SOP Number: 120
SOP Title: Safety Data Monitoring and Reporting Requirements for Clinical Trials

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Amendment History

Version	Date	Author/s	Amendment Details
1.0	1 June 2010	Katrina Brosnan	New
2.0	December 2017	Roberta Lusa & Bernadette Morris-Smith,	All sections, incorporating ICH GCP E6 (R2) and teletrials: QH TELETRIAL PILOT VERSION 1.0
3.0	June 2018	Roberta Lusa	All sections, refinement after CRC input: PUBLIC RELEASE VERSION 3.0
4.0	April 2019	Roberta Lusa	Amendments post Round 1 Health Service Directive Consultation

1 Purpose

To describe the procedures and requirements related to the safety data collection, verification and reporting requirements for clinical trials involving Investigational Medicinal Products (IMP) and Devices (IMD), conducted under the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) Scheme. This also includes company sponsored post registration / post marketing surveillance studies.

2 Responsibility / Scope

This standard applies to all Queensland Health employees (including visiting health professionals, contractors, consultants and volunteers) who propose to undertake, administrate, review and/or govern human research involving Queensland Health patients, facilities and/ or staff. All study personnel involved in the clinical study must operate within their scope of practice.

In 2016, important changes to regulatory and safety guidance documents pertaining to the Sponsor's responsibilities were released, which change the Sponsor's reporting responsibilities to the Australian regulatory body, the TGA and to HRECs. Consequently, this SOP refers to both the Sponsor's and Investigator's responsibilities relating to safety monitoring.

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

3 Glossary

For an explanation of acronyms and the definition of terms used in these SOPs, please refer to Chapter Two: Glossary of the Australian ICH GCP (Including Teletrials) Standard Operating Procedures (SOP) Compendium.

4 Procedure

Where Satellite Sites are involved, staff will report safety issues directly to the Sponsor as per the timelines specified in the protocol and the safety monitoring plan or similar document in the same way as the Primary site. Certified Copies of the relevant safety reports/documentation generated at the Satellite Site will be sent to the Primary Site for filing in the Site Master File. The rules will be pre-determined as per SOP 70: The Study Master File.

NOTE: where a sponsor delivers 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 but only after the sponsor confirms that the report has no bearing on participant safety or trial conduct. There no longer is a requirement for Investigators to print, review and

file these reports. See NHMRC Safety Monitoring and Reporting In Clinical Trials Involving Therapeutic Goods Guidelines (November 2016).

4.1 Sponsor responsibilities

The two documents The Australian Clinical Trial Handbook and the NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods Guidelines (November 2016) give clear direction to sponsor responsibilities.

A sponsor:

- must be identified for all clinical trials
- has ultimate responsibility for the ongoing safety evaluation of the IMP/ IMD
- is responsible for generating and disseminating all safety communications
- Must ensure that the trial protocol has clear sections describing:
    a) *the assessment and management of risk (if not in an alternative document);*
    b) *safety reporting definitions, procedures, responsibilities and reporting timelines;*
    c) *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 clinical 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 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).

4.1.1 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 Principal Investigator 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.

4.1.2 Sponsor Reporting Requirement

The outcome of various safety reviews is reported directly to HRECs, investigator and the Therapeutic Goods Administration (TGA), by the Sponsor and must indicate the impact of each report on patient safety, trial conduct or trial documentation. The reporting of safety reviews by the sponsor should be as per NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods 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.

4.1.2.1 Sponsor to Provide to Investigator

- updated Investigator's Brochure at least annually
- 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 (ie a measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety measure) should be notified within 72 hours, and all other significant safety issues should be notified within 15 calendar days of the sponsor instigating or being made aware of the issue.

4.1.2.2 Sponsor to Provide to Therapeutic Goods Administration (TGA)

- significant safety issues that meet the definition of an urgent safety measure (ie a measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety measure) should be notified within 72 hours, and all other significant safety issues should be notified within 15 calendar days of the sponsor instigating or being made aware of the issue

- all suspected unexpected serious adverse reactions (SUSAR) 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

4.1.2.3 Sponsor to Provide to HREC

- updated Investigator's Brochure at least annually which supports trial oversight, depicts a clear picture of evolving safety profile of the trial and provides evidence that the sponsor is conducting its safety monitoring appropriately.
- 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) 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.

4.2 Investigator responsibilities

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

- provide the sponsor with all relevant information so that an appropriate safety analysis can be performed
- capture and assess all local safety events and report 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 30.

4.2.1 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 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.

4.2.2 Reporting Requirement

The reporting of safety reviews by the investigator should be as per NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods or as detailed in the protocol. The safety reporting requirement in the protocol cannot be less than that required by the NHMRC.

4.1.2.1 To Sponsor

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

- all SAEs and SUSARs except those that are identified in the protocol, safety monitoring plan or similar document or Investigator 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

4.1.2.2 To Therapeutic Goods Administration (TGA)

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

- Advise TGA of any safety issues which emerge during this process. Such data do not need to be submitted on a routine basis to the TGA during the trial, but should be available for submission to the TGA on request, and where applicable, submitted as part of an application for registration.
- 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) 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.

4.1.2.3 To Institution/Research Governance Officer

Within 72 hours of becoming aware of the event:

- significant safety issues 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)
- 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.

5 Guidance Documents

1. National Mutual Acceptance. Single Ethical Review of Multi-centre Human Research Projects. MONITORING AND REPORTING TABLES
2. NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (November 2016)
3. Australian Government Department of Health Report of suspected adverse reaction to medicines or vaccines: "Blue Card"

4. NMHRC Guidance on Data Safety Monitoring Boards (DSMBs) 2018

6 Appendices

Appendix 1: Sponsor reporting of SUSARs and USADEs to TGA (for trials conducted under the CTN or CTX schemes)
Appendix 2: Safety Reporting Assessment Flow Chart: IMP trial
Appendix 3 Report Flowchart for Investigational Medicinal Products Trials
Appendix 4 Safety Reporting Assessment Flow Chart: IMD trial
Appendix 5 Report Flowchart for Investigational Medicinal Devices Trials