Safety Reporting

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Part A: Reporting Procedures

A-1 Reporting to the Austin Health HREC via the Office for Research (OfR)

Matters involved	When to report	How to report
Significant Safety Issue (SSI) *(relates to USM)*	Immediate, no later than 72 hours of the measure being taken	**For Projects approved by Austin HREC**: 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Safety Report" from the form type. 3. Click create and select "Significant Safety Issue (SSI) as the type of safety event. 4. Complete the form. **For externally approved project where the safety event occurred at the Austin Site:** 1. Follow the external HREC's reporting procedures. 2. Once the event report was finalized by the external HREC, log into ERM Application. 3. Under the SSA – Austin Health form, click "Create Sub-Form". Choose "Site Notification Form". 4. Click "Create" and complete the form.
Serious Breach	Immediate, no later than 72 hours after becoming aware of the event	**For Projects approved by Austin HREC:** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Serious Breach Report" from the form type. 3. Click create and complete the form. **For externally approved project where the safety event occurred at the Austin Site:** 1. Follow the external HREC's reporting procedures.

		2. Once the event report was finalized by the external HREC, log into ERM Application. 3. Under the SSA – Austin Health form, click "Create Sub-Form". Choose "Site Notification Form". 4. Click "Create" and complete the form.
Suspected Breach	Immediate, no later than 72 hours after becoming aware of the event	**For Projects approved by Austin HREC:** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Suspected Breach Report" from the form type. 3. Click create and complete the form. **For externally approved project where the safety event occurred at the Austin Site**: 1. Follow the external HREC's reporting procedures. 2. Once the event report was finalized by the external HREC, log into ERM Application. 3. Under the SSA – Austin Health form, click "Create Sub-Form". Choose "Site Notification Form". 4. Click "Create" and complete the form.
Investigator Brochure amendments	See how to report	Please follow the steps outlined in the SOP – Amendment requests.

A-2 Reporting to the Office for Research (OfR)

Matters involved	When to report	How to report
SSI *(results in Urgent amendment, Temporary Halt, Early Termination of study)*	Immediately, no later than 15 calendar days after becoming aware of the event	**For Projects approved by Austin HREC:** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Safety Report" from the form type. 3. Click create and select "Significant Safety Issue (SSI) as the type of safety event. 4. Complete the form. **For externally approved project where the safety event occurred at the Austin Site:** 1. Follow the external HREC's reporting procedures. 2. Once the event report was finalized by the external HREC, log into ERM Application. 3. Under the SSA – Austin Health form, click "Create Sub-Form". Choose "Site Notification Form". 4. Click "Create" and complete the form.
SUSARs	Immediately, no later than seven calendar days after becoming aware of the event	**For Projects approved by Austin HREC:** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Safety Report" from the form type. 3. Click create and select "Suspected Unexpected Serious Adverse Reaction (SUSAR) as the type of safety event. 4. Complete the form.

		For externally approved project where the safety event occurred at the Austin Site: 1. Follow the external HREC's reporting procedures. 2. Once the event report was finalized by the external HREC, log into ERM Application. 3. Under the SSA – Austin Health form, click "Create Sub-Form". Choose "Site Notification Form". 4. Click "Create" and complete the form.
USADEs	Immediately, no later than seven calendar days after becoming aware of the event	**For Projects approved by Austin HREC:** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Safety Report" from the form type. 3. Click create and select "Unanticipated Serious Adverse Device Effect (USADE)" as the type of safety event. 4. Complete the form. **For externally approved project where the safety event occurred at the Austin Site:** 1. Follow the external HREC's reporting procedures. 2. Once the event report was finalized by the external HREC, log into ERM Application. 3. Under the SSA – Austin Health form, click "Create Sub-Form". Choose "Site Notification Form". 4. Click "Create" and complete the form.
Annual Safety Reports	Along with Project Progress Report or after submission of Project Progress Report	**The Annual Safety Report is only needed for projects approved by the Austin Health HREC.** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Annual Safety Report" from the form type. 3. Click create and complete the form.
Data Safety Monitoring Board (DSMB) Reports		**The DSMB Report is only needed for projects approved by the Austin Health HREC.** 1. Log into ERM Application. 2. Under HREA form, click "Create Sub-Form". Choose the "Project Notification Form" from the form type. 3. Click create and complete the form.

A-3 Events that do not need to be reported to the Austin Health or OfR

- Single Serious Adverse Events (SAEs)
- Serious Adverse Reactions (SARs)
- Adverse Events (AEs) that do not affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Part B: Definitions & Responsibilities

1.1 Commercial Sponsor

A Commercial Sponsored project is defined when a project is funded by an Australian arm of an International Pharmaceutical and/or Biotechnology company, or an Australian Clinical Research Organisation (CRO) or an Australian Private Company.

I. When the Site Principal Investigator has reported a safety event to the Sponsor, the Sponsor must:
   a. Ensure the Site Principal Investigator has taken appropriate action to eliminate the hazard
   b. Report to Lead HREC
   c. Report to TGA
   d. Report to all Site Principal Investigators and the Coordinating Investigator (if different from the Site Principal Investigator).

II. If the Sponsor's causality assessment conflicts with the assessment made by the Site Principal Investigator, the opinions of both the investigator and the sponsor should be provided with any report sent to the TGA.

III. Reporting timelines for different safety event types are outlined.

1.2 Institution, including role of Institutional Delegate/s (e.g., staff within Office for Research)

The institution is a public or private entity that employs the Coordinating Investigator and/or Site Principal Investigator and/or any Associate Investigator/s. The institution is responsible for ensuring:

a) Assessing 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/governance 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. As outline in this document.

Some institutions may have delegated their authority staff within an Office for Research. This Office is responsible for receiving and triaging safety events, and alerting relevant departments within the institution, such that the institution has appropriately reviewed and assessed the impact on medico-legal risk, insurance and site feasibility.

The Site Institution is the place where the safety event occurred. The Site Institution must review the safety event to assess if the safety event impacts on their medico-legal risk, the responsible conduct of research, adherence to contractual obligations, and where applicable, facilitate the implementation of corrective and preventative action.

I. The Site Institution will often have a Delegated Officer (within the Office for Research) to report these events to. The Site Institution must:
   a. Immediately upon receiving the safety event, notify the relevant areas to the relevant areas that have oversight of:
      - Site Institution's Expert Review Committee /Independent Data Management Safety Monitoring Board
      - Legal & Insurance Departments
      - Quality and Safety
   b. Receive evidence from the Site Principal Investigator that they have reported the safety event to the Sponsor, lead HREC and TGA.

II. The Site Institution will provide any feedback in writing to the Site Principal Investigator, Sponsor, Coordinating Investigator and if appropriate, the lead HREC, within 28 calendar days of becoming aware of the event.

III. If the safety event impacts on the institution's ability to carry out the study in a safe manner in accordance with its insurance, legal/contractual and Quality & Safety requirements, the institution may choose to close the study in consultation with the Site Principal Investigator and Sponsor.

IV. The Site Institution Delegated Officer will maintain a confidential registry of all safety events which have occurred at their site.

1.3 Coordinating Investigator: Authorised person responsible on a day-to-day basis for the conduct of the study. This person is identified by the Pharmaceutical and/or Biotechnology Company or CRO.

I. In the event of a safety event (as defined in Table 1), the Site Principal Investigator is responsible for:
   a. Taking immediate action to eliminate the hazard
   b. Reporting the safety event to the Sponsor within 24 hours of becoming aware
   c. Reporting the safety event to the Site Institution according to the institutional policy
   d. Tracking the safety event using the Adverse Event Tracker provided for the site

II. As the Sponsor takes responsibility for reporting safety events, there is no need for the Site Principal Investigator to report the safety event to the Coordinating Investigator for Commercially Sponsored Clinical Trials.

III. If the SSI requires an immediate change to study documentation to address the safety hazard, this change can take place prior to receiving written approval from the Lead HREC. However, written approval must be applied for within 15 calendar days of becoming aware of the event.

1.4 Site Principal Investigator: The Site Principal Investigator is defined as the person who has taken responsibility of the clinical trial at the site but does not hold overall responsibilities across all sites. This person is identified by the Pharmaceutical and/or Biotechnology Company or CRO.

If the safety event occurred at the Coordinating Investigator's site, the reporting requirements are the same as the Site Principal Investigator requirements outlined in Section 1.3.

1.5 Lead Human Research Ethics Committee (HREC)

The lead HREC is the allocated HREC which provides ethical approval for the project. The lead HREC is identified based on the following information:

a) Where the study is conducted
b) Single or multisite
c) the Coordinating Investigator and Site Principal Investigator requirements (for multisite projects)

The lead HREC must receive a written report detailing (1) reasons for the SSI and (2) Plan for corrective and preventative action. The Lead HREC safety event report template must be used when reporting to them.

I. Reporting timeframes for safety events to the lead HREC are outlined in Table 1.

II. The lead HREC is not required to approve the urgent safety amendment prior to implementation. However, notifications of safety events should be reviewed at the meeting of the lead HREC or delegated sub-committee or executive.

III. The lead HREC should consider whether the measures taken are appropriate in relation to the apparent risk to participants, and what further action the Site Principal Investigator/Coordinating Investigator/Sponsor propose to take, for example, the submission of amendments to the protocol. Where any concern arise about the safety or welfare of participant or the conduct of the research, the lead HREC should address these with the site Principal Investigator/Coordinating Investigator/Sponsor and Site Institution (if appropriate) in writing.

1.6 Therapeutic Goods Administration (TGA)

The TGA must be notified of Clinical trials of unapproved therapeutic goods conducted in Australia under the Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) Schemes. The TGA may

1. Conduct an audit of clinical trials where there are safety concerns
2. Stop trial if it is in the public's interest

I. It is the Sponsor's responsibility to report safety events to the TGA.

II. The process to notify the TGA is outlined on the TGA's website. This information can be viewed at https://www.tga.gov.au/book-page/your-regulatory-reporting-requirements. Please note there are different processes for reporting SUSARs and USADEs.

III. The Sponsor must provide a copy of any correspondence from the TGA to Delegated Officer at the Site Institution.

IV. The TGA can decide to:

a. Conduct an audit of the clinical trial
b. Stop the clinical trial

1.7 Significant Safety Issue (SSI)

A SSI is a safety event that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. There are four types of actions you can report SSIs under. They are:

a) Urgent Safety measure (USM) is a measure required to be taken in order to eliminate an immediate hazard to participant's health and/or safety
b) Urgent amendments to Study Documentation that impact on Participant Safety
c) Temporary Halt
d) Early Termination of a study for safety reasons

1.8 Urgent Safety Measure (USM)

USM is a measure required to be taken in order to eliminate an immediate hazard to participant's health and/or safety.

1.9 Suspected Unexpected Serious Adverse Reaction Reports (SUSARs) (investigational products)

SUSARs are classified as events that lead to:

a) Death
b) Are life-threatening
c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability
e) Consists of a congenital anomaly or birth defect

1.10 Unanticipated Serious Adverse Device Effects (USADEs) for Medical Devices:

USADEs are classified as events that lead to that has not been identified in the risk report and has led to:

a) Death
b) Serious deterioration in the health of the participants that resulted in
    - Life-threatening illness or jury
    - Permanent impairment of a body structure or function
    - In-patient or prolonged hospitalisation
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function
c) Fetal distress, death or congenital abnormality or birth defect

1.11 Protocol Deviations and violations

A protocol deviation/violation is a failure to comply with the final study protocol as approved by the Human Research Ethics Committee. A violation is a serious non-compliance with the protocol that can result in the exclusion of a participant or their results from the study and in some cases a charge of research misconduct.

Changes to, or non-compliance with the research protocol without prior approval from the sponsor or the approving HREC that may (or has the potential to) impact or have a significant effect on the participants right to safety, welfare, privacy and/or on the integrity of the data. Deviations may result from the action of a researcher, research staff and/or the participant.

Examples of a protocol deviations:

- Failure to follow the HREC approved recruitment strategy, the use of unapproved recruitment materials or recruitment methods;
- Failure to obtain valid informed consent or complete study screening processes according to the approved protocol;
- Loss of laptop computer or portable storage devices that contained identifiable, private information about participants;
- Distribution of incorrect or study medication, dose or the use of expired study medications;
- Not following inclusion/exclusion criteria;
- A rescheduled study visits or follow up visit, failure to collect an ancillary self-report questionnaire;
- Participant's refusal to complete scheduled research activities;

- Failure to provide medical assistance, support or complete safety follow up to participants who request assistance;
- Changes to the research methodology, data collection methods, plan for disseminating the research results without prior approval from the sponsor or approving HREC.

Protocol deviations occurring at a site must be documented in Investigator Site Files and need to be reported by site principal investigator to the Coordinating Principal Investigator.

The Coordinating Principal Investigator must review the protocol deviation, along with the clinical trial protocol to establish the corrective actions and preventative steps to prevent the deviation from reoccurring.

The protocol deviation and corrective action plan must be reported to the Sponsor's Delegate by the Coordinating Principal Investigator or Coordinating Research Team using the protocol deviation report form.

1.12Serious Breach

A serious breach occurring at a participating site must be reported by the site Principal Investigator to the Coordinating Principal Investigator within a specified timeframe in the tables above.

The Coordinating Principal Investigator must review the serious breach, along with the clinical trial protocol to develop a Corrective and Preventive Action (CAPA) that defines the steps to prevent the serious breach from reoccurring.

The serious breach report and the CAPA is to be provided to the lead HREC and the sponsors delegate for review and approval.

A serious breach is defined as a breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial. Examples of serious breaches include but are not limited to:

- Persistent or systematic non-compliance with the instructions for completing consent forms, safety monitoring forms, case report forms or data collection tools that results in continued missed or incomplete data collection.
- Failure to record or report adverse events, serious adverse events, suspected unexpected serious adverse reactions, significant safety issues where urgent safety measures were implemented.
- Failure to conduct clinical trial procedures in accordance with the clinical trial delegation log.
- Widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects.
- Failure to report investigational medical product or device defects to the clinical trial sponsor or any relevant regulatory body.
- Failure to conduct research in conformity with the issued approvals, permits or licences in accordance with required laws, regulations, disciplinary standards and Austin Health policies relating to the responsible and/or safe conduct of research.
- Concealing or facilitating breaches (or potential breaches) of the Research Code by others.
- Conducting research without the requisite approvals, permits or licences required by laws, regulations, disciplinary standards and Austin Health policies related to the responsible and/or safe conduct of research.
- Failure to conduct Research as approved by an ethics review body where that conduct leads to (or has the potential to) results in participant harms.
- Conducting Research without ethics approval as required by the National Statement on Ethical Conduct in Human Research where that conduct leads to (or has the potential to) result in participant harms.
- Any breaches as outlined in the Austin Health Research Misconduct Procedure or the Australian Code for responsible conduct of research that leads to (or has the potential to) result in participant harms.

1.13 Research Misconduct Investigations as a result of safety reporting

Protocol deviation and/or serious breach reports where a Austin Health researcher, staff or student is responsible for the protocol deviation or the serious breach will be reviewed as per the Austin Health Research Misconduct Procedure to establish whether a breach of the Australian Code of Responsible Conduct of Research has occurred.

Protocol deviation and/or serious breach reports where the Austin Health's Delegate determines that the site Principal Investigator(s)/ site personnel are responsible for a protocol deviation or the serious breach will be referred onto their responsible institution for review under their own Research Misconduct procedures to establish whether a breach of the Australian Research Code for the Responsible Conduct of Research has occurred.

Part C: Version Control

Document History	
Version	**Summary of Changes**
2.0	• Part A – Change of section format • Part A – Included ERM submission steps • Part A – Revised reporting timeline and requirement for each type of safety report

Part D: Reference

- Australian Code For The Responsible Conduct Of Research (2018)
- National Statement on Ethical Conduct in Human Research (2007) - Updated 2018
- Safety monitoring and reporting in clinical trials involving therapeutic goods (2016)
- Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods (2018)