is shared in order to assist 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.

Investigation
- Description of the linked activity
- Root cause analysis
- Specification SAR/SAE
- **Evaluation of the impact/consequence**
- Reporting of notification to FAMHP (2/2)

Assign a score between 0 and 4 and consider mitigating this score once appreciated

3 perspectives of your interest

	IMPACT DESCRIPTION	INDIVIDUAL		SYSTEM		OTC SUPPLY
0	Insignificant	Insignificant	or	No effect	or	Insignificant
1	Minor	Non serious	or	Minor damage or some procedures postponed	or	Partial loss of gametes/embryos for one couple
2	Significant	Serious	or	Damage to system-services will be affected for short period Many procedures cancelled or postponed	or	Partial loss of gametes/embryos for some couples or total loss for one couple
3	Major	Life-threatening	or	Major damage to system – significant time needed to repair Significant numbers of procedures cancelled	or	Partial loss of gametes/embryos for for all couples or total loss for few couples
4	Severe	Fatal	or	System destroyed - need to rebuild All procedures cancelled	or	Total loss of gametes/embryos for all couples

SARE Model Canvas: window 4 (d) – All

Aim: such matrix is shared in order to assist 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.

Investigation
- Description of the linked activity
- Root cause analysis
- Specification SAR/SAE
- **Evaluation of the impact/consequence**
- Reporting to FAMHP (2/2)

We take this first score and multiply it by the other score

Impact matrix

Likelihood / 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

We take this score and multiply it by the other score

The result of the multiplication gives you an impact score on which you can base yourself for the mitigation and the formulation of the capa plan.

SARE Model Canvas: window 4 (e) – All

Don't forget: timing is essential → question of credibility, insurance, legal and vigilance at the national level.

Investigation
- Description of the linked activity
- Root cause analysis
- Specification SAR/SAE
- Evaluation of the impact/consequence
- **Reporting to FAMHP (2/2)**

- IF SAE meets definition and reporting criteria
- If SAR severity assessment is « serious » or above
- In two times: (I) after detection (II) after investigation

SARE Model Canvas: window 5 – All

CAPA Plan

→ Relevance of actions and reasonableness of deadlines

→ Largely dependent on reporting causes (RCA), final imputability and reporting assessed consequences / impact

→ Legally binding

SARE Model Canvas

Assess the likelihood of recurrence after CAPA

Effectiveness of the CAPA Plan should be assessed following implementation of corrective and preventive actions (for example by re-applying the impact matrix).

Remember: the impact can be reduced by

- Reducing the probability of recurrence through preventive measures; or
- Increasing the detectability of the risk; or
- Reducing the severity of the consequences, if it should recur.

→ Not legally binding, but seriously encouraged

SARE Model Canvas
Conclusions and take-home messages

The management of SARE can be like flying an airplane – a pragmatic checklist is useful every time - **Use carefully the SARE model canvas** each time you start or debrief a SARE situation.

In one view, you can **more easily manage** a key process. All steps should be assessed: severity / imputability / direct actions / likelihood of recurrence / consequences / impact matrix.

Administrative reporting to a competent authority is a legal obligation that **must be a continuation of a collaborative approach**. The **quality of the communication** between all stakeholders is essential for rapid action, when necessary, for the improvement of the system itself but also for **greater public transparency**.

SARE Model Canvas

Conclusions and take-home messages

Reporting adverse reactions or events should not be associated with punishment. **Achieving a 'no blame' culture** will result in greater participation by all those involved and more effective vigilance systems.

The role of a competent authority is to **assess a SARE and provide an appropriate regulatory response to the situation encountered**. To make a good assessment, a common basis of communication and shared expectations is needed.
--> Time and collaboration are the keys.

References

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- https://www.notifylibrary.org/background-documents

Abbreviations

1) **ORHA** means Organisation Responsible for Human Application

   Example: Orha = Hospital

2) **PO** means Procurement Organisation

3) **TE** means Tissue Establishment

4) **CA** means Competent Authority

5) **SAR** means Serious Adverse Reactions

6) **SAE** means Serious Adverse Events

7) **SARE** means Serious Adverse Reaction & Events

8) **NCA** means National Competent Authority

9) **MAR** means Medically Assisted Reproduction

10) **RCA** means Root Cause Analysis

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