TARGET AUDIENCE and SETTING

Sponsors, Principal Investigators and all staff conducting research at Monash Health, or research reviewed by Monash Health Human Research Ethics Committees (HREC).

PURPOSE

To describe the procedure for the management of safety information in clinical trials involving investigational products and in clinical research.

This document has been developed in accordance with International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R2) (2016), the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2023), and the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016).

DEFINITIONS

All definitions as per NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016).

Investigational Medicinal Products and Investigational Medical Devices	
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.

Investigational Medicinal 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 related to any dose administered.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	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.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI).

Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.

Investigational Medical Devices	
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.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device.
Serious Adverse Event (SAE)	An 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 • admission to hospital or prolonged hospitalisation, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function c. led to fetal distress, fetal death or a congenital abnormality or birth defect.
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.
Device Deficiencies	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

PRECAUTIONS/CONTRAINDICATIONS

All researchers at Monash Health must strive to conduct research in the manner indicated in the Human Research Strategic Policy.

RESPONSIBILITIES

It is the responsibility of sponsors, contract research organisations, investigators, institutions and their delegates, conducting clinical trials and clinical research projects to comply with the safety monitoring and reporting processes in the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016).

ICH GCP places the responsibility for the ongoing safety evaluation of the investigational product with the sponsor. Sponsors, through feedback from their safety committees or medical monitors, are responsible for generating safety communications.

For investigator-initiated research where the institution is acting as the sponsor, the Principal Investigator is responsible for submitting all safety reports to the HREC, the institution (Research Governance Office) or the Therapeutic Goods Administration (TGA).

The sponsor is required to:

- evaluate all safety information that is reported by investigators as well as safety information from other sources;
- when communicating safety information to investigators and HRECs, clarify the impact of each report on patient safety, trial conduct or trial documentation;
- 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;
- review the **investigator's brochure** at least annually, and provide any update/addenda of the investigator's brochure to the HREC and Principal Investigator;
- provide the HREC with an **annual safety report** including a clear summary of the evolving safety profile of the trial;
- report all **suspected unexpected serious adverse reactions/unanticipated serious adverse device effects** occurring in Australian participants to the TGA.

The Principal Investigator is required to:

- assess all local safety events and act on any events as clinical care dictates;
- provide the sponsor with all relevant information so that an appropriate safety analysis can be performed;
- capture and assess all **adverse events** that occur at the site as required and in accordance with the protocol;
- report safety critical **adverse events**, **serious adverse events**, and **urgent safety measures** instigated by the site to the sponsor;
- notify the institution (Research Governance Office) of all **significant safety issues**;
- report all **SUSARs/USADEs** occurring in Monash Health participants through RiskMan.

PROCEDURE

Monash Health endorses the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016) in its entirety.

Reporting Safety Events

Adverse Event (AE) and Serious Adverse Event (SAE)

The sponsor is required to:

- keep detailed records of all reported AEs and maintain up-to-date tabulations and/or line listings;
- assess and categorise the safety reports received from investigators.

The Principal Investigator is required to:

- 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 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);
    - all USMs instigated by the site.

Please note that while SAEs are not required to be reported on the Victorian Health Incident Management System (VHIMS) Feedback module (RiskMan), it is the responsibility of the Principal Investigator to report any research related fatal events that occur in Monash Health participants. Non research related fatal events do not reporting on RiskMan.

Suspected Unexpected Serious Adverse Reaction (SUSAR) and Unanticipated Serious Adverse Device Effect (USADE)

The sponsor is required to:

- report all SUSARs/USADEs occurring in Australian participants to the TGA;
    - for fatal or life threatening Australian SUSARs/USADEs, 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/USADEs, no later than 15 calendar days after being made aware of the case.

The Principal Investigator is required to:

- Report all SUSARs/USADEs, occurring in Monash Health participants, on the Victorian Health Incident Management System (VHIMS) Feedback module (RiskMan), within 72 hours of becoming aware of the event.

  Please note that all SUSARs/USADEs are to be reported on RiskMan and not through the Ethics Review Manager (ERM).

Upon SUSAR/USADE submission on RiskMan:

1. the SUSAR/USADE is assigned to the Research Support Services team in Riskman;
2. Research Support Services team will include the SUSAR/USADE in the upcoming HREC agenda;
3. the Pharmacist member on the HREC will review and advise the HREC;
4. Research Support Services will indicate the SUSAR/USADE outcome in Riskman and close the incident;
5. the SUSAR would be included in the monthly report provided to Clinical Governance

Significant Safety Issue (SSI) and Urgent Safety Measure (USM)

Significant safety issues usually require 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.

Urgent safety measures require sponsors or investigators to take immediate action to protect participants from a hazard to their health and safety, and are often instigated before the TGA and HREC are notified.

The sponsor is required to:

- notify the TGA, HREC and investigators of all SSIs that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial;
  - for SSIs that meet the definition of a USM, within 72 hours;
  - for all other SSIs, within 15 calendar days of the sponsor instigating or being made aware of the issue.

The Principal Investigator is required to:

- report SSIs to the institution (Research Governance Office) within 72 hours of becoming aware of the event;
- report USMs instigated by the site to the sponsor within 24 hours of becoming aware of the event.

Reporting External Safety Information

Annual Safety Report and Development Safety Update Report (DSUR)

The annual safety report should generally include:

- a brief description and analysis of new and relevant findings;
- for investigational products not on the Australian Register of Therapeutic Goods, a brief analysis of the safety profile of the investigational products 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.

The Sponsor is required to:

- provide the HREC with an annual safety report.

DSURs may be submitted to the Monash Health HREC as a supplementary document to the Annual Safety Report, but will not be accepted for review as a standalone item.

Investigator's Brochure (IB)

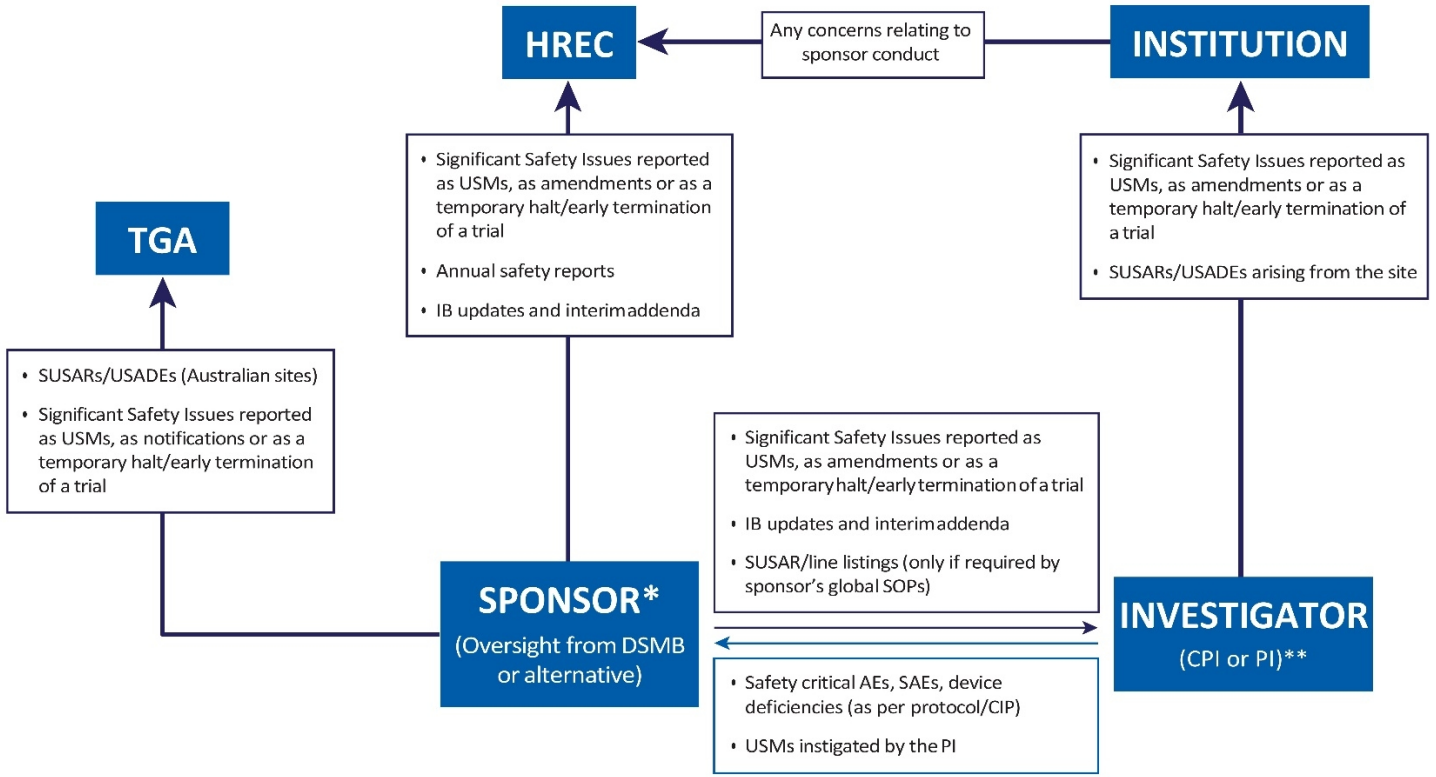
The Sponsor is required to:

- review the IB at least annually, and provide any updates to the HREC and Principal Investigator.

External Individual case SUSARs and six-monthly line listings

Sponsors may be required to follow global company policies that mandate the reporting of individual case SUSARs and six-monthly line listings to investigators and HRECs, however, this practice is not required by the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016). Individual case SUSARs and six-monthly line listings should not be submitted to Monash Health HREC or Research Governance Office.

SAFETY REPORTING FLOWCHART



KEY

AE – Adverse Event
CIP – Clinical Investigational Plan
CPI – Coordinating Principal Investigator
DSMB – Data Safety Monitoring Board
IB – Investigator's Brochure
PI – Principal Investigator
SAE – Serious Adverse Event
SOP – Standard Operating Procedure
SUSAR – Suspected Unexpected Serious Adverse Reaction
USADE – Unanticipated Serious Adverse Device Effect
USM – Urgent Safety Measure

*The sponsor (or their delegate) should report to all parties in accordance with the timelines indicated within the NHMRC guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016).

**The CPI should be provided with all correspondence sent by the sponsor to PIs and/or the HREC.

REFERENCES

1. Therapeutic Goods Administration (TGA) (2016) *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) - Annotated with TGA comments*.

2. National Health and Medical Research Council (NHMRC) (2023) *National Statement on Ethical Conduct in Human Research*.

3. National Health and Medical Research Council (NHMRC) (2016) *Safety monitoring and reporting in clinical trials involving therapeutic goods*.

Document Governance	
Supporting Policy	Human Research Strategic Policy
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