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Safety monitoring and reporting in clinical trials involving therapeutic goods

November 2016

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Australian Government
Department of Health
Therapeutic Goods Administration

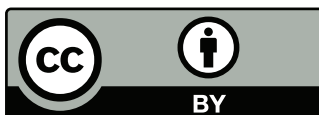
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Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods

1. Purpose

This guidance replaces the 2009 Position Statement: *'Monitoring and reporting of safety for clinical trials involving therapeutic products'* and adopts reporting arrangements for clinical trials that reflect current practice in the United States and European Union. This new guidance seeks to address widespread feedback from stakeholders that previous arrangements in Australia placed an unnecessary burden on investigators and Human Research Ethics Committees (HRECs) and did not genuinely contribute to patient safety.

2. Scope

This guidance addresses the collection, verification and reporting of adverse events and adverse reactions that occur in clinical trials involving **investigational medicinal products (IMPs)** and **investigational medical devices (IMDs)** for trials conducted under the Clinical Trial Exemption (CTX) or Clinical Trial Notification (CTN) schemes.¹

The safety monitoring and reporting requirements for **IMPs** and **IMDs** are broadly similar. However, in order to reflect the differing terminology and requirements of their respective Good Clinical Practice guidelines², the requirements for IMPs and IMDs have been detailed separately in Part 1 and Part 2 of this document respectively.

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)³ relative to standard care and the extent of knowledge about the IMPs/IMDs being tested. The sponsor's plans for safety monitoring should be documented and continually reviewed and adapted during the trial, as real time assessments of safety data are performed.

1 This guidance should be adopted as far as possible for other therapeutic goods trials (definitions, responsibilities and reporting pathways); however, reporting to the TGA should comply with the TGA's requirements for post marketing trials.

2 ICH GCP annotated by the TGA, for investigational medicinal products and ISO 14155: 2011, for investigational medical devices.

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

4. The Trial Sponsor and Ongoing Safety Monitoring

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*'. Many 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 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.

ICH GCP and ISO 14155 place the responsibility for the ongoing safety evaluation of the investigational product with the sponsor. To ensure there is appropriate independent oversight of safety within a clinical trial, sponsors should generally utilise an independent committee or independent individuals (e.g. a medical monitor) to review accruing safety data. When convened⁴, Data Safety Monitoring Boards are best placed to perform the review of trial safety data, as they are in the unique position of being able to review unblinded safety information to assess treatment exposure. In addition, they are often the only body with access to emerging efficacy data for the trial. As such, they have the clearest picture of the evolving balance of risks and benefits within the trial. It is **the outcome** of these reviews that are provided to HRECs, investigators, institutions and the Therapeutic Goods Administration (TGA).

Sponsors, through feedback from their safety committees or medical monitors, are responsible for generating safety communications. As such, placing the sponsor at the centre of the communication cascade will ensure timely and streamlined dissemination of information, and will align Australia with other world regions with single ethical review systems. In this model, sponsors report directly to HRECs⁵ and investigators, who forward any relevant information to their institution. Sponsors have the flexibility to delegate reporting responsibilities to third parties, for example, to a coordinating centre in a non-commercial trial.

4 The decision to convene a DSMB should be based on the potential risks and benefits to participants associated with the trial and the trial design.

5 In a multicentre trial, the Coordinating Principal Investigator should be provided with copies of correspondence sent by the sponsor to the HREC and investigators.

5. Summary of Main Changes to Reporting Requirements

Change from 2009 Position Statement	Rationale
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.	HREC are often not best placed to perform an analysis of these reports. The outcomes of the sponsor's analyses of accumulating safety data provides the HREC with more useful and useable information.
Removing the requirement to submit individual reports of AEs, SAEs, SUSARs/USADEs and six monthly line listings to investigators to align with EU Regulation. ⁶	Updated/addended investigator's brochures and spontaneous reports of significant safety issues 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, <i>external</i> SUSARs/USADEs and six monthly line listings to institutions.	Institutions are often not best placed to perform an analysis of these reports. The outcomes of the sponsor's analyses of accumulating safety data provides the institution with more useful and useable information.
Including the requirement for sponsors to provide HRECs with 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 and also evidence that the sponsor is conducting its ongoing safety monitoring appropriately.
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.

⁶ This revision aligns with EU Clinical Trial Regulation 536 which has removed the requirement for SUSARs and six monthly line listing to be reported to investigators. The revision is also consistent with Section F of ICH E2A.

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.

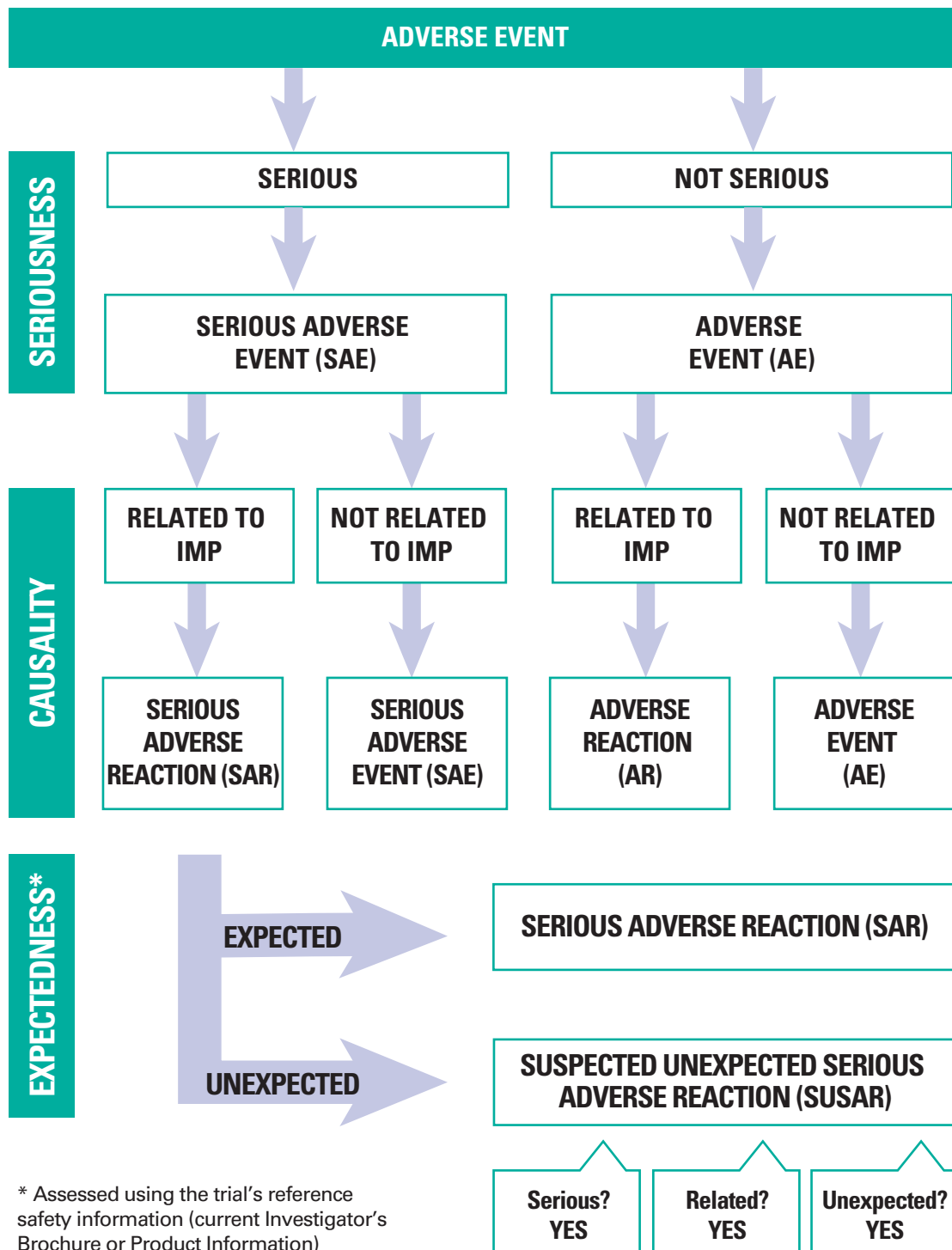
Term	Description
Investigational Medicinal Product (IMP)	<p>A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, a new patient group or when used to gain further information about an approved use.</p> <p>Note: This definition includes biologicals used as investigational medicinal products.</p>
Biological ⁷	<p>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).</p> <p>Examples include:</p> <ul style="list-style-type: none">• 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)	<p>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.</p>
Adverse Reaction (AR)	<p>Any untoward and unintended response to an investigational medicinal product related to any dose administered.</p> <p>Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a 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.</p> <p>Note⁸: The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event:</p> <ul style="list-style-type: none">• 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)

⁷ Sourced from Australian Regulatory Guidelines for Biologicals Part 1 - Introduction to the Australian Regulatory Guidelines for Biologicals.

⁸ Selected examples taken from 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.

Term	Description
	<ul style="list-style-type: none"> • 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 those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
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)	<p>The approved Australian summary of the scientific information relevant to the safe and effective use of a prescription medicine.</p> <p>Note: In a trial in which the IMP is an approved product, the Product Information may replace the investigator's brochure. If the conditions of use differ from those authorised, the PI should be supplemented with a summary of relevant clinical and non-clinical data that supports the use of the IMP in the trial.</p> <p>The Australian Product Information should be used where available for each trial IMP adopted across Australian sites.</p>
Reference Safety Information (RSI)	The information contained in either an investigator's brochure or an approved Australian 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 evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	<p>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.</p> <p>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.</p> <p>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.</p>
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.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Unexpected Adverse Reaction (UAR)	<p>An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI).</p> <p>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.</p>
Urgent Safety Measure (USM)	<p>A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.</p> <p>Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.</p>

B. Safety Reporting Assessment Flowchart: IMP Trial



Adapted from the NIHR Clinical Trials Toolkit

C. An Overview of Safety Monitoring and Reporting Responsibilities

1. Responsibilities of the Sponsor

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:

- a. ensure that the trial protocol has clear sections describing:
 - the assessment and management of risk (if not in an alternative document)⁹
 - safety reporting definitions, procedures, responsibilities and reporting timelines
 - any serious adverse events that do not require immediate reporting
- b. keep detailed records of all reported **adverse events** and maintain up-to-date tabulations and/or line listings¹⁰
- c. when communicating safety information to investigators and/or HRECs, clarify the impact of each report on patient safety, trial conduct or trial documentation
- d. assess and categorise the safety reports received from investigators, and report all **suspected unexpected serious adverse reactions** occurring in Australian participants to the Therapeutic Goods Administration
 - 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

Note 1: 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 guidance. Sponsors can discharge this responsibility by placing these reports on a portal or by sending them via e-mail. When the sponsor confirms that the report has no bearing on participant safety or trial conduct, confirmation of receipt of the communication may be requested, but there should be no requirement for investigators to print, review and file these reports.

Note 2: When determining whether a SUSAR has occurred, 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

⁹ The trial protocol or an alternative document such as a safety monitoring plan, should also describe the composition, roles and responsibilities of oversight committees and plans for ongoing safety monitoring.

¹⁰ The sponsor may be required to provide tabulations/line listings to the TGA on request.

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.

Note 3: When reporting a SUSAR to the TGA, the blind should generally¹¹ be broken by the sponsor. In order to avoid introducing biases, 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.

- e. review the investigator's brochure at least annually and update it when new and relevant information becomes available
- f. provide the HREC and investigators with any update/addenda of the investigator's brochure or where applicable, Product Information¹²
- g. provide the HREC with an **annual safety report**¹³ including a clear summary of the evolving safety profile of the trial. This report should allow the HRECs to assess whether ongoing safety monitoring is being conducted appropriately and that the trial's safety monitoring plans are being followed and where necessary, are being adapted to take into account new findings as the trial progresses

The annual safety report should generally include:

- 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 available safety data and the results of relevant clinical or non-clinical studies
- 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

Note 1: The Executive Summary of safety information produced for international regulators, such as a *Development Safety Update Report (DSUR)*, may serve as the annual safety report sent to HRECs (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: Development Safety Update Report.

- h. 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
- i. notify the TGA, HREC and investigators of all **significant safety issues** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Significant safety issues that meet the definition of an urgent safety measure should be notified **within 72 hours**, and all other significant safety issues should be notified **within 15 calendar days** of the sponsor instigating or being made aware of the issue. 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

¹¹ See Section D of ICH E2A: Managing Blinded Therapy Cases.

¹² When a Product Information is used in place of an investigator's brochure, any changes made by the Marketing Authorisation Holder should be reported to the HREC and investigators. Non-commercial sponsors should monitor for such changes.

¹³ HRECs have the discretion to request more frequent reporting for specific trials, such as early phase trials.

- 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.

Note 1: Often, significant safety issues (SSIs) do not fall within the definition of a SUSAR and thus are not subject to the reporting requirements for SUSARs. SSIs usually 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, SSIs often result in safety-related changes to trial documentation. These amendments should be submitted to the HREC **without undue delay**.¹⁴

Note 2: Urgent Safety Measures (USMs) are one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. Consequently, USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor **contact the TGA within 24 hours** of the measure being taken.

If this initial contact is by telephone, it should be followed-up with a written notification provided by facsimile or e-mail within 72 hours. Table 1 illustrates the types of action that result from SSIs and the associated timelines for **written notification**.

Table 1: Sponsor Reporting of Significant Safety Issues

Action	What is communicated	Recipients	Timelines and further review
a. Urgent safety measure (USMs) ¹⁵	<ul style="list-style-type: none"> • Reasons for the urgent safety measure • Measures taken • Further actions planned 	Notify the TGA, investigators and the HREC	<p>Without undue delay and no later than 72 hours of the measure being taken.</p> <p>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.</p>
b. Notification of an amendment	<ul style="list-style-type: none"> • Details of the significant safety issue • Further actions planned 	Notify the TGA ¹⁶ , investigators and the HREC	<p>Without undue delay and no later than 15 calendar days of the sponsor becoming aware of the issue.</p> <p>Sponsors should submit to the HREC an amendment relating to any revised trial documentation, without undue delay.</p>
c. Temporary halt of a trial for safety reasons ¹⁷	<ul style="list-style-type: none"> • 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	<p>Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial.</p> <p>Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), a letter describing these actions should be submitted to the HREC within 15 calendar days of the temporary halt</p>

¹⁴ Good Clinical Practice requires sponsors, through their investigators, to inform participants of new safety information in a timely fashion.

¹⁵ Temporary halts/early terminations implemented as urgent safety measures (USM) should be notified within USM timeframes.

¹⁶ The TGA should receive notification that a SSI has occurred but the amendment revising trial documentation does not require submission to the TGA.

¹⁷ Both the TGA and the HREC should be notified if the trial restarts, including evidence that it is safe to restart.

Action	What is communicated	Recipients	Timelines and further review
d. Early termination of a trial for safety reasons	<ul style="list-style-type: none"> • Reasons for the early termination • Measures taken • Further actions planned 	Notify the TGA, investigators and the HREC	Without undue delay and no later than 15 calendar days 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), a letter describing these actions should be submitted to the HREC within 15 calendar days of the early termination.

2. Responsibilities of the Principal Investigator

Investigators should assess¹⁸ all local safety events and should act on any events as clinical care dictates. 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.

The Principal Investigator should:

- a. capture and assess all AEs that occur at the site as required and in accordance with the protocol
- b. report to the sponsor **within 24 hours of becoming aware of the event:**
 - all SAEs, except those that are identified in the protocol as not needing immediate reporting
 - any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner)¹⁹
 - all urgent safety measure instigated by the site
- c. report to the sponsor as specified in the protocol:
 - all safety critical events
 - any additional requested information relating to reported deaths
- d. report to the institution **within 72 hours** of becoming aware of the event:
 - all significant safety issues
 - SUSARs²⁰ arising from the local site.

3. Responsibilities of the HREC

The sponsor, through their independent safety monitoring arrangements, has the primary responsibility for monitoring the ongoing safety of the investigational medicinal product. The HREC should be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial.

The approving HREC should:

- a. 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
- b. 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

¹⁸ Causality assessment decisions should be made by a qualified physician, or when appropriate, a qualified dentist.

¹⁹ Processes for handling consent for follow-up of participants (or pregnant partners of participants) should be in place.

²⁰ Reported when, in the investigator's judgement, a SUSAR has occurred. The investigator should not unblind the SUSAR for the purposes of reporting to their institution.

- c. keep under review the adequacy and completeness of the informed consent process and documentation in the light of new information about risks and benefits
- d. assess whether changes to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethical approval²¹
- e. advise the TGA, investigators and their institutions of any decision to withdraw approval

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.

4. Responsibilities of the Institution

An institution's responsibilities and oversight of safety information in clinical trials will differ depending on whether they are hosting externally sponsored clinical trials or sponsoring locally led non-commercial trials. In both cases they should help ensure that their site(s) understands and complies with sponsor requirements. Institutions should have oversight of any issues that may require management, such as disputes or litigation resulting from trials. **Where the institution is also named as the trial sponsor, the institution will also assume the sponsor responsibilities set out in this document.**

The Institution should:

- a. assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation and, where applicable, facilitate the implementation of corrective and preventative action
- b. develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document(s) should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator/initiated or collaborative group trials.

5. Responsibilities of the Therapeutic Goods Administration

Clinical trials of unapproved therapeutic goods are conducted in Australia under either the Clinical Trial Notification (CTN) Scheme or the Clinical Trial Exemption (CTX) Scheme. Responsibility for the regulatory control of therapeutic goods in Australia lies with the Therapeutic Goods Administration (TGA).

The TGA may:

- a. conduct an audit of a clinical trial where necessary on safety grounds
- b. stop a trial where that action is in the public's interest.

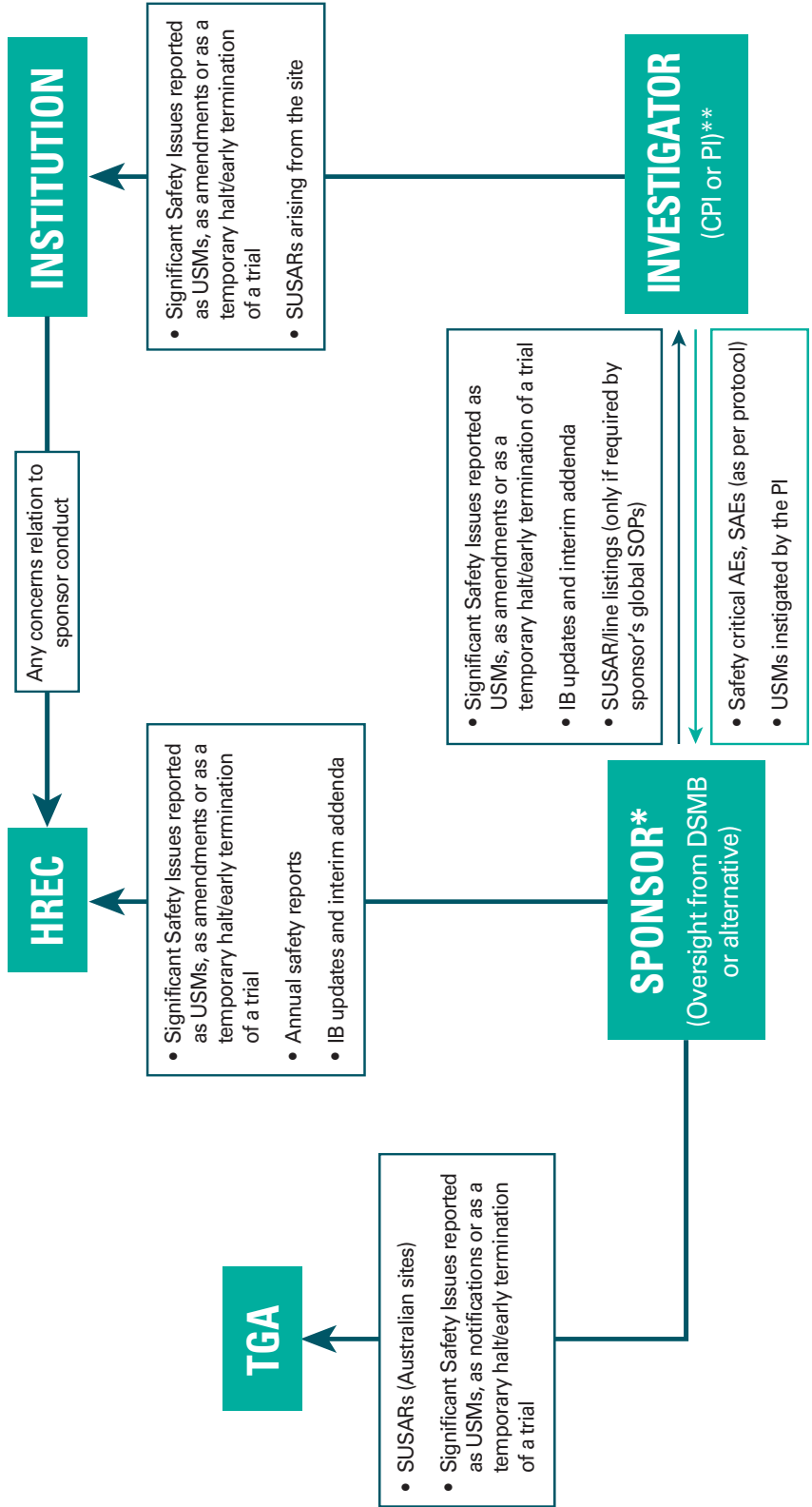
D. References

- 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
- 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)

²¹ An HREC may discuss any concerns it has with any aspect of a clinical trial with the TGA.

- 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: Report Flowchart for Investigational Medicinal Product Trials



KEY

- AE – Adverse Event
- DSMB – Data Safety Monitoring Board
- SAE – Serious Adverse Event
- SUSAR – Suspected Unexpected Serious Adverse Reaction
- IB – Investigator’s Brochure
- PI – Product Information
- PI – Principal Investigator
- CPI – Co-ordinating Principal Investigator
- SOP – Standard Operating Procedure
- USM – Urgent Safety Measure

* The sponsor (or their delegate) should report to all parties in accordance with the timelines indicated within this document.
 **The CPI should be provided with all correspondence sent by the sponsor to PIs and/or the HREC.

PART 2: Investigational Medical Devices (IMD) Trials

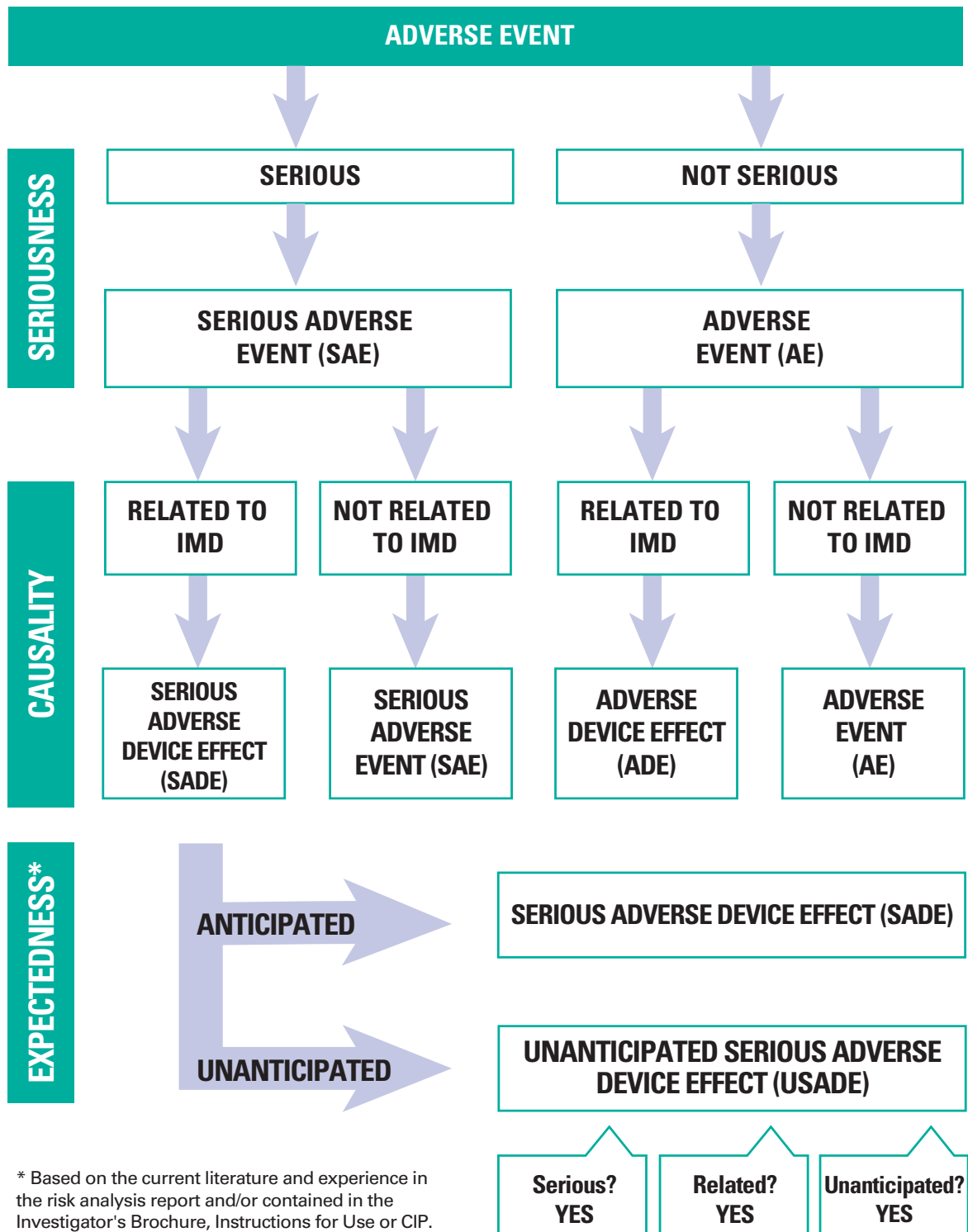
A. Definitions (IMDs)

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
Adverse Device Effect (ADE)	<p>Adverse event related to the use of an investigational medical device.</p> <p>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.</p>
Adverse Event (AE)	<p>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.</p> <p>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.</p>
Device Deficiencies	<p>Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.</p> <p>Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.</p>
Investigational Medical Device (IMD)	<p>Medical device being assessed for safety or performance in a clinical investigation</p> <p>Note: This includes medical devices already on the market, that are being evaluated for new intended uses, new populations, new materials or design changes.</p>
Investigator's Brochure (IB)	<p>Compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation.</p>
Medical Device	<p>Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article:</p> <ol style="list-style-type: none">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:<ul style="list-style-type: none">diagnosis, prevention, monitoring, treatment or alleviation of diseasediagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicapinvestigation, replacement or modification of the anatomy or of a physiological processsupporting or sustaining lifecontrol of conceptiondisinfection of medical devices, andthat 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.

Term	Description
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	<p>a. Adverse event that:</p> <p>b. led to death</p> <ul style="list-style-type: none"> • 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 <p>c. led to foetal distress, foetal death or a congenital abnormality or birth defect</p> <p>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.</p>
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.
Unanticipated Serious Adverse Device Effect (USADE)	<p>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</p> <p>Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.</p>
Urgent Safety Measure (USM)	<p>A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.</p> <p>Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.</p>

B. Safety Reporting Assessment Flowchart: IMD Trials



Adapted from the NIHR Clinical Trials Toolkit

C. An Overview of Safety Monitoring and Reporting Responsibilities

1. Responsibilities of the Sponsor

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. 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:

- a. ensure that the clinical investigation plan (CIP) has clear sections describing:
 - the assessment and management of risk (if not in an alternative document)²²
 - safety reporting definitions, procedures, responsibilities and reporting timelines
- b. review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device²³
- c. review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect²³
- d. keep detailed records of all **AEs** and **device deficiencies** that investigators have reported and maintain up to date tabulations and/or line listings²⁴
- e. when communicating safety information to investigators and/or HRECs, clarify the impact of each report on patient safety, trial conduct or trial documentation
- f. assess and categorise the information received from investigators, and report all **USADEs** occurring in Australian participants to the Therapeutic Goods Administration:
 - for fatal or life threatening Australian USADEs, 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 USADEs, no later than **15 calendar days** after being made aware of the case

Note 1: When determining whether a USADE has occurred, 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 sent to the TGA

²² The trial CIP or an alternative document should also describe the composition, roles and responsibilities of oversight committees and plans for ongoing safety monitoring.

²³ In case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties.

²⁴ The sponsor may be required to provide tabulations/line listings to the TGA on request.

- g. update the investigator's brochure or where applicable, the Instructions for Use (IFU), as significant new information becomes available
- h. provide the HREC and investigators with any update/addenda of the investigator's brochure or where applicable, the Instructions for Use²⁵
- i. provide the HREC with an **annual safety report**²⁶ including a clear summary of the evolving safety profile of the trial. This report should allow the HRECs to assess whether ongoing safety monitoring is being conducted appropriately and that the trial's safety monitoring plans are being followed and where necessary, are being adapted to take into account new findings as the trial progresses
 - 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

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

- j. 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
- k. notify the TGA, HREC and investigators of all **significant safety issues** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Significant safety issues that meet the definition of an **urgent safety measure** should be notified **within 72 hours**, and all other significant safety issues should be notified **within 15 calendar days** of the sponsor instigating or being made aware of the issue. Examples include²⁷:
 - 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 1: Often, significant safety issues (SSIs) do not fall within the definition of a USADE and thus are not subject to the reporting requirements for USADEs. SSIs usually 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, SSIs often result in safety-related changes to trial documentation. These amendments should be submitted to the HREC **without undue delay**.²⁸

Note 2: Urgent Safety Measures (USMs) are one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. Consequently, USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken.

²⁵ When the Instructions for Use document is used in place of an investigator's brochure, any changes made by the Marketing Authorisation Holder should be reported to the HREC and investigators. Non-commercial sponsors should monitor for such changes.

²⁶ HRECs have the discretion to request more frequent reporting for specific trials, such as early phase trials.

²⁷ 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.

²⁸ Good Clinical Practice requires sponsors, through their investigators, to inform participants of new safety information in a timely fashion.

If this initial contact is by telephone, it should be followed-up with a written notification provided by facsimile or e-mail within 72 hours. Table 1 illustrates the types of action that result from SSIs and the associated timelines for **written notification**.

Table 1: Sponsor Reporting of Significant Safety Issues

Action	What is communicated	Recipients	Timelines and further review
a. Urgent safety measure (USMs) ²⁹	<ul style="list-style-type: none"> • Reasons for the urgent safety measure • Measures taken • Further actions planned 	Notify the TGA, investigators and the HREC	<p>Without undue delay and no later than 72 hours of the measure being taken.</p> <p>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.</p>
b. Notification of an amendment	<ul style="list-style-type: none"> • Details of the significant safety issue • Further actions planned 	Notify the TGA ³⁰ , investigators and the HREC	<p>Without undue delay and no later than 15 calendar days of the sponsor becoming aware of the issue.</p> <p>Sponsors should submit to the HREC an amendment relating to any revised trial documentation without undue delay.</p>
c. Temporary halt of a trial for safety reasons ³¹	<ul style="list-style-type: none"> • 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	<p>Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial.</p> <p>Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), a letter describing these actions should be submitted to the HREC within 15 calendar days of the temporary halt.</p>
d. Early termination of a trial for safety reasons	<ul style="list-style-type: none"> • Reasons for the early termination • Measures taken • Further actions planned 	Notify the TGA, investigators and the HREC	<p>Without undue delay and no later than 15 calendar days of the sponsor's decision to terminate the trial.</p> <p>Where it is necessary to seek ethical review of related actions (e.g. informing participants or arranging continuing care and follow-up), a letter describing these actions should be submitted to the HREC within 15 calendar days of the early termination.</p>

2. Responsibilities of the Principal Investigator

Investigators should assess³² all local safety events and should act on any events as clinical care dictates. 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.

The Principal Investigator 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

²⁹ A temporary halt/early termination implemented as an urgent safety measure (USM) would be reported within USM timeframes.

³⁰ The TGA should receive notification that a SSI has occurred but the amendment revising trial documentation does not require submission to the TGA.

³¹ Both the TGA and the HREC should be notified if the trial restarts, including evidence that it is safe to restart.

³² Causality assessment decisions should be made by a qualified physician, or when appropriate, a qualified dentist.

- c. report to the sponsor within 24 hours any urgent safety measure instigated at the site
- d. report to the sponsor pregnancies that occur while a participant is on a clinical trial as specified in the clinical investigation plan
- e. follow-up any pregnancy until outcome (e.g. birth or spontaneous abortion) and report any incidents of congenital abnormality/birth defect as an SAE
- f. supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting
- g. report to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event:
 - All significant safety issues
 - USADEs³³ occurring at the site.

3. Responsibilities of the HREC

The sponsor, through their independent safety monitoring arrangements, has the primary responsibility for monitoring the ongoing safety of the investigational medical device. The HREC should be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial.

The approving HREC should:

- a. 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 in place to mitigate and manage any identified trial risks
- b. 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
- c. 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 process³⁴, and other information that may alter risks and benefits
- d. assess whether changes to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethical approval³⁵
- e. advise the TGA, investigators and their institutions of any decision to withdraw approval
- f. keep under review the adequacy and completeness of the informed consent process and documentation in the light of new information about risks and benefits.

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.

³³ Reported when, in the investigator's judgement, a USADE has occurred. The investigator should not unblind the USADE for the purposes of reporting to their institution.

³⁴ 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.

³⁵ An HREC may discuss any concerns it has with any aspect of a clinical trial with the TGA.

4. Responsibilities of the Institution

An institution's responsibilities and oversight of safety information in clinical trials will differ depending on whether they are hosting externally sponsored clinical trials or sponsoring locally led non-commercial trials. In both cases they should help ensure that their site(s) understands and complies with sponsor requirements. Institutions should have oversight of any issues that may require management, such as disputes or litigation resulting from trials. **Where the institution is also named as the trial sponsor, the institution will also assume the sponsor responsibilities set out in this document.**

The Institution should:

- a. assess whether any safety reports impact on medico-legal risk³⁶, adherence to contractual obligations or the trial's continued site authorisation
- b. develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document(s) should cover the requirements for both externally sponsored clinical trials and if applicable, internally sponsored investigator/initiated or collaborative group trials.

5. Responsibilities of the Therapeutic Goods Administration

Clinical trials of unapproved therapeutic goods are conducted in Australia under either the Clinical Trial Notification (CTN) Scheme or the Clinical Trial Exemption (CTX) Scheme. Responsibility for the regulatory control of therapeutic goods in Australia lies with the Therapeutic Goods Administration (TGA).

The TGA may:

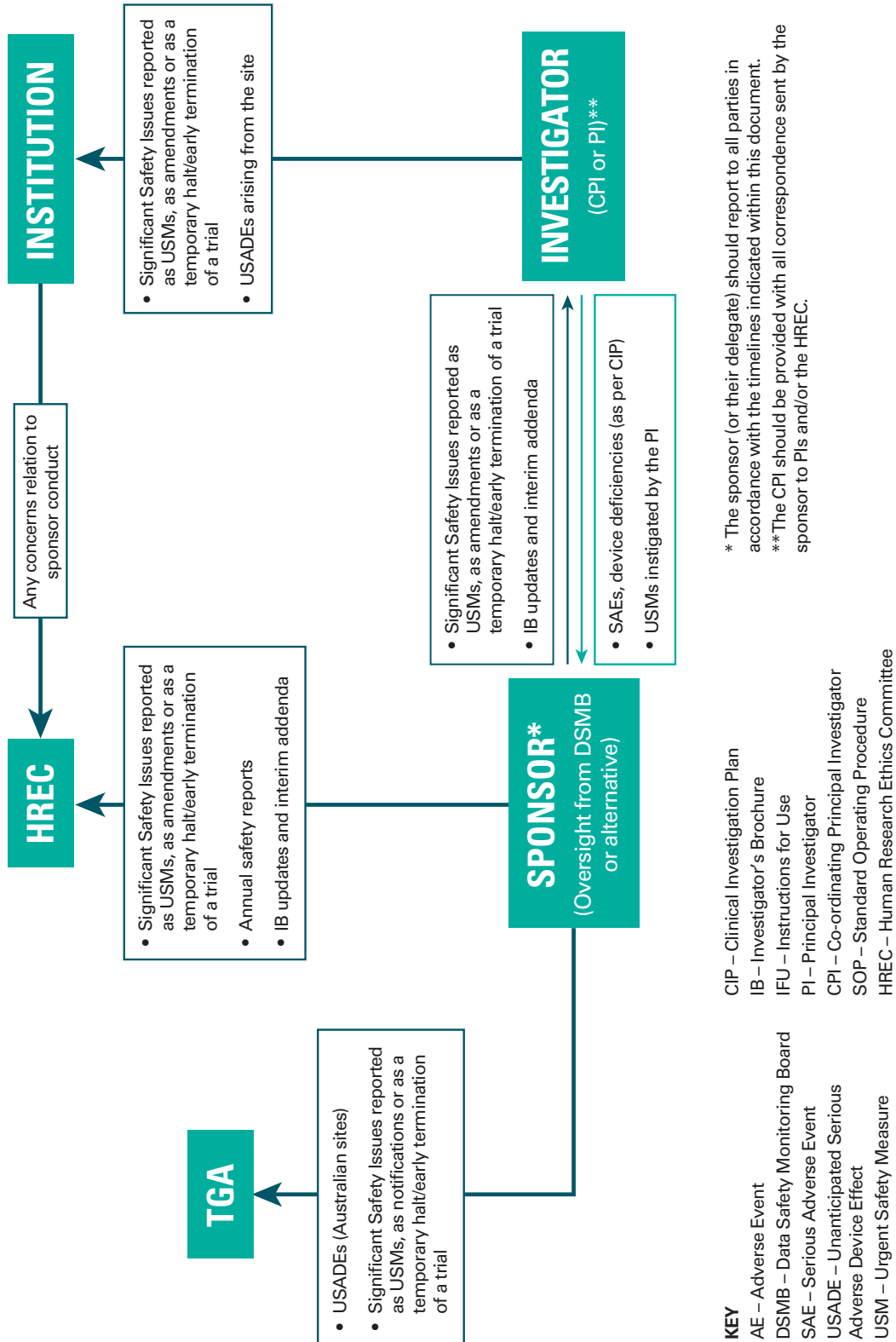
- a. conduct a regulatory inspection of a clinical trial where necessary on safety grounds
- b. stop a trial where that action is in the public's interest.

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)

³⁶ 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



Appendix 3: Document Revision and Working Party

The 2009 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.

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