GVHealth	**TITLE:**	**Clinical Trial Standard Operating Procedure 12: Safety Data Monitoring and Reporting Requirements for Clinical Trials**	
Document Type:	Procedure	**Approved by:**	CMO & EDMS
Directorate:	CMO & Medical Services	**Section:**	Research
Author/Prepared by:	Dr Ainsley Robinson	**Position:**	Clinical Trials Coordinator

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1.0	12 Nov 2020	16 June 2023	Dr Ainsley Robinson Research and Ethics	Reviewed and updated to v2.0

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1. PURPOSE:

To describe the procedures and requirements related to the safety data collection, verification and reporting requirements for clinical trials involving Investigational Medicinal Products (IMP) and Devices (IMD). This also includes post registration/post marketing surveillance studies.

2. SCOPE:

This Standard Operating Procedure (SOP) applies to all Goulburn Valley Health (GVH) employees, visiting health professionals, contractors, any external researchers, consultants, and volunteers who propose to undertake, administrate, review and/or govern human research involving GVH patients/participants, facilities and/or staff. All study personnel involved in the clinical study must operate within their scope of practice.

In 2016, the National Health and Medical Research Council (NHMRC) released important changes to regulatory and safety guidance documents pertaining to the Sponsor's responsibilities, which change the Sponsor's reporting responsibilities to the Australian regulatory body, the Therapeutic Goods Administration (TGA) and to Human Research Ethics Committees (HRECs). Refer to NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016). Consequently, this SOP refers to both the Sponsor's and Investigator's responsibilities relating to safety monitoring.

Reporting of all serious suspected adverse reactions that occur in post registration/marketing surveillance studies undertaken in Australia follow the same reporting lines and timelines as for serious adverse reactions. See Appendices 1-5.

International Council for Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (and requirements of the Integrated Addendum to this Guideline published by the Therapeutics Goods Administration (TGA)) (ICH GCP E6 (R2)) requires the site to report Adverse Events (AEs) to the Sponsor. In order for sites to ensure appropriate reporting, the PI (or their delegate) should ask participants at each visit (or as required by the Protocol) if they have experienced any Aes and record all Aes reported to them. All Aes should then be assessed for seriousness, for causality and for expectedness by the PI or their qualified delegate.

All Aes should be assessed for 'seriousness' against the definition of a Serious Adverse Event (SAE).

For Investigational Product (IP) trials, all Aes judged by the reporting Investigator as having a **reasonable causal relationship** with the IP would qualify as an adverse reaction, or in the case of a medical device, an adverse device effect. The expression 'reasonable causal relationship' means to convey, that there is evidence or argument to suggest a causal relationship. A similar principle applies to trials involving non-therapeutic goods. Any AE that is judged as having a reasonable causal relationship with the intervention being tested would qualify as a 'related AE'. For medicinal product/biological trials, the following are examples of types of evidence that would suggest a causal relationship between the IP and the AE:

- A single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with IP exposure but is otherwise uncommon in the population exposed (e.g. tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of the IP) that indicates those events occur more frequently in the IP treatment group than in a concurrent or historical control group.

Sponsors and sites also assess an event's **'expectedness'** to determine whether any Suspected Unexpected Serious Adverse Events (SUSARs) or the device/intervention equivalent, has occurred. This assessment should be performed using the Reference Safety Information chosen for the trial. This would be the IB/Product Information for therapeutic good trials or the Protocol for non-therapeutic good trials.

Significant Safety Issues (SSIs) are safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. SSIs are unplanned events (not already managed by the Protocol) and as such, result in an action, such as a Protocol amendment or the temporary or permanent halt in the trial. SSIs may arise from the Sponsor's analysis of aggregate data (e.g. a Data Safety Monitoring Board, finds an increase in frequency or severity of an AE) or may arise from a single case event such as a SUSAR.

Some SSIs may need to be implemented as an **Urgent Safety Measure (USM)**. A USM is defined as a measure required to eliminate an immediate hazard to the participant's health or safety (e.g., an occurrence of toxic epidermal necrolysis or hepatic failure). The PI should ensure the Sponsor is made aware of a USM within 72 hours of its occurrence at the site.

Any pregnancies (of trial participants or their partners) during the course of a therapeutic goods trial should be notified to the Sponsor as specified in the Protocol. Any pregnancy should be followed-up until its outcome as this ensures the detection and reporting of any congenital anomalies or birth defects.

3. PROCEDURE:

Where a Satellite Site(s) is/are involved, staff will report safety issues directly to the Sponsor as per the timelines specified in the Protocol and the safety monitoring plan or similar document in the same way as the Primary Site. Certified Copies of the relevant safety reports/documentation generated at the Satellite Site will be sent to the Primary Site for filing in the Site Master File (SMF). The rules will be pre-determined as per GVH_CT-SOP-07 The Study Master File and as documented in the Supervision Plan.

NOTE: Where a Sponsor delivers Suspected Unexpected Serious Adverse Reactions (SUSARs), analyses of accumulating safety data, annual safety reports and other safety communication through a web portal delivery system or via e-mail, as opposed to paper reports, acknowledgement of receipt by the Investigator/ HREC/Institution/TGA of such information will be required by the Principal Investigator (PI), but only after the Sponsor confirms that the report has no bearing on participant safety or trial conduct. There no longer is a requirement for

Investigators to print, review and file these reports. See NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016).

3.1. Sponsor Responsibilities:

The two documents, the Australian Clinical Trial Handbook (October 2018) and the NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016), give clear direction to Sponsor responsibilities.

A Sponsor:

- Must be identified for all clinical trials.
- Has ultimate responsibility for the ongoing safety evaluation of the IMP/IMD.
- Is responsible for generating and disseminating all safety communications.
- Must ensure that the trial Protocol has clear sections describing:
  a) the assessment and management of risk (if not in an alternative document);
  b) safety reporting definitions, procedures, responsibilities and reporting timelines; and
  c) any SAE that do not require immediate reporting.
- Must ensure the conduct of the trial, including the monitoring of safety and reporting of adverse outcomes, complies with the study Protocol as well as applicable guidelines.
- May delegate functions and duties to individuals or third parties, such as a Contract Research Organisation (CRO) or Data Safety Monitoring Board (DSMB), provided arrangements are in place for oversight of the delegated functions and duties, to ensure the integrity of the functions and duties performed and any data generated.
- Should evaluate and categorise all safety information that is reported by Investigators, as well as safety information received from other sources.
- Keep detailed records of all reported AEs and maintain up-to-date tabulations and/or line listings.
- Review the Investigator's Brochure (IB)/Instruction for Use or Clinical Investigation Plan (CIP) at least annually and update it when new and relevant information becomes available.
- Prepare and submit to relevant parties an annual safety report/Development Safety Update Report (DSUR).

3.1.1. Safety Data Monitoring:

The Sponsor's plans for safety data monitoring should be documented in a Safety Monitoring Plan or similar document and be given to the PI prior to the commencement of the clinical trial. It must be continually reviewed and updated during the trial, as real-time assessments of safety data are performed, and outcomes are made available.

A Sponsor may utilise an independent safety monitoring committee (e.g. DSMB) or independent individuals (e.g. a medical monitor) to:

- Review accruing trial safety data in either an unblinded or blinded manner to assess treatment exposure.
- Access, assess and review emerging efficacy data for the trial.
- Assess the balance of risks and benefits within the trial.
- Document the outcome of these reviews.

3.1.2. Sponsor Reporting Requirement:

The outcome of various safety reviews is reported directly to HRECs, Investigator and the TGA, by the Sponsor and must indicate the impact of each report on patient safety, trial conduct or trial documentation. The reporting of safety reviews by the Sponsor should be as per NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016) pages 7 and 17 or as detailed in the protocol. The safety reporting requirement in the Protocol **cannot** be less than that required by the NHMRC.

3.1.2.1. Sponsor to Provide to Investigator

- Updated IB, at least annually.
- Spontaneous reports of SSIs i.e., an issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
- Outcomes of analyses of accumulating safety data.
- SSIs: those that meet the definition of an USM (i.e., a measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety measure) should be notified within 72 hours, and all other SSIs should be notified within 15 calendar days of the Sponsor instigating or being made aware of the issue.

3.1.2.2. Sponsor to Provide to Therapeutic Goods Administration (TGA)

- SSIs that meet the definition of an USM (i.e., a measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety measure) should be notified within 72 hours, and all other SSIs should be notified within 15 calendar days of the Sponsor instigating or being made aware of the issue. It is strongly recommended that the Sponsor contact the TGA within 24 hours of an USM being taken, and if initial contact is by telephone, it should be followed-up with a written notification provided by facsimile or e-mail within 72 hours.
- All SUSARs occurring in Australian participants.
- 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.
- For all other Australian SUSARs, no later than 15 calendar days after being made aware of the case.

3.1.2.3. Sponsor to provide to HREC

- Updated IB at least annually which supports trial oversight, depicts a clear picture of evolving safety profile of the trial and provides evidence that the Sponsor is conducting its safety monitoring appropriately.

- SSIs: those that meet the definition of an USM (i.e., a measure required to be taken immediately in order to eliminate an immediate hazard to a participant's health or safety measure) should be notified within 72 hours, and all other SSIs should be notified within 15 calendar days of the Sponsor instigating or being made aware of the issue.

3.2. Investigator Responsibilities

The role of the Investigator with regard to safety reporting is to:

- Provide the Sponsor with all relevant information so that an appropriate safety analysis can be performed.
- Capture and assess all local safety events and report AEs that occur at the site as further clarified below.
- Ensure safety monitoring complies with the study protocol, safety monitoring plan if there is one as well as institutional and national guidelines.
- Act on any events as clinical care dictates.
- Maintain responsibility for oversight of the ongoing safety evaluation of the IMP/IMD.
- Ensure that if signing of safety documents has been delegated to another medical officer, that this is documented on the Delegation Log as per GVH_CT-SOP-03 Site Staff Qualifications, Training Records and Capability.

3.2.1. Safety Data Monitoring

- Keep detailed records of safety management.
- In the instance of device trials, maintain a permanent record of participant identification, study protocol number and device serial number or other tracking detail for the lifetime of the device, to enable a rapid response if a device safety issues arise.
- Review the adverse outcome in the context of known information on the medicine/device and make a determination as to whether the event was drug/device-related (i.e. an adverse reaction).
- Ensure that the immediate and follow-up reports identify participant by unique code number assigned to the trial participant and not by the participant's name, personal identification number, and/or address.
- Ensure any new information regarding safety events is updated on the AE page in the Case Report Form (CRF)/electronic (e)CRF and/or with a follow up SAE Form (paper or electronic), within 24 hours of the site becoming aware of the change of information and send to Sponsor.

3.2.2. Reporting Requirement

The reporting of safety reviews by the Investigator should be as per NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016) or as detailed in the protocol. The safety reporting requirement in the Protocol cannot be less than that required by the NHMRC.

3.2.2.1. To Sponsor

Within 24 hours of instigating or becoming aware of the event:

- All SAEs and SUSARs except those that are identified in the Protocol, Safety Monitoring Plan or similar document or IB as not needing immediate reporting.
- Any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner).
- Within 72 hours of instigating or becoming aware of the event:
- SSIs which meet the definition of an USM instigated by the Investigator (i.e. a measure required to be taken immediately in order to eliminate an immediate hazard to a participant's health or safety measure).
- All USMs instigated by the site as specified in the Protocol.
- All safety critical events/laboratory abnormalities identified in the Protocol as "critical to safety evaluations".
- Any additional requested information relating to reported deaths (e.g., autopsy reports and terminal medical reports).
- Additional requested information relating to reported deaths.
- Within 15 days of instigating or becoming aware of the event:
- All other significant issues.

3.2.2.2. To Therapeutic Goods Administration (TGA)

Use the Australian Government Department of Health Report of suspected adverse reaction to medicines or vaccines commonly known as the "Blue Card", CIOMS form or equivalent to report to the TGA. When submitting a SUSAR report to the TGA, submit via the TGA Business Services (TBS) ADR submission portal by email using a "Blue Card" or Sponsor provided CIOMS form to adr.reports@tga.gov.au.

- Advise TGA of any safety issues which emerge during this process. Such data do not need to be submitted on a routine basis to the TGA during the trial but should be available for submission to the TGA on request, and where applicable, submitted as part of an application for registration.
- SSIs: those that meet the definition of an USM (i.e., a measure required to be taken immediately in order to eliminate an immediate hazard to a participant's health or safety measure) should be notified within 72 hours, and all other SSIs should be notified within 15 calendar days of the Sponsor instigating or being made aware of the issue.

3.2.2.3. To Institution/Research Governance Officer

Within 72 hours of instigating or becoming aware of the event:

- SSIs that meet the definition of an USM (i.e., a measure required to be taken immediately in order to eliminate an immediate hazard to a participant's health or safety measure).
- SUSARs arising from the local site.

- any information received from the Sponsor that may be new and have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol, including monitoring of safety.

ABBREVIATIONS AND TERMS:
Please refer to GVH_CT-SOP-Abbreviations and Terms.

KEY ALIGNED DOCUMENTS:
GV Health Procedure:
- GVH_CT-SOP-07 The Study Master File

REFERENCES:
Australian Clinical Trial Handbook (October 2018)

ICH GCP E6 (R2)

NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods (November 2016)

APPENDICES:
Appendix 1: Sponsor Reporting of SUSAR and USADES To TGA (for Trials conducted under the CTN or CTA Schemes)
Appendix 2: Safety Reporting Assessment Flow Chart Investigational Medicinal Product Trials
Appendix 3: Report Flowchart for Investigational Medicinal Product Trial
Appendix 4: Safety Reporting Assessment Flowchart Investigational Medicinal Device Trials
Appendix 5: Report Flowchart for Investigational Medicinal Device Trial

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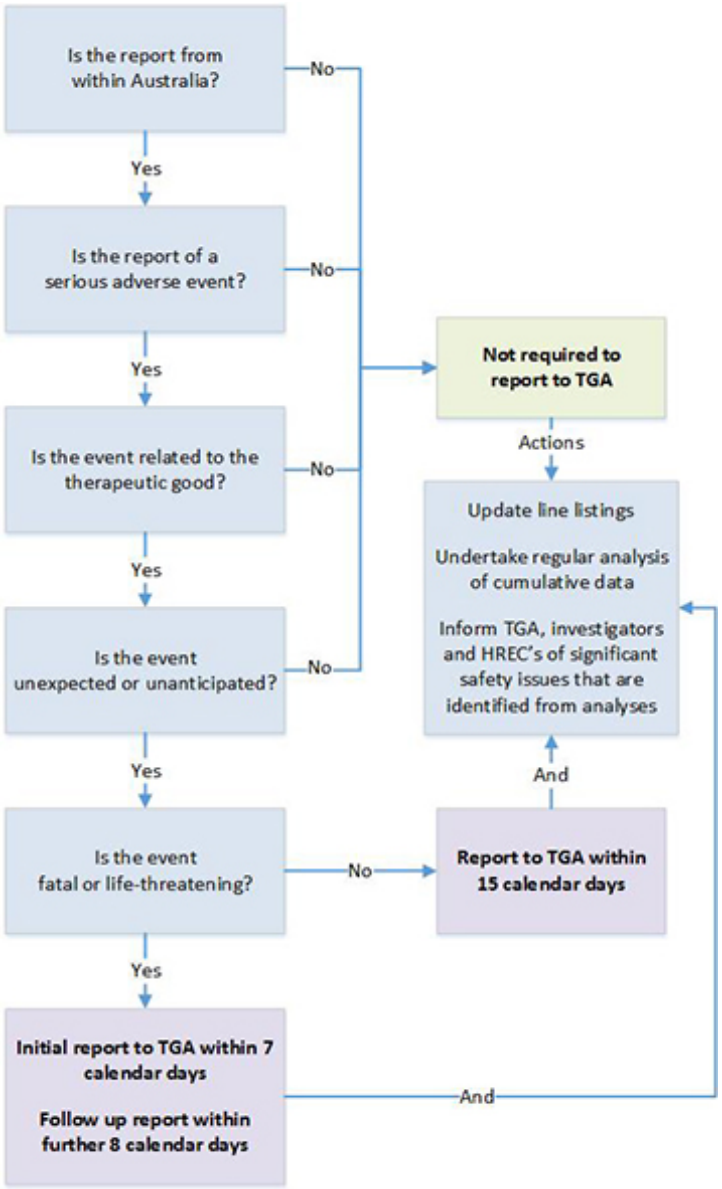
Appendix 1: Sponsor Reporting of SUSAR and USADES To TGA (for Trials conducted under the CTN or CTA Schemes)



Adapted from Australian Clinical Trials Handbook, page 37.

Text representation of flowchart with numbered steps

1. Is the report from within Australia?
   a. No: not required to report to TGA, but following actions required:
      - update line listings;
      - regular analysis of cumulative data;
      - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses.
   b. Yes: go to step 2.

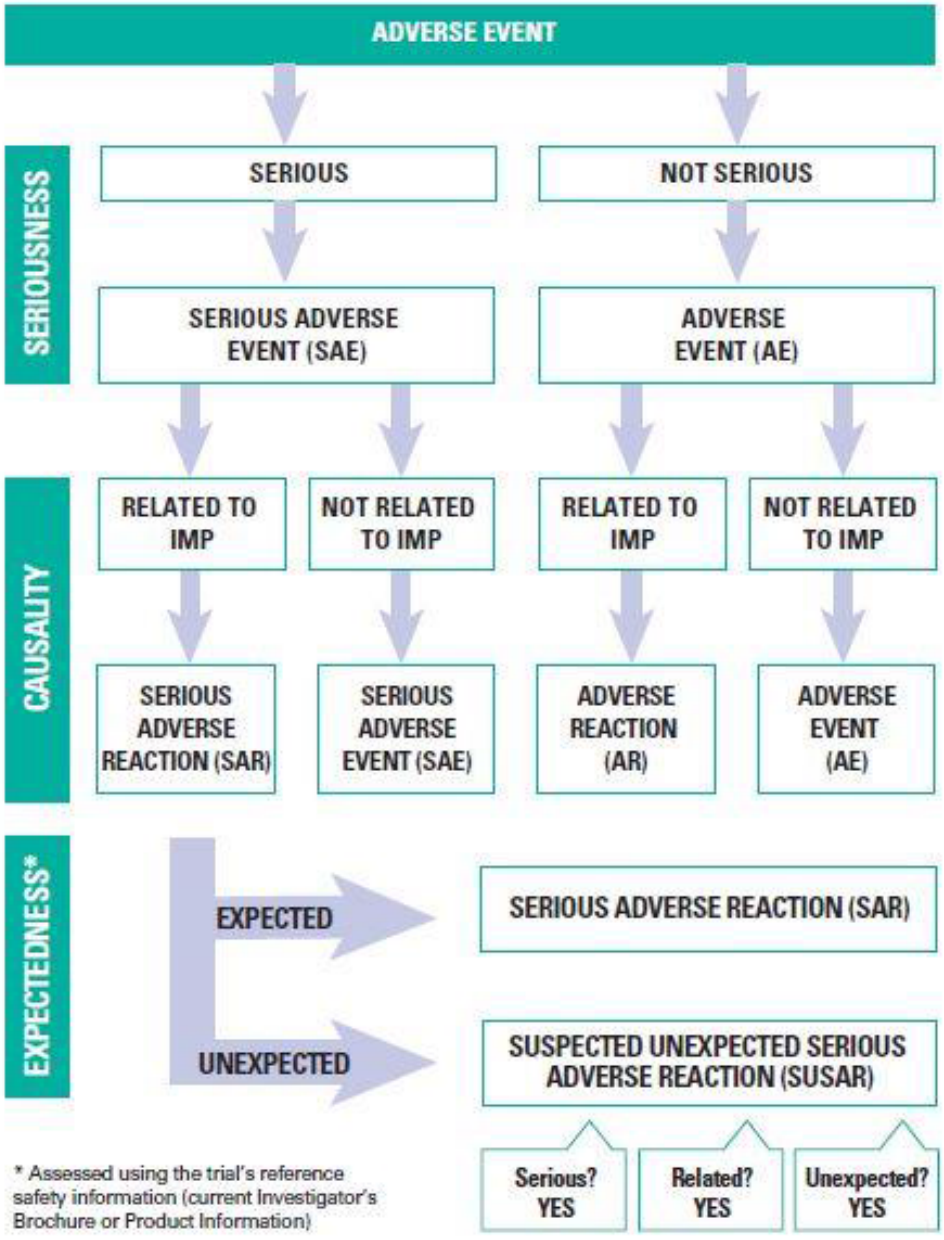
2. Is the report of a serious adverse event?
   a. No: not required to report to TGA, but following actions required:
      - update line listings;
      - regular analysis of cumulative data;
      - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses.
   b. Yes: go to step 3.

3. Is the event related to the therapeutic good?
   a. No: not required to report to TGA, but following actions required:
      - update line listings;
      - regular analysis of cumulative data;
      - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses.
   b. Yes: go to step 4.

4. Is the event unexpected or unanticipated?
   a. No: not required to report to TGA, but following actions required:
   - update line listings;
   - regular analysis of cumulative data;
   - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses.
   b. Yes: go to step 5.

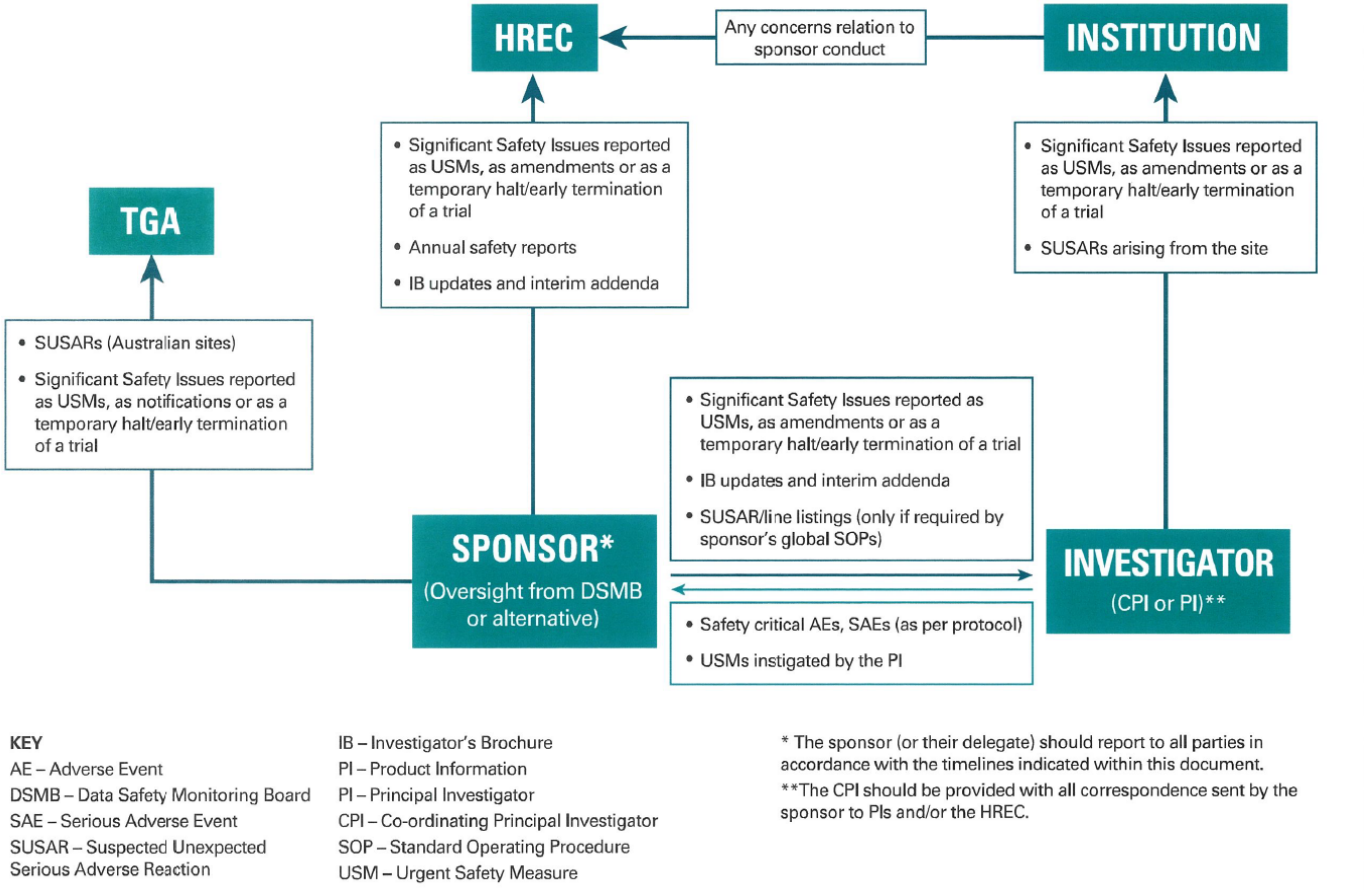
5. Is the event fatal or life threatening?
   a. Yes: report to TGA is required:
      - Initial report to TGA within 7 calendar days: and
        - update line listings;
        - regular analysis of cumulative data;
        - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses.
      - Follow up report within further 8 calendar days: and
        - update line listings
        - regular analysis of cumulative data
        - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses
   b. No: Report to TGA within 15 calendar days; and
      - update line listings;
      - regular analysis of cumulative data;
      - inform TGA, investigators and HREC's of significant safety issues (SSIs) that are identified from analyses.

Appendix 2: Safety Reporting Assessment Flow Chart Investigational Medicinal Product Trials



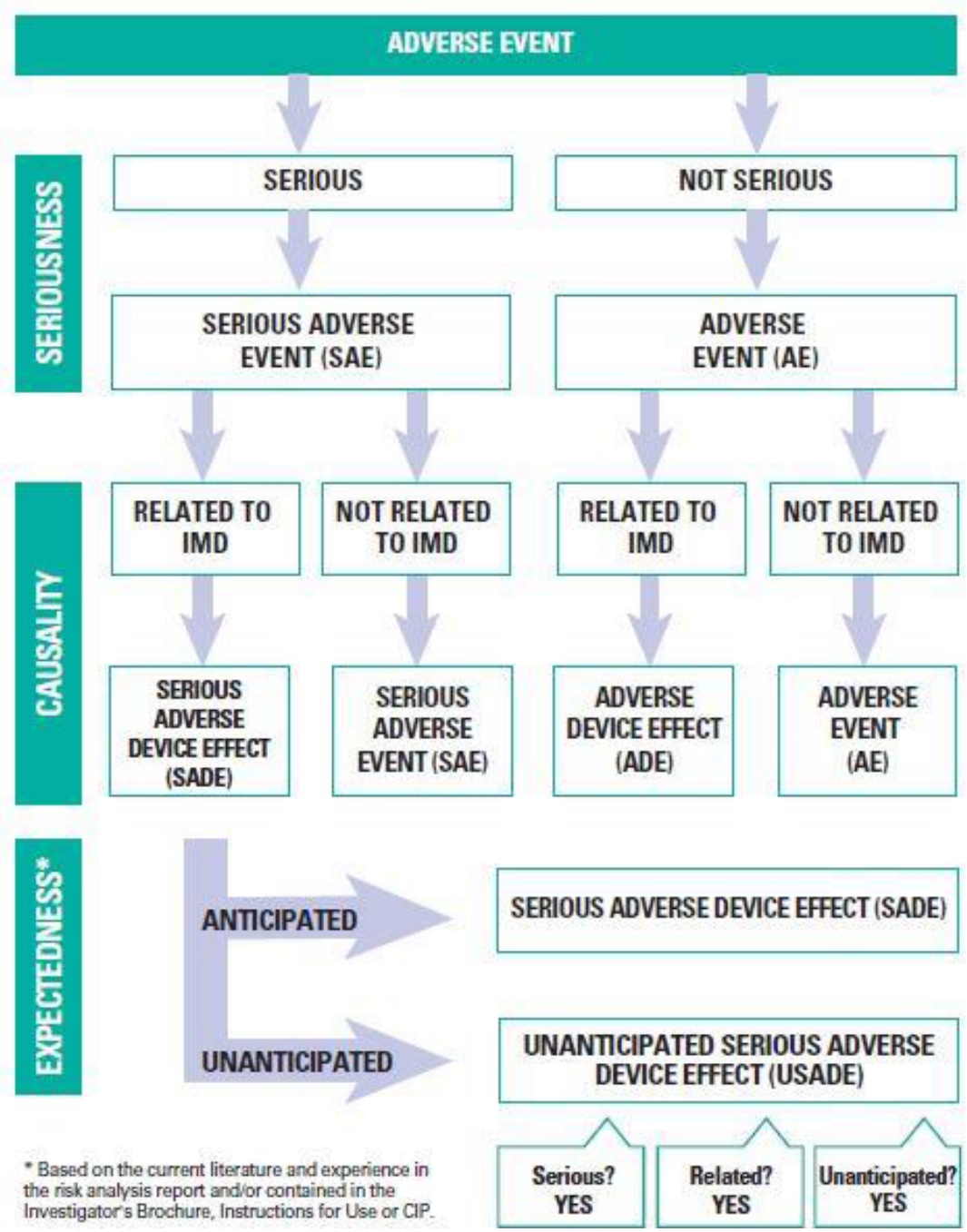
Adapted from NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016, page 6).

Appendix 3: Report Flowchart for Investigational Medicinal Product Trial



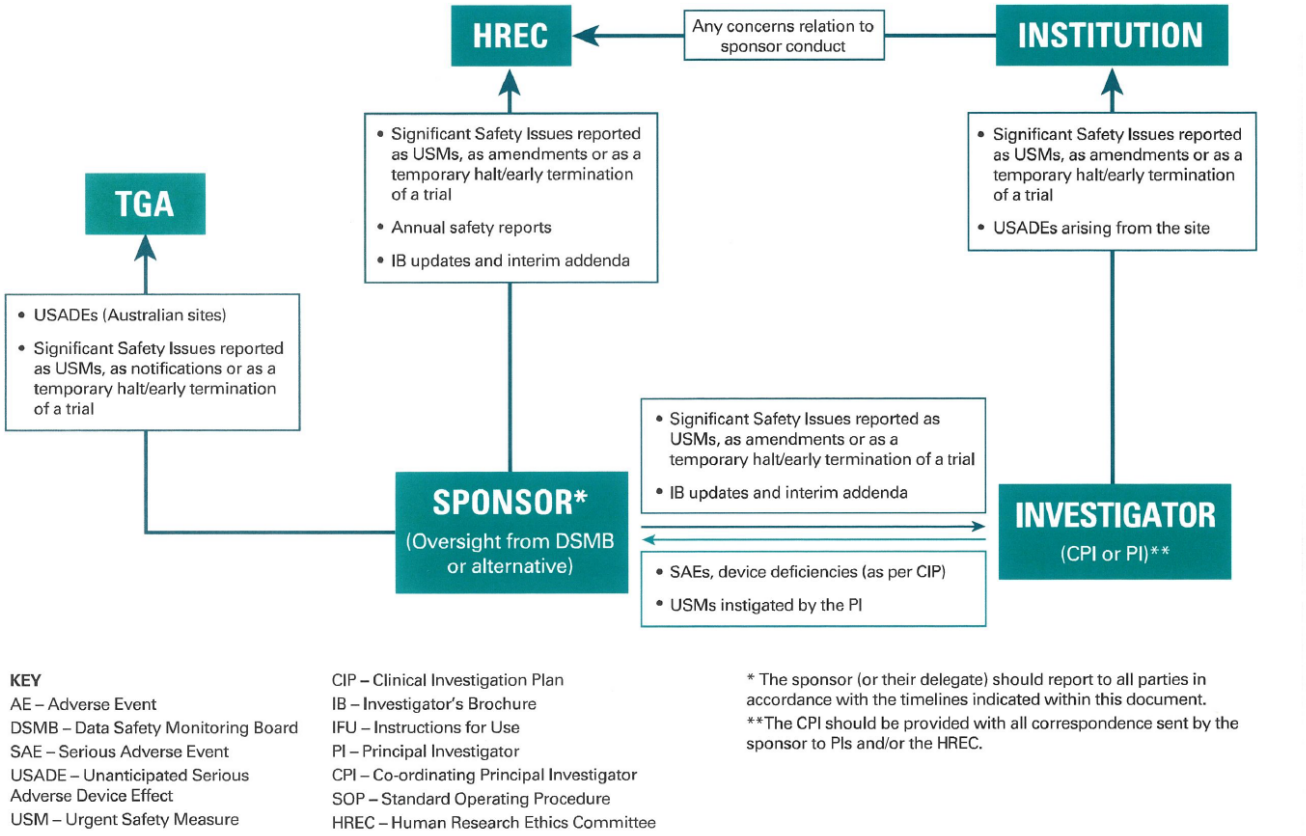
Adapted from NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016, page 13)

Appendix 4: Safety Reporting Assessment Flowchart Investigational Medicinal Device Trials



Adapted from NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016, page 16)

Appendix 5: Report Flowchart for Investigational Medicinal Device Trial



Adapted from NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016, page 22).