CLINICAL TRIAL SOP 7: Safety Data Monitoring and Reporting Requirements for Clinical Trials

Purpose

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

Scope

This SOP applies to all Investigators (Principal and Sub-Investigator), Study Coordinators, visiting medical officers (VMO), and other Research staff and volunteers who propose to undertake, administrate, review and/or govern human research involving patients/participants and staff. All study personnel involved in the clinical study must operate within their scope of practice.

This SOP refers to both the Sponsor's and Investigator's responsibilities relating to safety monitoring.
Reporting of all serious suspected adverse reactions that occur in post registration/marketing surveillance studies undertaken in Australia follow the same reporting lines and timelines as for serious adverse reactions.

Cabrini Health policies and regulatory requirements

This SOP should be read in conjunction with Safety Monitoring and Reporting in Research Policy and other documents provided by the Cabrini Research Governance Office (CRGO) relevant to the conduct of clinical research at Cabrini Health including but not limited to:

- Aboriginal and Torres Strait Islander Health – asking for Aboriginal and Torres Strait Islander identity
- Research Integrity and Misconduct Policy
- Cabrini Research Data Management, Access and Sharing Policy
- Data Classification and Labelling Standard
- Cabrini Authorship and Publications for Research Policy
- Research Participants Complaints and Compliments Procedures Policy
- Cabrini Research Governance Handbook

Researchers at Cabrini must foster quality research and abide by the following directives:

- The National Clinical Trials Governance Framework (NCTGF)
- National Statement on Ethical Conduct in Human Research (2023)
- Catholic Health Australia Code of Ethical Standards
- Act in accordance with Cabrini Research policies in order to protect the rights, safety and welfare of research participants
- Support patient and family carer involvement in their own research participation through abidance with the Australian open disclosure policy, and Charter of healthcare rights.
- Agree to comply with all reasonable directions and policies by Cabrini Research for Cabrini to meet or exceed the requirements of the NCTGF. To the extent that the NCTGF

applies to the position, compliance with the specified roles and functions of the workforce, as set out by the NCTGF.

Procedure

NOTE: where a Sponsor delivers Suspected Unexpected Serious Adverse Reactions (SUSARs), analyses of accumulating safety data, annual safety reports and other safety communication through a web portal delivery system or via e-mail, as opposed to paper reports, acknowledgement of receipt by the Investigator/HREC/Institution/TGA of such information will be required by the Principal Investigator (PI), but only after the Sponsor confirms that the report has no bearing on participant safety or trial conduct. There is no longer a requirement for Investigators to print, review and file these reports. See *NHMRC Safety Monitoring and Reporting In Clinical Trials Involving Therapeutic Goods (November 2016)*.

7.1 Sponsor Responsibilities

The two documents, the *Australian Clinical Trial Handbook (August 2021)* and the *NHMRC Safety Monitoring and Reporting In Clinical Trials Involving Therapeutic Goods (November 2016)* give clear direction to Sponsor responsibilities.

A Sponsor:

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

7.1.1 Safety Data Monitoring

The Sponsor's plans for safety data monitoring should be documented in a Safety Monitoring Plan or similar document and be given to the PI prior to the commencement of the clinical trial.

It must be continually reviewed and updated during the trial, as real-time assessments of safety data are performed, and outcomes are made available.
A Sponsor may utilise an independent safety monitoring committee (e.g. Data Safety Monitoring Board) or independent individuals (e.g. a medical monitor) to:

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

7.1.2 Sponsor Reporting Requirements

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

Sponsor to provide to Investigator:

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

Sponsor to provide to Therapeutic Goods Administration:

- Significant safety issues that meet the definition of an Urgent Safety Measure (i.e. a measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety measure) must be notified within 72 hours, and all other significant safety issues must be notified within 15 calendar days of the Sponsor instigating or being made aware of the issue. It is strongly recommended that the Sponsor contact the TGA within 24 hours of an Urgent Safety Measure being taken, and if initial contact is by telephone, it should be followed-up with a written notification provided by facsimile or e-mail within 72 hours.
- All SUSARs occurring in Australian participants.
- For fatal or life threatening Australian SUSARs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days.
- For all other Australian SUSARs, no later than 15 calendar days after being made aware of the case.

Sponsor to provide to HREC:

- Updated IB as available which supports trial oversight, depicts a clear picture of evolving safety profile of the trial and provides evidence that the Sponsor is conducting its safety monitoring appropriately.
- Significant safety issues: those that meet the definition of an Urgent Safety Measure (i.e. a measure required to be taken immediately in order to eliminate an immediate hazard to a participant's health or safety measure) must be notified within 72 hours, and all other significant safety issues must be notified within 15 calendar days of the Sponsor instigating or being made aware of the issue.

7.2 Investigator Responsibilities

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

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

7.2.1 Safety Data Monitoring

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

7.2.2 Reporting Requirements

The reporting of safety reviews by the Investigator should be as per *NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)* or as detailed in

the Protocol. The safety reporting requirement in the Protocol cannot be less than that required by the NHMRC.

Clinical Trial Team communication To Sponsor

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

- All SAEs and SUSARs except those that are identified in the Protocol, safety monitoring plan or similar document or Investigational Brochure as not needing immediate reporting.
- Any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner).

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

- Significant safety issues which meet the definition of an Urgent Safety Measure instigated by the Investigator (i.e. a measure required to be taken immediately in order to eliminate an immediate hazard to a participant's health or safety measure).
- All Urgent Safety Measures instigated by the site as specified in the Protocol.
- All safety critical events/laboratory abnormalities identified in the Protocol as "critical to safety evaluations".
- Any additional requested information relating to reported deaths (e.g. autopsy reports and terminal medical reports).
- Additional requested information relating to reported deaths.

Within 15 days of instigating or becoming aware of the event:

- All other significant issues.

To Therapeutic Goods Administration (as a sponsor)

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

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

Clinical Trial Team Communication to Institution/Research Governance Officer

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

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

- Any information received from the Sponsor that may be new and have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial Protocol, including monitoring of safety.
- Notify CRGO of any clinical incidents recorded in Riskman as per Monitoring of Research Policy.

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Professor Gary Richardson	Group Director, Cabrini Research		18 September 2024

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