Central Adelaide
Local Health Network

Safety Monitoring and Reporting for Clinical Trials Involving Therapeutic Goods and Reporting Serious Breaches of Good Clinical Practice or the Protocol for Clinical Trials Involving Therapeutic Goods

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Health
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Contents

1. Purpose

The purpose of this guideline is to describe the regulatory and good practice requirements for safety monitoring and reporting clinical trials involving therapeutic goods and reporting of serious breaches of Good Clinical Practice (GCP) or the protocol for clinical trials involving therapeutic goods.

This document sets a framework to define the roles and responsibilities of trial sponsors, investigators, the Human Research Ethics Committee (HREC), and the institution to ensure a consistent approach to safety monitoring and reporting across Central Adelaide Local Health Network (CALHN).

This guideline has been written in accordance with, and should be read in conjunction with, the National Health and Medical Research Council (NHMRC) *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Products November 2016* and the NHMRC *Reporting of Serious Breaches of GCP or the Protocol for Trials Involving Therapeutic Goods 2018.*

2. Scope

This guideline applies to both commercially and non-commercially sponsored clinical trials that are being conducted at CALHN which involve therapeutic goods. This guideline also applies to clinical trials involving therapeutic goods where the CALHN HREC is the approving HREC, but there are no CALHN sites participating.

3. Safety and Monitoring Reporting for Therapeutic Goods Clinical Trials

This section describes the framework for safety monitoring and reporting for clinical trials involving Investigational Medicinal Products (IMPs) and Investigational Medical Devices (IMDs), under the Clinical Trial Exemption (CTX) or Clinical Trial Notification (CTN) schemes.

3.1 Definitions/Acronyms

Definitions Specific to Investigational Medicinal Product Trials	
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, a new patient group or when used to gain further information about an approved use. **Note:** This definition includes biologicals used as investigational medicinal products.
Biological	An item made from, or containing, human cells or human tissues, and that is used to treat or prevent disease or injury, diagnose a condition of a person, alter the physiological processes of a person, test the susceptibility of a person to disease, replace or modify a person's body part(s). **Examples include:** • Human tissue therapy products (e.g. skin, tissues, bone for grafting) • Processed human tissues (e.g. demineralised bone, collagen) • Human cellular therapy products (e.g. cartilage cells, cultured skin cells) • Immunotherapy products containing human cells • Genetically modified human cellular 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. **Comment:** All Adverse Events (AEs) judged by either the reporting investigator or the sponsor as having a **reasonable possibility of a causal relationship** to an Investigational Medicinal Product (IMP) would qualify as adverse reactions.

	The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship. **Note:** The following are examples of types of evidence that would suggest a causal relationship between the IMP and the AE: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture) • An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
Investigator's Brochure (IB)	The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product that are relevant to the study of the product in humans.
Product Information (PI)	In relation to therapeutic goods, information relating to the safe and effective use of the goods, including information regarding the usefulness and limitations of the goods. **Note:** In a trial in which the Investigational Medicinal Product (IMP) is an approved product, the product information may replace the investigator's brochure. If the conditions of use differ from those authorised, the product information should be supplemented with a summary of relevant clinical and non-clinical data that supports the use of the IMP in the trial. The Australian product information should be used where available for each trial IMP adopted across Australian sites.
Reference Safety Information (RSI)	The information contained in either an investigator's brochure or approved Australian product information (or another country's equivalent) that contains the information used to determine what adverse reactions are to be considered **expected adverse reactions** and on the frequency and nature of those adverse reactions.
Safety Critical Adverse Events	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluation that should be reported to the sponsor according to the reporting requirements specified in the protocol.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	Any Adverse Event (AE)/Adverse Reaction (AR) 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. **Note:** Life-threatening in the definition of a serious AE or serious AR refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. **Note:** Medical and scientific judgement should be exercised in deciding whether an AE/AR should be classified as serious in other situations. **Important medical events** that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
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.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI). **Note:** The RSI should be contained in the investigator's brochure for an unapproved medicinal product or product information (PI), (or another country's equivalent of the PI) for an approved medicinal product.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. **Note:** This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from human research ethics committees or institutions.

Definitions Specific to Investigational Medical Device Trials	
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. **Note:** This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
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 (IMD). **Note:** This definition includes events related to the IMD or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to IMDs.
Device Deficiencies	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. **Note:** Device deficiencies include malfunctions, use errors, and inadequate labelling.
Investigational Medical Device (IMD)	Medical device being assessed for safety or performance in a clinical investigation. **Note:** This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials, or design changes.
Investigator's Brochure (IB)	Compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation.
Medical Device	Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article: a. Intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following: • Diagnosis, prevention, monitoring, treatment or alleviation of disease • Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap • Investigation, replacement or modification of the anatomy or of a physiological process • Supporting or sustaining life • Control of conception • Disinfection of medical devices, and

	b. That does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means
Serious Adverse Device Effect	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
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 • In-patient or prolonged hospitalisation, or • Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function c. Led to foetal distress, foetal death or a congenital abnormality or birth defect **Note:** Planned hospitalisation for a pre-existing condition, or a procedure required by the clinical investigation plan (protocol), without serious deterioration in health, is not considered a serious adverse event.
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.
Unanticipated Serious Adverse Device Effect (USADE)	A Serious Adverse Device Effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (and/or investigator's brochure/instructions for use). **Note:** Anticipated SADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report (and/or investigator's brochure/instructions for use).
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. **Note:** This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from human research ethics committees or institutions.

3.2 Assessment of Adverse Events

Each Adverse Event (AE) must be evaluated for:

Seriousness: An assessment of whether the AE meets the definition of serious or not serious.

Causality: A clinical assessment of whether the AE is related or not related to the IMP or to the use of the IMD.

Expectedness: An assessment of whether the Adverse Reaction (AR) or Adverse Device Effect (ADE) was expected or unexpected. Assessed using the trials reference safety information (current investigator's brochure or product information).

3.3 Responsibilities

3.3.1 Sponsor

Sponsors must have safety monitoring processes that are based on the risk, size and complexity of the proposed research. In trials with small numbers of participants, e.g. pilot or first in human trials, risks may more readily become apparent through close monitoring of AEs whereas in larger trials, risks are often better assessed through statistical comparisons of treatments. As such, sponsors must determine the most appropriate arrangements for ongoing monitoring and be prepared to justify these arrangements to the reviewing HREC.

Sponsors should evaluate all safety information that is reported by investigators as well as safety information from other sources. It is recognised that a non-commercial sponsor does not have access to all the safety data maintained by a commercial sponsor; however, non-commercial sponsors are responsible for evaluating all safety information available to them. To enhance the capacity of non-commercial sponsors to fulfil their responsibilities, entities that provide therapeutic goods to or receive therapeutic goods from other entities should share safety information with each other.

When the sponsor is CALHN, it may delegate some or all sponsor functions to the principal investigator or other third party (e.g. trial coordinator). When a principal investigator is delegated sponsor functions, they must undertake both the investigator and sponsor responsibilities.

For trials involving therapeutic goods, this guideline requires sponsors to adhere to the NHMRC *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods 2016* requirements as detailed in Part 1, Section C.1 for IMP trials and Part 2, Section C.1 for IMD trials.

3.3.2 Principal Investigator

Investigators must assess all local safety events and should act on any events as clinical care dictates. 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.

For IMP trials, the principal investigator must:

a. Capture and assess all AEs that occur at the site as required and in accordance with the protocol.

b. Report to the sponsor within **24 hours** of becoming aware of the event:
   - All Serious Adverse Events (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 Measures (USMs) instigated by the site.

c. Report to the sponsor as specified in the protocol:
   - All safety critical events.
   - Any additional requested information relating to reported deaths.

d. Report to the institution within **72 hours** of becoming aware of the event:
   - All Significant Safety Issues (SSIs).
   - SSI's occurring at an external site implemented as an USM, as an amendment or as a temporary halt/early termination of a trial.
   - Sudden Suspected Unexpected Serious Adverse Reactions (SUSARS).

For IMD trials, the principal investigator should:

a. Record every AE and observed device deficiency, together with an assessment and report to the sponsor as required by the clinical investigation plan.

b. Report to the sponsor without unjustified delay, all SAEs and device deficiencies that could have led to a serious adverse device effect.

c. Report to the sponsor within **24 hours** any USM instigated at the site.

d. Report to the sponsor pregnancies that occur while a participant is on a clinical trial as specified in the clinical investigation plan.

e. Follow-up any pregnancy until outcome (e.g. birth or spontaneous abortion) and report any incidents of congenital abnormality/birth defect as an SAE.

f. Supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting.

g. Report to their institution without undue delay and **no later than 72 hours** of the principal investigator becoming aware of the event.
   - All SSI's occurring at a local site
   - SSI's occurring at an external site implemented as an USM, as an amendment or as a temporary halt/early termination of a trial
   - Unexpected Serious Adverse Device Events (USADEs).

3.3.3 Human Research Ethics Committee

The sponsor, through their independent safety monitoring arrangements has the primary responsibility for monitoring the ongoing safety of the IMP or the IMD. The HREC must be satisfied that the sponsor's safety monitoring arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial.

The HREC will:

a. Assess the safety of proposed trials, including whether the evaluation of the anticipated benefits and risks is satisfactory and ensure that the sponsor has proportionate systems in place to mitigate and manage any identified risks.

b. Be satisfied that the sponsor's ongoing safety monitoring arrangements are adequate, including the justification for appointing/not appointing a data safety monitoring board, any 'stopping rules' and/or criteria for withdrawing individual participants from the trial.

c. Be satisfied that the sponsor understands their obligation to report to the HREC anything that may adversely affect the safety of participants or the conduct of the trial, particularly amendments relating to changes made to the device design and manufacturing process, and other information that may alter risks and benefits.

d. Keep under review the adequacy and completeness of the informed consent process and documentation in the light of new information about risks and benefits.

e. Assess whether changes to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethics approval.

f. Advise the Therapeutics Goods Administration (TGA), investigators and their institutions of any decision to withdraw approval.

3.3.4 Institution

The institution's responsibilities and oversight of safety information in clinical trials will differ depending on whether they are hosting externally sponsored clinical trials or supporting locally led non-commercial trials. In both cases the institution must ensure that their site(s) understand and comply with sponsor requirements. The institution will have oversight and act on any issues that may require management, such as disputes or litigation resulting from trials. Where the institution is also named as the trial sponsor, the institution will also assume the sponsor responsibilities.

The institution will:

a. Assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trials continued site 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. This supporting document(s) should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator-initiated or collaborative group trials.

3.4 Table 1: Summary of Reporting

3.4.1 Table 1: Sponsor and Investigator Safety Reporting to the Human Research Ethics Committee and the Institution for Clinical Trials Involving Therapeutic Goods

Responsible Party	Event	Timeline	To Who	How
Sponsor	SSI's implemented as an USM, as an amendment or as a temporary halt or early termination of a trial	Without undue delay and no later than **72 hours** of the measure being taken	The HREC	**Approved by CALHN HREC:** Complete the CALHN Research Safety Report, submit to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:** Refer to relevant HREC
Sponsor	All other SSI's	Within **15 days** of the sponsor instigating or being made aware of the issue	The HREC	**Approved by CALHN HREC:** Complete the CALHN Research Safety Report, submit to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:** Refer to relevant HREC
Sponsor	Annual safety report The Executive Summary of safety information produced for international regulators, such as a Development Safety Update Report (DSUR), may serve as the annual safety report (a full DSUR is not required)	May be aligned with the reporting cycles of global companies or aligned with the annual progress report	The HREC	**Approved by CALHN HREC:** Sponsor to provide written report or the executive summary of safety information produced for international regulators to the Principal Investigator for review. Submit the report to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:** Refer to relevant HREC
Sponsor	Investigator Brochure (IB) updates and interim addenda	When updates are generated	The HREC	**Approved by CALHN HREC:** Complete the CALHN Research Amendment Form and submit with the updated documentation to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:** Refer to relevant HREC
Principal Investigator	All SSI's occurring at a local site	**Without undue delay and no later than 72 hours** of becoming aware of the event	To the institution where the issue occurred	**Occurring at a CALHN site, approved by CALHN HREC:** Complete the CALHN Research Safety Report, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a CALHN site, approved by external HREC:** Complete the CALHN Research Safety Report, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a NALHN site, approved by CALHN HREC:** Contact HealthNALHNRgo@sa.gov.au **Occurring at an external site, approved by CALHN HREC:** Refer to relevant Research Governance Office
Principal Investigator	SSI's occurring at an external site implemented as an USM, as an amendment or as a temporary halt/early termination of a trial	**Without undue delay and no later than 72 hours** of becoming aware of the event	To the institution where the issue occurred	**Occurring at a CALHN site, approved by CALHN HREC:** Complete the CALHN Research Safety Report, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a CALHN site, approved by external HREC:** Complete the CALHN Research Safety Report, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a NALHN site, approved by CALHN HREC:** Contact HealthNALHNRgo@sa.gov.au

				Occurring at an external site, approved by CALHN HREC: Refer to relevant Research Governance Office
Responsible Party	**Event**	**Timeline**	**To Who**	**How**
Principal Investigator	Suspected Unexpected Serious Adverse Reactions (SUSARs) and Unanticipated Serious Adverse Device Effects (USADEs)	Within **72 hours** of becoming aware of the event	To the institution where the issue occurred	**Occurring at a CALHN site, approved by CALHN HREC**: Complete the CALHN Research Safety Report, submit to Health.CALHNResearchEthics@sa.gov.au **Occurring at a CALHN site, approved by external HREC:** Email notification to Health.CALHNResearchGovernance@sa.gov.au **Occurring at a NALHN site, approved by CALHN HREC:** Email notification to HealthNALHNRgo@sa.gov.au **Occurring at an external site, approved by CALHN HREC:** Refer to relevant Research Governance Office

3.4.2 Table 2: Investigator Safety Monitoring Reporting to the Sponsor for Clinical Trials Involving Therapeutic Goods

Responsible Party	Event	Timeline	To Who	How
Investigational Medicinal Procedures				
Principal Investigator	All Serious Adverse Events (SAEs), except those that are identified in the protocol as not needing immediate reporting	Within **24 hours** of becoming aware of the event	Sponsor	As defined by the sponsor
Principal Investigator	All safety critical Adverse Events (AEs)	As specified in the protocol	Sponsor	As defined by the sponsor
Principal Investigator	Urgent Safety Measures (USMs) instigated at a site	Within **24 hours**	Sponsor	As defined by the sponsor
Investigational Medical Devices				
Principal Investigator	All Serious Adverse Events (SAEs) and device deficiencies	As per the Clinical investigation plan and without unjustified delay	Sponsor	As defined by the sponsor
Principal Investigator	Urgent Safety Measures (USMs) instigated by the principal investigator	Within **24 hours**	Sponsor	As defined by the sponsor

4. Reporting of Serious Breaches of GCP or the Protocol for Clinical Trials Involving Therapeutic Goods

Although GCP requires all deviations to be reported to the trial sponsor, not all deviations require reporting to review bodies. HRECs need only be made aware of the small sub-set of deviations that have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the clinical trial (hereinafter referred to as serious breaches). Serious breaches occurring at a site must also be reported by the investigator to their institution, as they may impact on medico-legal risk, the responsible conduct of research, or adherence to contractual obligations.

This section describes the framework for reporting of serious breaches of GCP or the protocol for trials involving IMPs and IMDs, under the CTX or CTN schemes.

4.1 Definitions/Acronyms

Definitions Specific to Breaches in Therapeutic Goods	
Audit	A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures, Good Clinical Practice, and the applicable regulatory requirement(s).
Clinical Trial	Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.
Commercial Trial	A trial that is funded and sponsored by a commercial company, where the company designs the protocol and owns the results and intellectual property rights arising from the trial.
Coordinating Principal Investigator (CPI)	a. In relation to a clinical trial conducted at a single trial site, the principal investigator at that site b. In relation to a clinical trial conducted at more than one trial site, the health professional, whether or not he or she is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.
Deviation	Any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol.
Principal Investigator (PI)	The person responsible, individually or as a leader of the research team at a site, for the conduct of a trial at that site. In a single centre trial, the principal investigator may also be the coordinating principal investigator.
Non-Commercial Trial	A trial where a non-commercial (not for profit) organisation retains control of the protocol and is the trial sponsor. Non-commercial trials are usually publically funded (e.g. by government/charities), but may also be funded/supported by a commercial company.
Serious Breach	A breach of good clinical practice or the protocol that is likely to affect to a significant degree: a. The safety or rights of a trial participant, or b. The reliability and robustness of the data generated in the clinical trial. **Note:** this guidance's definition of **serious breach** differs from the definition in the National Health and Medical Research Council *Australian Code for the Responsible Conduct of Research* and is about deviations from the requirements of Good Clinical Practice or the clinical trial protocol.
Significant Safety Issue	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.
Suspected Breach	A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor.

Third Party	Any entity (other than the trial sponsor) wishing to report a suspected breach.
Urgent Safety Measure	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. **Note**: An urgent safety measure can be instigated by either the investigator or sponsor and can be implemented before seeking approval from human research ethics committees or institutions.

4.2 Responsibilities

4.2.1 Sponsor

Sponsors have primary responsibility for determining whether any suspected breach meets the definition of a serious breach. In practice, this assessment is often conducted or overseen by the group tasked with monitoring the general quality of the trial and its adherence to the protocol. In particular, the judgement on whether a breach is likely to have a significant impact on the reliability and robustness of trial data should be made by the sponsor and depends on a variety of factors; for example, the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, and the impact of excluding the data from the analysis. However, if the sponsor is unsure whether a potential serious breach has significant impact on the rights or safety of participants, they should contact the reviewing HREC for advice.

When the sponsor is CALHN, it may delegate some or all sponsor functions to the principal investigator or other third party (e.g. trial coordinator). When a principal investigator is delegated sponsor functions, they would undertake both the investigator and sponsor responsibilities.

For trials involving therapeutic goods, this guideline requires sponsors to adhere to the NHMRC *Reporting of Serious Breaches of GCP or the Protocol for Trials Involving Therapeutic Goods 2018* requirements as detailed in Section 4.

4.2.2 Third Parties

The majority of suspected breaches will be identified by the sponsor either through routine monitoring or through direct reporting of deviations from trial sites. Sponsors may also identify serious breaches that have occurred as a result of a failure of their own quality systems, which they should report in the same manner. However, some serious breaches may be identified by third parties (e.g. trial sites) who wish to report directly to the reviewing HREC. This would usually be appropriate if:

a. The investigator/institution has good evidence that a serious breach has occurred but the sponsor disagrees with their assessment and is unwilling to notify the HREC.

b. The investigator/institution has become aware that the sponsor may have committed a serious breach.

4.2.3 Principal Investigator

The principal investigator must:

a. Ensure that the trial team is aware of the process for reporting serious breaches

b. Report any suspected breaches to the sponsor within **72 hours** of becoming aware of the suspected breach. Note: Exceptionally, the investigator, in liaison with their institution, may report the suspected breach directly to the HREC.

c. Report all serious breaches that have been confirmed by the sponsor as occurring at the site to their institution within **72 hours** of being notified of the serious breach.

d. Provide any follow-up information as required.

e. Work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions that may be indicated.

3.2.4 Human Research Ethics Committee

The role of the HREC in reviewing serious breaches is to evaluate the impact of the serious breach on the continued ethical acceptability of the study and to satisfy itself that the serious breach is managed appropriately; for example, through an amendment to trial documentation. Serious breaches may raise issues on which ethical advice is required; for example, whether participants should be re-consented if a report of a serious breach has identified inadequacies in the consent process. HRECs may also assess whether any corrective and/or preventative actions implemented or planned are appropriate and have adequately addressed the underlying issue.

Where the sponsor has notified the HREC of the serious breach, the HREC will:

a. Assess the report, including any corrective and preventative actions implemented, and provide any necessary feedback to the sponsor.

b. For trials conducted under the CTX/CTN scheme, inform the TGA and the sponsor if the notification of a serious breach leads to the suspension or withdrawal of the ethics approval for the trial.

Where a third party has notified the HREC of a suspected breach, the HREC will:

a. Inform the sponsor of the suspected breach report.

b. If the sponsor confirms to the HREC that a serious breach has not occurred, but the rationale for not reporting the serious breach is unclear or contested by the HREC, request a written justification or explanation from the sponsor.

c. For trials conducted under the CTX/CTN scheme, inform the TGA and the sponsor if the notification of a serious breach leads to the suspension or withdrawal of the ethical approval for the trial.

4.2.5 Institution

The institution will:

a. Develop clear guidance for investigators detailing the reporting and management of serious breaches that is consistent with the framework set out in NHMRC document.

b. Assess each serious breach to determine its impact e.g. any impact on other trials conducted by the institution/investigator.

c. Facilitate the implementation of any corrective and preventive actions if required by the sponsor.

d. Take advice from the reviewing HREC regarding its assessment of the breach.

e. Inform the HREC if a serious breach leads to withdrawal of the site's authorisation.

f. Consider whether the conduct determined to be a serious breach requires the application of the Australian Code for the Responsible Conduct of Research.

4.3 Summary of Reporting

4.3.1 Table 4: Summary of Sponsor and Investigator Serious Breach Reporting to the Human Research Ethics Committee and the Institution for Clinical Trials Involving Therapeutic Goods

Responsible Party	Event	Timeline	To Who	Reporting Pathway
Sponsor	Serious breach	Within **7 calendar days** of confirming a serious breach has occurred and provide follow-up reports when required	The HREC	**Approved by CALHN HREC:**: Complete the CALHN Research Serious Breach Report Form, submit to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:**: Contact relevant HREC
Sponsor	Third party serious breach notification provided to the sponsor by the Human Research Ethics Committee (HREC) determined by the sponsor to **meet** the definition of a serious breach	Within **7 calendar days** of making a decision	The HREC	**Approved by CALHN HREC:**: Complete the CALHN Research Serious Breach Report Form, submit to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:**: Contact relevant HREC
Sponsor	Third party serious breach notification provided to the sponsor by the HREC determined by the sponsor to **not meet** the definition of a serious breach	Within **7 calendar days** of confirming a serious breach has not occurred	The HREC	**Approved by CALHN HREC:**: By letter or e-mail including a justification for the decision submit to Health.CALHNResearchMonitoring@sa.gov.au (the PI and research team contact must be copied into the submission email) **Approved by external HREC:**: Contact relevant HREC
Third Parties	Suspected breach	-	The HREC	**Approved by CALHN HREC:**: Complete the CALHN Research Suspected Breach Report Form (Third Party), submit to Health.CALHNResearchMonitoring@sa.gov.au **Approved by externa HREC:**: Contact relevant HREC
Principal Investigator	Serious breach confirmed by the sponsor as occurring at the site	Within **72 hours** of being notified of the serious breach	To the institution where the issue occurred	**Occurring at a CALHN site, approved by CALHN HREC:** Complete the CALHN Research Serious Breach Report Form, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a CALHN site, approved by external HREC:** Complete the CALHN Research Serious Breach Report Form, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a NALHN site, approved by CALHN HREC:** Contact HealthNALHNRgo@sa.gov.au **Occurring at an external site, approved by CALHN HREC:** Refer to relevant Research Governance Office

4.3.2 Table 4: Summary of Investigator Suspected Breach Reporting to the Sponsor for Clinical Trials Involving Therapeutic Goods

Responsible Party	Event	Timeline	To Who	Reporting Pathway
Principal Investigator	Suspected breach	Within **72 hours** of becoming aware of the suspected breach	The sponsor	As defined by the sponsor
Principal Investigator	Protocol Deviation (not related to IMP/IMD) – Investigator Initiated trials	Within 7 calendar days	To the institution where the issue occurred	**Occurring at a CALHN site, approved by CALHN HREC:** Complete the CALHN Research Protocol Deviation Form, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at a CALHN site, approved by external HREC:** Complete the CALHN Research Protocol Deviation Form, submit to Health.CALHNResearchMonitoring@sa.gov.au **Occurring at an external site, approved by CALHN HREC:** Refer to relevant Research Governance Office

5. References

NHMRC *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Products November 2016*

NHMRC *Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018*

NHMRC *National Statement on Ethical Conduct in Human Research 2007* (updated 2018)

NHMRC *Australian Code for the Responsible Conduct of Research 2018*

TGA *Note for Guidance on Good Clinical Practice (ICH GCP) – Annotated with TGA Comments*

TGA *Integrated Addendum to ICH GCP Current Step 2 version dated 11 June 2015*

TGA *Access to Unapproved Therapeutic Goods – Clinical Trials in Australia*

6. Document Control

Version	Date	Summary	Approved By
1.0	July 2019	New	Bernadette Swart Manager CALHN Research Services
1.1	November 2019	Various minor changes and further clarification to 3.5.1, sponsor annual safety reporting	Bernadette Swart Manager CALHN Research Services
2.0	July 2020	Changes to SSI reporting and serious breach reporting	Bernadette Swart Manager CALHN Research Services
3.0	September 2021	Changes to Annual Safety Report and Protocol Deviation reporting	Bernadette Swart Manager CALHN Research Services