

Title: Adverse event documentation and reporting

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1. PURPOSE

To document the procedure for the documentation and reporting of adverse events in research participants.

2. RESPONSIBILITY AND SCOPE

This standard applies to all Melbourne Children’s campus employees (including visiting medical officers, visiting health professionals, contractors, consultants and volunteers) who propose to undertake, administrate, review and/or govern human research involving Melbourne Children’s research participants and staff.

3. APPLICABILITY

The designated SOP writer and all relevant research staff.

4. INTRODUCTION

4.1. Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a study participant, regardless of whether or not it is thought to be related to study procedures or to a study intervention (e.g. an experimental drug or device; a behavioural intervention; a procedural intervention). An example of an AE that is not necessarily related to a study intervention is the hypothetical case of a research participant in a clinical trial, who sustains a fracture after being hit by a falling tree branch. The fracture is considered an adverse event even though it may have nothing to do with the clinical trial intervention.

4.2. Serious Adverse event

An adverse event is defined as **serious** if it results in:

- Death
- A life threatening event
- Hospitalisation or prolongation of hospitalisation
- Significant disability or incapacity
- Birth defect

Other important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the research participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. This can include diagnosis of cancer.

4.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is a serious adverse event:

- Where there is at least a reasonable possibility of a causal relationship between an intervention and an adverse event (in other words the relationship of the SAE to the trial drug/device/other intervention cannot be ruled out)
and
- That is unexpected, meaning that the nature or severity of the reaction is not consistent with the known scientific information (e.g. Investigator's Brochure for an unapproved investigational product or product information document or similar for an approved, marketed product)

4.4. Other significant events

This category includes any other significant event which: has an impact on the research; requires action; or raises ethical implications.

5. PROCEDURE

5.1. Non-serious adverse events (AE)

Adverse events can be identified through:

- Participant report (open-ended questioning should be used)
- Observation of the participant (e.g. blood pressure)
- Reports (e.g. laboratory, ECG and others)

The process for adverse event management and reporting will be clearly defined in the trial protocol and will include:

- The time period during which new AEs should be recorded (e.g. *from* the time of consent or from the time that the drug/device intervention commences *until* the final visit)
- The requirement for reporting AEs to the investigator/associate investigator for review of the AE and assignment of whether there is a causal relationship (i.e. whether or not the AE is considered related to the trial drug/device/other intervention). Categories of causality should be defined in the protocol and the categories can include definitely related, probably related, possibly related, unlikely to be related and definitely unrelated.

- Note that in a trial of an investigational drug or device the causality must be assessed by a medically-qualified investigator
- How and where the AE is documented (e.g. trial data collection forms and/or trial database plus source documents such as trial-specific participant notes and/or hospital record)
- The requirement to document any intervention required to treat the AE
- The time period for follow up of AEs (an AE should be followed until it resolves or stabilises except where the trial participant is lost to follow up)

5.2. Serious adverse events (SAE)

The process for serious adverse event management and reporting should be clearly defined in the study protocol. The process will be as above for the reporting of AEs but the following requirements will apply to the timing of reporting:

- Report to the investigator/associate investigator immediately
- Where there is an external sponsor (i.e. where the sponsor is not MCRI or RCH) report to the sponsor immediately - note that where the sponsor requests additional information/documentation confidentiality must be maintained when sending this (i.e. no identifying information about the participant to be sent to the sponsor)
- Report to the approving HREC within the HREC's required timeframe (note that for RCH HREC this is within 72 hours of occurrence)

When the RCH site is involved in a multi-site trial, reporting requirements may vary depending on the role of the RCH site. This is detailed in section 5.4.

5.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

The process for SUSAR reporting should be clearly defined in the study protocol. The process will be as above for the reporting of SAEs but the following requirements will apply to the timing of reporting:

- Where there is an external sponsor (i.e. where the sponsor is not MCRI or RCH) report to the sponsor immediately - note that where the sponsor requests additional information/documentation confidentiality must be maintained when sending this
- For investigator-initiated trials of investigational drugs or devices where MCRI or RCH is the sponsor, the investigator must also report the SUSAR to the TGA per its expedited reporting timeframes (for minimum requirements and notification methods see <https://www.tga.gov.au/publication/reporting-adverse-drug-reactions>)
 - For fatal or life-threatening SUSARs – the initial report should be submitted as soon as possible but must be within 7 calendar days after first knowledge by the investigator and this should be followed by as complete a report as possible within a further 8 calendar days
 - For all other SUSARs – as soon as possible but not later than 15 calendar days after first knowledge by the investigator
- For all SUSARs RCH Research Ethics and Governance Office will:
 - Forward the SUSAR to a nominated member of the RCH Drug Trials Sub-Committee (RCH DTSC) for review by the RCH DTSC
 - Report to VMIA (copying in the Secretary of the MCRI Risk Management Committee)

When the RCH site is involved in a multi-site trial, reporting requirements may vary depending on the role of the RCH site. This is detailed in section 5.4.

Reporting requirements for multi-site trials

Where an SAE or SUSAR occurs in an RCH participant:

- If RCH HREC is the approving HREC and RCH/MCRI is the lead site, reporting requirements are as previously outlined
- If the approving HREC is external to RCH and another site is the lead site
 - The RCH/MCRI investigator should submit the SAE/SUSAR to
 - The Coordinating Principal Investigator at the lead site who will submit to the approving HREC
 - The RCH Research Governance and Ethics Office

Where an SAE or SUSAR occurs at a site other than RCH (i.e. at an accepting site) and where the RCH HREC is the approving HREC and RCH/MCRI is the lead site:

- The accepting site investigator submits the initial and follow up reports to the Coordinating Principal Investigator at RCH/MCRI
- The Coordinating Principal Investigator
 - Submits all reports to RCH HREC via the Research Governance and Ethics Office
 - Ensures all subsequent correspondence with RCH HREC is provided to the accepting site
- The accepting site investigator should submit all correspondence to their institutional governance office.

With regard to periodic line listings of SUSARs (i.e. periodic listings of all SUSARs reported during use of the investigational drug or device):

- Where RCH/MCRI is the lead site, the CPI at RCH should submit to HREC via the RCH Research Governance and Ethics Office and also circulate to accepting sites
 - The accepting site investigator should submit all correspondence to their institutional governance office
- Where RCH/MCRI is an accepting site, the RCH PI should submit to the RCH Research Governance and Ethics Office

5.4. Other significant events

Report to HREC any other significant event which: has an impact on the research; requires action; or raises ethical implications.

6. GLOSSARY

Clinical Trial

A form of human research designed to find out the effects of an intervention(s), involving allocation of participants to treatments. A clinical trial can involve testing a drug, a surgical procedure, other therapeutic procedures and devices, a preventive procedure, or a diagnostic device or procedure.

External Sponsor

An individual, company, institution or organization (i.e. not RCH, MCRI or University of Melbourne) that takes responsibility for the initiation, management, monitoring, and/or financing of a research project. The external sponsor may be, for example, a collaborating group or a commercial entity. For projects with no external sponsor the RCH or MCRI will act as the project sponsor.

Investigational Product

A drug or device which is being tested or used as a reference in a clinical trial. This includes a product when it is being used or assembled (formulated or packaged) in a way different from the TGA approved form; **or** when it is being used for an unapproved indication; **or** when it is being used to gain further information about an approved use.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that trial participants are protected. The TGA has adopted the GCP requirements of the International Conference on Harmonisation (ICH) with some modifications (see “Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB” - section 8). Compliance with the “Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB” is mandatory for clinical trials of investigational drugs/devices being conducted under the TGA’s clinical trial schemes. However, compliance is strongly recommended for all research staff involved in human research.

International Conference on Harmonisation (ICH)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator

An individual responsible for the conduct of a clinical trial at a trial site and ensures that it complies with GCP guidelines. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

- **Associate Investigator (AI)** Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows, clinical research coordinators). The Principal Investigator will designate who will be nominated as associate investigators for that site.
- **Chief or Coordinating Principal Investigator (CPI)** A CPI is the investigator who, in a multi-site trial, takes overall responsibility for the research project across sites.

Melbourne Children’s

This term encompasses The Royal Children’s Hospital Melbourne, the Murdoch Childrens Research Institute and the University of Melbourne’s Department of Paediatrics.

Participant

A participant is a person that is the subject of the research.

Research Ethics and Governance Office (REG)

REG supports the HREC and institutional research governance processes at Melbourne Children’s.

Standard Operating Procedure (SOP)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Therapeutic Goods Administration (TGA)

The role of the TGA is to provide a national framework for the regulation of therapeutic goods in Australia and to ensure their quality, safety and efficacy.

The National Health and Medical Research Council (NH&MRC)

NHMRC is Australia's leading expert body for: supporting health and medical research; developing health advice for the Australian community, health professionals and governments; and providing advice on ethical behaviour in health care and in the conduct of health and medical research.

Victorian Managed Insurance Authority (VMIA)

VMIA is the insurance agency for RCH & MCRI.

7. ACRONYMS NOT ELSEWHERE SPECIFIED

HREC

Human Research Ethics Committee

MCRI

Murdoch Childrens Research institute

RCH

The Royal Children's Hospital Melbourne

8. REFERENCES

TGA

Note for guidance on Good Clinical Practice (CPMP/ICH/135/96) annotated with TGA comments DSEB, July 2000 available at

http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm#U_L1r62_mUI

Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) available at <https://www.tga.gov.au/sites/default/files/ich37795.pdf>

Department of Health and Community Services Victoria

Information on multi-site reporting requirements for trials can be found in "Research governance and Site specific assessment – process and practice" available at

<http://www.health.vic.gov.au/clinicaltrials/site-specific.htm>

The Royal Children's Hospital

RCH Standard Operating Procedure "Investigators Responsibilities in Research (SOP RCH0498)" available at http://www.rch.org.au/policy/policies/Investigators_Responsibilities_in_Research/

RCH Regulatory Ethics and Governance Office adverse event reporting guidelines and forms available at http://www.rch.org.au/ethics/existing_applications/Adverse_events/

9. APPENDICES

9.1. Process flow

Refer to process map at http://www.rch.org.au/ethics/existing_applications/Adverse_events/)

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