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The Department of Research and Innovation, in collaboration with the Cancer Centre Clinical Trials Unit, has developed a series of standard operating procedures (SOPs) designed to facilitate good clinical trials practice and compliance with applicable regulatory requirements for clinical trial research at Bendigo Health. These SOPs are based on those developed by the Parkville Cancer Clinical Trials Unit (PCCTU) who have kindly granted permission for adaptation and use at Bendigo Health.

SOP 6: Management of Safety Information for Clinical Trial Research

Version No: 2.0
Effective Date: 20-Dec-2021
Supersedes: 01-Sep-2020
Review Date: 20-Dec-2023

	Final revisions by:	Approved on behalf of the Interdisciplinary Research Steering Committee by Chair:
Name	Dr. Rani Watts	Dr. Angela Crombie
Position Title	Clinical Trials Research Manager	Director of Research and Innovation
Signature		
Date	20-Dec-2021	20-Dec-2021

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1. Introduction and Background

International Council for Harmonisation (ICH) of Good Clinical Practice (GCP) guidelines defines the requirements to ensure that all clinical trial participants taking part in a clinical trial are safe and their rights protected.

The National Health and Medical Research Council (NHMRC) and local Human Research Ethics Committee (HREC) and ICH GCP safety reporting guidelines should be followed for the reporting of all internal and external safety information.

2. Objective

To describe the procedure related to the management of safety information for clinical trials research.

3. Scope

This standard operating procedure (SOP) applies to all clinical trials conducted by Bendigo Health.

4. Ownership and Responsibility

The sponsor has primary responsibility for monitoring the ongoing investigational product safety and reporting. The sponsor is expected to:

- Evaluate all safety information that is reported by investigators as well as safety information from other sources (NHMRC, 2016)
- Notify the Therapeutic Goods Administration (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 (NHMRC, 2016)
- Review the investigator brochure annually, providing the ethics committee and PI with any updates
- Submit an annual safety report to the ethics committee

The investigator reviews local safety events, responding as clinical care dictates, and reports to the sponsor all relevant information for safety analysis. The PI is expected to:

- Capture and assess all adverse events (AEs) that occur at the site as required and in accordance with the protocol (NHMRC, 2016)
- Report to the sponsor all serious adverse events (SAEs)

The relevant ethics committee assess the safety of proposed clinical trials and monitors the sponsor's ongoing safety monitoring arrangements.

The institution oversees any safety issues that may require local management.

5. Glossary of Terms

Please refer to Bendigo Health's *Clinical Trial Research Standard Operating Procedures Glossary of Terms* for a full supporting glossary.

6. Procedure

Bendigo Health endorses the NHMRC safety monitoring and reporting in clinical trials involving therapeutic goods guidance (2016).

6.1 Reporting Safety Events

6.1.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

The PI is responsible to:

a. Capture and assess all AEs that occur at the site as required and in accordance with the protocol. Where a paper medical record is used clarification of AE term, grade, causality and start and stop dates are documented in a supplementary source log.
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)
   - All urgent safety measure instigated by the site (NHMRC, 2016)

6.1.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The sponsor should:

- Assess and categorise SUSARs from investigator reports
- Report any Australian clinical trial participant SUSARs to the TGA, no later than 15 calendar days after being made aware of the event

The PI should:

- Report any SUSARs arising from site to the institution, within 72 hours of becoming aware of the event

6.1.3 Significant Safety Issues (SSIs) and Urgent Safety Measures (USMs)

Any safety information which has a bearing on patient safety or clinical trial conduct should be emailed to the PI and Research team.

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 (NHMRC, 2016).

USM require immediate action to eliminate an immediate hazard to a clinical trials participant's health or safety and are often acted on before being reported to the ethics committee, institution or TGA.

The sponsor should:

- Notify investigators, TGA and ethics committee within 72 hours

The investigator should:

- Report to the sponsor within 24 hours of USMs
- Report all SSIs to the institution within 72 hours of becoming aware of the event

Dear investigator letters (DILs) are used to notify investigators about new or updated safety information. When a dear investigator letter is determined to be a SSI requiring a USM by the PI, investigators should:

- Notify clinical trial participants immediately

When a DIL is determined not to be an SSI by the PI, investigators should:

- Notify clinical trial participants at their next visit

Sponsors should:

- Submit DILs to the ethics committee as a noting item

6.2 Reporting Safety Information

Any safety reports which have a bearing on patient safety or clinical trial conduct should be emailed to the PI and members of the research team.

6.3 Annual Safety Reports

The annual safety report should generally include:

- A brief description and analysis of new and relevant findings
- For IPs not on the Australian Register of Therapeutic Goods, a brief analysis of the safety profile of the investigational product (IP) 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 (NHMRC, 2016)

Sponsors should:

- Submit an annual safety report to the ethics committee

Drug safety update reports (DSUR) may be submitted as the annual safety report.

These reports along with the acknowledgement should be sent to site via email and will be filed in the electronic investigator site file.

6.4 Investigator Brochure (IB)

The sponsor should review the IB annually, providing the ethics committee and PI with any updates.

6.5 External Individual and Combined Reports

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 email. 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 (NHMRC, 2016).

Bendigo Health will not access sponsor portals to receive safety information. Safety information that has bearing on clinical trial participant safety or clinical trial conduct should only be communicated to site via SSI or USM as outlined in section 6.1.3. Individual case SUSARs or six monthly line listings will not be received, acknowledged or filed in the electronic investigator site file.

6.6 Training on Safety Information

Training on updated safety information will not be undertaken or documented, as outlined in *SOP 3: Clinical Trial Research Training* (see Related Documents).

7. Dissemination and Implementation

The Department of Research and Innovation at Bendigo Health is responsible for the dissemination and implementation of the Bendigo Health SOPs related to clinical research. Any content updates will be tabled at the Clinical Trials Sub-Group and the Interdisciplinary Steering Committee meetings. Content updates will be accompanied by relevant promotions and training.

Approved SOPs will be published on the Bendigo Health intranet and available through the SiteDocs portal. SOPs will be made available in hard copy format upon request to: clinicaltriasresearchsupport@bendigohealth.org.au.

Any updates to the existing approved SOPs will be disseminated internally, and will be effective immediately.

8. Monitoring Compliance and Effectiveness

SOP compliance will be monitored as part of the Bendigo Health SOP monitoring and audit process, initiated by the Clinical Trials Sub-group.

Any queries concerning the effectiveness of the SOP identified during the Bendigo Health monitoring and audit process or through use will be escalated to the Interdisciplinary Research Steering Committee to advise.

9. Review and Updating

This SOP will be reviewed every two years, or when changes to legislation or working practices impact upon the content of this document. This SOP may be merged with another SOP if appropriate or removed entirely if it becomes redundant.

10. Reference(s)

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) (2016)

National Health and Medical Research Council. (2016). Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods.

11. Related Document(s)

SOP Glossary of Terms
SOP 3: Clinical Trial Research Training

12. Amendment History

Version	Date	Amended By	Details of Amendment
2	20-Dec-2021	Jasmine Gillingham Dr. Rani Watts	• Revisions in line with amendments to those made by the Parkville Precinct Clinical Trial Unit; • Minor administrative amendments