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COMMON APPROACH

FOR DEFINITION OF REPORTABLE SERIOUS ADVERSE EVENTS AND REACTIONS (SARE) AS LAID DOWN IN THE TISSUES AND CELLS DIRECTIVE 2004/23/EC AND COMMISSION DIRECTIVE 2006/86/EC

VERSION 2024

This Common Approach document comprises **recommendations** for a harmonised approach for the completion of the annual web-reporting template by the competent authorities in Member States to the European Commission for Serious Adverse Reaction(s) and Event(s) Tissues and Cells - Directive 2006/86/EC and has no legally binding status for Member States.

A **Vigilance Expert Subgroup (VES)** of the Competent Authorities on Substances of Human Origin (CASoHO E01718) proposes changes and updates to the SARE reporting template and to this set of instructions. The subgroup presents and discusses its proposals with the full meetings of Competent Authorities and agrees a programmed approach for improvements with DG SANTE.

The common approach laid down here aims to facilitate comparisons between data sent to the Commission from Member States, and associated countries. The guidelines are meant to reduce the reporting burden on all parties concerned (reporting establishments, competent authorities, and the European Commission) by clarifying issues before data collection is undertaken each year.

Furthermore, due to the complexity of data collection, annual reporting of SARE has been and will continue to be a learning exercise over the coming years.

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1. SCOPE OF REPORTING

Legal framework

Article 11(1) of the Tissues and Cells Directive (2004/23/EC) describes the types of serious adverse reactions and events (SARE ([1])) that are reportable.

Reportable SAR are those '***observed in a donor during or after the procurement which may influence the quality and safety of of tissues and cells or in the recipient during or after clinical application which may be linked to the quality and safety of tissues and cells.***'

Reportable SAE 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'***.

Article 7 of Directive 2006/86/EC requires that Member States shall submit to the Commission an annual report, on the notification of serious adverse events and reactions received by the competent authority, using the formats in Parts A and B of Annex V. **The report should include data collected during the previous calendar year.**

The following are **not subject to mandatory reporting** under the Tissues and Cells Directives:

- adverse reactions in recipients which are not linked to the quality and safety of the tissues or cells applied (e.g., surgical error, infection due to a contaminated surgical instrument, viral infection from another source).

- events or reactions in living donors which do not influence the quality and safety of the tissues or cells.

As a general principle, the Commission cannot require the Member States to report more information than that specified in the Tissues and Cells Directive. However, the Commission is supporting Member States in their efforts to improve data collection and analysis in the vigilance field, and therefore, a facility has been included to report donor reactions in the annual report on a voluntary basis, for those who collect them nationally (see section 13 of this document).

2. IMPORTANT INFORMATION FOR COMPLETION OF THE ELECTRONIC REPORT

SARE data submission is performed electronically using the SANTE Data Collection Platform. The form is stored in SANTE Data Collection Platform and access to the report is limited to authorised users. Technical instructions for the SARE web reporting form are available in the User Guide.

Where a Member State has two or more different competent authorities responsible for SARE reporting for tissues and cells***, it is not possible to submit separate electronic forms***. In these

([1]) DIRECTIVE 2004/23/EC:

'serious adverse event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity;

'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;

circumstances, one competent authority should enter their data on the electronic form and **save it without submitting;** the other competent authority/authorities should then add and save their data and **the last must submit** the form.

IMPORTANT: please make sure to **distinguish correctly** between:

- **"0"** - when there were no activities in this reporting period for this type of tissues/cells, or when there was no reportable SAR or SAE.
- **"N/A" – data not available** (there was activity and/or SARE for this type of tissues/cells, but data are not available/are partial at the time of the reporting). **"N/A" does not mean Not Applicable and is not used for Not Assessable**.

3. DEFINITIONS TO BE APPLIED FOR SAR IN REPLACEMENT T&C AND HAEMATOPOIETIC STEM CELLS

The web-reporting form/template includes several terms that are taken from Annex V, part A of Directive 2006/86/EC (Annual notification for serious adverse reactions). The following definitions/interpretations are proposed to ensure a common approach to reporting this data.

3.1. Type of tissue/cell

Tissues or cells should be included using the descriptions in the drop-down menus on the web reporting form.

Following the agreement of Competent Authorities for tissues and cells and Competent Authorities for organ transplantation ([2]), vascularised composite tissues (e.g., face, arm) are considered to be covered by the Directive 2010/53/EC, therefore SAR following transplantation of such tissues should not be reported here.

3.2. Number of tissues and cells of this type distributed (if available)

Article 3 (k) of Directive 2004/23/EC defines "distribution" (see Glossary).

In the annual report, the number of tissues and cells of this type distributed should be understood as 'the total number transported or delivered to a clinical unit, even if the clinical unit is in the same building or the same floor'.

- If tissues and cells are returned to the Tissue Establishment (TE) without use and for subsequent redistribution, they should be counted only when subsequently redistributed.
- Where tissues or cells pass from one TE to another TE before distribution, they should not be included in this total until finally distributed for clinical application.

[2] https://ec.europa.eu/health/events/meeting-competent-authorities-tissues-and-cells-3-4-december-2012-summary-report_en

The quantity of tissues and cells distributed by a TE could be extracted from the annual activity report that TEs submit to the CA in accordance with Article 10 of Directive 2004/23/EC. This is the national distribution activity that provides a denominator for the frequency of reactions for this type of tissue or cells.

The following is a proposed common approach to **counting units distributed**:

T&C	**One (1) unit equals to:**
Skeletal Tissues	One individually packaged graft (e.g., one femoral head, one unit of demineralised bone, one container of bone chips, one femoral strut, one osteochondral allograft, one individually packaged tendon or part of a tendon)
Haematopoietic Stem Cells	One single bag or container of cells
Ocular Tissues	One individually packaged or contained graft (e.g., one cornea, one piece of sclera)
Cardiovascular Tissues	One individually packaged or contained graft (e.g., one valve, one package containing one or more lengths of vessel)
Skin	One container of skin, regardless of the area of skin it contains **([3])**.
Amniotic Membrane	One container of tissue, regardless of the area of tissue it contains[2].

The category of '**Multiple Tissues or Cells**' should be used where a recipient received several different types of tissues or cells simultaneously and experiences a reaction, but it is not evident which T&C type was implicated. Denominator data (numbers distributed, recipients etc.) are not required in this section, as this data is included in the individual tissue/cell types (see section 3).

3.3. Total number of recipients for this type tissues and cells (number of recipients affected)

In the annual report, this should be understood to mean the total number of patients who had at least one unit of tissues or cells applied during the year concerned in a given country, **regardless of whether they had a reaction or not**. This is the national activity that provides a denominator for the frequency of reactions for this type of tissue or cells.

It is acknowledged that not all Member States currently collect data on the total number of patients treated with each type of tissue or cells.

If this information is not available, N/A should be selected in the relevant type of T&C and it should be noted in the comments space provided.

3.4. Number of serious adverse reaction(s)

Each individual adverse reaction in an individual recipient following the application of human tissues or cells, and where the reaction is 'serious' and can be linked to the quality and safety of the tissues or cells applied, should be counted as **1 adverse reaction report**, i.e., one report for

(3) If this data is recorded by cm^2 in your MS, you should divide the total by the average number of cm^2 included in a single package. Although this will be an estimate, it will be adequate for the purposes of providing a denominator for SARE monitoring. If you do not have data on the average number of cm^2 included in a single package, please provide the total area of distributed skin in the comments box only.

each relevant category of SAR (see 5.9 SAR Type). Therefore, multiple reaction types in one recipient should be reported as multiple SARs.

Only one report (SAR or SAE) should be notified for each incident. Thus, when an SAR is the result of an adverse event, only the SAR should be reported, i.e., from the moment when a recipient or donor has been harmed, this takes precedence. [The only exception to this is where an adverse event results in a reaction in a donor and where that reaction does not fall within the mandatory reporting criteria, i.e., not caused by or resulting in a quality or safety defect in the tissues or cells donated. In this case, it is recommended that the event is reported as an SAE (mandatory) and the reaction is reported in the non-mandatory category of donor reactions if that is the procedure applied in that MS. Example: *PBSC donor who should have been excluded from donation, has a serious adverse reaction during apheresis. The cells are suitable for transplantation. In this case, the SAR in the donor can be reported as a non-mandatory reaction as there is no impact on the quality or safety of the cells but the SAE (the error in donor selection) must also be reported as it meets the criteria for mandatory reporting.*]

3.5. Severity assessment

Reactions should be included in this number only if they were serious in nature. Directive 2004/23/EC defines serious as "fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization or morbidity."

The following **severity assessment** tool should be applied:

NOT REPORTABLE	Insignificant	No harm to the recipient or living donor
	Non-serious	Mild clinical consequences that do not necessitate hospitalization and do not result in long-term disability or consequences for the recipient or living donor.
TO BE REPORTED	**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 (see guidance in 5.10)

3.6. Imputability assessment

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 included in the annual report. The following **imputability (see glossary) assessment** tool should be applied:

NOT REPORTABLE	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*	**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 or when there is no evidence for attributing imputability, but it cannot be excluded
	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)

* Occasionally a confirmed SAR is submitted, where even after investigation the imputability cannot be assigned but cannot be excluded. In such cases the default assignment Possible can be selected.

3.7. Pending Reports

It should be understood that only SARs for which the investigation has been completed should be included in the annual report. SARs which are still pending should remain for the report of the following year and should only be included once they have been investigated and closed. Suspected serious adverse reactions must be communicated to the competent authority, but they should not be included in the annual report to the European Commission unless they have been fully confirmed at the date of submission.

3.8. T&C exchanged between Member States

Where implicated tissues or cells have been distributed to more than one EU Member State, the CA in the Member State where the tissues or cells originated, and where the reactions occur, should communicate with each other. They should include in their respective reports only the affected recipients and reactions that occurred in their respective country, to ensure that recipients affected are included in just one report.

3.9. SAR Type

The annual report template includes the following main categories:

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

Serious adverse reactions not involving a disease transmission should be reported in the 'Other SAR' category (these fall under the definition of SAR in the Directive); under this category, the following sub-categories are available:

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

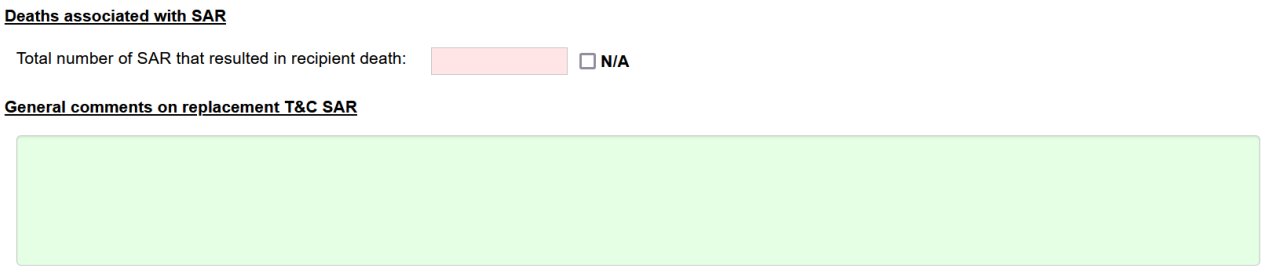
3.10. Deaths associated with SAR in recipients

Where a SAR has resulted in a recipient death, use the box to highlight the number of cases. A total number should be inserted in the box to indicate how many SAR resulted in recipient deaths. Please type "0" if no death has occurred or, if there is no data on recipients' deaths, please, tick the N/A box. Additional information should always be provided in the 'General comments on replacement T&C/Haematopoietic stem cell SAR' box available just below giving relevant details such as:

- a brief description of patient initial illness details
- a brief description of the occurrences that led to the fatality and the level of imputability
- list of the tissue or cell products applied and any relevant information regarding the preparation of the implicated product(s)
- the conclusions and follow-up actions (corrective and preventive), if appropriate.

Deaths associated with a patient's underlying condition or any other cause not possibly attributable to the tissues or cells applied should not be included.

In the "General comments on Replacement T&C / Haematopoietic Stem Cells SAR" please enter also general comments related to your reports giving additional details where necessary. This field can also be left blank, apart from a case where the SAR resulted in a death.



4. DEFINITIONS TO BE APPLIED FOR SAR IN REPRODUCTIVE T&C

The electronic report includes several terms which are taken from Annex V, part A of Directive 2006/86/EC (Annual notification for serious adverse reactions). The following definitions/interpretations are proposed to ensure a common approach to reporting this data.

4.1. Number of tissues and cells of this type distributed (if available)

Article 3 (k) of Directive 2004/23/EC defines "distribution" (see Glossary).

In the annual report, **the number of tissues and cells of this type distributed** should be understood as distributed for application to a patient in your Member State i.e., 'the total number transported or delivered to a clinical unit, even if the clinical unit is in the same building or on the same floor'. In the MAR context, it should be understood to mean the number of sperm units that have been delivered to a clinic for insemination or the number of embryos delivered to a clinical setting for transfer to patients.

- If gametes or embryos are returned to the Tissue Establishment (TE) without use and for subsequent redistribution, they should be counted only when subsequently redistributed.

- Where tissues or cells pass from one TE to another TE before distribution for clinical use, they should not be included in this total until finally distributed for clinical application.

The quantity of gametes or embryos distributed by a TE could be extracted from the annual activity report that TEs submit to the CA in accordance with Article 10 of Directive 2004/23/EC. The following is a proposed common approach to counting units distributed for the purpose of inclusion in the annual report to the Commission:

- one unit of **sperm** is one individual straw, the contents of which will be applied at once (for IUI) or

- one individual **embryo**

If you don't have the number of units distributed, please provide the number of cycles only in the comments box, otherwise your data will distort the total.

This is the national distribution activity that provides a denominator for the frequency of reactions for this type of tissue or cells.

4.2. Total number of recipients for this type of tissues and cells (number of recipients affected)

In the annual report, this should be understood to mean the total number of patients who had at least one unit of tissues or cells applied during the year concerned in a given country, regardless of whether they had a reaction or not. In the context of Medically Assisted Reproduction, this means the number of patients who have been inseminated with sperm (IUI only) or have had an embryo transfer. This is the national activity that provides a denominator for the frequency of reactions for this type of tissue or cells.

It is acknowledged that not all Member States currently collect data on the total number of patients treated with each type of tissue or cells. If this information is not available for a type of tissues or cells, N/A should be selected in the Total number of recipients column, and it should be noted in the comments space provided.

4.3. Number of serious adverse reaction(s) in recipients or offspring

Each individual adverse reaction in an individual recipient or offspring following the donation or application of human tissues or cells, and where the reaction is 'serious' and can be linked to the safety or quality of the tissues or cells donated or applied, should **be counted as 1 adverse reaction report**.

4.4. Severity assessment

Reactions should be included in this number **only if they were serious in nature**. Directive 2004/23/EC defines serious as "fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization or morbidity."

The following **severity assessment** tool has been adapted by the SOHO V&S project for use in the field of Medically Assisted Reproduction (MAR) and should be applied.

NOT REPORTABLE	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	**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 (see guidance in 4.8)

4.5. Imputability assessment

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 included in the annual report. The following **imputability (see glossary) assessment** tool which was adapted in the SOHO V&S project for the field of MAR should be applied.

NOT REPORTABLE	**Not assessable**	Insufficient data for imputability assessment
	Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the MAR process
	Unlikely	Evidence clearly in favour of attributing to other causes than the MAR process
TO BE REPORTED*	**Possible 1***	Evidence is indeterminate but cannot be excluded or when there is no evidence for attributing imputability, but it cannot be excluded
	Likely 2	Evidence in favour of attributing to the MAR process
	Certain 3	Conclusive evidence beyond reasonable doubt for attributing to the MAR process

*Occasionally a confirmed SAR is submitted, where even after investigation the imputability cannot be assigned but cannot be excluded. In such cases the default assignment Possible can be selected.

4.6. Pending Reports

It should be understood that only SARs for which the investigation has been completed should be included in the annual report.
SARs which are still pending should remain for the report of the following year and should only be included once they have been investigated and closed. Suspected serious adverse reactions must be communicated to the competent authority, but those should not be included within the annual report to the European Commission unless they have been fully confirmed at the date of submission.

4.7. T&C exchanged between Member States

Where implicated tissues or cells have been distributed to more than one EU Member State, **the CA in the Member State where the tissues or cells originated and where the reactions occur should communicate with each other and include in their respective reports only the affected recipients and reactions** that occurred in their respective country, so as to ensure that recipients affected are included in just one report.

4.8. Serious adverse reactions in donors

In this section of the template, only those donor reactions which fall within the strict interpretations of the EU Directives should be counted, i.e., only those that impacted on the quality and safety of the T&C procured. For donor reactions falling outside the legal requirement, i.e., without an impact on the T&C procured (e.g., Ovarian Hyperstimulation Syndrome), a separate section is provided at the end of the webform.

4.9. SAR Type

The annual report template includes the following categories:

1) Transmitted infections

- Bacterial infection,
- Viral infection (HBV, HCV, HIV, other),
- Parasitical infection (malaria or other),
- Fungal infection,
- Prion disease,
- Other transmitted infections.

2) Transmitted malignant diseases

3) Transmitted genetic conditions

4) Other SAR
not involving a disease transmission should be reported in this category (these fall under the definition of SAR in the Directive).

There is a dropdown list under this subtype of SARs, for the different reproductive tissues and cells. Specifically, the following sub-categories are available:

Partner sperm or donor sperm (IUI)

(1) Other SAR: Anaphylactic reaction

(2) Other SAR: Ectopic pregnancy[3] (requiring surgical intervention or hospitalization)

(3) Other SAR (None of the above, please specify)

Embryo (all combinations of partner/donor gametes)

(1) Other SAR: Ectopic pregnancy ([4]) (requiring surgical intervention or hospitalization)

(2) Other SAR: Molar pregnancy ([5])

(3) Other SAR (None of the above, please specify)

Other reproductive tissues and cells (e.g., ovarian or testicular tissue)

(1) Rejection

(2) Other SAR (None of the above, please specify)

It should be understood that, as stated in Article 6(2) of Directive 2006/86/EC, 'in the case of assisted reproduction, ***any type of gamete or embryo misidentification or mix-up shall be considered as a serious adverse event.'***

- If a SAR occurred as a result of gamete or embryo misidentification i.e., disease transmission, then it should be reported as an adverse reaction.
- Psychological damage following gamete or embryo misidentification, or mix-up of gametes should not be reported as a serious adverse reaction.

4.10. Deaths associated with SAR in recipients or offspring

Where a SAR has resulted in a recipient or offspring death, use the box to highlight the number of cases. A total number should be inserted in the box to indicate how many SAR resulted in recipient or offspring deaths. Please type "0" if no death has occurred or, if there is no data on recipients' or offsprings' deaths, tick the N/A box. Additional information should always be provided in the

([4]) In-vitro fertilization (IVF) and Intrauterine Insemination (IUI) are known risk factors for ectopic pregnancies. The cause can be multifactorial. As aetiology is not clear, quality and safety of embryos or sperm may be involved.

([5]) Molar pregnancies are caused by 3PN embryos (triploidy) or 2PN embryos with only paternal chromosomes. Those embryos can be transferred in IVF cycles, causing a molar pregnancy. PN scores are not always possible and 2PN could be only paternal.

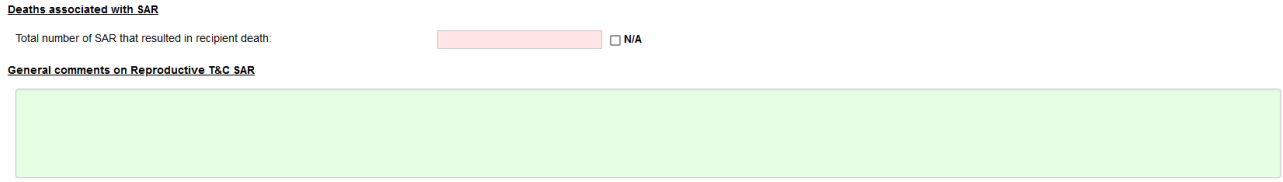
'General comments on reproductive T&C SAR (in donors)' box available just below giving relevant details such as:

- a brief description of patient initial illness details
- a brief description of the occurrences that led to the fatality and the level of imputability
- list of the tissue or cell products applied and any relevant information regarding the preparation of the implicated product(s)
- the conclusions and follow-up actions (corrective and preventive), if appropriate.

Deaths associated with a patient's underlying condition or any other cause not possibly attributable to the tissues or cells applied should not be included.

Note that spontaneous or elective abortions where the foetus has a genetic condition that caused the death should be included if an investigation has indicated that imputability to non-partner donated gametes or embryos was possible, likely or certain.

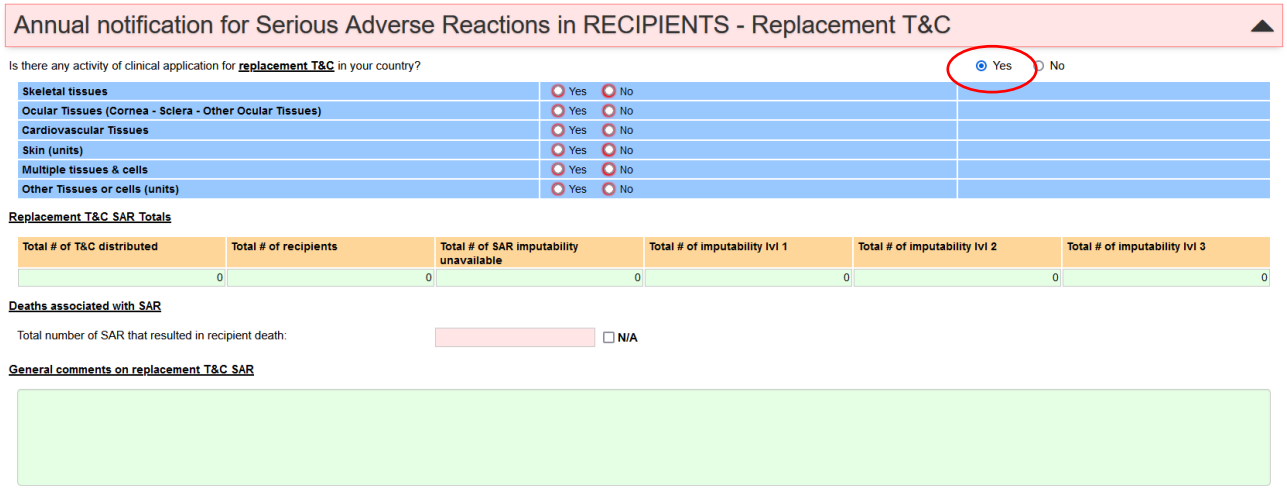
In the General comments on Reproductive T&C SAR please enter also general comments related to your reports giving additional details where necessary. This field can also be left blank, apart from a case where the SAR resulted in a death.



5. GUIDANCE ON REPORTING SERIOUS ADVERSE REACTIONS (SAR)IN RECIPIENTS – REPLACEMENT T&C

The first section is where all reaction data associated with 'replacement' T&C should be inserted, i.e.: bone, skin, heart valves, corneas etc.

If your MS had any activity of clinical application for these tissues and cells select 'yes' even if no SAR were reported. This will open a table for completion.



In row 1, for Skeletal tissues, select 'Yes' if any skeletal tissues were applied in your Member State. This will open additional rows where you should insert data relating to the numbers of units distributed and the numbers of recipients (see definitions/interpretations in chapter 5 below) for each skeletal tissue category.

- If you only have aggregated data for skeletal tissue, please complete the 'General' row only. The remaining rows will be automatically locked.

- If you have distribution and clinical application data for each category of skeletal tissue, then fill in each relevant row and the 'General' row will be automatically locked.

For each skeletal tissue category, select in the SAR column 'Yes' if any SAR has been reported for this tissue category, 'No' if no SAR occurred. Clicking on 'Yes' will open additional rows with a list of SAR types where you should click 'Yes' to each type of SAR that has been reported for that tissue. This will open an additional row where you should insert information relating to subtypes of SAR (where appropriate) and enter a specification for each SAR subtype (Description/Comments) with the number of SARs with that specification for that type of tissue.

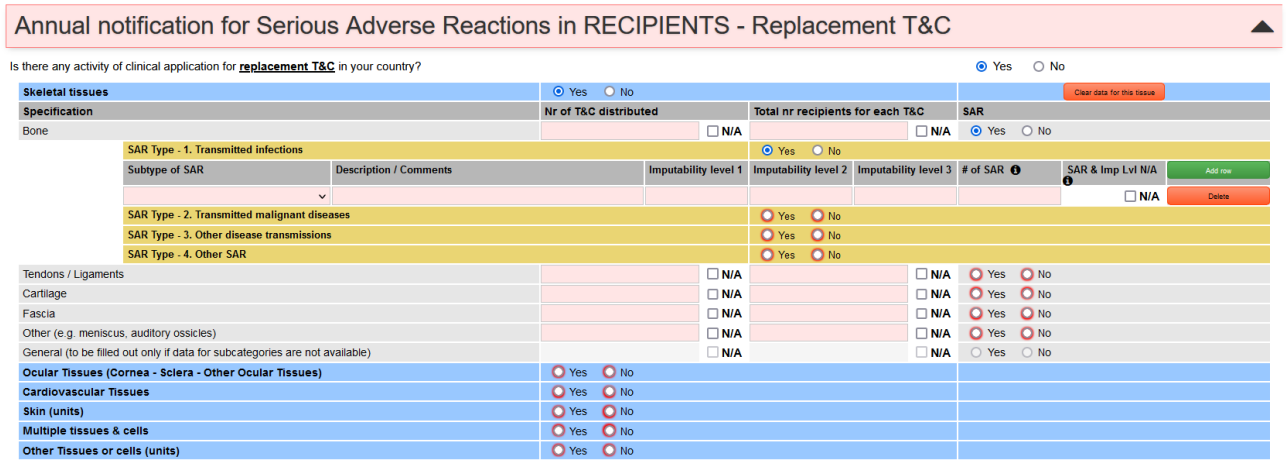
- If you know the imputability level for each SAR, please provide the number of SAR for each level of imputability and the '# of SAR' field will be locked automatically.

- If SARs have been confirmed as reportable, but even after investigation the imputability cannot be assigned but cannot be excluded, in such cases the default assignment "Possible" can be selected.

- If you only have the number of SARs occurred, but you don't know their imputability levels, please complete the '# of SAR' field only, the other fields will be locked automatically.

- If you know that SARs occurred, but you do not know the number nor the imputability level, tick the N/A box under 'SAR & Imp Lvl N/A'.

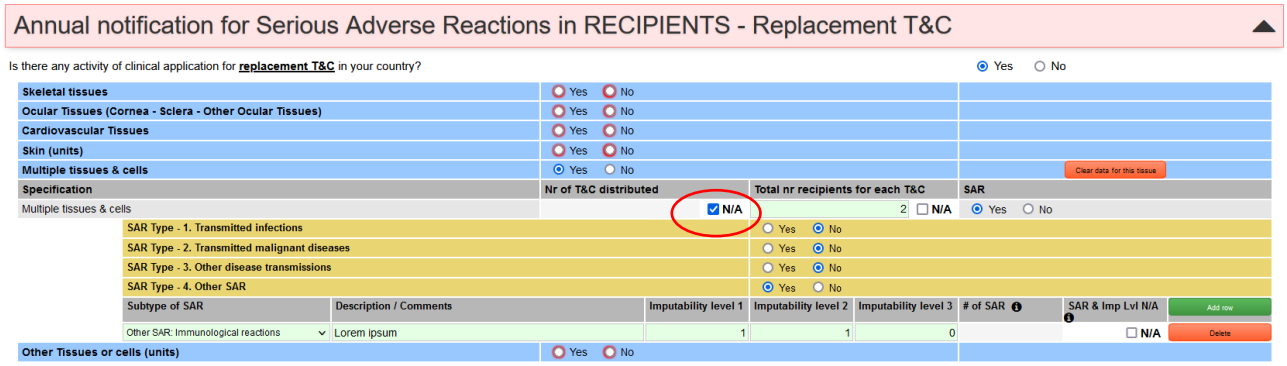
Click on the green 'Add row' button on the right to add an additional row or on the orange 'Delete' button to delete a row.



Donor reactions are captured elsewhere in the template; see section 13 for clarification.

Move to the next tissue/cell types by clicking 'Yes' if any ocular tissue, cardiovascular tissue, skin unit have been applied to recipients in your MS. Proceed with the completion of the table as before.

Please use the **'Multiple Tissues & Cells' category** to include any SAR(s) occurring when patients have been treated simultaneously with different types of T&C and it is not evident which T&C type was implicated. The units of Tissue and Cells applied in patients who received multiple T&C types should be counted under the figures for each individual type of T&C. Example: *if there is an immunological reaction in a patient that received multiple types of T&C, and the reaction cannot be attributed to a specific T&C type, then the reaction should be reported under 'Multiple Tissues and Cells', and the number of units distributed and number of recipients should be included under the sections for each type of T&C*. Therefore, under 'Nr of T&C distributed' please click the option N/A.



Please note that pancreatic islets, hepatocytes, amniotic membrane, and others (e.g., adipose tissue, tympanic membrane) are within the 'Other tissues or cells' section.

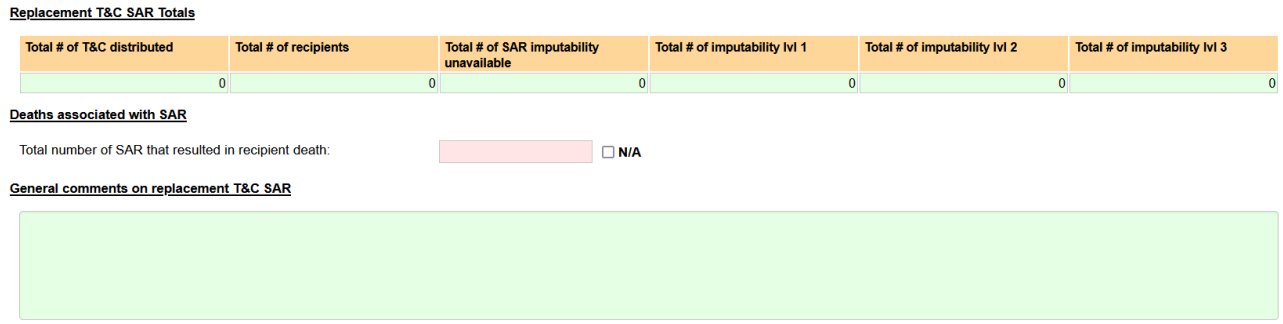
The 'Replacement T&C SAR Totals' in the next table will be automatically calculated for the following categories:

Total # of SAR Imputability unavailable: it is the total of the SARs occurred and for which imputability levels are not available or not assessable (it does not include SARs that have been confirmed as reportable, but where the imputability after assessment is unknown, as they are included in imputability 1).

Total # of imputability level 1, 2 or 3: they are the individual totals of SARs occurred per level of imputability assigned.

A separate box is available to highlight the number of deaths associated with SAR.

In the 'General comments on replacement T&C SAR' box, please enter comments related to your reports giving additional details where necessary. This field can also be left blank, apart from a case where the SAR resulted in a death.



Replacement T&C SAR Totals

Total # of T&C distributed	Total # of recipients	Total # of SAR imputability unavailable	Total # of imputability lvl 1	Total # of imputability lvl 2	Total # of imputability lvl 3
0	0	0	0	0	0

Deaths associated with SAR

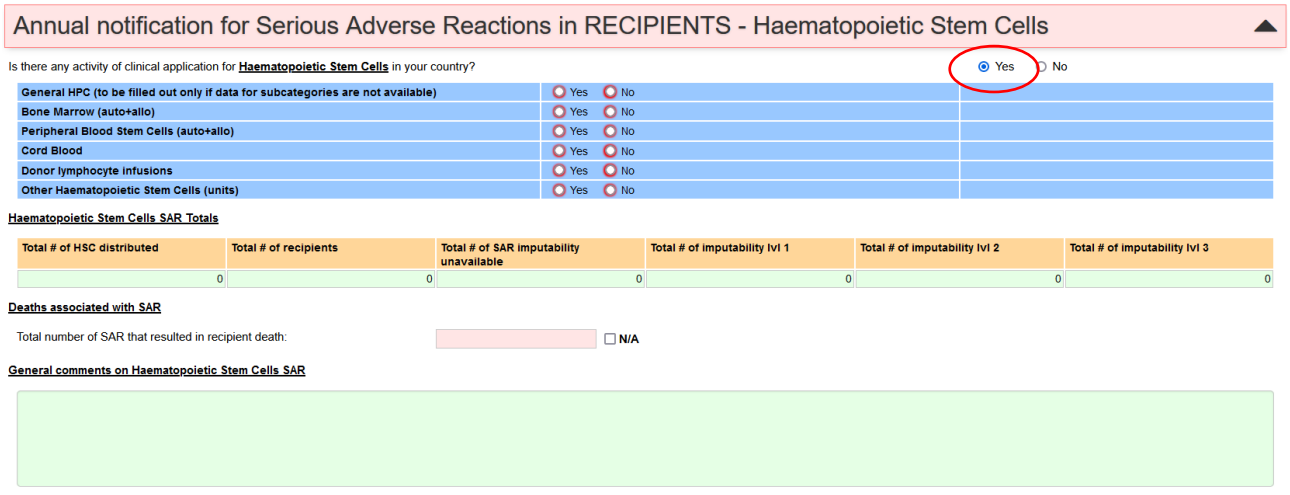
Total number of SAR that resulted in recipient death: ☐ N/A

General comments on replacement T&C SAR

6. ANNUAL NOTIFICATION FOR SERIOUS ADVERSE REACTIONS IN HAEMATOPOIETIC STEM CELLS

The second section is where all reaction data associated with haematopoietic stem cells should be inserted, i.e.: bone marrow, cord blood, etc.

If your MS had any activity of clinical application for these tissues and cells select 'yes' even if no SAR were reported. This will open a table for completion.



Annual notification for Serious Adverse Reactions in RECIPIENTS - Haematopoietic Stem Cells

Is there any activity of clinical application for Haematopoietic Stem Cells in your country? ◉ Yes ○ No

General HPC (to be filled out only if data for subcategories are not available)	○ Yes ○ No	
Bone Marrow (auto+allo)	○ Yes ○ No	
Peripheral Blood Stem Cells (auto+allo)	○ Yes ○ No	
Cord Blood	○ Yes ○ No	
Donor lymphocyte infusions	○ Yes ○ No	
Other Haematopoietic Stem Cells (units)	○ Yes ○ No	

Haematopoietic Stem Cells SAR Totals

Total # of HSC distributed	Total # of recipients	Total # of SAR imputability unavailable	Total # of imputability lvl 1	Total # of imputability lvl 2	Total # of imputability lvl 3
0	0	0	0	0	0

Deaths associated with SAR

Total number of SAR that resulted in recipient death: ☐ N/A

General comments on Haematopoietic Stem Cells SAR

- If you only have aggregated data for haematopoietic stem cells, please complete the 'General HPC' row only. The remaining rows will be automatically locked.

- If you have distribution and clinical application data for each category of haematopoietic stem cells, then fill in each relevant row and the 'General' row will be automatically locked.

In addition:

- If you only have aggregated data for subcategories (autologous, allogeneic related and unrelated), please complete the ‘General’ row only clicking on ‘Yes’. The remaining rows will be automatically locked.

- If you have distribution and clinical application data for each subcategory of haematopoietic stem cells, then click ‘Yes’ for each relevant row and the ‘General’ row will be automatically locked.

If this category or any subcategory had any activity, select ‘Yes’ (SAR column) if any SAR were reported for this category or any subcategory. This will open additional rows where you should click ‘Yes’ to each type of SAR that was reported for that tissue. This will open additional rows where you should insert information relating to subtypes of SAR (where appropriate) and enter a specification for each SAR subtype with the number of SARs with that specification for that type of tissue.

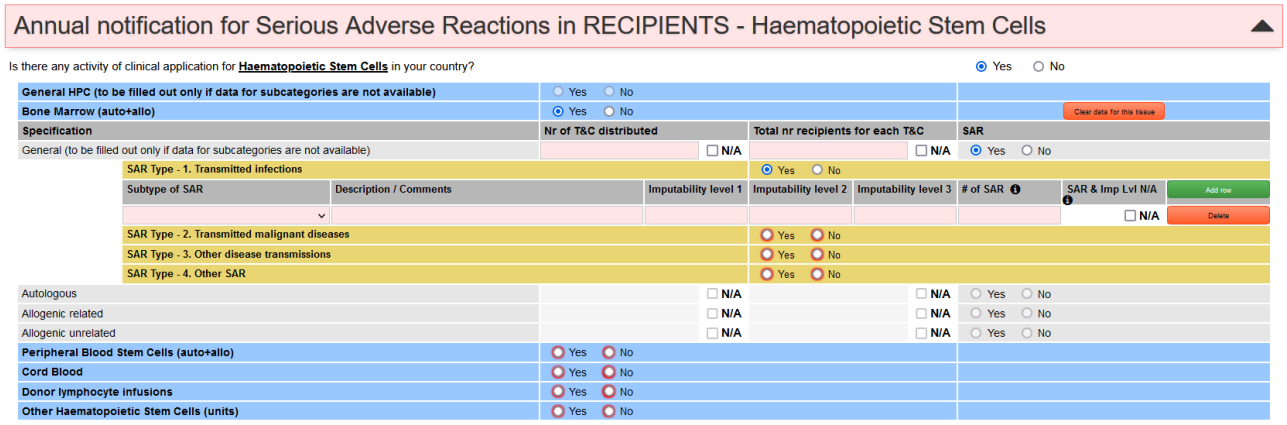
- If you know the imputability level for each SAR, please provide the number of SAR for each level of imputability and the ‘# of SAR’ field will be locked automatically.

- If SARs have been confirmed as reportable and where, even after investigation, the imputability cannot be assigned but cannot be excluded, in such cases the default assignment "Possible" can be selected.

- If you only have the number of SARs occurred, but you don't know their imputability levels, please complete the '# of SAR' field only, the other fields will be locked automatically.

- If you know that SARs occurred, but you do not know the number, tick the N/A box under ‘# of SAR N/A’.

Click on the green ‘Add row’ button on the right to add an additional row or on the orange ‘Delete’ button to delete a row.



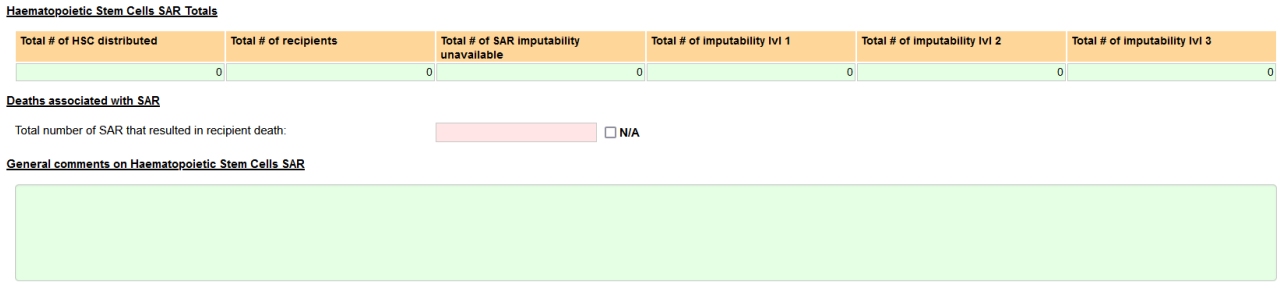
Donor reactions are captured elsewhere in the template; see section 13 for clarification.

Move through the different tissue/cell types by clicking ‘Yes’ if any bone marrow, peripheral blood stem cells etc. were procured, distributed or applied in your MS. Proceed with the completion of the table as before.

The ‘Haematopoietic Stem Cells SAR Totals’ in the next table will be automatically calculated. The totals are calculated as for serious adverse reactions in recipients of replacement T&C.

A separate box is available to highlight the number of deaths associated with SAR. Additional information should always be provided in the general comments box.

In the ‘General comments on Haematopoietic Stem Cells SAR’ box, please enter comments related to your reports giving additional details where necessary. This field can also be left blank, apart from a case where the SAR resulted in a death.


Haematopoietic Stem Cells SAR Totals

Total # of HSC distributed	Total # of recipients	Total # of SAR imputability unavailable	Total # of imputability lvl 1	Total # of imputability lvl 2	Total # of imputability lvl 3
0	0	0	0	0	0

Deaths associated with SAR

Total number of SAR that resulted in recipient death: ☐ N/A

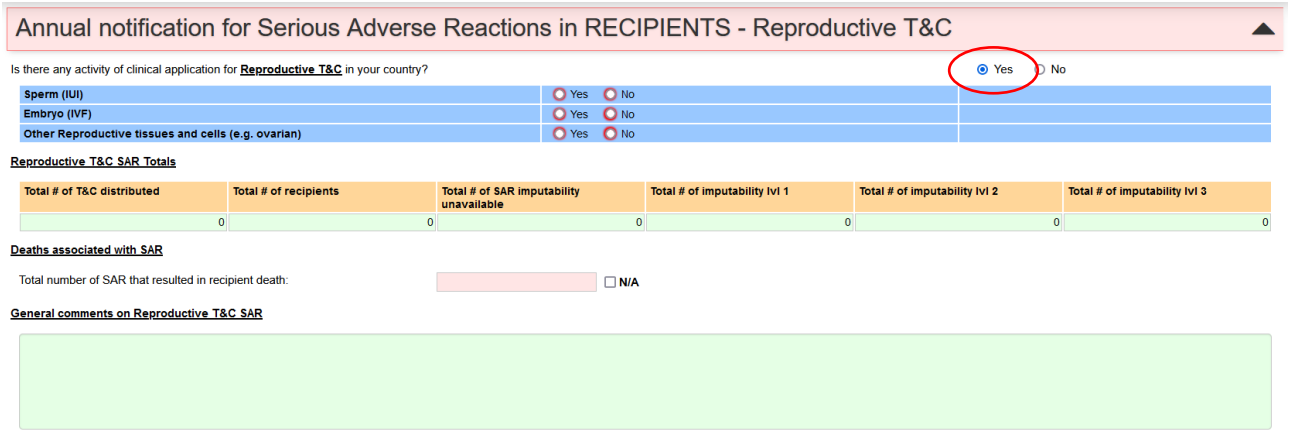
General comments on Haematopoietic Stem Cells SAR

7. ANNUAL NOTIFICATION FOR SERIOUS ADVERSE REACTIONS – REPRODUCTIVE T&C

In this section all reaction data associated with ‘reproductive’ T&C should be inserted, i.e., sperm, oocytes, embryos, ovarian and testicular tissue.

Recipients for sperm are those women who received sperm with IUI (partner or donor sperm) in the year concerned. Recipients for embryos are the women who received embryo(s) by embryo transfer (fresh or thawed). A recipient who had multiple IUIs or embryo transfers should be counted as ONE.

If your MS has had any activity of distribution and clinical application for these tissues and cells select ‘yes’ even if no SAR have been reported. This will open a table for completion.


Annual notification for Serious Adverse Reactions in RECIPIENTS - Reproductive T&C

Is there any activity of clinical application for Reproductive T&C in your country? ◉ Yes ○ No

Sperm (IUI)	○ Yes ○ No	
Embryo (IVF)	○ Yes ○ No	
Other Reproductive tissues and cells (e.g. ovarian)	○ Yes ○ No	

Reproductive T&C SAR Totals

Total # of T&C distributed	Total # of recipients	Total # of SAR imputability unavailable	Total # of imputability lvl 1	Total # of imputability lvl 2	Total # of imputability lvl 3
0	0	0	0	0	0

Deaths associated with SAR

Total number of SAR that resulted in recipient death: ☐ N/A

General comments on Reproductive T&C SAR

Only data for sperm relating to IUI is collected in the SAR section and not data on sperm used for IVF. All other sperm related data is captured in the relevant embryo section.

In row 1, select ‘yes’ if any sperm is distributed in your Member State for partner or non-partner use for IUI treatment. This will open additional rows where you should insert data relating to the numbers of units distributed and the numbers of recipients (see definitions/interpretations for ‘distributed’ and ‘number of recipients’ in chapter 7 below) for each category.

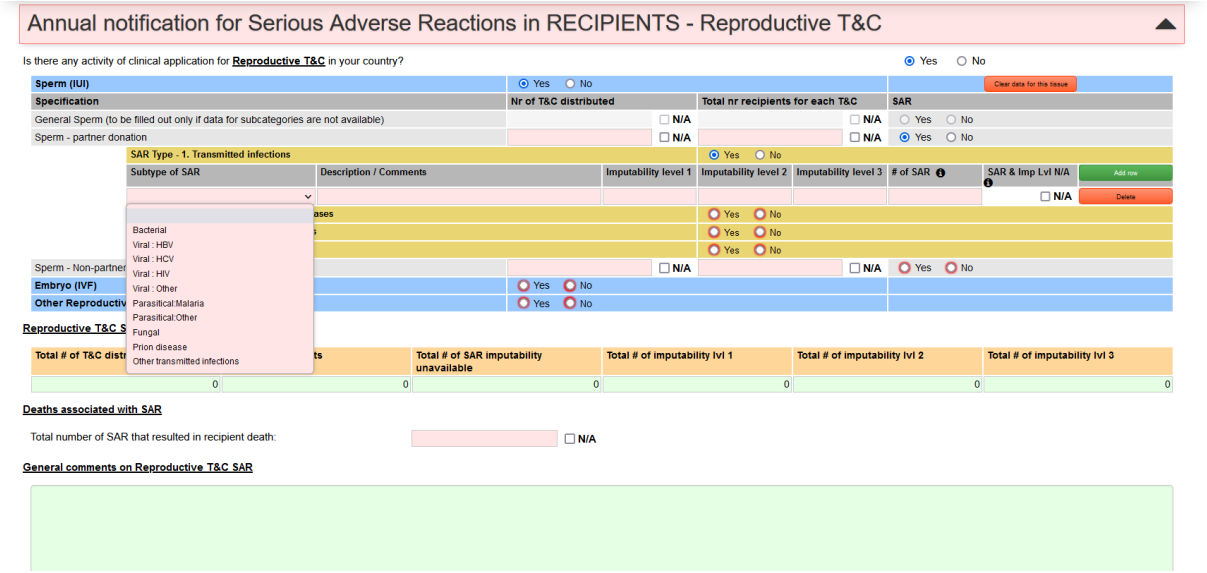
- If you only have aggregated data for partner and non-partner collections, then please complete the ‘General’ row only. The remaining rows will be automatically locked.

- If you have distribution and clinical application data for both partner and non-partner donation or for only one of these, then complete each relevant row and the ‘General’ row will be automatically locked.

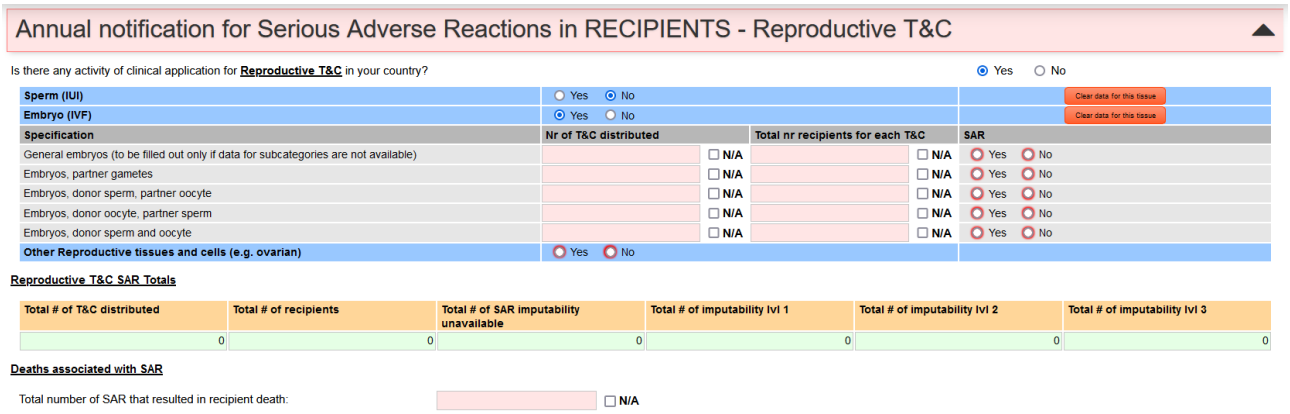
For each sperm row, select ‘Yes’ in the Column “SAR” if any SAR has been reported for this T&C category. This will open additional rows where you should click ‘yes’ to each type of SAR that has been reported for partner sperm or non-partner sperm. Each click will open additional rows where you should insert information relating to subtypes (where appropriate) and enter a specification for each SAR type with the number of SARs with that specification for that type of tissue. Click on the green ‘Add row’ button on the right to add an additional row or on the orange ‘Delete’ button to delete a row.

- If you only have the number of SARs occurred, but you don't know their imputability levels, please complete the '# of SAR' field only, the other fields will be locked automatically.

- If you know the imputability level for each SAR, please provide the number of SAR for each level of imputability and the ‘# of SAR’ field will be locked automatically.



Reactions related to embryos should be captured within the relevant embryo category, including data on the number of embryos distributed and the number of recipients for each of the four specific embryo categories. Please provide the data for embryos according to the specific categories provided, leaving the ‘General embryos’ blank. If the data by specific category is not available, you can complete the ‘General embryos’ category instead.



Donor reactions are captured elsewhere in the template; see section 13 for clarification.

The 'Reproductive T&C SAR Totals' in the next table will be automatically calculated. The totals are calculated as for serious adverse reactions in recipients of replacement T&C.

A separate box is available to highlight the number of deaths associated with SAR. Additional information should always be provided in the general comment box.

In the 'General comments on Reproductive T&C SAR' box, please enter comments related to your reports giving additional details where necessary. This field can also be left blank, apart from a case where the SAR resulted in a death.

8. DEFINITIONS TO BE APPLIED FOR SAE IN REPLACEMENT T&C AND IN HAEMATOPOIETIC STEM CELLS

The web-reporting template includes terms which are taken from Annex V, part B of Directive 2006/86/EC (Annual notification for serious adverse events). The following definitions/interpretations are proposed to ensure consistency in the reporting of this data. Please provide the data by category and specification of replacement tissues and cells and haematopoietic stem cells using the descriptions in the drop-down menu.

8.1. Number of tissues or cells processed

Article 3(g) of Directive 2004/23/EC defines processing as 'all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications'. In the annual report, this term refers to replacement tissues and cells and haematopoietic stem cells processed in TEs but not necessarily distributed. These data will allow the calculation of SAE rates in relation to numbers of tissues or cells processed in the European Union**.**

8.2. Definitions of SAE

Each event *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,* and where the event is 'serious' and can be linked to the safety or quality of the tissues or cells processed, should **be counted as 1 adverse event report**. Many SAE result

in SAR in recipients or donors; in these circumstances, only the SAR, not the SAE, should be reported.

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 (replacement tissues and cells and haematopoietic stem cells)**:

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

(2) The event could have implications for other patients or donors because of shared practices, services, 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 ([6]) of unmatched allogeneic tissues or cells.

When multiple tissues are affected by a single SAE, this should be reported as **1 adverse event report** in the row of Multiple tissues or cells. For 'Multiple Tissue and Cells, denominators should be counted under the "individual type of T&C" figures. For example, if there is a tissue or cell defect, and the event cannot be attributed to a specific T&C type, then the event should be reported under 'Multiple Tissues and Cells', and the number of processed tissues should be included under the sections for each type of T&C.

8.3. 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.

[6] A significant quantity should be understood as a quantity that has caused patient treatments to be cancelled or delayed.

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.

8.4. Specification of SAEs

The following categories are provided in the electronic report.

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

Examples
- Sporadic CJD diagnosed and reported in a living femoral head donor several years after procurement.

- Significant loss (80%) of stem cells in an allogeneic bone marrow graft following freezing/thawing (viability and CD34+ measured). Graft infused (no other option)

- Cytogenetic abnormalities in donor cells discovered after stem cell transplantation that didn't result in malignancy or genetic disease transmission to the recipient.

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: 150 heart valves thawed due to simultaneous failure of liquid nitrogen automatic filling system and alarm system.

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 washing solution used during procurement.

- 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.

- Cardiac valve distributed for surgery was mis-sized, rendering it unusable.
- Bone irradiated twice – grafts distributed for clinical application.
- Cryopreserved skin past its expiry date is distributed and used on a burned patient.
- A frozen femoral head is held by a courier company for 72 hours in a holding depot rather than being delivered immediately (Courier company used by many Tes in the country).

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.

8.5. Description and number of tissues/cells affected

Please describe the event and specify how many non-reproductive tissues/cells were affected as an indicator of the impact of the event. This is particularly important if the reported event resulted in the loss of irreplaceable autologous tissues or cells, highly matched (i.e., recipient specific) allogeneic tissues or cells or a significant quantity of unmatched tissues or cells or the release of a large quantity of tissues or cells that were not compliant with the established quality criteria.

9. DEFINITIONS TO BE APPLIED FOR SAE IN REPRODUCTIVE T&C

The electronic report includes terms which are taken from Annex V, part B of Directive 2006/86/EC (Annual notification for serious adverse events). The following definitions/interpretations are proposed to ensure consistency in the reporting of this data. Please provide the data by category and specification of reproductive tissue and cell type using the descriptions in the drop-down menus on the electronic report.

9.1. Number of tissues or cells processed

Article 3(g) of Directive 2004/23/EC defines processing as '*all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications*'. In the annual report, this term refers to tissues and cells processed in Tes but not necessarily distributed. These data will allow the calculation of SAE rates in relation to numbers of tissues or cells processed in the European Union**.**

9.2. Definitions of SAE

Each event *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,* and where the event is 'serious' and can be linked to the safety or quality of the tissues or cells processed, should **be counted as 1 adverse event report**. Many SAE result in SAR in recipients, offspring or donors; in these circumstances, only the SAR, not the SAE, should be reported.

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.

9.3. 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, collection or pick-up of gametes.

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 gametes or embryos 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)
It means the provision of tissues or cells by a tissue establishment or organisation responsible for transplantation, infusion, insemination or transfer. It is the process of linking the correctly selected gametes or embryos 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 organization 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 which may affect quality and safety of tissues and cells or potentially harm the patient.

9.4. Specification of SAEs

The following categories are provided in the electronic report.

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.

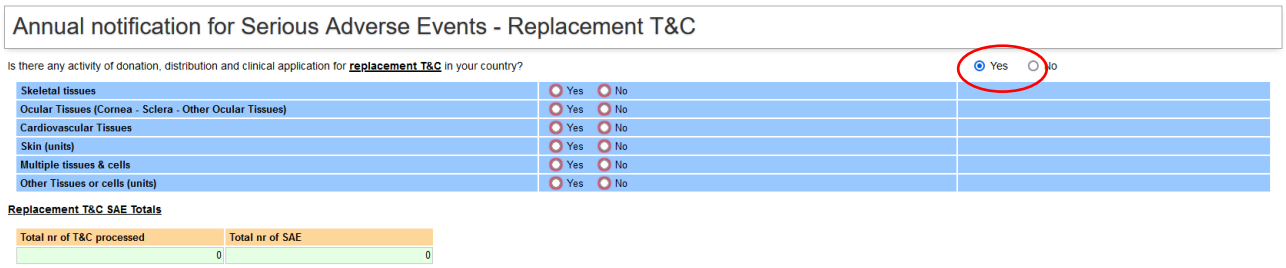
Example
An air company/ Pilot refused to accept cells in liquid nitrogen on board.

9.5. Description and number of tissues/cells affected

Please describe the event and specify how many reproductive tissues/cells were affected as an indicator of the impact of the event. This is particularly important if the reported event resulted in the loss of irreplaceable autologous/partner tissues or cells, or a significant quantity of non-partner tissues or cells or the release of a large quantity of tissues or cells that were not compliant with the established quality criteria.

10. GUIDANCE ON REPORTABLE SERIOUS ADVERSE EVENTS (SAE) ASSOCIATED WITH REPLACEMENT TISSUES AND CELLS

If your MS has had any activity in replacement tissues and cells for human application select 'yes', <u>even if no SAE have been reported</u>, to open **the corresponding tables for reporting the activity data.**

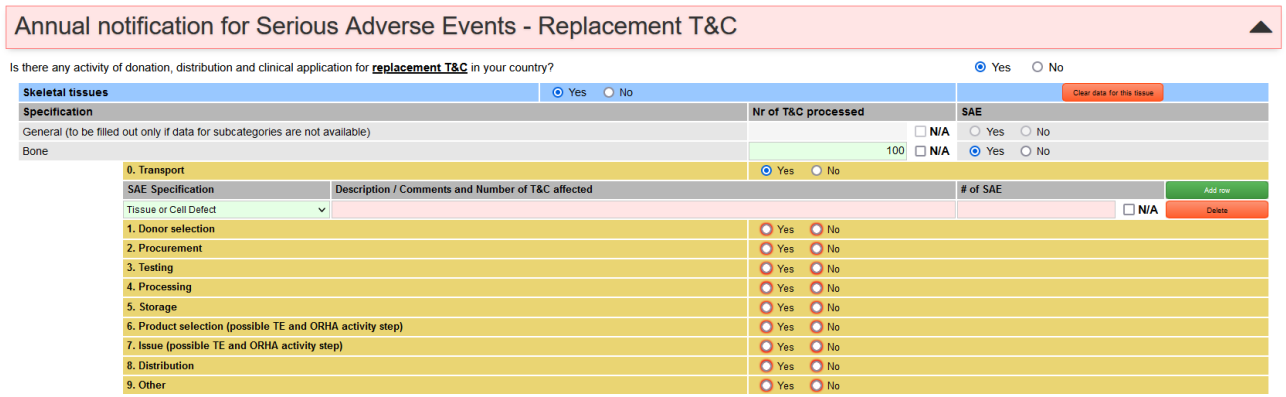


In row 1, for Skeletal tissues, select 'Yes' if any skeletal tissues were donated, distributed or applied in your Member State. This will open additional rows where you should insert data relating to the numbers of units processed (see definitions/interpretations in chapter 10 below) for each skeletal tissue category.

- If you only have aggregated data for skeletal tissue, please complete the 'General' row only. The remaining rows will be automatically locked.

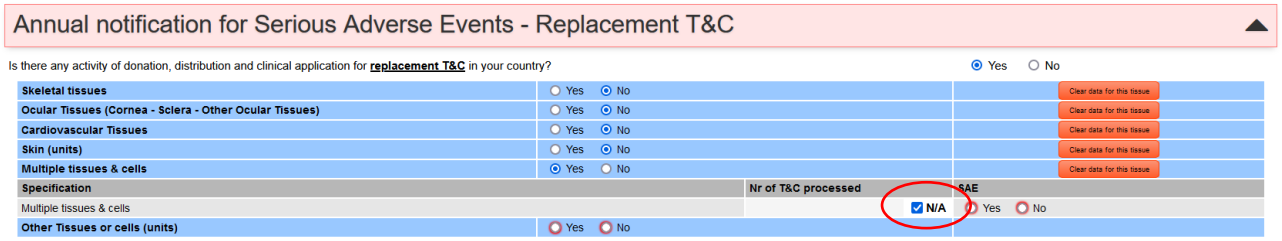
- If you have processing data for each category of skeletal tissue, then fill in each relevant row and the 'General' row will be automatically locked.

For each skeletal tissue category, select 'Yes' (SAE column) if any SAE has been reported for this tissue category. This will open additional rows where you should click 'Yes' to each activity step in which a SAE has occurred. This will open additional rows where you should insert information relating to SAE specifications and enter description / comments and number of T&C affected and the number of SAE. Click on the green 'Add row' button on the right to add an additional row or on the orange 'Delete' button to delete a row.



Move to the next tissue/cell types by clicking 'Yes' if any ocular tissue, cardiovascular tissue, skin unit have been processed in your MS. Proceed with the completion of the tables as before.

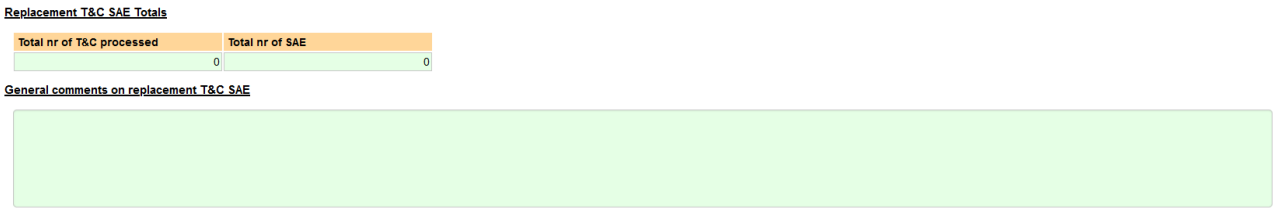
When multiple tissues are affected by a single SAE, this should be reported as **1 adverse event report** in the row of Multiple tissues or cells. For 'Multiple Tissue and Cells, denominators should be counted under the "individual type of T&C" figures. For example, if there is a tissue or cell defect, and the event cannot be attributed to a specific T&C type, then the event should be reported under 'Multiple Tissues and Cells', and the number of processed tissues should be included under the sections for each type of T&C.



Please note that pancreatic islets, hepatocytes, amniotic membrane, and others (e.g., adipose tissue, tympanic membrane) are within the 'Other tissues or cells' section.

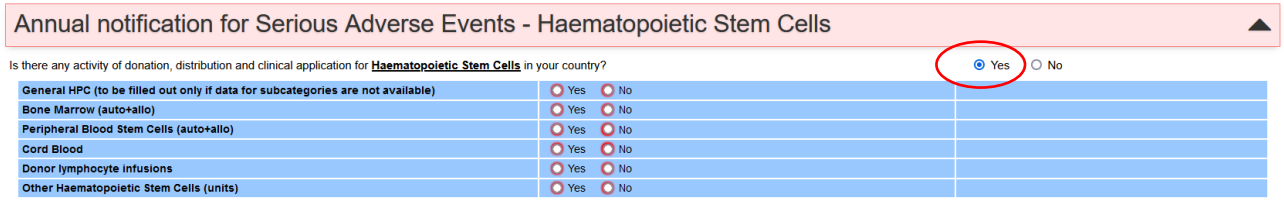
The 'Total nr of T&C processed' and the 'Total nr of SAE' will be automatically calculated.

In the 'General comments on replacement T&C SAE' box, please enter comments related to your reports giving additional details where necessary. This field can also be left blank.



11. GUIDANCE ON REPORTABLE SERIOUS ADVERSE EVENTS (SAE) ASSOCIATED WITH HAEMATOPOIETIC STEM CELLS

If your MS has had any activity in haematopoietic stem cells for human application select 'yes', <u>even if no SAE have been reported</u>, to open the corresponding tables for reporting the activity data.



- If you only have aggregated data for haematopoietic stem cells, please complete the 'General HPC' row only. The remaining rows will be automatically locked.

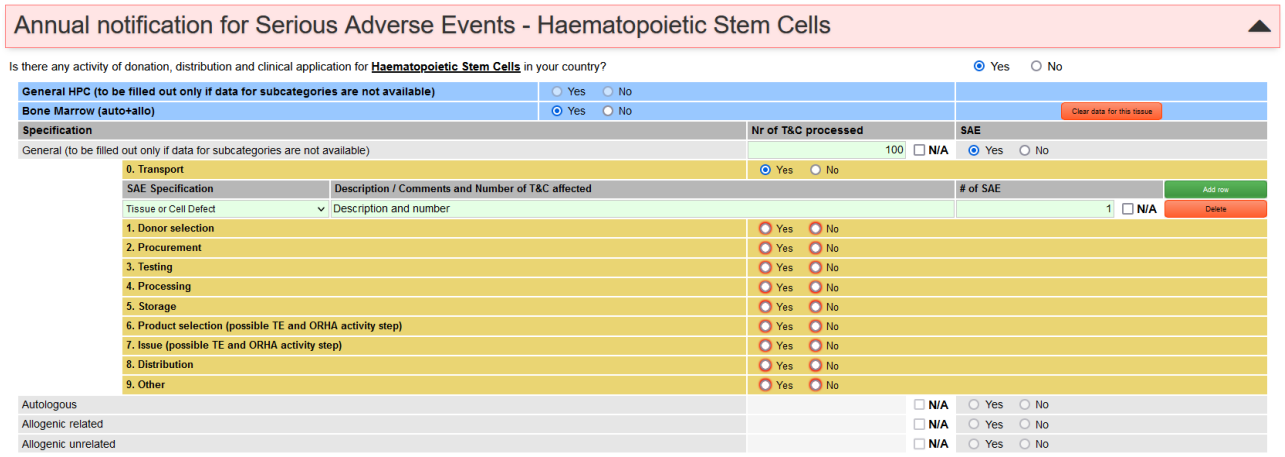
- If you have processing data for each category of haematopoietic stem cells, then fill in each relevant row and the 'General' row will be automatically locked (see definitions/interpretations in chapter 10 below).

In addition:

- If you only have aggregated data for subcategories (autologous, allogeneic related and unrelated), please complete the 'General' row only clicking on "Yes". The remaining rows will be automatically locked.

- If you have processing data for each subcategory of haematopoietic stem cells, then click "Yes" for each relevant row and the 'General' row will be automatically locked.

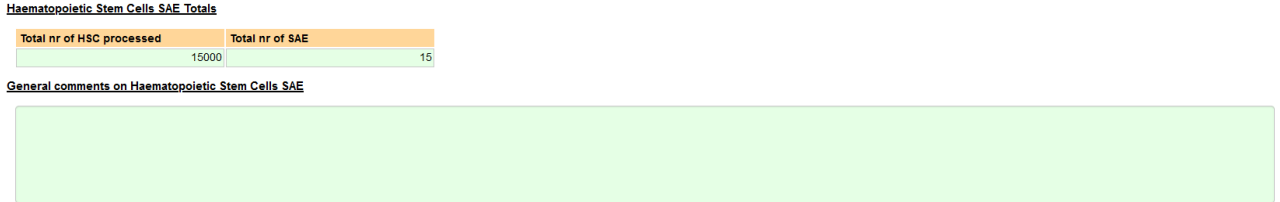
For each haematopoietic stem cell category, select 'Yes' (SAE column) if any SAE has been reported. This will open additional rows where you should click 'Yes' to each activity step in which a SAE has occurred. This will open additional rows where you should insert information relating to SAE specifications and enter description / comments and number of T&C affected and the number of SAE. Click on the green 'Add row' button on the right to add an additional row or on the orange 'Delete' button to delete a row.



Move through the different tissue/cell types by clicking 'Yes' if any bone marrow, peripheral blood stem cells etc. have been processed in your MS. Proceed with the completion of the table as before.

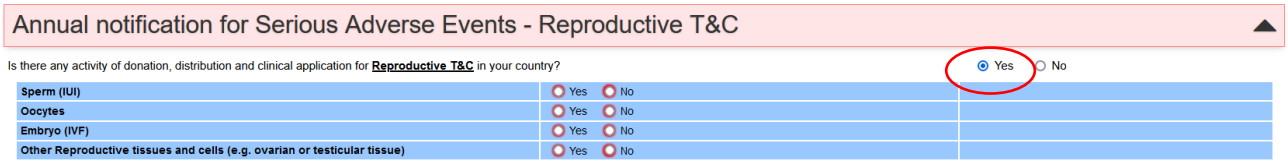
The 'Total nr of HSC processed' and the 'Total nr of SAE' will be automatically calculated.

In the 'General comments on Haematopoietic Stem Cells SAE' box, please enter comments related to your reports giving additional details where necessary. This field can also be left blank.



12. GUIDANCE ON REPORTABLE SERIOUS ADVERSE EVENTS (SAE) ASSOCIATED WITH REPRODUCTIVE TISSUES AND CELLS

If your MS has had any activity in reproductive tissue and cells for human application select 'yes' <u>even if no SAE have been reported</u>. This will open a table for completion of the processing activity data.

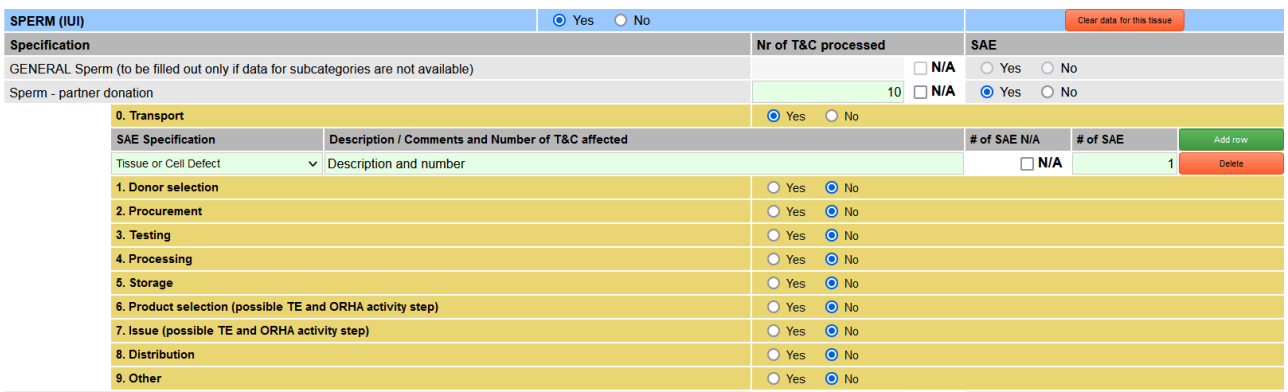


In row 1, for Sperm (IUI), select 'Yes' if there was any activity of donation, processing, distribution and clinical application in your Member State. This will open additional rows where you should insert data relating to the numbers of T&C processed (see definitions/interpretations in chapter 12 below).

- If you only have aggregated data for sperm (IUI), please complete the 'General' row only. The remaining rows will be automatically locked.

- If you have processing data for each category of sperm (IUI) then fill in each relevant row and the 'General' row will be automatically locked.

Select 'Yes' (SAE column) if any SAE has been reported for this tissue category. This will open additional rows where you should click 'Yes' to each activity step in which a SAE has occurred. This will open additional rows where you should insert information relating to SAE specifications and enter description / comments and number of T&C affected and the number of SAE. Click on the green 'Add row' button on the right to add an additional row or on the orange 'Delete' button to delete a row. Repeat these steps for all categories.



13. 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, medical device), for example:

- Ovarian Hyper-Stimulation Syndrome (OHSS) as an exaggerated response to the use of ovulation induction medications

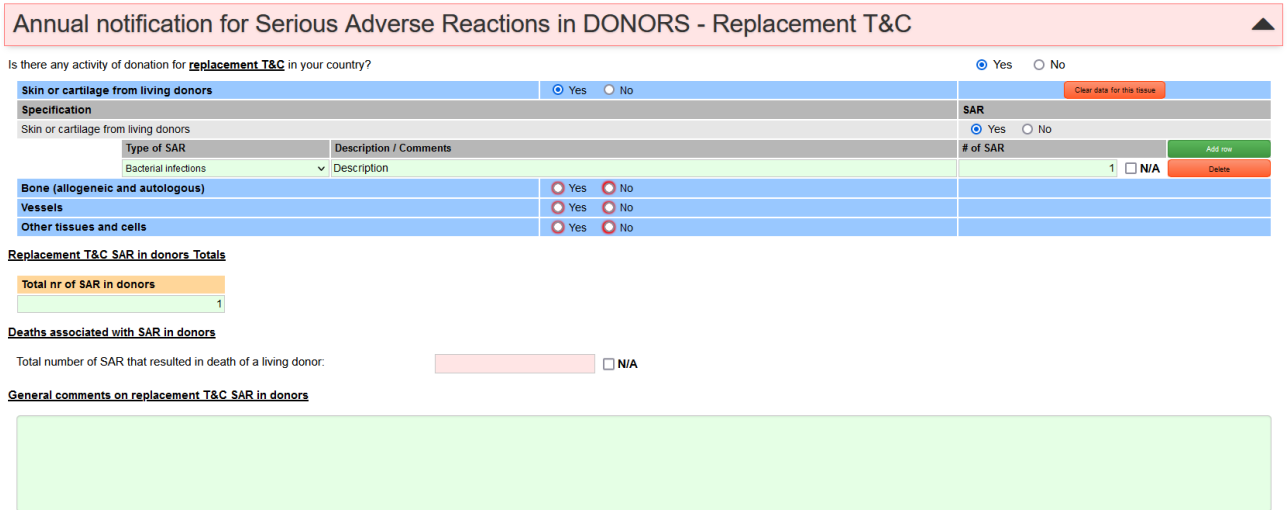
- Reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection.

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. The declared data will not be calculated as part of the total number of SARs.

SAR in donors can be reported separately for replacement tissues and cells, haematopoietic stem cells and reproductive tissues.
There are corresponding dropdown lists of donor SAR types according to tissue/cell types. As in the Recipient SAR sections of the reporting form, select ‘yes’ in the SAR Column if any donor SAR has been reported for that specific tissue/cell category. This will open an additional row with a dropdown list (Type of SAR) where you should select the type of donor SAR that has been reported for that tissue. It is mandatory to select the type of SAR and add a description or comment. If there are no comments, just type “No”.

13.1. Replacement tissues and cells

For donors of replacement tissues and cells, the following table is provided.



The replacement tissues and cells SAR types for donors are listed below.

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

For 'Other tissues and cells' no dropdown list is available and descriptions have to be added manually.

Click on the green 'Add row' button on the right to add an additional row or on the orange 'Delete' button to delete a row.

The replacement tissues and cells SAR totals for donors will be automatically calculated.

Where a SAR has resulted in a donor death, the total number of deaths associated with donation of replacement tissues and cells should be inserted in the appropriate box.

Please insert a comment in the 'General comments on Replacement T&C SAR in donors' box and provide relevant details such as:

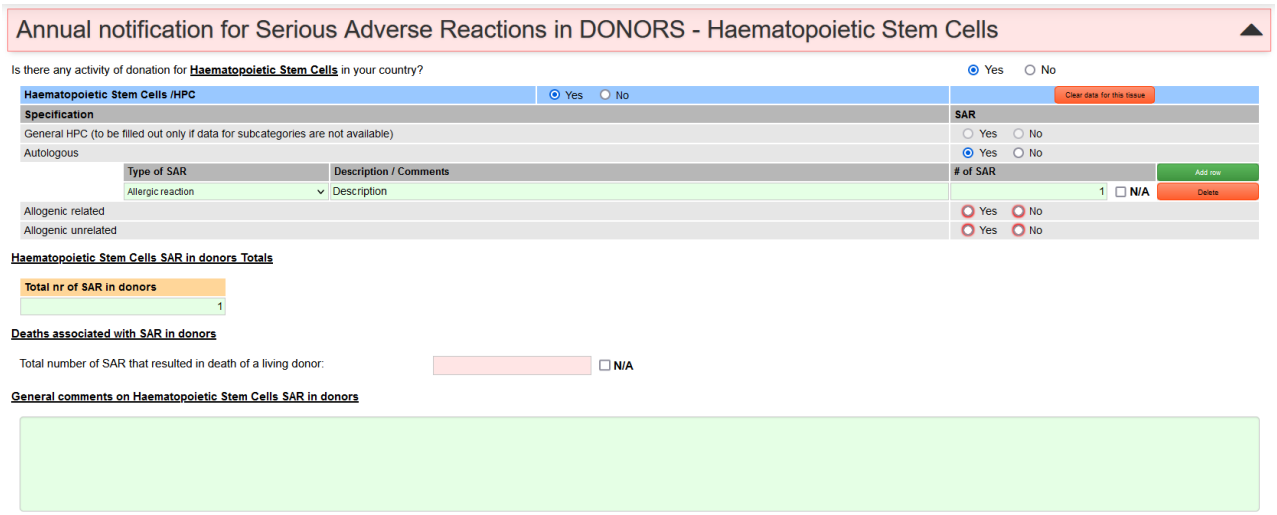
– a brief description of type of donation and donor medical history

– a brief description of the occurrences that led to the fatality and the level of imputability

– the conclusions and follow-up actions (corrective and preventive), if appropriate.

13.2. Haematopoietic stem cells

For donors of haematopoietic stem cells, the following table is provided.



When data are not available by specific type of haematopoietic stem cells (autologous, allogeneic related, allogeneic unrelated), total number of haematopoietic stem cells processed can be filled out in the General category and the other rows will be automatically locked. When data are available by specific type of haematopoietic stem cells (autologous, allogeneic related, allogeneic unrelated), the corresponding rows can be filled out and the General category row will be automatically locked.

The haematopoietic stem cells SAR types for donors are listed below:

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

Click on the green ‘Add row’ button on the right to add an additional row or on the orange ‘Delete’ button to delete a row.

The haematopoietic stem cells SAR totals for donors in the next table will be automatically calculated.

Where a SAR has resulted in a donor death, the total number of deaths associated with donation of haematopoietic stem cells should be inserted in the appropriate box.

Please insert a comment in the ‘General comments on Haematopoietic Stem Cells SAR in donors’ box and provide relevant details such as:

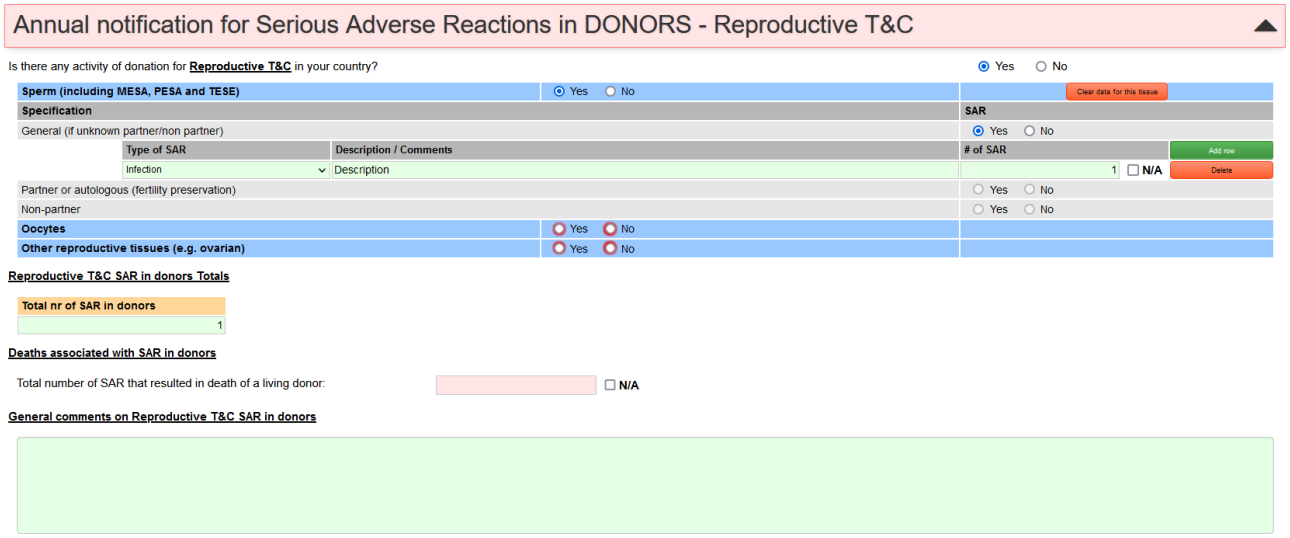
– a brief description of type of donation and donor medical history

– a brief description of the occurrences that led to the fatality and the level of imputability

– the conclusions and follow-up actions (corrective and preventive), if appropriate.

13.3. Reproductive tissues and cells

For donors of reproductive tissues and cells the following table is provided.



When data are not available by specific type of reproductive tissues and cells (partner or autologous, non-partner), total number of reproductive tissues and cells processed can be filled out in the General category and the other rows will be automatically locked. When data are available by specific type of reproductive tissues and cells, the corresponding rows can be filled out and the General category row will be automatically locked.

The reproductive tissues and cells SAR types for donors are listed below.

Sperm (including Microsurgical Epididymal Sperm Aspiration MESA, Percutaneous Epididymal Sperm Aspiration PESE, TEsticular Sperm Extraction TESE) and other reproductive tissues (ovarian or testicular tissue):
1. Infection
2. Surgical complications
3. Reaction to anaesthetic
4. Reactions other than the above

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

Click on the green ‘Add row’ button on the right to add an additional row or on the orange ‘Delete’ button to delete a row.

The reproductive tissues and cells SAR totals for donors in the next table will be automatically calculated.

Where a SAR has resulted in a donor death, the total number of deaths associated with donation of reproductive tissues and cells should be inserted in the appropriate box.

Please insert a comment in the ‘General comments on Reproductive T&C SAR in donors’ box and provide relevant details such as:

– a brief description of type of donation and donor medical history

– a brief description of the occurrences that led to the fatality and the level of imputability

– the conclusions and follow-up actions (corrective and preventive), if appropriate.

14. GLOSSARY

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 or cells, is undertaken. It may also be responsible for the procurement or testing of tissues and cells" (*Article 3(o) of Directive 2004/23/EC).

Procurement organization "*means a healthcare establishment or a 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. (*Article 2(i) of Directive 2006/86/EC)"

Organisation responsible for human application "*means a health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells*". (Article 2(j) of Directive 2006/86/EC)

Distribution *"means transportation and delivery of tissues or cells intended for human applications"* (Article 3 (k) Directive 2004/23/EC), whereas '**human application'** is defined in the same article as follows: "*means the use of tissues or cells on or in a human recipient and extracorporeal applications*".

Imputability: 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.

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 MAR, relates to individuals or couples seeking treatment.