HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to

Reporting Serious Adverse Reactions and Serious Adverse Events Associated with Human Tissues and Cells

SUR-G0005-5

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

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1 INTRODUCTION

The following document is intended to provide guidance for tissue establishments (TEs), including importing tissue establishments (ITEs) and/or other relevant organisations, on the procedure to follow for submission of a suspected serious adverse reaction (SAR) or serious adverse event (SAE) report to the Health Products Regulatory Authority (HPRA).

The HPRA has been designated as the national competent authority (CA) for the purpose of implementing EU and national legislation related to human tissues and cells, including the following:

- Directive 2004/23/EC of the European Parliament and of the Council of 3 March 2004 on setting the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as amended.
- Directive 2006/17/EC of the 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells as amended.
- Directive 2006/86/EC of the 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.
- Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells.
- Directive 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells.
- Directive 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.
- S.I. No. 158 of 2006, European Communities (Quality and Safety of Human Tissues and Cells) Regulations 2006, as amended.
- S.I. No. 598 of 2007, European Communities (Human Tissues and Cells) Traceability Requirements, Notification of Serious Adverse Reactions and Events and Certain Technical Requirements) Regulations 2007, as amended.
- S.I. No. 209 of 2014, European Communities (Quality and Safety of Human Tissues and Cells) (Amendment) Regulation 2014.
- S.I. No. 32 of 2019, European Communities (Human Tissues and Cells Traceability Requirements, Notification of Serious Adverse Reactions and Events and Certain Technical Requirements) (Amendment) Regulations 2019.
- S.I. No. 33 of 2019, European Communities (Quality and Safety of Human Tissues and Cells) (Amendment Regulations 2019.

2 REPORTING SYSTEMS INCLUDING ANNUAL NOTIFICATION TO THE EUROPEAN COMMISSION

In accordance with this legislation, the HPRA is obliged to establish a reporting system for the notification of SARs and SAEs. The TE/ITE is obliged to notify and provide the HPRA with a report analysing the cause and ensuing outcome of SARs and SAEs.

It is important to note that under the legislative requirements, a procurement organisation or organisation responsible for human application is not precluded from also notifying the competent authority if it so wishes (refer to section 4).

As required by Article 7 of Directive 2006/86/EC, on an annual basis the HPRA submits a report to the European Commission, collating national information relating to adverse reactions and events.

Summaries of cumulative EU data from the ANSAR/E reports are available on the EU Commission website. Further information on the regulation of tissues and cells can be found on the European Commission website at https://ec.europa.eu/health/blood_tissues_organs/tissues_en.

3 DEFINITIONS (FROM DIRECTIVES 2004/23/EC, 2006/86/EC AND 2015/566/EC)

Procurement organisation

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.

Organisation responsible for human application

A health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells.

Serious adverse reaction (SAR)

An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs hospitalisation or morbidity.

Serious adverse event (SAE)

Any untoward occurrence associated with the procurement, testing, processing, storage or distribution of tissue 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.

Tissue Establishment (TE)

A tissue bank or unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues or cells are undertaken. It may be responsible for procurement or testing of tissues and cells.

Importing Tissue Establishment (ITE)

A tissue bank or unit of a hospital or another body established within the Union which is a party to a contractual agreement with a third country supplier for the import into the Union of tissues and cells coming from a third country intended for human application.

Further relevant definitions may be found in the above referenced legislation.

4 REPORTING SARS AND SAES TO THE HPRA

Each TE/ITE should designate a responsible person with responsibility for ensuring that human tissues and cells intended for human application comply with the terms of the legislation including reporting obligations.

Article 11(1) (2004/23/EC) provides further information on the type of serious adverse reaction and events (SAR/E) that are reportable. Through the responsible person (or designee), TEs/ITEs, are responsible for notifying and providing the HPRA with a report analysing the cause and ensuing outcome of reportable SAR/Es, i.e.:

- any SAR or SAE which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, preservation, storage and distribution of tissues and cells. (This includes 'near miss' reports where the event was detected prior to transplantation.)
- any SARs observed during or after clinical application which may be linked to the quality and safety of tissues and cells.

When multiple tissues are affected by a single SAE, this should be reported as one adverse event.

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 one adverse reaction report, i.e. one report for each SAR (see section 4.1 below).

Therefore, multiple reaction types in one recipient should be reported as multiple SARs.

When an SAR is the result of an adverse event, only the SAR(s) should be reported, i.e. from the moment when a recipient or donor has been harmed, this takes precedence. Details of the event should be included in the report.

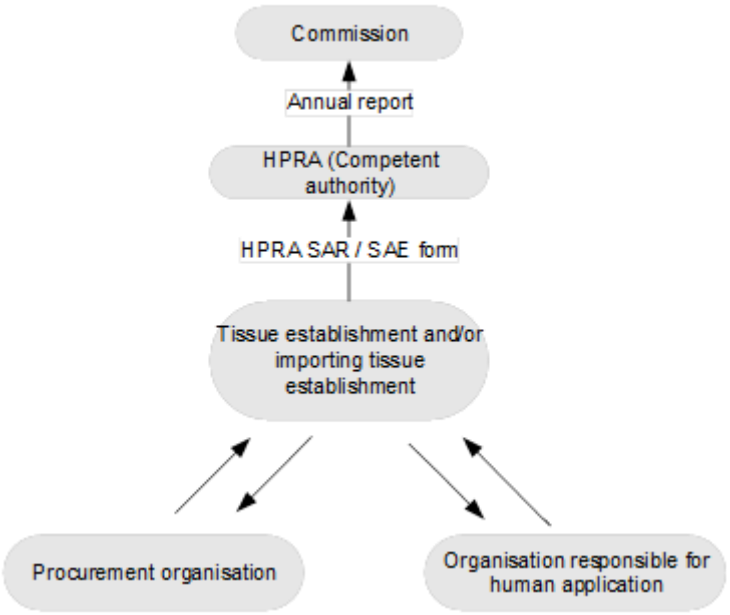
4.1 Tissue Establishment/Importing Tissue Establishment reporting

Directive 2006/86/EC recognises the central role of the TE/ITE in SAR/SAE reporting and investigation, particularly as this may involve quarantine, recall or look back for patients who have received implicated tissues and cells.

Where a report involves tissues or cells that have been distributed to another establishment, please provide as much information as possible to the HPRA to facilitate communication between all relevant parties.

Procurement organisations or organisations responsible for human applications should report SAR/Es that have occurred at their facility to the associated TE. The ITE should ensure their agreements with third country suppliers include receipt of notification of any SAR/Es which may influence the quality and safety of the tissues and cells imported or to be imported by the ITE, as detailed in Directive 2015/566/EU.

The responsible person (or designee) at the Irish TE/ITE is responsible for subsequent submission of relevant reports in a timely manner to the HPRA. Ideally, reports should only be submitted by a TE/ITE to avoid duplicate reporting, however, reports received by the HPRA directly from a procurement organisation or an organisation responsible for human application will also be accepted. In such cases, it remains the responsibility of the reporting organisation to inform the relevant TE of the incident and to share the local/HPRA assigned case reference numbers to facilitate report linkage.



4.2 Points to Note

If there is doubt as to whether an event or reaction is reportable, it is preferable that it is reported. The HPRA will provide feedback if the case is considered to fall outside the remit for reporting and outline the associated rationale. The HPRA may also be contacted by email for queries in relation to the reporting of SAR/SAEs using the details in section 7 below.

All reports should be submitted as soon as possible, providing the most complete case information available at the time of reporting. It is appreciated that follow up actions, e.g. corrective and preventative actions, may be undertaken in parallel and that information on the outcome of these actions may be incomplete at the time of initial reporting. In such cases, this additional information may be provided at a later date (including appropriate reference numbers) to ensure timely notification of reports and subsequently support case closure.

5 SERIOUS ADVERSE REACTIONS (SARs)

5.1 Recipient SARs

SARs should be reported according to the criteria outlined below:

SAR categories

- Transmitted bacterial infection
- Transmitted viral infection
- Transmitted parasitical infection
- Transmitted fungal infection
- Transmitted prion disease
- Other transmitted infection
- Transmitted malignant disease
- Other transmitted disease (e.g. immunological disease, other donor derived disease)
- In the case of assisted reproductive technologies (ART), any disease transmission to the offspring (e.g. genetic disorder or infection as listed above)
- Other adverse reactions (not involving a disease transmission), e.g.:
    - Cardiovascular reactions
    - Pulmonary reactions
    - Renal complications
    - Neurological reactions
    - Toxicity (e.g. due to DMSO)
    - Immunological reactions (including allergic reactions, rejection, haemolytic reactions, or other immunological reactions)
    - Graft failure/delayed engraftment (Note: GvHD to be reported if unexpectedly serious and/or linked to product preparation)
    - Undue exposure to risk
    - Infusion related non-specific symptoms (including febrile reaction)
    - Ectopic pregnancy (ART)
    - Molar pregnancy (ART)
    - Reactions other than those listed above.

For additional information on donor reactions, see section 5.2.

For additional information on ART specific reactions, see section 5.3.

Severity

Reactions should be reported if they were serious in nature. Directive 2004/23/EC defines serious as ‘fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity’.

The severity assessment tool from the European Commission document ‘tissues and cells - Common approach for definition of reportable Serious Adverse Events and Reactions (SARE)’ (available at https://health.ec.europa.eu/publications) has been adapted by the SOHO V&S project.

The severity tool contained in the SOHO V&S Guidance for Competent Authorities:

Communication and Investigation of Serious Adverse Events and Reactions associated with human tissues and cells (2013) may be useful. You can find this guidance at https://notifylibrary.org under 'search'. The following table 1 contains more information on the severity assessment tool.

Table 1 - Severity assessment tool

NOT REPORTABLE	**Insignificant**	No harm to the recipient or living donor
	Non-serious	Mild clinical consequences, which do not necessitate hospitalisation 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 and/or - birth of a child with a serious genetic disease following ART with non-partner gametes or donated embryos.
	Life-threatening	Adverse reaction resulted in: - 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 and/or - birth of a child with a life-threatening genetic disease following ART with non-partner gametes or donated embryos.
	Fatal	Adverse reaction resulted in: - death in a living donor or a tissue/cell recipient.

Imputability

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 HPRA.

The imputability assessment tool from the European Commission document 'tissues and cells - Common approach for definition of reportable Serious Adverse Events and Reactions (SARE)' has been adapted by the SOHO V&S project.

The SOHO V&S Guidance for Competent Authorities: Communication and Investigation of Serious Adverse Events and Reactions associated with human tissues and cells (2013) imputability tool should be applied. The following table 2 contains more information on the imputability assessment tool.

Table 2 - Imputability assessment tool

NOT ASSESSABLE*	**Not assessable**	When there is insufficient data for imputability assessment
NOT REPORTABLE	**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
	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)

*Where there is insufficient data for the imputability assessment, i.e. considered 'not assessable', particularly for cases where the severity is serious, life threatening or fatal, there should be a predisposition to submit a case report to the HPRA for further review.

5.2 Donor SARs

Donor reactions which have no potential impact on the quality and safety of the tissues and cells fall outside the strict interpretation of the legislation. However, the European Commission recognises the value of such reports and encourages inclusion of such in the annual reports collated and submitted by CAs. The HPRA requests TEs/ITEs to voluntarily submit any such reports of SARs in donors fulfilling the imputability and severity assessment criteria.

The types of donor reactions that most commonly require reporting are reactions associated with granulocyte colony-stimulating factor (GCSF), calcium toxicity associated with peripheral blood stem cell collection, ovarian hyperstimulation syndrome (OHSS) or 'other' types of donor reactions resulting in harm, requiring additional medical intervention, or hospitalisation of a donor.

Any donor reaction reports which are associated with the administration of medicinal products should include details of the medicinal product concerned, including information on the product/brand name, dose, route of administration and therapy dates. The HPRA will liaise internally with pharmacovigilance colleagues to review and follow up on relevant cases, as appropriate.

5.3 SARs Specific to Assisted Reproductive Technology (ART)

SARs or SAEs that meet the reporting obligations for recipients or donors as outlined above should be reported in addition to the following considerations unique to ART.

In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered as a serious adverse event (as applicable) and should be reported to the HPRA (see section 6.3).

If an adverse reaction occurred as a result of gamete or embryo misidentification i.e. disease transmission, then it should be reported as a SAR.

Psychological damage following gamete or embryo misidentification, or mix-up of gametes should not be reported as a serious adverse reaction.

5.3.1 Transmission of genetic disease

The birth of a child (or creation of a foetus), following ART treatment in the Republic of Ireland, with a genetic disease inherited/possibly inherited from a non-partner donor, should be reported to the HPRA and to the supplying TE as a suspected SAR. An investigation to establish

if this is considered an inherited/possible inherited condition which could be associated with the non-partner donor should be undertaken.

In relation to the transmission of genetic diseases following the use of non-partner gametes, where appropriate the HPRA will liaise with national establishments and other European CAs to support appropriate communication. Notifications relating to treatment in Ireland involving non-partner gametes originating outside of the EU may necessitate contact with the third-party supplier, or other ITEs as necessary (see section 6.3.1 for further information on donor block notifications).

5.3.2 Donor Reactions Specific to ART

Examples of SAR types for donors of reproductive tissues and cells are:

- Ovarian Hyperstimulation Syndrome (OHSS) (see below)
- Infection
- Surgical complications
- Reaction to anaesthetic
- Torsion of the ovary (leading to surgery with or without removal of fallopian tube and/or ovary)
- Reactions other than the above

Ovarian Hyperstimulation Syndrome (OHSS)

All severe cases of OHSS and all OHSS cases that require hospitalisation should be reported as donor reactions. Information regarding the circumstances (e.g. if occurring in a non-partner oocyte donor, or in a patient undergoing an oocyte retrieval for their own treatment) and the time of occurrence (i.e. prior to or after embryo transfer) should be included in the report.

The Guidance on Vigilance and Surveillance in ART (Work Package 5 Deliverable 5) (2011) in the EU developed by the SOHO V&S project provides guidance and references for the classification of ovarian hyperstimulation syndrome and should be followed for this purpose.

As OHSS reports involve the use of medicinal products, the HPRA will liaise internally with pharmacovigilance colleagues to review and follow up on relevant cases, as appropriate. Please include details of the medicinal product concerned, including information on the product/brand name, dose, route of administration and therapy dates.

6 SERIOUS ADVERSE EVENTS (SAEs)

Any incident which has implications or potential implications for the quality and safety of tissues and cells should be considered reportable as an SAE to the HPRA.

Examples of such include but are not limited to:

- the distribution of inappropriate tissues/cells for clinical use, even if not used
- an event which could have implications for other patients or donors because of shared practices, services, supplies or donors
- an event which resulted in the loss of any irreplaceable autologous tissues or cells, or any highly matched (i.e. recipient specific) allogeneic tissues or cells
- an event which resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

6.1 SAE Activity steps (deviation occurring at)

The following categories are provided in the reporting template:

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 of tissues or cells.

Testing

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

Transport

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

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

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

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

Other (specify)

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.

6.2 Specification of SAE

The following categories are provided in the reporting template:

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 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, failure of liquid nitrogen automatic filling system and alarm system leading to the thawing of 150 heart valves in cryostorage.

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:

- Contaminated washing solution used during procurement or processing.
- Material defect leading to damage or loss of tissues and cells.

System failure

This should be understood as a failure of the quality management system.

- Inadequate training, education
- Under-resourced staffing, excessive workload or inadequate skill-mix
- Inadequate process, procedures or documentation. Procedure shortcuts allowed, e.g. no second witness for critical steps
- Other (please specify)

Human error

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, inadequate SOPs, or staff not having been trained properly, they would be classified as system failure.

- Cardiac valve distributed for surgery mis-sized, rendering it unusable.

- Bone irradiated twice – grafts distributed for clinical application.
- Cryopreserved skin past its expiry date distributed and used on a burned patient.
- Container of embryos accidentally dropped.

Other (specify)

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 airline company/pilot refused to accept cells in liquid nitrogen on board.

6.3 SAEs specific to assisted reproductive technology (ART)

Examples of SAEs specific to assisted reproductive technology include, but are not limited to:

- the release of inappropriate gametes, embryos or germinal tissues for clinical use, even if not used
- an event which could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors
- an event which resulted in a mix-up of gametes or embryos
- contamination or cross contamination
- accidental loss of gametes, embryos, germinal tissues (e.g. break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle

Please note there should be a predisposition to submit a report to the HPRA for further review. Following assessment, the HPRA will decide if the case is to be included in the annual report for submission to the European Commission. The reporter will be informed of the final case classification.

6.3.1. Donor block notifications

Where a risk or potential risk has been identified following the use of non-partner gametes (e.g. regarding the birth of a child elsewhere with a genetic disease inherited/possibly inherited from the donor), the supplying TE must inform all TEs/ITEs who have received the associated product. The supplying TE should confirm if a donor block has been applied, and confirm the type of block, e.g. temporary or permanent/conditional. A temporary donor block is applied where a risk/potential risk has been identified and is under investigation. A permanent/conditional donor block is where the investigation is complete, and a risk has been confirmed. The conditions of further use of the implicated donor following the performance of a risk assessment should be included.

All confirmed permanent/conditional donor block notifications should be submitted to the HPRA as an SAE report. A copy of the notification and consent form should be included, as received from the supplying gamete bank / establishment, whether in the EU or a third country. Confirmation of the tissues and cells supplied, used, stock remaining in storage and information on any offspring or ongoing pregnancies which have resulted from the use of the donor, should be included in the information provided to the HPRA.

The HPRA will forward on any donor notification reports received via the EC Rapid Alert for Tissues and Cells (RATC) system to the ART clinics. This communication includes a list of questions regarding the use of the non-partner gametes, for which a response is requested from all impacted ART clinics.

The birth of a child (or creation of a foetus), following ART treatment in the Republic of Ireland, with a genetic disease inherited/possibly inherited from the donor, should be reported to the HPRA as a suspected SAR (see section 5.3). The supplying TE should also be informed.

7 INSTRUCTIONS FOR COMPLETION AND SUBMISSION OF FORMS

How to report:

- Ideally by using the online form, accessible from the HPRA website at www.hpra.ie under the 'Report an Issue' tab.
- By downloading a copy of the report form available via the Blood Tissues and Organs section of the HPRA website. Completed forms should be emailed to btosafety@hpra.ie.
- By printing, completing and posting a copy of the report form to the HPRA by freepost to the address at the bottom of the form.

Further information is available from:

Tissues and Cells
Health Products Regulatory Authority,
Pharmacovigilance Section,
Kevin O' Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2
Ireland

Telephone +353 1 6764971
Fax +353 1 6762517
Email address: btosafety@hpra.ie

All reports should be submitted in line with this guide.

7.1 Completion of the SAR/E form

All available information should be included on the report form.

- If information requested is not available, the term N/A or the words 'not available' should be included, where appropriate.
- Supplementary information may be appended with the initial report form for clarification if considered relevant/deemed necessary by the reporter. Supplementary information may also be sent to btosafety@hpra.ie. Please ensure the report ID number is included on all documentation provided. See below for information on reporting identification number (assigned at reporting site) and HPRA case reference number.
- A contact name, telephone number and email address must be provided to facilitate the HPRA to follow up cases, as appropriate.
- All reports should be dated (note that reports submitted online will receive an automatic date-stamp).

For online reports, once submitted, a hyperlink is provided which allows a PDF of the report to be generated as a record. A PDF of the report is also attached to the automatic acknowledgement email.

Confirmation of a successfully submitted email or postal report occurs by the provision of a HPRA case reference number.

For further information on the form fields, refer to the following sections:

7.1.1 EU Tissue Establishment Code

The person submitting the SAR/SAR report should include the EU Tissue Establishment code assigned on the EU Tissue Establishment Compendium.

7.1.2 Report identification number (assigned at reporting site)

The person submitting the SAR/SAE report should assign a local unique report identification number, which may be used to link information back to the case and to support traceability. The responsibility for assigning a system of numbering rests with the individual TE/ITE or organisation, as long as it allows for traceability and record linkage. This number will be kept on file at the HPRA for future reference.

N.B. Please do not include any information that would identify the patient, healthcare professional, or other individuals involved. Personal data is processed only when necessary. Donor, recipient and staff names (other than the reporter), are not required, and this information should be anonymised.

7.1.3 HPRA case reference number

Individual case reference numbers will also be allocated by the HPRA (i.e. the HPRA case reference number) for reference purposes and the reporting organisation will be informed of this number in any relevant correspondence.

7.1.4 Classification of events/reactions

Only one box should be ticked, indicating whether the report refers to an SAR or SAE.

Please note that if a reaction occurs as a result of an event, it should be considered as a reaction and reported as such, with relevant background information provided.

7.1.5 Donor/recipient information

This information should be provided if known. If unknown, please state this on the form. Donor, recipient and staff names (other than the reporter) are not required, and this information should be anonymised.

7.1.6 Dates

All relevant dates should be included. Please indicate if not available.

7.1.7 Unique Donation Identification Number

A single identifying code should be allocated to all donated material by the TE/ITE. This code should incorporate at least the information set out in Annex VII Directive 2006/86/EC.

7.1.8 Single European Code (SEC) (if applicable)

If applicable, the SEC should be applied, as per Directive 2015/565 and included in the report form.

7.1.9 Notification of relevant establishments/site manufacturers

Procurement organisations or organisations responsible for human application should have procedures in place to notify the associated TE or other relevant parties. TEs should notify other associated TEs or organisations as appropriate. There should be procedures in place between the third country supplier and the importing tissue establishment to notify the ITE of SAR/Es.

Information on parties notified should be included in the report. Details should be provided under the SAR/SAE sections of the form.

7.1.10 Implicated tissues and cells

The implicated tissues and cells should be selected. A separate section is provided for assisted reproductive technology and non-assisted reproductive technology tissues and cells. Please indicate if the tissues and cells are autologous or allogeneic, or in the case of ART, whether partner or non-partner treatment is involved.

7.1.11 Categorisation of SAE Activity Step and Specification

The activity step and specification of the SAE should be included in the report form (see section 6.1 and 6.2).

7.1.12 Categorisation of SARs

Provide the final clinical outcome if known. See section 4 for further information on the list of reactions.

7.1.13 Risk analysis

Details of the root cause analysis and any corrective and preventative actions taken should be provided, however this information may be provided at a later date if not available at the time of the initial report.

8 PROCESSING OF REPORTS AT THE HPRA

On receipt of report forms, the HPRA will:

- enter anonymised information provided onto the HPRA database and assign a unique HPRA case reference number to the case. Both this number and the reference number assigned by the TE/ITE or other reporting organisation will be referenced in all correspondence.
- review the data provided and consider the status of the report, any need for follow up and/or additional information to facilitate case report completion.
- follow up with the reporting establishment as necessary.

On completion of assessment and review of all relevant data, the HPRA will close the case and send an email to this effect along with the case classification. It is important to note that although a case may have been closed, it may be revisited on the basis of further follow up information or issues arising with the report(s) or associated reports.

A privacy notice in relation to the personal data collected by the HPRA is available on the HPRA website (www.hpra.ie) under the 'Report an Issue' tab and by clicking on 'Tissues and Cells Adverse Reaction'.