HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Serious Adverse Reaction/Event Reporting for Human Organs Intended for Transplantation

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

CONTENTS

1 INTRODUCTION

Effective vigilance systems for serious adverse reactions and events (SAR/Es) reporting rely on appropriate communication and coordination between the healthcare professionals involved in organ donation and transplantation including procurement organisations, retrieval teams, transplantation centres, donor hospitals, testing laboratories, transplant co-coordinators and other transplant staff. It is important to acknowledge that the reporting of suspected SAR/Es is not associated with blame and is essential for ensuring the quality and safety of organs for transplantation.

The reporting of SAR/Es is important to highlight any unexpected complication, particularly if recipients may be at risk. It provides a mechanism for monitoring the quality and safety of organs during the entire chain from donation to transplantation through report investigation and implementation of corrective and preventative actions (CAPA).

This document is intended to provide guidance for procurement organisations / transplantation centres and/or other relevant organisations on the procedure to follow for reporting suspected SAR/Es, by providing guidance on how to complete the SAR/E report form with the required information, giving definitions of reportable reactions and events and providing examples of SAR/Es.

2 LEGAL FRAMEWORK

The European Directive on the Quality and Safety of Human Organs intended for Transplantation (EU Directive 2010/53/EC) was adopted by the European Parliament and the Council on 7 July 2010 and transposed into Irish legislation by Statutory Instrument (S.I.) No. 325 of 2012; European Union (Quality and Safety of Human Organs intended for Transplantation) regulations 2012.

The Commission Implementing Directive 2012/25/EU of 9 October 2012, laying down information procedures for the exchange, between Member States, of human organs intended for transplantation, sets out the requirements for the transmission of information when organs are exchanged between Member States. These additional requirements are transposed into Irish legislation in S.I. No. 198 of 2014 (Quality and Safety of Human Organs intended for Transplantation) (Amendment) Regulations 2014.

The Health Products Regulatory Authority (HPRA) and the Health Service Executive (HSE) have been appointed for implementing different aspects of this legislation. The HSE has established the Office for Organ Donation and Transplant Ireland (ODTI) as the delegated body responsible for the implementation of the obligations applicable to the HSE under the Directive and national regulations.

The legislation sets out the obligation for all procurement organisations / transplantation centres to establish a system for the notification and management of SAR/Es.

3 DATA PROTECTION

It should be noted that the recording of data from SAR/E report forms is carried out securely and strictly in accordance with the data protection and privacy provisions. Personal and contact information is used solely for the purposes of necessary interaction and follow up related to SAR/E reports. For the purposes of complying with statutory and legal reporting requirements, details of reports submitted may be shared across organisations involved in monitoring the quality and safety of human organs for transplantation. This ensures that relevant information is exchanged with relevant responsible bodies in a timely manner.

The processing of personal data in the context of vigilance monitoring activities associated with human organs for transplantation is considered justified as the protection of public health constitutes a substantial public interest. In accordance with data protection requirements, identifiable personal data are processed only when necessary and all of the parties involved are responsible for assessing this necessity at each stage of the monitoring process.

The individual has the right to request a copy of personal data held by the HPRA and to have any inaccuracies in such data corrected or deleted as appropriate.

4 DEFINITIONS

Serious Adverse Reaction

A serious adverse reaction (SAR) is defined in the legislation as 'an unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation:

- that is fatal, life-threatening, disabling, incapacitating, or
- which results in, or prolongs, hospitalisation or morbidity.

Serious Adverse Event

A serious adverse event (SAE) is defined in the legislation as 'any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation:

- that might lead to the transmission of a communicable disease;
- that might lead to death or life-threatening, disabling or incapacitating conditions for patients; or
- which results in, or prolongs, hospitalisation or morbidity.

Responsible Person

In accordance with the legislative requirements, the procurement organisation or transplantation centre shall ensure that organs intended for transplantation comply with the terms of the legislation. They shall ensure there is a reporting system in place to report, investigate, register and transmit relevant information concerning SAR/Es to the HPRA and HSE/ODTI.

5 REPORTING SERIOUS ADVERSE REACTIONS AND EVENTS

In accordance with the legislative requirements, a system to facilitate reporting, evaluation and the management measures applied to SAR/Es has been developed, in collaboration with the HSE/ODTI.

Procurement organisations / transplantation centres are requested to report:
- SAE(s) that may influence the quality and safety of organs intended for transplantation and is attributable to the donation, testing, characterisation, procurement, preservation, transport or transplantation activities;
- SAR(s) observed during or after transplantation which may be attributed to such activities;
- Living donor reactions – any SAR(s) in the living donor that may result from the donation.

A report form is available for download, completion and submission to the HPRA and may be accessed under the Publications and Forms section on the HPRA website.

Completed forms should be forwarded by email to btosafety@hpra.ie and to odti@hse.ie.

Alternatively they may be sent by freepost to the following address:

Organ Donation Transplant Ireland
Ground Floor
Bridgewater House
Bridgewater Business Centre
Conyngham Road
Islandbridge
Dublin 8
D08 T9NH

Organs - Pharmacovigilance Section
FREEPOST
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

The HPRA and HSE/ODTI each acknowledge receipt of all reports submitted. The HSE/ODTI is responsible for case evaluation and follow-up of clinical SAR/Es, for example the inability to characterise donor malignancy at donor hospital due to limited pathology cover. The HPRA is

responsible for evaluation and follow up of non-clinical SAR/Es, for example, mislabelling of organ boxes resulting in the wrong organs being delivered to a transplant centre. The HPRA and HSE/ODTI liaise in relation to the review and follow-up of relevant reports as considered appropriate and a response will be provided to the reporter(s) by the relevant organisation dealing with evaluation of the case.

Note:

Although not directly authorised by the HPRA, testing laboratories involved in organ and donor characterisation should report any relevant SAR/Es to the procurement organisation, which is then responsible for onward reporting to the HPRA and HSE/ODTI. Likewise, any SAR/E discovered by a procurement organisation / transplantation centre which involves a testing laboratory must also be reported to HPRA.

Donor hospitals (hospitals where the donor/organ is characterised and retrieved) should report detected SAR/Es to the procurement organisation, which is then responsible for onward reporting to the HPRA and HSE/ODTI. Likewise, any SAR/Es discovered by a procurement organisation / transplantation centre which involves a donor hospital should also be reported to the HPRA and HSE/ODTI.

This guidance is not comprehensive and other events and reactions not included as examples below may fall within the definitions. If in doubt, reporting procurement organisations / transplantation centres are encouraged to contact the HPRA or HSE/ODTI at the contact points listed above.

6 INSTRUCTIONS FOR COMPLETION OF FORMS

All available information should be included on the form. The following points should be taken into account when completing the form:

- All reports should be completed comprehensively and dated;
- All dates should be included;
- A unique report ID number to support traceability at the reporting establishment should be assigned;
- Supplementary information may be appended with the initial report form for clarification if considered relevant/deemed necessary by the reporter (please ensure the unique report ID number is included on all documentation provided, see 6.2);
- If information requested is not available, the term N/A or the words ‘not available’ should be included, where appropriate.

6.1 Reporter details

The reporting establishment name and address, contact name, telephone number and email

address should be provided to facilitate the HPRA and /or HSE/ODTI to follow up on cases, as appropriate.

6.2 Report information

The person submitting the SAR/E report form should assign a unique report identification number, which may be used to link information back to this case. This helps to support traceability of the report in the future. The responsibility for assigning a system of numbering rests with the individual procurement organisation or transplantation centre, as long as it allows for traceability. Please note that individual case record numbers are also allocated by the HPRA for reference purposes and the reporting organisation will be informed of this number.

Only one box should be ticked, indicating whether the case is classified as an SAR or SAE.
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.

Only one box should be ticked, indicating whether the SAR/E involves the donor/recipient or both. The N/A box should be ticked, in cases that do not directly involve either the donor or recipient but had an effect on the quality and safety of the organ intended for transplantation. The type of donor, whether living or deceased, should be indicated.

The affected/related organ should be indicated. If other than liver, pancreas, heart, lung or kidney, a detailed specification should be provided.

The name of the retrieval team (name of hospital) should also be provided for traceability purposes.

6.3 Donor/Recipient details

All organs procured, allocated and transplanted must be fully traceable from donor to the recipient and vice versa in order to safeguard the health of both the donors and recipients. In order to facilitate traceability throughout the entire transplantation chain, a number of identification details must be provided, as applicable, to the HPRA and HSE/ODTI when submitting SAR/E reports.

The name of the donor hospital should be supplied. This is the hospital where the donor is characterised and the organ is both characterised and retrieved. The national donor number, the medical record number assigned by the donor hospital along with the date of organ retrieval should also be supplied.

The name of the transplantation centre should be supplied. This is the authorised establishment that has performed the transplant. The medical record number given to the recipient by the transplantation centre should be supplied along with the date of transplantation.

Providing the HPRA and HSE/ODTI with these specified identifiers allows for greater traceability in cases where follow up investigation of the event/reaction, outside of the transplantation centre, is required.

In the case where the SAR/E relates to organ(s) received from or provided to another EU member state, the details of the exchange should be provided including the name of establishment, the date of exchange, and any relevant contact details.

Note:

Organs exchanged overseas should be accompanied by information for the receiving establishment on how to report any SAR/Es relating to donation, testing, characterisation, procurement, preservation or transport carried out in Ireland.

6.4 SAR/E details

The date and time of occurrence of the SAR/E and the date and time of SAR/E detection should be supplied. These times are not necessarily the same in all cases. It is possible that some time may have elapsed before the SAR/E was detected. Distinguishing between the two allows for a further characterisation of the type of event/reaction to be investigated and facilitates the development of risk/cause analysis and implementation of corrective and preventative actions.

If the SAR/E occurs at a different place than the reporting establishment, details of the place should be supplied in order to facilitate the appropriate follow up on corrective and preventative actions, directly with the site involved.

Each SAR/E should be investigated by the procurement organisation / transplantation centre. The procurement organisation / transplantation centre may tick the completed box if they consider that they have performed sufficient risk/cause analysis and have implemented the appropriate corrective and preventative actions in order to close out the case. Further investigation may not be deemed necessary by the HPRA and HSE/ODTI if the correspondence indicates that the investigation has been appropriately completed.

The SAR/E may have implications for other recipients/potential recipients. For example, complications with one donor may have implications for many potential recipients. Details as to whether any other organs/tissues or cells obtained from this donor had been transplanted to other recipients should be provided to allow for notification to other sites of any potential risks that may be associated with this donor. Procurement organisations / transplantation centres should have procedures in place to notify associated establishments or other relevant parties as appropriate. Establishments should notify other associated establishments or organisations as appropriate. Information on the parties notified should be included in the report.

The HPRA transmits all relevant information available to us to support an interconnection between SAR/E reporting systems for organs and those for tissues and cells.

6.5 Serious Adverse Reactions (SAR)

SARs are unintended responses or effects in a recipient or living donor to anything that occurs in the transplantation chain. Unintended responses, in this context, entail any reaction by any patient during the chain that may not be considered by the professional medical community as 'calculated risk'.

Clinical symptoms or situations suggesting that any of the following reactions might have occurred in an organ recipient should be seen as triggers for an SAR report. When completing the form, the reporter(s) will be asked to select from a number of options listed below:

- Infection possibly transferred from the donor to the recipient (e.g. viral, bacterial, prion) that was not known at the time of transplantation (e.g. due to incorrect donor characterisation information).
- Infections possibly transferred due to contamination or cross-contamination by an infectious agent on the organ or associated materials from procurement to transplantation.
- Malignant disease possibly transferred from the donor to the recipient that was not known at the time of transplantation.
- Any unintended consequence for the recipient, including recurrence of recipient illness, early graft failure or delayed graft function, which may be connected to the testing, characterisation, procurement, preservation and transport of the organ.
- Unexpected immunological reactions that were not anticipated and may be connected to the testing, characterisation, procurement, preservation and transport of the organ.
- Aborted transplantation procedure due to any issue with the organ supplied, discovered after recipient is anaesthetised, where the issue may be attributable to the testing, characterisation, procurement, preservation and transport of the organ.

Note:

The HPRA and HSE/ODTI recognise that organs may have complications for a number of reasons, and a specific cause may be difficult to determine. Delayed graft function and early graft failure should only be reported as an SAR when there are grounds for suspecting that the failure may be connected to the donation, testing, characterisation, procurement, preservation, transport or transplantation of the organ, or a serious adverse event.

If following evaluation of a known risk, a clinical decision is taken to continue with transplantation, in such cases there is no need to report associated SAR/Es, unless there are implications for other recipients.

Examples of reportable and non-reportable SARs are shown below in Table 1.

Table 1: Examples of reportable and non-reportable SARs

DESCRIPTION	REPORTABLE AS AN SAR?
Suspected transfer of infection or malignant disease from donor to recipient, that was not known at the time of donation	Yes
Suspected transfer of infection to a recipient due to the contamination in the preservation of the organ	Yes
Aborted transplantation procedure where the recipient is already anaesthetised, due to an issue at the transplant centre, which affected the quality and safety of the organ	Yes
Aborted transplantation procedure where the recipient is already anaesthetised, due to an issue with the organ supplied that may be attributable to the testing, characterisation, procurement, preservation and transport of the organ	Yes – there is an impact for the recipient, however the reaction is likely to have been caused by an SAE
Early graft failure or delayed graft function suspected to be attributable to the testing, characterisation, procurement, preservation and transport of the organ	Yes
Recurrence of recipient illness (e.g. CMV) suspected to be attributed to the quality and safety of the transplanted organ	Yes
Suspected transfer of infection from donor to recipient where the implanting surgeon made a decision to proceed on the basis of an unknown test result	No
Post-operative infection NOT suspected to be attributable to the testing characterisation, procurement, preservation and transport of the organ	No
Early graft failure or delayed graft function NOT suspected to be attributed to the testing characterisation, procurement, preservation and transport of the organ	No

This list has been adapted from guidelines outlined by the Human Tissue Authority, UK and the European Committee of Experts on Organ Transplantation (CD-P-TO). See references in Appendix 1.

The probability of recurrence is intended to assist practitioners and regulators in planning their response to a given adverse reaction. An assessment is made based on the likelihood of recurrence using the following scale:

- Rare (difficult to believe it could happen again)
- Unlikely (not expected to happen again)
- Possible (may occur occasionally)
- Likely (expected to happen but not persistent)
- Almost certain (expected to happen on many occasions)

Further facilitating the planning of a response to a given reaction, an additional assessment is made based on the severity of the reaction using the following scale:

- Death
- Life-Threatening (major intervention to prevent death, evidence of a life threatening transmitted infection)
- Serious (hospitalisation or prolongation of hospitalisation, persistent or significant disability or incapacity, intervention to preclude permanent damage, evidence of a serious transmitted infection)
- Non Serious (mild clinical/psychological consequences, no hospitalisation, no anticipated long term consequences/disability)

6.5.1 Living Donor Reactions

Donor adverse reactions with a possible direct effect on the quality and safety of the donated organ or that may have resulted from the donation should be reported as a serious adverse reaction. These may be immediate, within a few days post donation, or they may be delayed, i.e. identified weeks/months after the donation.

The procurement organisation / transplantation centre should provide information to living donors on how to identify and report SAR/Es that may have resulted from donation or transplant.

A living donor should notify the procurement organisation / transplantation centre of any suspected SAR/E. It is the responsibility of the procurement organisation / transplantation centre to report the suspected SAR/E to the HPRA and HSE/ODTI without delay.

6.6 Serious Adverse Events (SAE)

A brief description of the type of event is to be provided. This should include the suspected reasons as to why the event may have occurred and if any corrective or preventative actions have been put in place in order to facilitate and close out the investigation.

The probability of recurrence is intended to assist practitioners and regulators in planning their response to the given adverse event. An assessment is made based on the likelihood of recurrence using the following scale:

- Rare (difficult to believe it could happen again)
- Unlikely (not expected to happen again)
- Possible (may occur occasionally)
- Likely (expected to happen but not persistent)
- Almost certain (expected to happen on many occasions)

It is important to indicate the stage at which the event occurred (donation, testing, characterisation, procurement, preservation, transport, transplantation or other) and the specifics of the SAE, for example if it was an organ defect, equipment failure, human error or

other. This facilitates risk/cause analysis, allows for the implementation of corrective actions and can pinpoint risk areas for the development of preventative strategies.

6.6.1 Triggers for reporting Serious Adverse Events

Deviations from standard operating procedures or other adverse events should be reported as a serious adverse event when one or more of the following criteria apply:

- The event could have implications for the quality and safety of organs
- The event could have implications for other patients, recipients or donors because of shared practices, services, supplies or donors.
- The event resulted in the loss of any organs.

Table 2: Example of reportable and non-reportable SAEs

DESCRIPTION	REPORTABLE AS AN SAE?
Transcription error when recording test results	Yes
Positive virology result post-transplantation that was not known at the time of donation and has implications for the recipients of organs or tissues and cells	Yes
Unlabelled samples sent to a testing laboratory which resulted in consequences for the quality and safety of the organ	Yes
Mislabelling of organ boxes resulting in the wrong organs being delivered to transplant centre	Yes
Tumour discovered at post mortem or by Transplant Centre that was not known or communicated at the time of donation	Yes
Damage to organ, during retrieval or transplant, which resulted in an impact on the recipient (significant delay/unable to transplant/graft failure) or loss of organ	Yes
Problems with transport or arranging transport resulting in a loss of organ due to prolonged cold ischemic time (CIT)	Yes
Donor or recipient data reporting incident	Yes
Equipment malfunction or iatrogenic damage during living laparoscopic donor nephrectomy requiring conversion to an open operation and consequent delayed graft function.	Equipment malfunction should be classified as an SAE – any clinical consequences for the donor or recipient should be classified as an SAR
Damage to an organ which has no consequence for the recipient	No

DESCRIPTION	REPORTABLE AS AN SAE?
Mislabelling of boxes with no consequence for the quality and safety of the organ or transplant recipient.	No

This list has been adapted from guidelines outlined by the Human Tissue Authority, UK and the European Committee of Experts on Organ Transplantation (CD-P-TO). See references in Appendix 1.

APPENDIX 1 REFERENCES

1. Directive 2010/53/EC
2. Directive 2012/25/EU
3. Directive 95/46/EC
4. Statutory Instrument No. 325 of 2012
5. Statutory Instrument No 198 of 2014
6. Serious Adverse Reaction/Event Report Form for Human Organs Intended for Transplantation
7. Human Tissue Authority – The Quality and Safety of Organs Intended for Transplantation – a Documentary Framework - July 2012, (Updated 2014)
8. Human Tissue Authority – Guidance for licence holders; Reporting serious adverse event and reaction in relation to organs intended for transplantation – June 2015
9. European Directorate for the Quality of Medicines & Health Care of the Council of Europe (EDQM) – Guide to the Quality and Safety of Organs for Transplantation – 5th Edition
10. Organ Donation and Transplant Ireland, Health Service Executive in conjunction with the Health Products Regulatory Authority - A Framework for Quality and Safety of Human Organs Intended for Transplantation – Version 1 -2014
11. Data Protection Act, 1988 and the Data Protection (Amendment) Act, 2003