NHMRC Australian Health Ethics Committee (AHEC) Position Statement

Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (Medicinal Products and Medical Devices)
&
The Reporting of Serious Breaches of the Protocol/Good Clinical Practice

Draft prepared for public consultation, April 2016

Contents

1. Purpose

In the seven years since the release of the 2009 AHEC Position Statement: '*Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009*', both the United States and the European Union have updated their safety monitoring and reporting arrangements for clinical trials. In response to this, and also in response to the widespread feedback from stakeholders that current arrangements in Australia place an unnecessary burden on investigators and Human Research Ethics Committees (HRECs) that do not genuinely contribute to patient safety, the National Health and Medical Research Council (NHMRC) conducted a consultation to review these arrangements. This Position Statement replaces the 2009 Position Statement and incorporates the recommendations made in the consultation's final report provided to NHMRC in May 2015.

2. Scope

This Position Statement addresses the collection, verification and reporting of adverse events and adverse reactions that occur in clinical trials involving medicinal products and medical devices, whether conducted under the Clinical Trial Exemption (CTX) or Clinical Trial Notification (CTN) schemes or used within the terms of their marketing authorisation. Post marketing trials conducted by Marketing Authorisation Holders (MAHs) of medicinal products will also be subject to the requirements laid down in the Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines.

The safety monitoring and reporting requirements for **Investigational Medicinal Products (IMPs)** and **Investigational Medical Devices (IMDs)** are broadly similar; however, in order to reflect the differing terminology, the requirements for IMPs and IMDs have been detailed separately in Part 1 and Part 2 of this document respectively.

This Position Statement also clarifies requirements for the categorisation and reporting of non-compliances (protocol deviations and violations) as non-compliance may impact on the safety of participants.

3. Risk-Adapted Safety Monitoring

The *National Statement on Ethical Conduct in Human Research* (2007) (National Statement) permits monitoring arrangements to be commensurate to the risk, size and complexity of the trial. The nature and extent of participant safety monitoring should be based on the assessment of the risks of the trial intervention(s)[1] relative to standard care and the extent of knowledge about the IMPs/IMDs being tested. A safety monitoring plan should be developed for all trials based on an assessment of the specific risk factors identified.

4. The Trial Sponsor

The sponsor of a clinical trial is defined as '*an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study*'. Sponsor functions may be delegated to third parties, such as clinical research organisations/centres, Data Safety Monitoring Boards or Coordinating Principal Investigators, provided that arrangements are in place for oversight of any delegated activities.

A sponsor should be identified for all clinical trials. Although the definition of trial sponsor allows an individual to be named as sponsor, for non-commercial trials it is usually more appropriate for an institution, rather than an investigator, to perform this role. It is also common practice for a group of non-commercial partners to

[1] The term trial intervention means either the IMP/IMD or additional study procedures required by the protocol.

make collaborative arrangements to initiate, manage and fund trials and, in such circumstances, it is important to ensure that all sponsor functions, including safety monitoring and reporting, are clearly allocated or delegated.

5. Summary of Main Changes

Change from 2009 Position Statement	Rationale
Clarifying that the sponsor has primary responsibility for the ongoing safety evaluation of the trial usually through a Data Safety Monitoring Board, Independent Medical Monitor or alternative committee.	The sponsor[2] has access to data that gives the clearest picture of the emerging balance of risks and benefits for each trial.
Removing the requirement to submit individual reports of adverse events (AEs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), unanticipated serious adverse device effects (USADEs) and six monthly line listings to HRECs.	HRECs do not have the expertise or resources to perform an analysis of individual case reports or line listings. Single case events and partial datasets of events do not provide HRECs with useful or usable information.
Removing the requirement to submit individual reports of AEs, SAEs, SUSARs/USADEs and six monthly line listings to investigators.	Updated/addended Investigator's Brochures provide investigators with the most relevant information on the use of the medicinal product or medical device.
Removing the requirement to submit individual reports of AEs, SAEs, *external* SUSARs/USADEs and six monthly line listings to institutions[3].	Institutions do not have the expertise or resources to perform an analysis of individual case reports or line listings.
Including the requirement for sponsors to send HRECs an annual safety report.	Provides HRECs with a report that supports trial oversight, including: • A clear summary of the evolving safety profile of the trial • Reassurance that the sponsor is conducting its ongoing safety monitoring appropriately and as outlined in the protocol/HREC application
Clarifying requirements and terminology for the reporting of significant safety issues.	Ensures that significant safety issues are communicated to all parties in a consistent manner and timeframe.
Placing the sponsor at the centre of the communication cascade.	Removes the administrative burden on the Coordinating Principal Investigator (CPI) by allowing sponsors to report safety information directly to HRECs and Principal Investigators (PIs).
Clarifying that the sponsor has primary responsibility for collating all trial-related non-compliance and rationalising the reporting of non-compliance to HRECs and institutions	Aligns with international guidance and legislation and reduces the administrative burden on investigators, HRECs and institutions by reporting only instances of non-compliance that impact on trial approval/authorisation.

[2] The term sponsor in this document means sponsor or their delegate.

[3] Institutions should still receive SUSARs/USADEs originating from their site for information purposes.

6. The Categorisation and Reporting of Non-Compliance

Non-compliance with the protocol, clinical investigation plan or good clinical practice at the trial site should lead to prompt action by the sponsor to secure compliance and all instances of non-compliance should be reported to, and collated by the sponsor. HRECs should be made aware of any non-compliance that impacts on the continued safety and wellbeing of participants or the credibility of the trial data. Institutions should be made aware of any non-compliance that impacts on medico-legal risk, the responsible conduct of research or adherence to contractual obligations.

There is no internationally accepted definition of the terms *protocol deviation* or *protocol violation* but both are used to describe non-compliance. With respect to reporting to approval bodies, international guidelines[4,5] and international regulation[6] refer to the reporting of *Serious Breaches of the Protocol or Good Clinical Practice (GCP):*

> **Serious Breach**
>
> *A breach of the protocol or Good Clinical Practice that is likely to affect to a significant degree:*
>
> *a) The safety or physical or mental integrity of the trial participant*
> *b) The reliability and robustness of the data generated in the clinical trial*

Serious breaches are reported by the trial site to the sponsor or detected by the sponsor, or other bodies, during monitoring or audit.

Reporting of Serious Breaches to the HREC that approved the study[7]

The sponsor should report serious breaches to the HREC **within 7 days** of being made aware of the breach. The HREC should assess the impact of the breach on the continued ethical acceptability of the study. The HREC should be made aware of any corrective and preventative actions that result from the serious breach and may take any further action they deem necessary. Trial sites (or any other third party) may also communicate serious breaches directly to the HREC if they become aware of any serious breach that may have been perpetrated by the sponsor.

Reporting of Serious Breaches to the institution where the breach occurred

The site investigator should report serious breaches to their own institution which should assess the impact of the breach including its potential to generate a medico-legal claim or amount to research misconduct. The institution may also work with the investigator to devise a formal plan of corrective action, such as further training of site staff. Institutions should develop clear guidance for investigators detailing the reporting and management of serious breaches.

Note: HRECs and institutions should only receive reports of non-compliance that meet the definition of a serious breach.

[4] Integrated Draft Addendum to ICH GCP: July 15 (5.20.1)
[5] ISO 14155 – Clinical investigation of medical devices for human subjects (9.4 e)
[6] EU Regulation No 536/2014 (Article 52)
[7] For multi-centre trials conducted under the single ethical review model, only the HREC that reviewed the trial would be involved in the review of serious breaches.

7. Safety Monitoring and Reporting

PART 1: Investigational Medicinal Product (IMP) Trials

a) Definitions (IMPs)

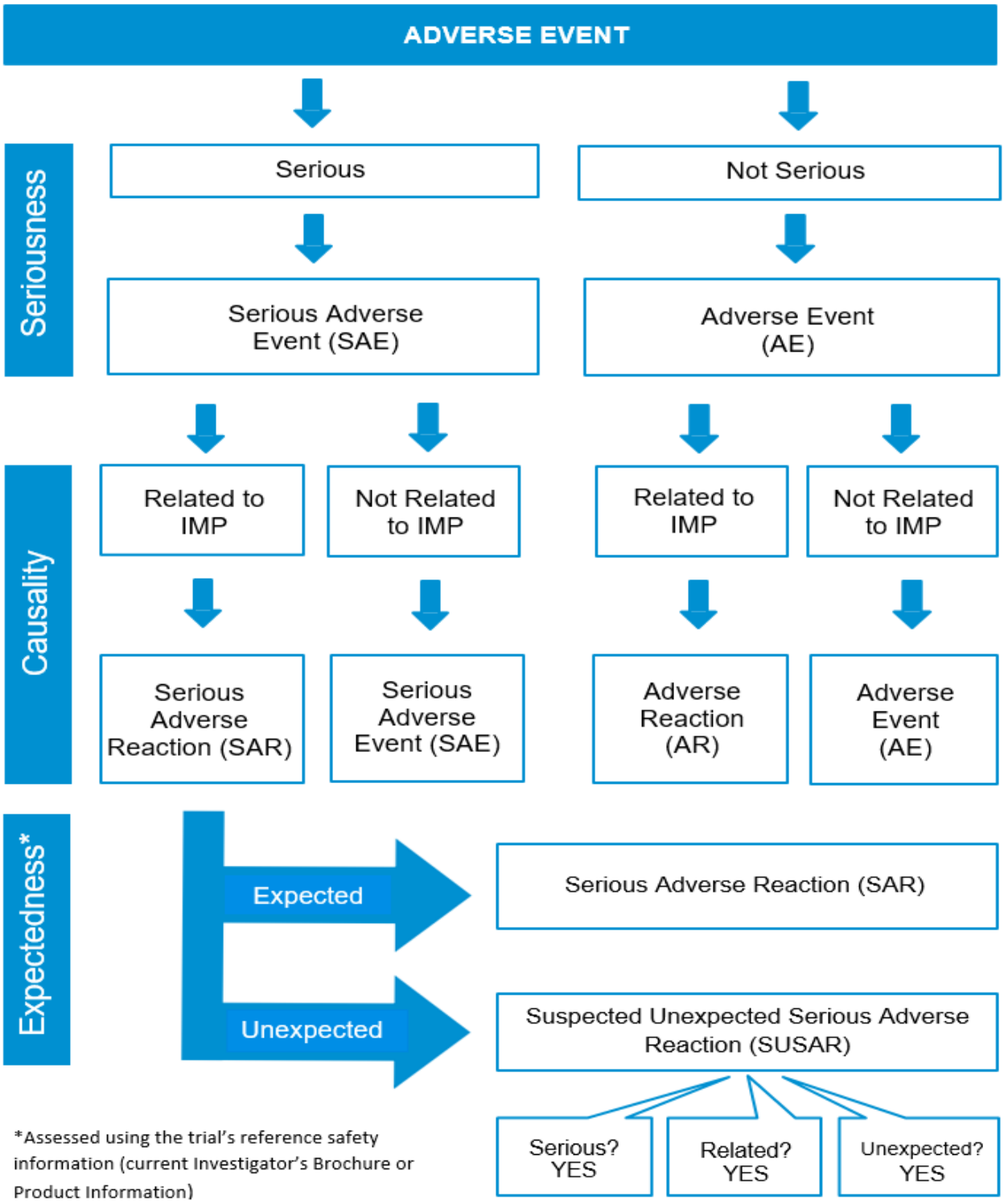
The terminology associated with safety reporting is subject to global variation and companies conducting international trials may be required to use definitions outlined in their company policies. However, in order to promote consistency in Australia and a common understanding of safety reporting requirements, the following definitions for the categorisation of safety events for IMPs should be adopted wherever possible.

Term	Description
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. **Note:** This definition includes biologicals used as investigational medicinal products.
Biological[8]	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). **Examples include:** human tissue therapy products (e.g. skin, tissues, bone for grafting) · processed human tissues (e.g. demineralised bone, collagen) · human cellular therapy products (e.g. cartilage cells, cultured skin cells) · immunotherapy products containing human cells · genetically modified human cellular products.
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product[9] related to any dose administered. **Comment**: All adverse events judged by either the reporting investigator or the sponsor as having a **reasonable causal relationship** to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship. **Note[10]:** The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (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 drug therapy) that indicates

[8] Sourced from Australian Regulatory Guidelines for Biologicals Part 1 - Introduction to the Australian Regulatory Guidelines for Biologicals.
[9] The definition of investigational medicinal product includes both test product(s) and any comparator(s).
[10] Extract from FDA Safety Reporting Guidance clarifying the types of evidence that would suggest a causal relationship between the investigational medicinal product and the adverse event.

	those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR) Important Medical Event	Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. **Note:** Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. **Note:** Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI). **Note:** The RSI should be contained in the Investigator's Brochure for an unapproved medicinal product or Product Information (or another country's equivalent of the Product Information) for an approved medicinal product.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Investigator's Brochure (IB)	The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product that are relevant to the study of the product in humans.
Product Information (PI)	A summary of the scientific information relevant to the safe and effective use of a prescription medicine. **Note:** In a trial in which the IMP is an approved product, the Product Information may replace the Investigator's Brochure. One Product Information (or another country's equivalent) should be chosen for each trial IMP and adopted across all sites (national or international).
Reference Safety Information (RSI)	The information contained in either an Investigator's Brochure or a Product Information (or another country's equivalent) that contains the information used to determine what adverse reactions are to be considered **expected adverse reactions** and on the frequency and nature of those adverse reactions.
Safety Critical Adverse Events	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluation that should be reported to the sponsor according to the reporting requirements specified in the protocol. **Note**: May also be known as Adverse Events of Special Interest.
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. **Note**: This type of measure can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

b) Safety Reporting Assessment Flowchart: IMP Trials



Adapted from the NIHR Clinical Trials Toolkit

c) An Overview of Safety Monitoring and Reporting Responsibilities

i. Responsibilities of the Sponsor or Delegate

Sponsors should establish safety monitoring processes that are based on the risk, size and complexity of the proposed research. In trials with small numbers of participants, e.g. phase I trials, risks may more readily become apparent through close monitoring of adverse events whereas, in larger trials, risks are often better assessed through statistical comparisons of treatments. As such, sponsors should determine the most appropriate arrangements for ongoing monitoring and be prepared to justify these arrangements to the reviewing HREC.

Sponsors should evaluate all safety information that is reported by investigators as well as safety information from other sources. It is recognised that a non-commercial sponsor does not have access to all the safety data maintained by a commercial sponsor; however, non-commercial sponsors are responsible for evaluating all safety information available to them. To enhance the capacity of non-commercial sponsors to fulfil their responsibilities, entities that provide therapeutic goods to or receive therapeutic goods from other entities should share safety information with each other.

Sponsors should:

- ensure that the trial protocol has clear sections describing
    - the assessment and management of risk (if not outlined in a separate document)
    - safety reporting definitions, procedures, responsibilities and reporting timelines
- keep detailed records of all reported **adverse events** and maintain up-to-date tabulations and/or line listings[11]
- assess and categorise the safety reports received from investigators, and report all **suspected unexpected serious adverse reactions** occurring in Australian participants to the Therapeutics Goods Administration12
    - for fatal or life threatening Australian SUSARs, no later than **7 days** after being made aware of the case, with any follow-up information within a further 8 days
    - for all other Australian SUSARs, no later than **15 days** after being made aware of the case

  Note: Sponsors may be required to follow global company policies that mandate the reporting of individual case SUSARs and six monthly line listings to investigators; however, this practice is not required by this Position Statement. Sponsors can discharge this responsibility by placing these reports on a portal or by sending them via e-mail so that investigators have access to them. For routine reports that have no impact on participant safety or trial conduct, there should be no requirement for investigators to print, file or confirm review[13] of these reports.

- provide HRECs with an **annual safety report**[14] written in lay language and including a clear summary of the evolving safety profile of the trial, specifically:
    - A brief description and analysis of new and relevant findings
    - For IMPs not on the Australian Register of Therapeutic Goods, a brief analysis of the safety profile of the IMP and its implications for participants, taking into account all safety data as well as the results of any relevant non-clinical studies

[11] The sponsor may be required to provide tabulations/line listings to the TGA on request.

[12] Where the sponsor's causality assessment conflicts with the assessment made by the site investigator, the site investigator's assessment cannot be downgraded by the sponsor (i.e. altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a SUSAR, the opinion of both the investigator and the sponsor should be provided with any SUSAR report sent to the TGA.

[13] Confirmation of review of any updates/addenda to the investigator's brochure would be required.

[14] HRECs have the discretion to request more frequent reporting for specific trials, such as early phase trials.

- A brief discussion of the implications of the safety data to the trial's risk-benefit ratio
- A description of any measures taken or proposed to minimise risks
- Confirmation that the sponsor is adequately monitoring the trial's risk-benefit ratio in accordance with the safety monitoring plans described in the protocol, trial risk assessment or HREC application.

Note 1: The above information may be submitted as the Executive Summary of a Development Update Safety Report (a full DSUR is not required). The timing of the annual safety report may be aligned with the reporting cycles of global companies or aligned with the annual progress report sent to the HREC.

Note 2: Where combination therapies are being investigated, options for annual safety reporting are described in section 2.5 of the ICH Guideline E2F on the Developmental Safety Update Report.

- report to the HREC within 7 days of being made aware of the breach, all **Serious Breaches of the Protocol or GCP**, that are likely to affect to a significant degree:
  - the safety or physical or mental integrity of the trial participant
  - the reliability and robustness of the data generated in the clinical trial
- ensure that the Investigator's Brochure (IB) is reviewed at least annually and provide:
  - to the HREC, any annual update of the IB
  - to investigators, any annual update of the IB and any spontaneous updates or addenda to the IB
- ensure that all sponsor responsibilities for safety monitoring and reporting (e.g. reporting SUSARs and significant safety issues to the TGA) are appropriately allocated or delegated.
- report to the TGA, HREC and investigators, all **significant safety issues** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Examples include:
  - 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.

Note: Significant safety issues are not usually reported as SUSARs, but require other action such as the reporting of an urgent safety measure, an amendment, a temporary halt or an early termination of a trial. In addition, significant safety issues often result in safety-related changes to trial documentation or other aspects of the overall conduct of the trial. Such amendments should be submitted to the HREC without undue delay.

Where a significant safety issue is implemented as an urgent safety measure, sponsors and trial investigators must act immediately to protect participants from any immediate risk to their health and safety. It is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken, in order to discuss the case with a safety scientist. This initial contact should be followed-up with a written notification provided by facsimile or e-mail. Table 1 outlines the timelines for written notifications and also illustrates the types of action that result from significant safety issues.

Table 1: Sponsor Reporting of Significant Safety Issues			
Action	**What is communicated**	**Recipients**	**Timelines and further review**
Urgent safety measure (USMs)[15]	• Reasons for the urgent safety measure • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the measure being taken[16]. The HREC is not required to approve USMs but may consider whether any proposed actions are appropriate, such as the submission of an amendment relating to revised trial documentation.
Amendment	• Details of the significant safety issue • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the sponsor becoming aware of the issue. Sponsors should submit to the HREC an amendment relating to any revised trial documentation, as soon as the relevant documentation has been internally approved.
Temporary halt of a trial for safety reasons[17]	• Reasons for the halt • The scope of the halt (e.g. suspension of recruitment or cessation/interruption of trial treatment) • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the sponsor's decision to terminate the trial. Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), an amendment should be submitted to the HREC within **15 days** of the temporary halt.
Premature termination of a trial for safety reasons	• Reasons for the premature termination • Measures taken • Further actions planned	Notify the TGA, Investigators and the HREC	Without undue delay and no later than **72 hours** of the sponsor's decision to terminate the trial. Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), an amendment should be submitted to the HREC within **15 days** of the premature termination.

ii. Responsibilities of the Principal Investigator(s) or Delegate

The PI or Delegate should:

- capture and assess all AEs that occur at the site as required and in accordance with the protocol
- report to the sponsor within 24 hours all SAEs, except those that are identified in the protocol as not needing immediate reporting

[15] By definition, urgent safety measures may be instigated at sites before the TGA and HREC are notified. A temporary halt/early termination may also meet the definition of an urgent safety measure.

[16] Urgent safety measures instigated by investigators should be reported immediately to the sponsor to enable compliance with the 72 hour reporting timeline.

[17] Both the TGA and the HREC should be informed if the trial restarts. An amendment should be submitted to the HREC providing evidence that it is safe to restart the trial.

- report to the sponsor adverse events identified in the protocol as critical to safety evaluations in accordance with the protocol
- supply the sponsor with any supplementary information as requested
- report to the sponsor within 24 hours any urgent safety measure instigated at the site
- report to the sponsor pregnancies that occur while a participant is on a clinical trial in accordance with the protocol
- follow-up any pregnancy until outcome[18] (e.g. birth or spontaneous abortion) and report any incidents of congenital anomaly/birth defect as an SAE
- report to their institution without undue delay and no later than 72 hours of the PI instigating or becoming aware of the event:
  - all significant safety issues
  - any confirmed[19] SUSAR that has occurred at the site
  - any serious breach that has occurred at the site.

iii. Responsibilities of the HREC

The approving HREC should:

- assess the safety of proposed trials, including whether the evaluation of the anticipated benefits and risks is satisfactory and ensure that the sponsor has proportionate systems in place to mitigate and manage any identified risks
- satisfy itself that the sponsor's ongoing safety monitoring arrangements are adequate, including the justification for appointing/not appointing a Data Safety Monitoring Board and any 'stopping rules' or criteria for withdrawing individual participants from the trial
- satisfy itself that the sponsor understands their obligation to report to the HREC anything that may adversely affect the safety of participants or the conduct of the trial
- assess whether changes to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethical approval
- keep under review the adequacy and completeness of the informed consent process and documentation in the light of new information about risks and benefits
- assess any reports of serious breaches, including any corrective and preventative actions taken by the sponsor and take any action deemed necessary.

  Note: While HRECs must keep approvals under review in light of safety information it receives, the responsibility for proactively monitoring the ongoing risk-benefit ratio of the trial remains with the sponsor at all times.

iv. Responsibilities of the Institution

The Institution should:

- assess whether any reports received (e.g. safety reports and serious breaches) impact on medico-legal risk[20], the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation

[18] If evidence exists to suggest foetal exposure to a particular IMP may cause a longer term safety issue, then the follow up period should be defined appropriately and these timeframes and any follow-up requirements should be described in the protocol.

[19] 'Confirmed' means that the sponsor has communicated to the site investigator that a SUSAR has been/will be reported to the TGA.

[20] Research-related events that meet the definition of a clinical incident, should be processed in keeping with any organisation-wide reporting of incidents relating to patient safety.

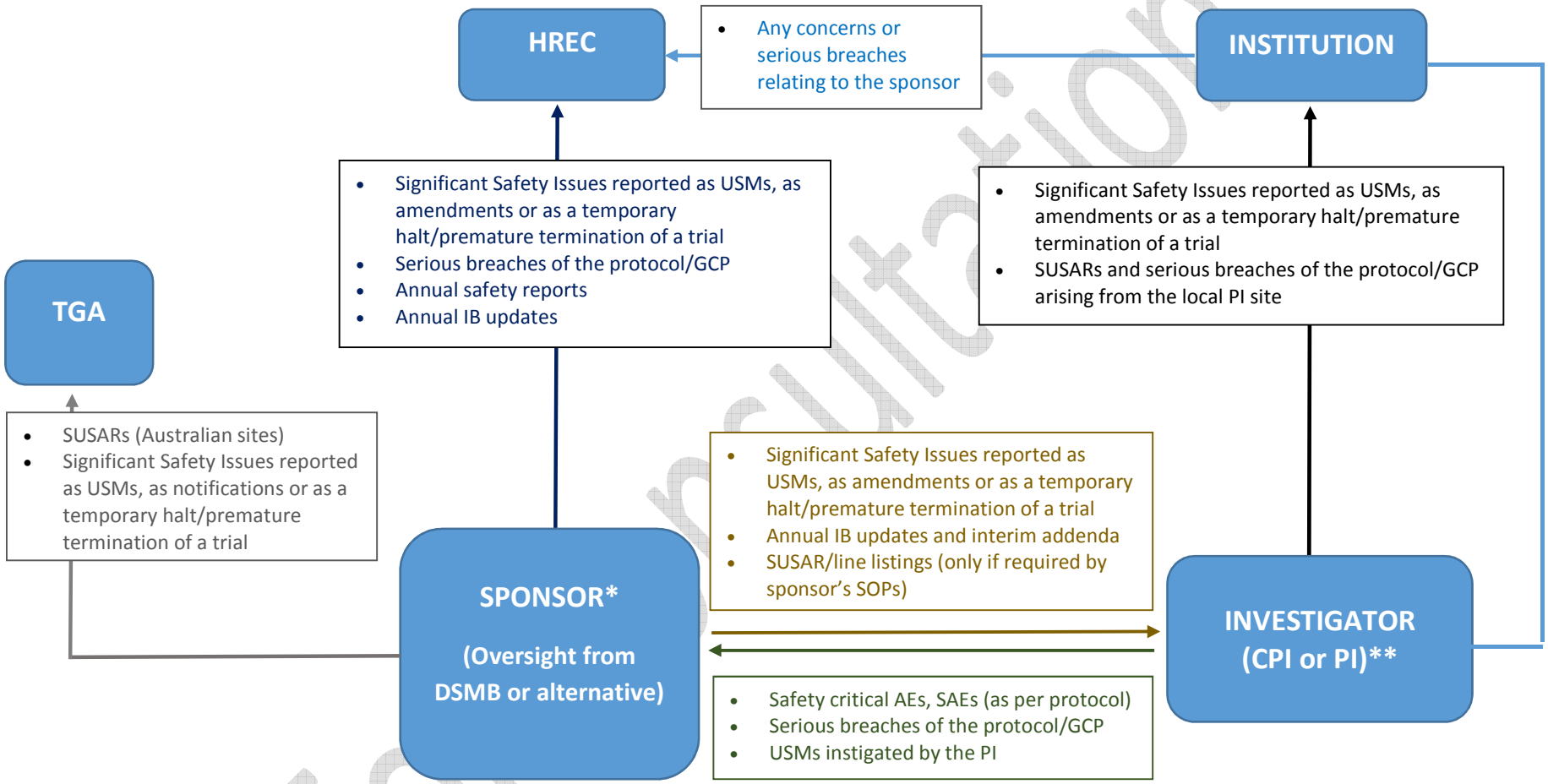
- develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator/initiated or collaborative group trials.

  Note: Where the institution is also named as the trial sponsor, the institution will assume the sponsor responsibilities set out in this document.

d) References

- Note for Guidance on Good Clinical Practice (ICH GCP) – Annotated with TGA Comments
- Integrated Addendum to ICH GCP Current Step 2 version dated 11 June 2015
- Regulation No 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC
- The National Statement on Ethical Conduct in Human Research (2007), as amended
- Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies (FDA)
- Guidance for Industry and FDA staff: Dear Healthcare Letters – Improving Communication of Important Safety Information
- EMA Guidelines on Strategies to Identify and Mitigate Risks for First in Human Clinical Trials With Investigational Medicinal Products
- Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (CT-3 2011)
- Development Safety Update Report ICH E2F
- EU Detailed Guidelines on Good Clinical Practice Specific to Advanced Therapy Medicinal Products
- Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines dated June 14

APPENDIX 1: Reporting Flowchart for Investigational Medicinal Product Trials



KEY:
AE - Adverse Event
SAE - Serious Adverse Event
SUSAR - Suspected Unexpected Serious Adverse Reaction
USM - Urgent Safety Measure
IB - Investigator's Brochure
PI - Product Information
PI - Principal Investigator
CPI - Coordinating Principal Investigator
SOP - Standard Operating Procedure
HREC - Human Research Ethics Committee

*The sponsor (or their delegate) should report to all parties in accordance with the timelines indicated within this document.

** The CPI is copied in to all correspondence sent by the sponsor to PIs and/or the HREC. The sponsor will only send PIs correspondence relevant to their role.

PART 2: Investigational Medical Devices (IMD) Trials

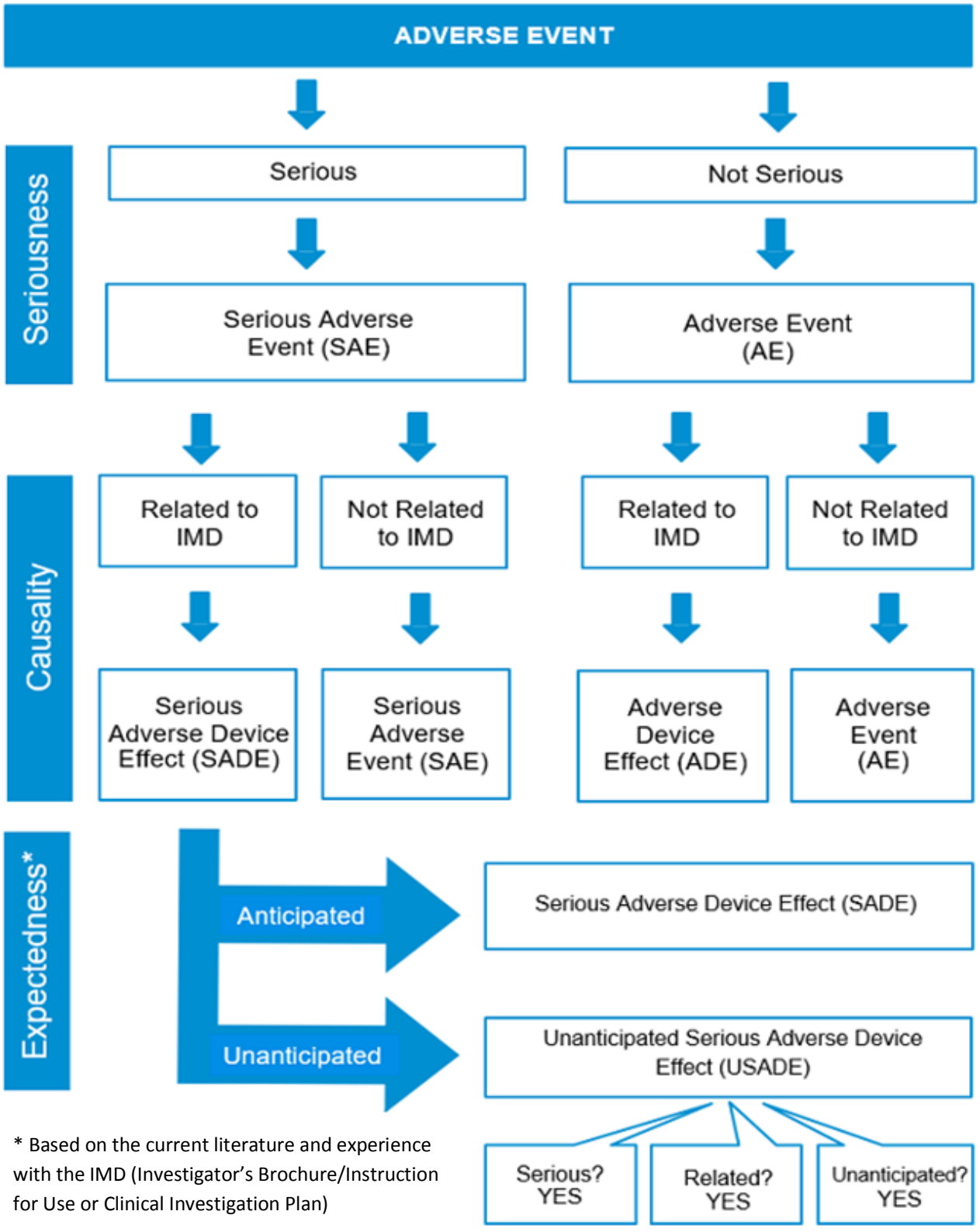
a) Definitions (IMDs)

The terminology associated with clinical trial safety reporting is subject to global variation and companies conducting international trials may be required to use definitions outlined in their company policies. However, it is recommended that the following definitions are adopted to promote consistency in Australia and a common understanding of safety reporting requirements. Where available, the definitions for IMDs have been sourced from ISO 14155 (2011): Clinical Investigation of medical devices for human subjects – Good Clinical Practice.

Term	Description
Investigational Medical Device (IMD)	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 of or 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.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device. **Note:** This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. **Note:** This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **Note:** Although not specific to clinical trials, Section 5.1.1 B of the EU MEDDEV 2.12-1 rev 8 provides some guidance to assist with the assessment of whether a causal relationship with the investigational medical device exists.
Serious Adverse Event (SAE)	Adverse event that: a. led to death b. 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 hospitalization, or - medical or surgical intervention to prevent life-threatening illness or injury or

	permanent impairment to a body structure or a body function c. led to foetal distress, foetal death or a congenital abnormality or birth defect **Note:** Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report, the Investigator's Brochure or for marketed devices, the Instructions for Use (IFU) or contained in the clinical investigation plan based on the current literature and experience with the investigational device.
Device Deficiencies	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.
Investigator's Brochure (IB)	Compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation.
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. **Note**: This type of measure can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

b) Safety Reporting Assessment Flowchart: IMD Trials



* Based on the current literature and experience with the IMD (Investigator's Brochure/Instruction for Use or Clinical Investigation Plan)

Adapted from the NIHR Clinical Trials Toolkit

c) An Overview of Safety Monitoring and Reporting Responsibilities

i. Responsibilities of the Sponsor or Delegate

Sponsors should establish safety monitoring processes that are commensurate with the risk, size and complexity of the proposed research. In trials with small numbers of participants, e.g. pilot or first in human trials, risks may more readily become apparent through close monitoring of adverse events whereas in larger trials, risks are often better assessed through statistical comparisons of treatments. As such, sponsors should determine the most appropriate arrangements for ongoing monitoring and be prepared to justify those arrangements to the reviewing HREC.

Sponsors should evaluate all safety information that is reported by investigators as well as safety information from other sources. It is recognised that a non-commercial sponsor may not have access to complete safety data maintained by a commercial sponsor; however, non-commercial sponsors are responsible for evaluating all safety information available to them. To enhance the capacity of non-commercial sponsors to fulfil their responsibilities, entities that provide therapeutic goods to or receive therapeutic goods from other entities should share safety information with each other.

Sponsors should:

- ensure that the clinical investigation plan (CIP) has clear sections describing:
    - the assessment and management of risk (if not outlined in a separate document)
    - safety reporting definitions, procedures, responsibilities and reporting timelines.
- review all **AEs** and **device deficiencies** and determine and document in writing whether they could have led to a **SADE**
- keep detailed records of all **AEs** and **device deficiencies** that investigators have reported and maintain up to date tabulations and/or line listings[21]
- assess and categorise the information received from investigators, and report all **USADEs** occuring in Australian participants to the Therapeutics Goods Administration:[22]
    - for fatal or life threatening Australian USADEs, no later than **7 days** after being made aware of the case, with any follow-up information within a further 8 days
    - for all other Australian USADEs, no later than **15 days** after being made aware of the case.
- provide HRECs with an **annual safety report**[23] written in lay language and including a clear summary of the evolving safety profile of the trial:
    - a brief description and analysis of new and relevant findings
    - a brief discussion of the implications of safety data to the risk-benefit ratio for the trial
    - a description of any measures taken or proposed to minimise risks
    - confirmation that the sponsor is adequately monitoring the trial's risk-benefit ratio in accordance with the safety monitoring plans described in the CIP, trial risk assessment or HREC application.

  Note: The timing of the annual safety report may be aligned with the reporting cycles of global companies or aligned with the annual progress report sent to the HREC.
- report to the HREC within 7 days of being made aware of the breach, all **Serious Breaches of the Clinical Investigation Plan or GCP**, that are likely to affect to a significant degree:

[21] The sponsor may be required to provide tabulations/line listings to the TGA on request.

[22] Where the sponsor's causality assessment conflicts with the assessment made by the site investigator, the site investigator's assessment cannot be downgraded by the sponsor (i.e. altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a USADE, the opinion of both the investigator and the sponsor should be provided with any report made.

[23] HRECs have the discretion to request more frequent reporting for specific trials, such as early phase trials.

- the safety or physical or mental integrity of the trial participant
- the reliability and robustness of the data generated in the clinical trial.

- ensure that the Investigator's Brochure (IB) is reviewed at least annually and provide:
  - to the HREC, any annual update of the IB
  - to investigators, any annual update of the IB and any spontaneous updates or addenda to the IB.
- ensure that all sponsor responsibilities for safety monitoring and reporting (e.g. reporting USADEs and significant safety issues to the TGA) are appropriately allocated or delegated
- report to the TGA, HREC and investigators, all **significant safety issues** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Examples include[24]:
  - 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 resulting from a lack of effectiveness of an IMD used in a trial
  - a major safety finding from a newly completed study using the same IMD
  - 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 anticipated adverse device effect.

Note: Significant safety issues are not usually reported as USADEs, but require other action such as the reporting of an urgent safety measure, an amendment, a temporary halt or an early termination of a trial. In addition, significant safety issues often result in safety-related changes to trial documentation or other aspects of the overall conduct of the trial. Such amendments should be submitted to the HREC without undue delay.

Where a significant safety issue is implemented as an urgent safety measure, sponsors and trial investigators must act immediately to protect participants from any immediate risk to their health and safety. It is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken, in order to discuss the case with a safety scientist. This initial contact should be followed-up with a written notification provided by facsimile or e-mail. Table 1 outlines the timelines for written notifications and also illustrates the types of action that result from significant safety issues.

Table 1: Sponsor Reporting of Significant Safety Issues

Action	What is communicated	Recipients	Timelines and further review
Urgent safety measure (USMs)[25]	• Reasons for the urgent safety measure • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the measure being taken[26]. The HREC is not required to approve USMs but may consider whether any proposed actions are appropriate, such as the submission of an amendment relating to revised trial documentation.

[24] Although not specific to clinical trials, Annex 1 MEDDEV 2 12-1 rev. 8 provides examples of events that may meet the definition of a significant safety issue.

[25] By definition, urgent safety measures may be instigated at sites before the TGA and HREC are notified. A temporary halt/early termination may also meet the definition of an urgent safety measure.

[26] Urgent safety measures instigated by investigators should be reported immediately to the sponsor to enable compliance with the 72 hour reporting timeline.

Amendment	• Details of the significant safety issue • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the sponsor becoming aware of the issue. Sponsors should submit to the HREC an amendment relating to any revised trial documentation, as soon as the relevant documentation has been internally approved.
Temporary halt of a trial for safety reasons[27]	• Reasons for the halt • The scope of the halt (e.g. suspension of recruitment or cessation/interruption of trial treatment) • Measures taken • Further actions planned	Notify the TGA, investigators and the HREC	Without undue delay and no later than **72 hours** of the sponsor's decision to terminate the trial. Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), an amendment should be submitted to the HREC within **15 days** of the temporary halt.
Premature termination of a trial for safety reasons	• Reasons for the premature termination • Measures taken • Further actions planned	Notify the TGA, Investigators and the HREC	Without undue delay and no later than **72 hours** of the sponsor's decision to terminate the trial. Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), an amendment should be submitted to the HREC within **15 days** of the premature termination.

ii. Responsibilities of the Principal Investigator(s) or Delegate

The PI or Delegate should:

- record every AE and observed device deficiency, together with an assessment and report to the sponsor as required by the clinical investigation plan
- report to the sponsor without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect
- supply the sponsor with any supplementary information relating to safety reports, as requested
- report to the sponsor within 24 hours any urgent safety measure instigated at the site
- report to the sponsor pregnancies that occur while a participant is on a clinical trial as specified in the CIP
- follow-up any pregnancy until outcome (e.g. birth or spontaneous abortion) and report any incidents of congenital abnormality/birth defect as an SAE
- report to their institution without undue delay and no later than 72 hours of the Principal Investigator instigating or becoming aware of the event:
  - All significant safety issues
  - Any confirmed[28] USADEs that has occurred at the site
  - Any serious breach that has occurred at the site.

[27] Both the TGA and the HREC should be informed if the trial restarts. An amendment should be submitted to the HREC providing evidence that it is safe to restart the trial.

[28] Confirmed means that the sponsor has communicated to the site investigator that a USADE has been/will be reported to the TGA.

iii. Responsibilities of the HREC

The approving HREC should:

- assess the safety of the proposed trial and whether the evaluation of the anticipated benefits and risks is satisfactory, and ensure that the sponsor has proportionate systems are in place to mitigate and manage any identified trial risks
- satisfy itself that the sponsor has adequate ongoing safety monitoring arrangements in place including the justification for appointing/not appointing a Data Safety Monitoring Board and any 'stopping rules' and criteria for withdrawing individual participants from the trial
- satisfy itself that the sponsor understands their obligation to report to the HREC anything that may adversely affect the safety of participants or the conduct of the trial, particularly amendments relating to changes made to the device design and manufacturing process[29], and other information that may alter risks and benefits
- assess whether changes to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethical approval
- keep under review the adequacy and completeness of the informed consent process and documentation in the light of new information about risks and benefits
- assess any reports of a serious breach, including any corrective and preventative actions taken by the sponsor and take any action deemed necessary.

  Note: While HRECs must keep approvals under review in light of safety information it receives, the responsibility for proactively monitoring the ongoing risk-benefit ratio of the trial remains with the sponsor.

iv. Responsibilities of the Institution

The Institution should:

- assess whether any reports received (e.g. safety reports and serious breaches) impact on medico-legal risk[30], adherence to contractual obligations or the trial's continued site authorisation
- develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document should cover the requirements for both externally sponsored clinical trials and if applicable, internally sponsored investigator/initiated or collaborative group trials.

  Note: Where the institution is also named as the trial sponsor, the institution will assume the sponsor responsibilities set out in this document.

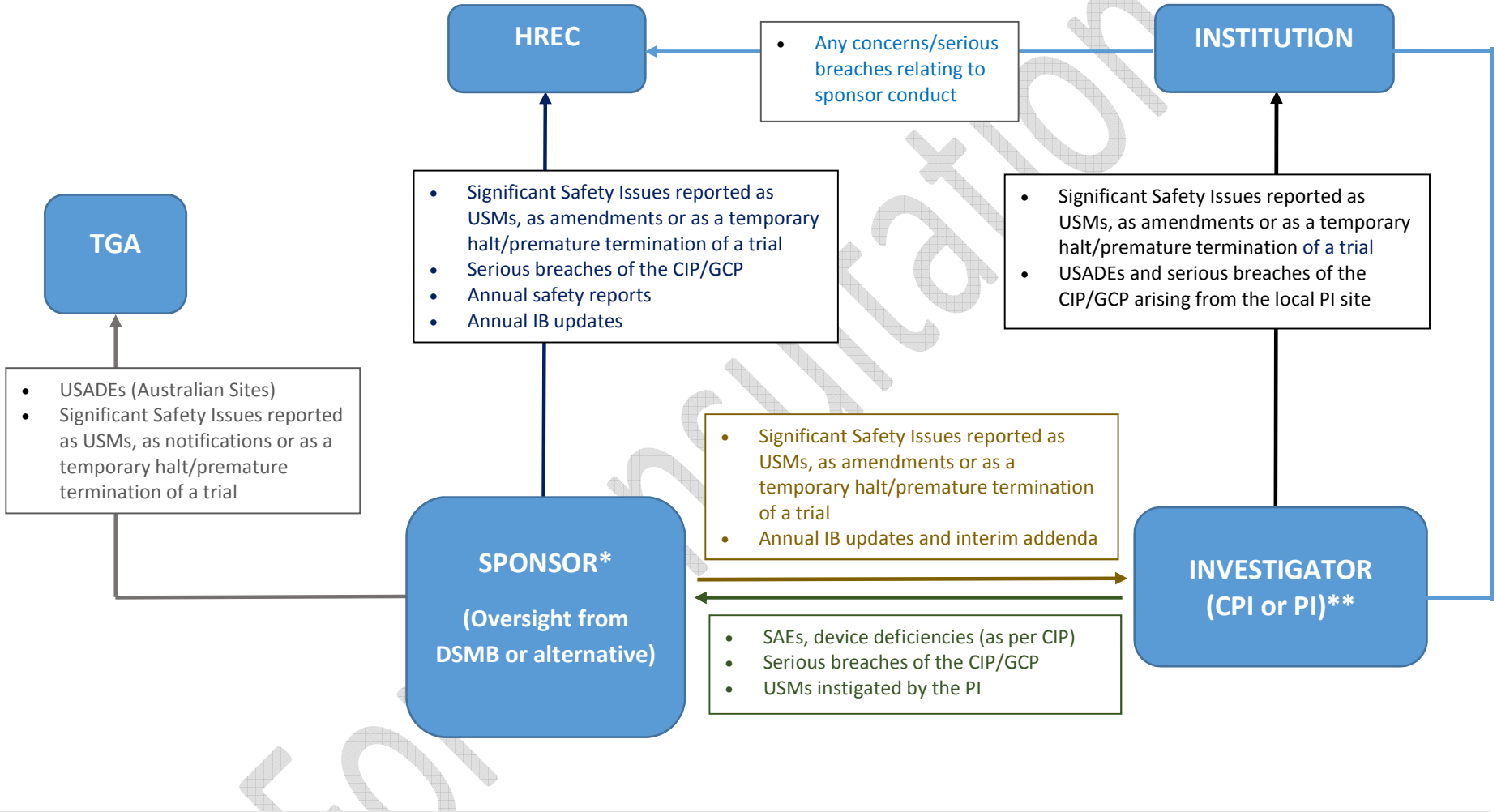
d) References

- ISO 14155 (2011) = Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice
- Regulation of the European Parliament and of the Council on Medical Devices, and Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 /EEC – (Section 1.5.4 Creating Synergies with Clinical Trials on Medicinal Products)

[29] Sponsors/manufacturers should provide clear evidence to the HREC that the proposed change(s) do not predictably increase the risk to the patient, user or third party.

[30] Research-related events that meet the definition of a clinical incident should be processed in keeping with any organisation-wide reporting of incidents relating to patient safety.

APPENDIX 2: Reporting Flowchart for Investigational Medical Device Trials



KEY

AE - Adverse Event
SAE - Serious Adverse Event
USADE – Unanticipated Serious Adverse Device Effect
USM - Urgent Safety Measure
IB - Investigator's Brochure
IFU - Instructions for Use
PI - Principal Investigator
CPI - Coordinating Principal Investigator
SOP - Standard Operating Procedure
HREC - Human Research Ethics Committee

*The sponsor (or their delegate) should report in parallel to all parties in accordance with the timelines indicated within this document.

** The CPI is copied in to all correspondence sent by the sponsor to PIs and/or the HREC. The sponsor will only send PIs correspondence relevant to their role.

APPENDIX 3: Document Revision and Working Party

The NHMRC Australian Health Ethics Committee (AHEC) Position Statement has been revised in line with the National Health and Medical Research Council (NHMRC) policy that all its guidelines be reviewed at least every five years.

Working Party:

Professor Ingrid Winship	Executive Director of Research for Melbourne Health and AHEC Member
Tanya Symons	Director, T Symons Associates Pty Ltd
Adjunct Professor Nikolajs Zeps	Director of Research at SJGHC Subiaco Hospital
Melissa Hagan	Manager, Health and Medical Research at Queensland Health
Professor James Toouli	Emeritus Professor of Surgery at Flinders University Adelaide
Val Theisz	Medical Technology Association of Australia (MTAA)
Adelina Tan	Therapeutic Goods Administration (TGA)
Dr Wendy Hague	Clinical Trials Program Director, NHMRC Clinical Trials Centre

Mrs Tanya Symons	Consultant Technical Writer