

Title: SOP Safety Monitoring and Reporting Procedure for MCRI-sponsored Investigator-Initiated Trials of Medicines/Medical Devices

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Document History

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1.0	[Author]	N/A	New Issue
2.0	Kate Scarff		Updated to align with requirements of NHMRC document <i>Safety monitoring and reporting in clinical trials involving therapeutic products (EH59)</i> , dated November 2016 Updated to provide clear guidance on how to assess and report safety events to different stakeholders. Updated to include reporting requirements for medicines and devices used within conditions of their registration. Updated to include reporting requirements for RCH ADR Committee.

Table of Contents

1	PURPOSE	2
2	RESPONSIBILITY AND SCOPE.....	3
3	APPLICABILITY	4
4	ACRONYMS LIST	4
5	PROCEDURE.....	5
5.1	MONITORING SAFETY – OVERVIEW	5
5.2	ADVERSE EVENTS	6
5.3	ASSESSMENT OF ADVERSE EVENTS	7
5.3.1	Assessment of severity.....	7
5.3.2	Assessment of seriousness	7
5.3.3	Assessment of causality	8
5.3.4	Assessment of expectedness.....	9
5.3.5	Other considerations when assessing AEs	10
5.4	SIGNIFICANT SAFETY ISSUES	10
5.5	EXPEDITED REPORTING PROCEDURES	11
5.5.1	Site PI – Reporting to the Sponsor-Investigator and local Research Governance Office.....	11
5.5.2	Sponsor-Investigator – Reporting to the approving HREC.....	13
5.5.3	Sponsor-Investigator – Reporting to the RCH ADR Committee.....	13
5.5.4	Sponsor-Investigator – Unapproved IMP/IMD Safety Reporting to the TGA.....	14
5.5.5	Sponsor-Investigator – Registered Medicine Safety Reporting to the TGA.....	16
5.5.6	Sponsor-Investigator – Registered Device Safety Reporting to the TGA.....	16
5.5.7	Sponsor-Investigator – Reporting SUSARs in blinded trials of IMPs.....	17
5.5.8	Sponsor-Investigator – Reporting new safety information to Site PIs	17
6	ASSOCIATED DOCUMENTS & FORMS.....	18
7	GLOSSARY	18
8	REFERENCES	23
9	APPENDICES	24
9.1	PROCESS FLOW – SAFETY ASSESSMENT, DOCUMENTATION AND REPORTING FOR MCRI-SPONSORED IITs: RESPONSIBILITIES OF THE SITE PI	25
9.2	PROCESS FLOW – SAFETY ASSESSMENT, DOCUMENTATION AND REPORTING FOR MCRI-SPONSORED IITs: RESPONSIBILITIES OF THE SPONSOR-INVESTIGATOR	27

1 PURPOSE

To provide the pharmacovigilance/medical device vigilance procedure for the Coordinating Principal Investigator (CPI) and their research team working on MCRI-sponsored investigator-initiated trials (IITs) involving investigational medicinal products (IMPs)/investigational medical devices (IMDs), respectively. *Note: The collective term, investigational products (IPs), is used throughout this SOP to refer to both IMPs and IMDs.*

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines with a view to identifying information about potential new hazards and preventing harm to participants.

Medical device vigilance is the equivalent of pharmacovigilance for medicines and involves evaluating reported adverse events, disseminating information that could be used to prevent or minimise the consequences of adverse events, and modifying the medical device or removing the medical device from the market, where appropriate.

An investigational medicinal product (IMP) is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. This includes both TGA-approved medicines that are listed on the Australian Register of Therapeutic Goods [ARTG]) and unapproved medicines. Unapproved medicines may be new medicines, approved medicines investigated for new uses or medicines that are not new but are approved by other regulatory agencies such as the Food and Drug Administration (FDA) or European Medicines Agency (EMA). New uses include an unapproved indication, a new patient group, new dose form or packaging or when used to gain further information about an approved use.

An investigational medical device (IMD) is a medical device being assessed for safety or performance in a clinical investigation. This includes TGA-approved medical devices and unapproved medical devices. Unapproved medical devices include new medical devices and medical devices that are being evaluated for new intended uses, new populations, new materials or design changes and may or may not be approved by other regulatory agencies such as the FDA.

Adherence to this SOP will facilitate appropriate monitoring, reviewing, and documentation of safety events that occur during trials of IPs and appropriate reporting of safety events to the approving Human Research Ethics Committee (HREC), RCH Governance Office, Investigators at participating sites and the Therapeutic Goods Administration (TGA).

This SOP does not cover how to document safety events in source documents or the case report form (CRF). Instructions for documenting safety events should be provided in the trial Source Document Plan and instructions/help tools for completing the trial CRF.

2 RESPONSIBILITY AND SCOPE

This SOP applies to Melbourne Children's campus employees who undertake any of the following roles in an MCRI-sponsored clinical trial with an IP:

- Coordinating Principal Investigator (CPI), herein referred to as the Sponsor-Investigator.
Note: For MCRI-sponsored IITs, CRDO have replaced the term Coordinating Principal Investigator with the term Sponsor-Investigator. The latter better reflects the dual role of Sponsor and Investigator.
- Members of the research team who have been delegated responsibility for pharmacovigilance activities by the Sponsor-Investigator.

This SOP may also be used by campus staff where RCH/MCRI is a site in an IIT sponsored by another institution if the external Sponsor does not have their own SOP.

The Sponsor-Investigator is responsible for reviewing all safety events reported by members of the lead site research team and Investigators from participating sites (applicable for multi-centre research).

For multi-centre trials, the Principal Investigator at each site is responsible for local safety monitoring and reporting.

The Sponsor-Investigator and site Principal Investigators are responsible for supervising any individual to whom they have delegated safety monitoring or reporting duties.

3 APPLICABILITY

This SOP covers how to monitor, assess and report safety events that occur in IITs involving medicine or medical device interventions conducted under a Clinical Trial Notification (CTN) or Clinical Trial Exemption Scheme (CTX). The SOP is aligned with the requirements of the NHMRC Guidance: *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods [EH59]*, dated November 2016.

This SOP is also relevant to trials of medicines and medical devices that are not conducted under the CTN/CTX schemes because they are to be used in accordance with the TGA-approved product information (applicable to medicines)/Instructions for Use (applicable to medical devices). In these trials, the Sponsor-Investigator and the research team should conduct safety monitoring and reporting to Investigators, the approving HREC and local research governance office in accordance with the EH59 guidance but reporting to the TGA is in accordance with the relevant TGA Guidance as listed below:

Medicines: [Pharmacovigilance responsibilities of medicine sponsors, Australian recommendations and requirements, Version 2.1, June 2018](#).

Biologics: [Biovigilance responsibilities of sponsors of biologicals, Version 1, December 2017](#).

Devices: [Australian regulatory guidelines for medical devices \(ARGMD\) Part 3 – Post market, Version 1.1, May 2011](#) (Note this document was labelled “Under review” at time of finalising this SOP)

This SOP does not cover how to monitor, assess, or report safety events that occur in clinical trials involving interventions other than a drug or device, e.g. surgery, radiotherapy or psychotherapy interventions. A CRDO SOP for safety monitoring and reporting in trials of interventions that are not a drug or device will be available in early 2019.

4 ACRONYMS LIST

ADR/AR	Adverse drug reaction/adverse reaction (interchangeable terms)
AE	adverse event
AI	Associate Investigator
ARGMD	Australian Regulatory Guidelines for Medical Devices
ARTG	Australian Register of Therapeutic Goods
CPI	Coordinating Principal Investigator
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IFU	Instructions for Use
IIT	Investigator-initiated trial
IMD	Investigational medical device
IMP	Investigational medicinal product
IP	Investigational Product
IRB	Institutional Review Board
MCRI	Murdoch Children's Research institute
MCTC	Melbourne Children's Trials Centre
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
RCH	The Royal Children's Hospital Melbourne
REG	Research Ethics and Governance Office
RSI	Reference Safety Information
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration (TGA)
USM	Urgent Safety Measure

5 PROCEDURE

5.1 Monitoring Safety – Overview

The Sponsor-Investigator is responsible for establishing the process by which safety of participants will be monitored during the trial.

Sponsor-Investigator is a term used for investigator-initiated studies. It is an individual who is responsible for both the initiation and conduct of a study. The term does not include any person other than an individual. This person will be:

- the Principal Investigator for single-site investigator-initiated studies
- the Coordinating Principal Investigator for multi-centre investigator-initiated studies

The safety monitoring plan and justification for the approach chosen, should be based on the trial specific Risk Assessment and Risk Management Plan and consider the following:

- The registration status of the investigational product in Australia (i.e. whether the product has been evaluated by the Therapeutics Goods Administration [TGA] for quality, safety and efficacy and entered into the Australian Register of Therapeutic Goods [ARTG] enabling marketing in Australia), outside Australia, or not previously reviewed by a regulatory body, i.e. a new investigational product.
- The plan for use of the investigational product:
 - product listed on the ARTG and will be used within its current approved indication
 - product listed on the ARTG but which will be used outside its current indication

- product which is not listed on the ARTG but will be used in accordance with approved registration by an overseas regulator (e.g. FDA, EMA)
 - product that is still in early development with no/limited safety or efficacy data in humans
- Risks that are associated with the conduct of the trial, e.g. risks involved in procedures conducted as part of the study).

The risk assessment will be used to justify the following:

- The time period for collecting adverse events. Examples include:
 - From Screening or randomisation/administration of investigational product (IP)
 - End 30 days or 5 elimination half-lives after last administration of IP
 - End after completion of all study-related procedures
- Is it appropriate to have reduced/targeted safety data collection? **Important: Regardless of the answer, all non-serious adverse reactions still need to be captured in the participant's medical record.**
- Is it appropriate to only expedite reports of serious and unexpected adverse reactions (SUSARs) to stakeholders rather than all serious adverse events?
- What is the justification for having/not having a Data Safety Monitoring Committee (DSMC)?

The safety monitoring plan should be detailed in the protocol or a separate document and include the role and composition of any oversight committees.

5.2 Adverse Events

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 must be clearly defined in the trial protocol and include:

- The time period during which new AEs should be recorded as per the trial specific Risk Assessment and Risk Management Plan
- The requirement for site PI/delegate for assessment of:
 - Severity
 - Expectedness
 - Causality
 - Seriousness

See Section 5.3 for how to assess AEs.

- How and where the AE is documented. e.g. AE Case Report Form (CRF) plus source documents such as trial-specific participant notes and/or hospital record. The source document for recording AEs should be specified in the trial specific Source Document Plan (see CRDO's Source Document Plan Guidance and Template available from the CRDO website).
- The requirement to document in the source document any intervention required to treat the AE
- The time period for follow up of any AEs ongoing after the last study visit. This may be expressed in number of days or half-lives. This data is important both for

the safety profile of the investigational product and for monitoring the welfare of participants.

- The requirements for expedited reporting for the Sponsor-Investigator and site PIs. See section 5.5 for reporting requirements.

5.3 Assessment of adverse events

The Site PI/delegate is responsible for assessing all AEs with regards to severity, seriousness and causality (see sections 5.3.1 -5.3.3). Generally the Sponsor-Investigator will perform the assessment of expectedness but this can be delegated to Site PIs (see section 5.3.4).

Following receipt of an expedited safety report from a site, the Sponsor-Investigator/delegate should also review and assess the report to ensure severity, seriousness, causality and expectedness have been appropriately determined.

Note: If the Sponsor's causality assessment conflicts with the assessment made by the site PI, the site PI's assessment cannot be downgraded by the sponsor (i.e. from 'related' to 'not related'). In this case, if the Investigator's assessment triggers the reporting of a SUSAR, the opinion of both the investigator and the sponsor should be provided on any SUSAR report sent to the TGA (see Section 5.3.3).

It may also be necessary to request further information from the site to complete the review.

Seriousness and causality must always be assessed by a medically qualified doctor.

Following the review and assessment, the Sponsor-Investigator and Site PIs should report those events identified as SSIs, USMs or SUSARs to stakeholders within the relevant timelines (see section 5.5).

5.3.1 Assessment of severity

The protocol must describe how severity will be graded. Options include standard toxicity grading scales, e.g. CTCAE or WHO. Alternatively it may be appropriate to develop a trial-specific grading scale such as the one below.

Intensity	Description
Mild	An event tolerated by the patient, causing minimal discomfort and not interfering in everyday activities
Moderate	An event sufficiently discomforting to interfere with normal everyday activities
Severe	An event that prevents normal everyday activities

5.3.2 Assessment of seriousness

Medicines

An adverse event/reaction is a serious adverse event (SAE)/serious adverse reaction (SAR) if it:

- Results in death
- Is life-threatening
- Requires hospitalisation
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

Some medical events may also be considered as serious if they impact participant safety or require an intervention to prevent one of the defined criteria for seriousness. For example treatment for allergic bronchospasm in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Devices

An adverse event/adverse device effect is a serious adverse event (SAE)/serious adverse device effect (SADE) if it:

- Led to death
- Led to serious deterioration in the health of the participant, that either resulted in:
 - A life-threatening illness or injury, or
 - A permanent impairment of a body structure or a body function, or
 - In-patient or prolonged hospitalisation, or
 - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

5.3.3 Assessment of causality

Causality refers to the likelihood that an adverse event is related to the administration/use of the IP. An adverse event that is judged by the Investigator or the Sponsor-Investigator to have a reasonable possibility of a causal relationship to the IMP/IMD is considered an adverse reaction (AR)/ adverse device effect (ADE).

The Site PI/delegate must use medical and scientific judgement and knowledge of the participant when making a causality assessment for IMPs and IMDs, including factors such as:

- Underlying or concurrent illness/disease
- Concomitant therapy
- Any other risk factors
- Known safety profile of the investigational product – consult the protocol, IB, Product Information, published literature
- Timing of the AE and the administration/use of IP
- Effect withdrawal/discontinuation of IP, or reduction in exposure/dose and reintroduction of use/increase in exposure/dose has on the event

For IMDs only, the Site PI/delegate must also consider the following:

- Is the body-site or organ expected to be affected by the device?
- Could the event be due to use error?
- Does the event depend on a false result given by a device used for diagnosis?

The protocol must describe the scale use to record the causality of an event and this must be consistent with the safety reporting options contained in the trial-specific Expedited Safety Reporting Form (see section 5.5.1) and the CRF. See below for an example of a causality assessment scale used for IMPs.

Causality	Description
Unrelated	There is no association between the trial intervention and the reported event. AEs in this category do not have a reasonable temporal relationship to

	exposure to the test product, or can be explained by a commonly occurring alternative aetiology
Possible	The event could have cause or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the intervention and/or follow a known response pattern to the test article, but could also have been produced by other factors.
Probable	The association of the event with the trial intervention seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and are consistent with the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigators clinical experience.
Definite	The AE is a consequence of administration of the trial intervention. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the test product or that they occur after rechallenge

The Sponsor-Investigator may also assess the causality of adverse events occurring in participants enrolled through participating sites. It is important the site Investigator's assessment is independent of the Sponsor-Investigator. If there is disagreement between the two assessments, the opinion of both parties must be provided on the report to the approving HREC, local governance office and TGA.

5.3.4 Assessment of expectedness

Expectedness is related to what is expected for the side effects of the IP, not to what is anticipated for a particular disease/illness, participant population or individual participant history. Expectedness also relates to the severity and specificity of known adverse events. An increase in the specificity or severity of an expected AE constitutes an unexpected adverse event.

The Sponsor-Investigator and site PIs have responsibilities for expedited reporting of those safety events that are serious, related and unexpected (see Section 5.5). For IMPs, such events are known as Suspected Unexpected Serious Adverse Reactions (SUSARs). For IMDs, the equivalent term is Unanticipated Serious Adverse Device Effect (USADE).

The Sponsor-Investigator is responsible for performing the assessment of expectedness using the current Reference Safety Information (RSI). For IMPs, the RSI specifically references what AEs are considered expected. For IMDs, the RSI lists adverse device effects by their nature, incidence, severity and outcome.

The protocol must identify the source of the RSI used for the clinical trial. For IMPs, the RSI may be an Investigator's Brochure (IB), TGA-approved Product Information, publication or some other document that contains information on the safety profile of the IP. For IMDs, the RSI is contained in the risk analysis report and/or contained in the Investigator's Brochure, Instructions for Use or Clinical Investigation Plan (ISO 14155 term for protocol). If the only safety information available is from published preceding clinical trials, this information should

be provided in the protocol. The same RSI must be used for all sites, including international sites.

If the RSI is generated by a third party, it is important that the Sponsor-Investigator has a process in place to regularly check for any updates.

Updates to the RSI need to be communicated in a timely manner to Investigators and the approving HREC, clearly identifying the version of the updated document to enable confirmation of the date the updated RSI is used at sites. Old versions of the RSI must be archived to ensure they are not used for making expectedness assessments.

The Sponsor-Investigator may delegate the assessment of expectedness to other Investigators but this will require processes are in place to ensure individual Investigators receive consistent training in using the RSI and the interpretation of expectedness to facilitate accurate identification and reporting of SUSARs / USADEs, rather than under- or over-reporting.

5.3.5 Other considerations when assessing AEs

- If there is a possible drug-drug interaction between the study IMP and a concomitant medication this must be reported as a SUSAR.
- SUSARs causally associated with a study placebo should be reported as a SUSAR, e.g. an allergic reaction to an excipient.
- SUSARs associated with registered comparator products used within the conditions of their marketing approval should be reported to the Sponsor-Investigator, approving HREC and relevant regulatory authority(ies) as normal.

5.4 Significant Safety Issues

The Sponsor-Investigator has additional safety monitoring responsibilities beyond the collection of individual AEs, SAEs and SUSARs. They are responsible for monitoring all adverse events to enable timely identification of any significant safety issues (SSIs). An SSI is a safety issue that could adversely affect the safety of participants or material impact on the continued ethical acceptability of the trial. By their nature, SSIs will result in actions, such as reporting of an urgent safety measure, safety-related changes to the protocol and other trial documents, a temporary halt or an early termination.

Urgent Safety Measures (USMs) are a subset of SSI where the Sponsor or Investigator acts immediately to protect participants from an immediate hazard to their health and safety. They are often instigated before the TGA or HREC are notified. Where there are specific safety concerns for a trial or an IP before a trial starts, the protocol should have stopping rules built in to the study design. In this circumstance, triggering of stopping rules will not constitute an USM.

SSIs may be readily apparent in trials with small participant numbers. However larger trials may warrant statistical comparisons of treatments to detect a new, emerging safety risk.

Examples of SSIs included in the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59), November 2016, are included below:

- A serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- A hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- A major safety finding from a newly completed animal study (such as carcinogenicity)

- A temporary halt/termination of a trial for safety reasons
- Recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction
- Single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure

5.5 Expedited Reporting Procedures

The Sponsor-Investigator and site PIs have responsibilities for expedited reporting of safety events to stakeholders in accordance with the NHMRC EH59 guidance and as specified in the protocol. Expedited reporting of safety events facilitates the safety of participants in clinical trials.

5.5.1 Site PI – Reporting to the Sponsor-Investigator and local Research Governance Office

Site PIs must report safety events to the Sponsor-Investigator and local Research Governance Office as well as SSIs identified by the Sponsor-Investigator in accordance with the NHMRC EH59 guidance and as specified in the protocol.

The Sponsor-Investigator is responsible for generating the SSI, USM and SUSAR reports and sending them to the local Research Governance Office via the Site PI.

The Investigator is responsible for forwarding the reports identified above and sending expedited SAE reports to the Sponsor-Investigator.

The Sponsor-Investigator can define in the protocol and risk assessment those SAEs that do not require expedited reporting. These non-expedited SAEs must still be collected and monitored, e.g. collection in the CRF and monitored by DSMB.

Examples of SAEs that may not require expedited reporting include:

- Events common in the patient population being studied, e.g. as a consequence of their age or medical condition
- Trial endpoints that will be captured and monitored by a DSMB, e.g. death in a stroke trial
- Well characterised adverse reactions, e.g. neutropenic sepsis in a chemotherapy trial
- Pre-planned surgery.

The Sponsor-Investigator may identify in the protocol non-serious AEs that require expedited reporting because they are important to the evaluation of safety of the trial. For example, changes in ECGs or changes in liver function tests. Non-serious AEs do not require expedited reporting to the TGA. The protocol must define these non-serious AEs and detail the reporting requirements (what needs to be reported and in what timeframe) to the Sponsor-Investigator.

Types of events to be reported and their associated timeframe are provided in Table 1.

Table 1. Site PI Expedited Reporting Requirements		
Safety Event/Report	Research Governance Office	Sponsor-Investigator
SSIs *identified by the Sponsor-Investigator	≤ 72 hours of receiving report	N/A

USMs	≤ 72 hours of instigation	≤ 24 hours of instigation
SUSARs/USADEs *identified by the Sponsor-Investigator (local participants only)	≤ 72 hours of becoming aware of event	N/A
SAEs (IMPs) SAEs and device deficiencies that could have led to a SADE (IMDs)	N/A	≤ 24 hours of becoming aware of the event Without unjustified delay
AEs/lab evaluations critical to safety (IMPs) AEs/device deficiencies (IMDs)	N/A	Per protocol

* The Sponsor-Investigator is responsible for identifying SSIs and evaluating expectedness of SARs and SADEs with subsequent identification of SUSARs/USADEs.

Safety events reported to the local RGO should use the locally-approved process. For example, safety reporting to the RCH Research Governance Office requires completing the safety report form accessed within ERM and submission through the [ERM portal](#). A copy of the safety report and accompanying correspondence must be sent to the Sponsor-Investigator. It is the responsibility of the site PI to understand the process for reporting safety events to their local research governance office.

Safety events reported to the Sponsor-Investigator should use a trial-specific Expedited Safety Report Form. A template Expedited Safety Report Form is available from the CRDO website. The information collected in this form must include:

- The Participant ID, date of birth and sex
Important: Confidentiality of the participant must be maintained. Ensure any accompanying information (e.g. lab reports, imaging) is de-identified. If this is not possible, you must have consent from participant to provide identifying data to nominated third party (ies).
- Site details
- SAE/SUSAR – full description including event start date and resolution date (if resolved).
- Suspected IMP/IMD
- Causality assessment
- Assessment of seriousness
- Relevant medical history/concurrent medical conditions
- Concomitant medications
- Dates of suspect drug administration/device use and whether any changes made as result of event
- Date the investigator/team became aware of the event
- If report is an initial or follow-up report

5.5.2 Sponsor-Investigator – Reporting to the approving HREC

The Sponsor-Investigator must report safety events to the approving HREC in accordance with the NHMRC E59 guidance, protocol and additional requirements stipulated as a condition of ethics approval.

In addition to expedited reporting of SSIs and USMs, the Sponsor-Investigator must submit an Annual Safety Report to the approving HREC. The annual safety report should provide the following:

- A clear summary of the evolving safety profile of the trial
- Evidence that the Sponsor-Investigator is conducting ongoing safety monitoring appropriately
- Evidence that the Sponsor-Investigator is following the trial-specific safety monitoring plan
- Evidence that the Sponsor-Investigator has adapted the safety monitoring plan to address any emerging safety issues throughout the trial

The Sponsor-Investigator is responsible for reporting SSIs, USMs and Annual Safety Reports to the approving HREC using forms developed by the relevant state department of health. The process for submitting forms may be via a portal, e.g. ERM in Victoria or by submitting a form via email to the approving HREC. RCH HREC requires the Sponsor-Investigator to submit safety reports through ERM. It is the responsibility of the Sponsor-Investigator to ensure they use the preferred process of the relevant approving HREC. Updated IBs/Product Information should be provided in accordance with local HREC requirements.

Timeframes for reporting safety events/reports to the approving HREC are provided in Table 2.

Table 2. Sponsor-Investigator Expedited Reporting Requirements to HREC

Safety Event/Report	Reporting Timeframe
SSIs (excluding USMs)	≤ 15 days
USMs	≤ 72 hours
Annual Safety Report	Same time as Annual Progress Report
Updated IB/PI	As applicable

5.5.3 Sponsor-Investigator – Reporting to the RCH ADR Committee

For participants enrolled at Melbourne Children’s only, the Sponsor-Investigator must report all adverse reactions (expected and unexpected, serious or not serious) to the RCH Adverse Drug Reaction (ADR) Committee.

The ADR Committee provides oversight of adverse drug reactions occurring in patients at The Royal Children’s Hospital (RCH). The ADR Committee involves a multidisciplinary team, coordinated by the Pharmacy Department and Clinical Pharmacology. The team aims to:

- Identify any ARs occurring within the hospital
- Review suspected ARs and provide advice on management

- Refer patients with suspected drug allergies to the RCH Allergy Clinic for follow up, where appropriate
- Provide patients with an ADR Alert Card, where appropriate
- Document ARs in a patient's medical history and on the Pharmacy Department's medication dispensing system
- Report ARs to the Advisory Committee on Medicines (ACM) of the Therapeutic Goods Administration (TGA). *Note: The ADR Committee is not responsible for reporting ARs to the TGA that occur in participants participating in clinical research/clinical trials. In this case, the Sponsor-Investigator is responsible for reporting to the TGA (See Section 5.5.4 and 5.5.5 for details).*

Reports should be submitted via https://www.rch.org.au/pharmacy-intranet/Adverse_Drug_Reaction_Report/ as soon as possible. Please refer to the RCH pharmacy intranet for further information at [https://www.rch.org.au/pharmacy-intranet/medicines-information/Adverse_Drug_Reaction_\(ADR\)_reporting/](https://www.rch.org.au/pharmacy-intranet/medicines-information/Adverse_Drug_Reaction_(ADR)_reporting/)

5.5.4 Sponsor-Investigator – Unapproved IMP/IMD Safety Reporting to the TGA

There are different procedures for reporting safety events to the TGA for SUSARs, USADEs and SSIs used under the CTN/CTX schemes. Details for each of these types of event are provided below. Regardless of the type of safety event, please retain a copy of the submitted report, and any associated correspondence including acknowledgement of receipt, in the Trial Master File.

SUSARs and USADEs

SUSARs should be reported to the TGA through the TGA Business Services Adverse Event Management System (AEMS) portal at <https://aems.tga.gov.au/privacy/>. Users will need to have a TGA Business Services account. Please contact CRDO at crdo.info@mcri.edu.au to request a user account. Users will be able to draft the report form and then contact CRDO to arrange for the report to be submitted to the TGA.

Alternatively SUSARs can be reported directly to the TGA by the site PI/delegate using either of the following forms:

- [Blue Card](#)
- or
- [CIOMS form](#)

emailed to adr.reports@health.gov.au

USADEs should be reported to the TGA using the online Users [Medical Device Incident Report form](#).

Alternatively, USADEs can be reported to the TGA using the Users [Medical Device Incident Report form](#) available for download in PDF or Word version from the TGA website. The completed form should be emailed to iris@tga.gov.au

Timeframes for reporting SUSARs and USADEs to the TGA are provided in Table 3.

Table 3. Sponsor-Investigator Reporting SUSARs/USADEs to TGA

Serious Unexpected Related Safety Event	Reporting Timeframe
SUSARs (Australian sites only)	<p>For fatal or life threatening Australian SUSARs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days</p> <p>For all other Australian SUSARs, no later than 15 calendar days after being made aware of the case</p>
USADEs (Australian sites only)	<p>For fatal or life threatening Australian SUSARs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days</p> <p>For all other Australian SUSARs, no later than 15 calendar days after being made aware of the case</p>

SSIs (All therapeutic goods – IMPs and IMDs)

SSIs should be reported in writing to the TGA's Pharmacovigilance and Special access Branch via email to clinical.trials@health.gov.au within the timeframes provided in Table 4.

Table 4. Sponsor-Investigator Reporting SSIs to TGA

Type of SSI	Reporting Timeframe
USM	≤ 24 hours (where possible) but no later than 72 hours of measure being taken
Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia)	Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action
All other significant safety issues (SSIs): <ul style="list-style-type: none"> • Notification of an amendment • Temporary halt of a trial for safety reasons • Early termination of a trial for safety reasons 	Without undue delay and no later than 15 calendar days of the trial sponsor becoming aware of the issue or temporary halt or early termination

5.5.5 Sponsor-Investigator – Registered Medicine Safety Reporting to the TGA

In accordance with the TGA guidance, *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements*, V2.1 June 2018 (page 23), serious adverse reactions (SARs) (both expected and unexpected) related to registered medicines used in accordance with the TGA-approved product information or label indications, must be reported to the TGA by the Sponsor-Investigator within 15 calendar days from receipt.

Only SARs occurring in Australia must be reported.

Individual adverse reaction reports do not need to be submitted for:

- Non-serious adverse reactions
- Adverse events not suspected to be related to the medicine
- Adverse reactions that occurred overseas during the trial.

BUT the Sponsor-Investigator must retain records of these non-reportable cases to be considered in ongoing global analysis of the benefit-risk ratio of the medicine and provide to the TGA upon request.

SARs must be reported to the TGA through the TGA Business Services Adverse Event Management System (AEMS) portal at <https://aems.tga.gov.au/privacy/>. Users will need to have a TGA Business Services account. Please contact CRDO at crdo.info@mcri.edu.au to request a user account. Users will be able to draft the report form and then contact CRDO to arrange for the report to be submitted to the TGA.

5.5.6 Sponsor-Investigator – Registered Device Safety Reporting to the TGA

In accordance with the TGA guidance, [Australian Regulatory Guidelines for Medical Devices \(ARGMD\), V1.1 May 2001](#) page 305, AEs related to registered medical devices that meet the following three basic reporting criteria, even if they do not involve a patient or user, should be reported to the TGA:

- AE has occurred in Australia
- and the medical device is associated with the AE
- and the event led to or might lead to death or serious injury, or might lead to death or serious injury if it were to occur again

There are eight exemption rules for reporting AEs to the TGA. Please refer to the ARGMD (pages 308-311) for details.

In accordance with the ARGMD, the timeframes for submitting AE reports to the TGA are provided in Table 5.

Table 5. Sponsor-Investigator Reporting Registered Medical Device AEs to the TGA

Type of AE	Reporting Timeframe
Represents a serious threat to public health	within 48 hours of receipt
AE that led to death or a serious deterioration in health of a patient, user of the device or another person	within 10 days of receipt

AE that recurrence may lead to death, serious deterioration in health of a patient, user of the device or another person	within 30 days of receipt
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Medical device AEs may be reported to the TGA using the same process that applies to USADEs described in Section 5.5.3.

5.5.7 Sponsor-Investigator – Reporting SUSARs in blinded trials of IMPs

For blinded IMPs, SUSARs should generally be unblinded before reporting to the Research Governance Office and the TGA and/or other relevant regulatory authority(ies).

However, retention of the blind for a participant is understandable when the serious outcome is identical to or closely resembles the primary efficacy endpoint of the study. These outcomes would be considered disease-related and exempted from expedited reporting. However if monitoring detects the number of cases exceeds what would reasonable be expected, the Sponsor-Investigator should reconsider the issue of blinding and report to the TGA. The trial protocol should state how these issues will be handled.

The Sponsor-Investigator should have in place procedures for unblinding for expedited reporting purposes without compromising the blinded members of the team. The blind should be maintained for all other persons involved in the conduct or management of the trial, including those responsible for data analysis and/or interpretation of results. The blind should only be broken for the specific participant concerned.

If after unblinding it is evident that the participant received IMP (rather than a comparator that is used within conditions of registration or a placebo), the SUSAR should be reported using procedure described in section 5.5.3. If the participant received placebo or a comparator product, follow the procedure described in section 5.3.5.

5.5.8 Sponsor-Investigator – Reporting new safety information to Site PIs

The Sponsor-Investigator/delegate must notify the PI at each site of all SSIs and USMs (occurring at any site) and SUSARs/USADEs (local site participants only) in accordance with the process detailed in Table 6.

Table 6. Sponsor-Investigator Reporting of New Safety Information to Site PIs

Safety Event	Report Format	Timeframe
USM	Copy of safety report provided to HREC	≤ 72 hours of measure being taken
All other significant safety issues (SSIs) that result in: <ul style="list-style-type: none"> • Notification of an amendment • Temporary halt of a trial for safety reasons 	Copy of safety report provided to HREC	Without undue delay and no later than 15 calendar days of the sponsor becoming aware of the issue/decision to halt/terminate trial

- Early termination of a trial for safety reasons

Local site SUSARs/USADEs	Complete safety report form in accordance with local site state/territory requirements	*≤ 24 hours receiving expedited safety report from the site
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* Sites have < 72 hours to submit local SUSARs to the local Research Governance Office. Therefore the Sponsor-Investigator must review all SARs reported by sites within 24 hours to facilitate rapid reporting.

6 ASSOCIATED DOCUMENTS & FORMS

CRDO Risk Assessment and Management Tool

[CRDO Source Document Plan Guidance and Template](#)

[RCH Procedure “Investigators Responsibilities in Research” \(RCH0498\).](#)

Note at time of finalising this SOP this RCH procedure was in process of being updated to reflect the NHMRC EH59 requirements.

7 GLOSSARY

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).

Adverse Reaction (AR) / Adverse Drug Reaction (ADR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Biological

An item made from, or containing, human cells or human tissues, and that is used to treat or prevent disease or injury, diagnose a condition of a person, alter the physiological processes of a person, test the susceptibility of a person to disease, replace or modify a person’s body part(s).

Clinical Trial

Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. (WHO definition)

Clinical Trial Exemption (CTX)/Clinical Trial Notification (CTN)

Clinical trials conducted using ‘unapproved therapeutic goods’ in Australia – that is, therapeutic goods that have not been evaluated by the Therapeutics Goods Administration (TGA) for quality, safety and efficacy and entered into the Australian Register of Therapeutic

Goods (ARTG) for general marketing – are required to make use of the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes.

Under the CTN scheme, scientific and ethical review is provided by a human research ethics committee (HREC), with subsequent notification to the TGA. In the CTX scheme, the TGA has a direct role in the review of trial scientific data and must give an ‘approval’ for the proposed trial program to go ahead; however, HREC review is still required.

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 Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) 2016 – Annotated with TGA comments available at <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>). Compliance with the guideline 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.

Human Research Ethics Committee (HREC)

Human Research Ethics Committees (HRECs) play a central role in the Australian system of ethical oversight of research involving humans. HRECs review research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. Also known as institutional review board (IRB) and institutional ethics committee (IEC).

Instructions for Use (IFU)

Document containing a device’s intended use/purpose; how the device should be used, maintained and stored; and any residual device risks, warnings, limitations or contraindications.

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.

Investigational Product (IP)

An investigational medicinal product or investigational medical device which is being tested or used as a reference in a clinical trial.

An investigational medicinal product (IMP) is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. This includes both TGA-approved medicines and biologicals that are listed on the Australian Register of Therapeutic Goods [ARTG]) and unapproved medicines and unapproved biologicals. Unapproved medicines/biologicals may be new medicines/biologicals, approved medicines/biologicals investigated for new uses or medicines/biologicals that are not new but are approved by other regulatory agencies such as the Food and Drug administration (FDA) or European Medicines Agency (EMA). New uses include an unapproved indication, a new patient group, new dose form or packaging or when used to gain further information about an approved use.

An investigational medical device (IMD) is a medical device being assessed for safety or performance in a clinical investigation. This includes TGA-approved medical devices and unapproved medical devices. Unapproved medical devices include new medical devices and medical devices that are being evaluated for new intended uses, new populations, new materials or design changes and may or may not be approved by other regulatory agencies such as the FDA.

Instructions for Use (IFU)

Document containing a device's intended use/purpose; how the device should be used, maintained and stored; and any residual device risks, warnings, limitations or contraindications.

Investigator / Principal Investigator/ Coordinating Principal Investigator/ Associate Investigator

An Investigator is an individual responsible for the conduct of a study, ensuring that the study complies with GCP guidelines. There are different terms used to distinguish the varying role of Investigators as described below.

- If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the Principal Investigator (PI). In this instance they may delegate tasks to other team members.
- A senior 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 may be called an Associate Investigator. The Principal Investigator will designate who will be nominated as Associate investigators for the site.
- If a study is conducted at more than one study site, the Principal Investigator taking overall responsibility for the study and for the coordination across all sites is known as the Coordinating Principal Investigator (CPI); the Principal Investigator at each site will retain responsibility for the conduct of the study at their site.

Note that for investigator-initiated research, the PI or CPI leading the research takes on responsibilities of the Sponsor and the term "Sponsor-Investigator" should be adopted to highlight the dual sponsor and investigator role.

Investigator-initiated trials (IITs)

Trials where the investigator initiates and organises a trial with minimal involvement of the institution are referred to as investigator-initiated trials (IITs). In this case, the institution will be usually be responsible for the medico-legal risk and delegate the remaining Sponsor responsibilities to the lead investigator (i.e. Sponsor-Investigator), including the initiation, financing (or arranging the financing) conduct and management (including compliance with GCP and applicable regulatory requirements) of the trial.

Investigator's Brochure (IB)

The document containing a summary of the scientific information relevant to the safe and effective use of an investigational medicine or device.

MCRI

Murdoch Children's Research Institute

Medical Device

Any instrument, apparatus, implement, machine, appliance, implant, software, material, or other similar or related article:

- a. Intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:
 - Diagnosis, prevention, monitoring, treatment or alleviation of disease
 - Diagnosis, monitoring, treatment, alleviation or of compensation for an injury or handicap
 - Investigation, replacement or modification of the anatomy or of a physiological process
 - Supporting or sustaining life
 - Control of conception
 - Disinfection of medical devices, and
- b. That does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means.

Medical Device Vigilance

Medical device vigilance is the equivalent of pharmacovigilance for medicines and involves evaluating reported adverse events, disseminating information that could be used to prevent or minimise the consequences of adverse events, and modifying the medical device or removing the medical device from the market, where appropriate. *Note: Definition obtained from TGA Guideline: Australian regulatory guidelines for medical devices (ARGMD) Part 3 – Post-market, Version 1.1, May 2011. Under review when accessed on 09 October 2018.*

Melbourne Children's

Melbourne Children's is a collaboration between campus partners The Royal Children's Hospital (RCH), Murdoch Children's Research Institute (MCRI) and The University of Melbourne.

Melbourne Children's Trials Centre (MCTC)

Melbourne Children's Trials Centre (MCTC) is a unique collaboration between the Royal Children's Hospital, The Murdoch Children's Research Institute, The Royal Children's Hospital Foundation and The University of Melbourne. These institutes bring together expertise in research, clinical practice and education.

The centre provides Investigators and industry Sponsors with support for all types of clinical research ranging from trials of novel therapeutic agents to large public health prevention trials. MCTC aims for excellence in the design and conduct of clinical trials and leadership in paediatric health research.

Participant

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

Pharmacovigilance

Process of ongoing monitoring of the safety profile, combined with the ongoing assessment and evaluation of the risk-benefit of medicines. The process is important to identify adverse reactions/adverse device effects and changes in the known safety profile.

Product Information

In relation to therapeutic goods, the TGA-approved Australian summary of the scientific information relating to the safe and effective use of the goods. Note in trials in which the IMP is an approved product, the approved Product Information may replace the Investigator's Brochure.

RCH

The Royal Children's Hospital Melbourne

Reference Safety Information

The information used to determine what adverse reactions/adverse device effects are considered expected. For IMPs this information may be contained in either an Investigator's Brochure or approved Australian Product Information (or another country's equivalent). For IMDs, this information may be contained in either a risk analysis report, Investigator's Brochure, Instructions for Use (IFU) or Clinical Investigation Plan (ISO 14155 term for protocol).

Research Ethics and Governance Office (REG)

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

Risk Analysis Report

Documented risk analysis of the IMD carried out before the study starts. The report should:

- include or refer to review of the published and available unpublished medical/scientific data.
- risks identified as well as the risks to participants in the proposed trial, and should be balanced against the anticipated benefits to participants.
- be updated with new information that comes to light during the trial.

Serious Adverse event (SAE)

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

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or 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.

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability of the trial.

Sponsor

An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, MCRI or RCH will act as the Sponsor but delegate many sponsor responsibilities to the Coordinating Principal

Investigator. In this case the CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Standard Operating Procedure (SOP)

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

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)

Therapeutic Good

In relation to the evaluation, assessment and monitoring done by the TGA, therapeutic goods are broadly defined as products for use in humans in connection with:

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury
- influencing inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling or preventing conception
- testing for pregnancy

This includes things that are:

- used as an ingredient or component in the manufacture of therapeutic goods
- used to replace or modify of parts of the anatomy

Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods.

The National Health and Medical Research Council (NHMRC)

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.

Urgent Safety Measure

A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

8 REFERENCES

NHMRC

NHMRC: Safety monitoring and reporting in clinical trials involving therapeutic goods, EH59, Nov 2016, available at: <https://nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods>

TGA

Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (2) 2016 – Annotated with TGA comments available at <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>

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

TGA Guidance: Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australian using “unapproved” therapeutic goods, Version 2.2 October 2018, available at <https://www.tga.gov.au/publication/australian-clinical-trial-handbook>

TGA Guidance: Pharmacovigilance responsibilities of medicine sponsors. Australian recommendations and requirements. Version 2.1, June 2018. Available at <https://www.tga.gov.au/sites/default/files/pharmacovigilance-responsibilities-medicine-sponsors.pdf>

TGA Guidance: Australian Regulatory Guidelines for Medical Devices, Version 1.1 May 2011, under review, available at <https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd>

Department of Health and Human Services Victoria, Coordinating Office for Clinical Trial Research

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 Regulatory Ethics and Governance Office safety reporting guidelines and links to the Victorian safety reporting forms available at https://www.rch.org.au/ethics/existing-applications/Safety_reporting/

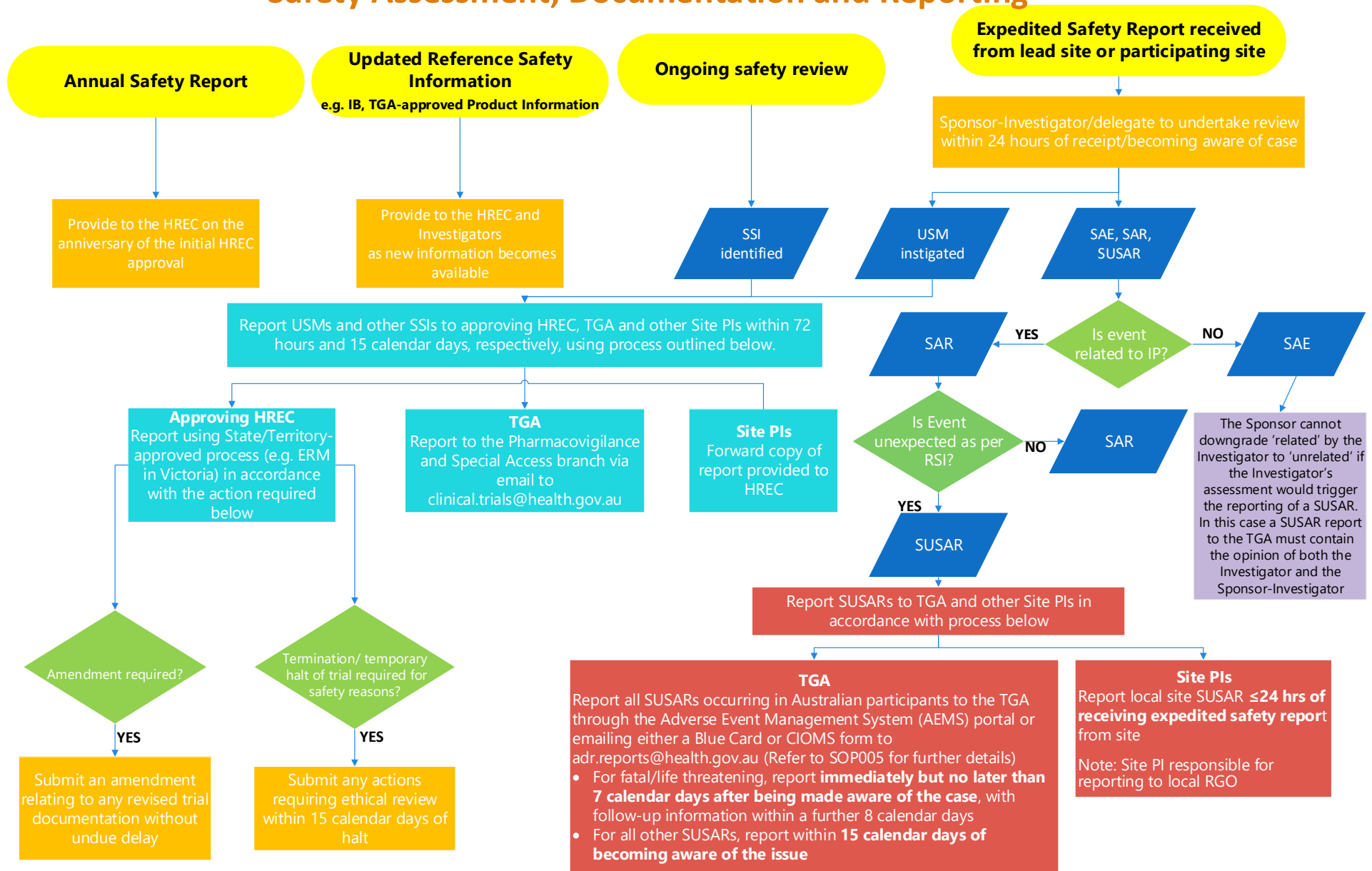
RCH Procedure, “Investigator Responsibilities in Research” RCH0498, dated 08 September 2017, available from https://www.rch.org.au/policy/policies/Investigators_Responsibilities_in_Research/

RCH Pharmacy ADR Reporting requirements available at [https://www.rch.org.au/pharmacy-intranet/medicines-information/Adverse_Drug_Reaction_\(ADR\)_reporting/](https://www.rch.org.au/pharmacy-intranet/medicines-information/Adverse_Drug_Reaction_(ADR)_reporting/)

9 APPENDICES

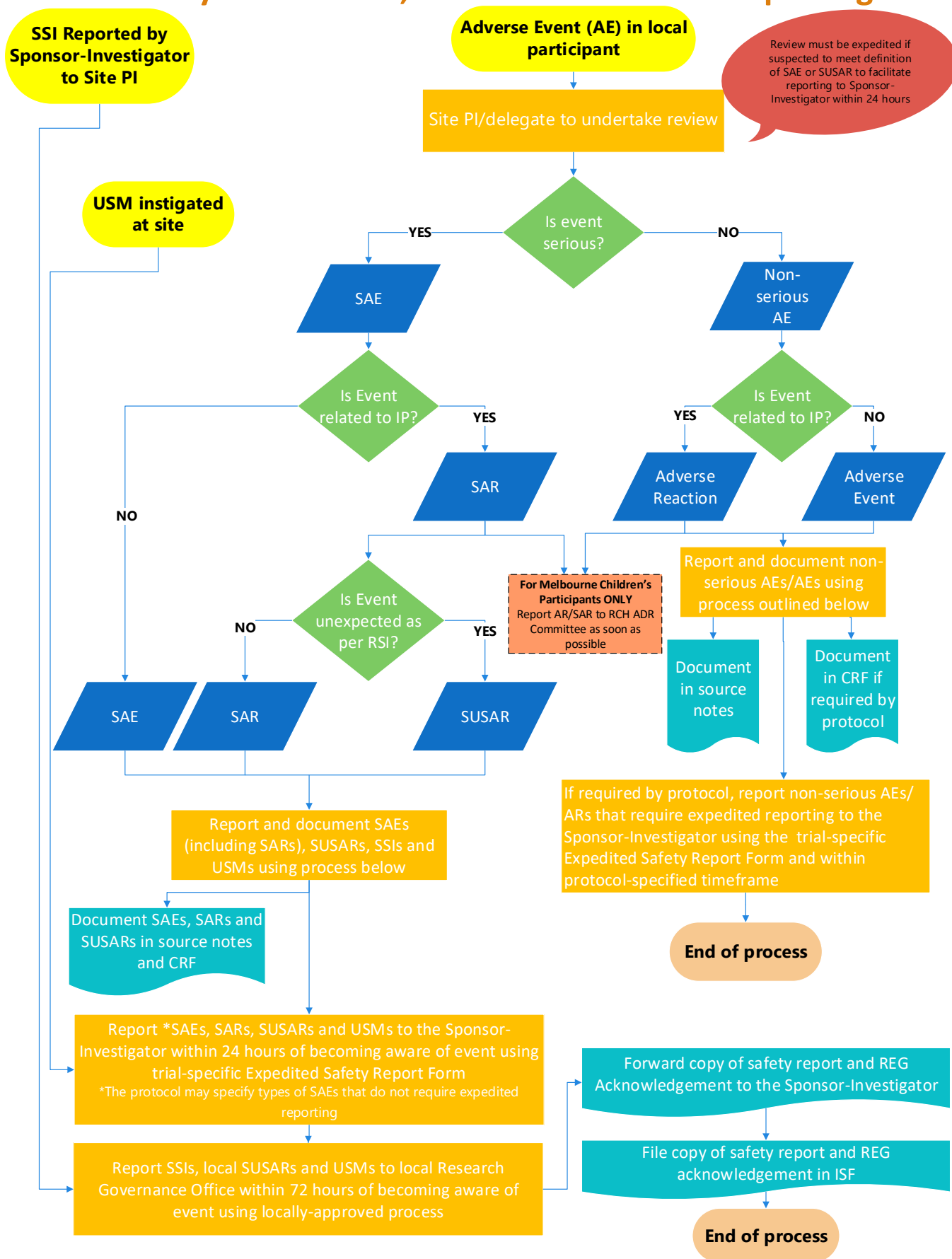
9.1 Process flow – Safety Assessment, Documentation and Reporting for MCRI-sponsored IITs: Responsibilities of the Site PI

Responsibilities of the Sponsor-Investigator in MCRI-sponsored IITs: Safety Assessment, Documentation and Reporting



9.2 Process flow – Safety Assessment, Documentation and Reporting for MCRI-sponsored IITs: Responsibilities of the Sponsor-Investigator

Responsibilities of Site PIs in MCRI-sponsored IITs: Safety Assessment, Documentation and Reporting



DOCUMENT END