Policy Directive

Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations

Summary This document applies to all clinical trials conducted within Public Health Organisations (PHOs) in NSW. It outlines the safety monitoring and reporting requirements for trials involving investigational medicinal products or investigational medical devices (referred to as therapeutic good trials) and also the safety monitoring and reporting requirements for trials involving other types of intervention (referred to as non-therapeutic goods trials).

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Applies to Affiliated Health Organisations, Cancer Institute, Local Health Districts, NSW Ambulance Service, Public Hospitals, Specialty Network Governed Statutory Health Corporations

Distributed to Divisions of General Practice, Ministry of Health, NSW Ambulance Service, Private Hospitals and Day Procedure Centres, Public Health System, Tertiary Education Institutes

Audience Clinical, Public health organisation, Nursing, Research departments, Hospitals, Pharmaceuticals, Research ethics committees, Clinical trial researchers, Medical research groups

Secretary, NSW Health

This Policy Directive may be varied, withdrawn or replaced at any time. Compliance with this directive is mandatory for NSW Health and is a condition of subsidy for public health organisations.

POLICY STATEMENT

SAFETY MONITORING AND REPORTING FOR CLINICAL TRIALS CONDUCTED IN NSW PUBLIC HEALTH ORGANISATIONS

PURPOSE

This policy describes the regulatory and good practice requirements for safety monitoring and reporting for clinical trials conducted within NSW Public Health Organisations (PHOs). It sets out the roles and responsibilities of PHOs, investigators, Human Research Ethics Committees (HRECs) and clinical trial sponsors. It provides a standard framework for all clinical trials to ensure a consistent approach to safety monitoring and reporting across NSW PHOs.

MANDATORY REQUIREMENTS

Mandatory requirements for safety and monitoring reporting is outlined below:

Therapeutic Goods Trials

For trials conducted under the Clinical Trial Notification and Clinical Trial Exemption Schemes (CTX/CTN Scheme), safety monitoring and reporting activities must be conducted in accordance with the NHMRC Guidance: *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods 2016 (the NHMRC Guideline)* and any relevant requirements for unapproved therapeutic goods published by the Therapeutic Goods Administration (TGA).

For trials not conducted under the CTX/CTN Scheme, safety monitoring and reporting activities must be conducted in accordance with the NHMRC Guidance: *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods 2016 (the NHMRC Guideline)*; however, when reporting to the TGA, sponsors should comply with the TGA's requirements for post marketing trials.

Non-Therapeutic Goods Trials

For trials involving interventions other than therapeutic goods, this policy requires safety monitoring and reporting activities to be aligned, as far as possible, with the requirements for therapeutic goods trials and conducted within the framework described in Attachment 1: *Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations: Procedures* (Section 1 and Section 3).

All Clinical Trials

This policy requires any research related adverse events that meet the definition of clinical incident to be processed in accordance with the NSW Health Incident Management Policy (PD2014_004).

IMPLEMENTATION

The protection of participant safety in clinical trials is a shared responsibility and is outlined in Attachment 1: *Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations: Procedures*

- Sponsors are responsible for the ongoing safety evaluation of their trials and for reporting changes in the risk/benefit ratio to all concerned parties (Section 2.3.1 and 3.3.1).
- Investigators are responsible for the ongoing medical care of trial participants and for reporting safety events to the sponsor and their institution (Section 2.3.2 and Section 3.3.2).
- HRECs are responsible for oversight of the risk benefit balance of approved clinical trials (Section 2.3.3 and Section 3.3.3).
- Research governance offices are responsible for acting on any information arising from clinical trials that may impact on the institution's duty of care to trial participants (Section 2.3.4 and Section 3.3.4).

REVISION HISTORY

Version	Approved by	Amendment notes
October 2017 (PD2017_039)	Deputy Secretary & CHO, Population and Public Health	First version.

ATTACHMENTS

1. Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations: Procedures.

Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations

NSW GOVERNMENT Health

PROCEDURE

Issue date: October-2017

PD2017_039

1. BACKGROUND

1.1 About this document

This Policy Directive applies to all clinical trials conducted within NSW Public Health Organisations (PHOs). It outlines the safety monitoring and reporting requirements for trials involving investigational medicines, biologicals and medical devices (referred to as therapeutic good trials) as well as the safety monitoring and reporting requirements for trials involving other types of intervention (referred to as non-therapeutic goods trials).

The requirements for therapeutic goods trials and non-therapeutic goods trials are detailed separately in Section 2 and Section 3 respectively.

1.2 About the regulatory and governance environment in Australia

Australian guidelines[1] set out the responsibilities of Human Research Ethics Committees (HRECs) and institutions[2] overseeing clinical trials. These bodies must ensure that the risks posed by clinical trials are acceptable before granting approval and that any change in the risk-benefit ratio of ongoing trials is compatible with continued approval. International Good Clinical Practice Guidelines[3] set out the responsibilities of sponsors and investigators who must have processes in place for the collection, verification, classification, reporting and management of clinical trial adverse events. Investigators working within NSW PHOs should also ensure that any research-related adverse events that meet the definition of an incident are reported in accordance with the Incident Management Policy (PD2014_004).

Where a clinical trial involves unapproved therapeutic goods supplied under the Clinical Trial Notification/Clinical Trial Exemption Schemes (CTN/CTX Schemes), all stakeholders must comply with any relevant requirements outlined within the *Therapeutic Goods Act* 1989 (Cth) and associated regulations.

[1] Including the National Statement on Ethical Conduct in Human Research and the NHMRC Guidelines for Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods.
[2] For the purpose of this policy, the term 'institution' refers to the Research Governance Office (RGO) within a NSW Public Health Organisation.
[3] Guidelines for Good Clinical Practice (ICH E6 R2) and ISO 14155 (2011): Clinical Investigation of Medical Devices for Human Subjects: Good Clinical Practice.

2. SAFETY MONITORING AND REPORTING FOR THERAPEUTIC GOODS TRIALS

2.1 Key Definitions

Definitions For All Clinical Trials	
(Clinical) Incident[4]	Any unplanned event resulting in, or with the potential for, injury, damage or other loss. This includes a near miss.
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.
Coordinating Principal Investigator (CPI)	The Coordinating Principal Investigator is; a) In relation to a clinical trial conducted at a single trial site, the investigator for 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.
CTN/CTX Schemes	The principal schemes that provide access to unapproved therapeutic goods for clinical trials conducted in Australia (see TGA website).
Data Safety Monitoring Board (DSMB)	A committee that reviews the accumulating data in a trial and recommends to the sponsor (either directly or indirectly) whether to continue, modify, or stop a trial for either safety or ethical reasons.
Good Clinical Practice (GCP)	An international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials.
Near Miss	Any event that could have had adverse consequences but did not. An arrested or interrupted sequence where the incident was intercepted before causing harm e.g. an incorrect medication added to an infusion but not administered.
Non-Therapeutic Goods Trials	Trials other than Therapeutic Goods Trials.
Principal Investigator (PI)	The person responsible, individually, or a leader of the researchers at a site, for the conduct of a trial at that site. In a single centre trial, may also be the Coordinating Principal Investigator.
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.
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.
Therapeutic Goods Trials	Trials investigating the safety and/or efficacy/effectiveness of medicines, biologicals or medical devices (therapeutic goods).
Unapproved Therapeutic Goods	A product not entered on the Australian Register of Therapeutic Goods (ARTG), including: - Any new formulation of an existing product - Any new route of administration, - In the case of an existing medical device, any new technology, new material or a new treatment modality A product being used beyond the conditions of its marketing authorisation, including: - New indications extending the use of a medicine to a new population group - Extension of doses or duration of treatments outside the approved range See TGA website.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

[4] NSW Health Policy: PD2014_004 Incident Management Policy

Definitions Specific to Investigational Medicinal and Biological Trials (IMP Trials)	
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. **Note:** All adverse events judged by either the reporting investigator or the sponsor as having a **reasonable causal relationship** to an investigational medicinal product 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.
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 to gain further information about an approved use.
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 some trials, the approved Product Information may replace the Investigator's Brochure.
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/Reaction	Any untoward medical occurrence (AE/AR) that at any dose:
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.
Adverse Device Effect (ADE)	An 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.

Definitions Specific to Investigational Medical Device Trials (IMD Trials)	
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. **Note:** This definition includes events related to the investigational medical device 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
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.
Reference Safety Information (RSI)	The information used for assessing whether an adverse device effect is expected.
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 hospitalization, 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.
Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect 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 serious adverse device effect (ASADE) 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).

2.2 Assessment of Adverse Events

Each adverse event must be evaluated for:

- **Seriousness:** An assessment of whether the adverse event meets the definition of a Serious Adverse Event (SAE)[5].
- **Causality:** A clinical assessment of whether there is a reasonable causal relationship between the adverse event and the investigational medicinal product (IMP) or to the use of the investigational medical device (IMD).
- **Expectedness:** An assessment of whether the adverse reaction or adverse device effect is consistent with information previously described in the trial's Reference Safety Information (RSI).

2.3 Responsibilities

2.3.1 Sponsor Responsibilities

Clinical trial sponsors should have documented processes to manage the ongoing safety evaluation of their trials. Trial risks should be determined through a risk assessment and sponsors should ensure that their safety monitoring plans are proportionate to the level of risk identified. The trial protocol (or other document) should clearly demonstrate to those reviewing safety monitoring plans, that appropriate measures to monitor the safety of participants are in place.

When the sponsor is a NSW PHO, it may delegate some or all sponsor functions to the Coordinating Principal Investigator (CPI) or other third party (e.g. a coordinating centre). When CPIs are delegated sponsor functions, they would undertake both the investigator and sponsor responsibilities referenced in this document.

For trials involving therapeutic goods, this procedure requires sponsors to adhere to the NHMRC Guidance requirements as detailed in Part 1, Section C.1 for investigational medicinal products trials and Part 2, Section C.1 for investigational medical device trials.

[5] The term 'severe' is often used to describe the intensity (clinical severity) of a specific event. This is not the same as 'serious', which is based on patient/event outcome or action criteria.

2.3.2 Investigator Responsibilities

Investigators must have the necessary training[6] and experience to undertake their GCP responsibilities for safety monitoring and reporting. They are responsible for supervising any individual or party to whom they have delegated safety monitoring or reporting duties or functions and must ensure that any members of their trial team are appropriately qualified and trained to undertake those activities.

For trials involving therapeutic goods, this procedure requires investigators to adhere to the NHMRC Guidance requirements as detailed in Part 1, Section C.2 for IMP trials and Part 2, Section C.2 for IMD trials.

Investigators should also ensure that any research-related events that meet the definition of a clinical incident are processed in keeping with any organisation-wide reporting of incidents relating to patient safety as required by the Incident Management Policy (PD2014_004).

2.3.3 Human Research Ethics Committees (HREC) Responsibilities[7]

HRECs must assess whether the sponsor's safety monitoring plans are acceptable and whether any changes to the risk-benefit ratio reported as the trial progresses are compatible with continued ethics approval.

HRECs should:

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

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

[6] There is an expectation that investigational site staff conducting therapeutic goods trials receive GCP training that meets the minimum criteria for ICH GCP investigator site personnel training identified by TransCelerate BioPharma, Inc as such training would cover the investigational site's safety reporting responsibilities.
[7] Adapted from Part 1 Section C3 of the NHMRC Guidelines.

e) For CTX/CTN trials, advise the Therapeutics Goods Administration (TGA), investigators and their institutions of any decision to withdraw approval.

f) Acknowledge receipt of any safety-related communication.

2.3.4 Research Governance Office (RGO) Responsibilities[8]

Research governance staff must act on any information received during the course of a trial that may impact on the institution's duty of care to patients and other clinical trial participants.

Research governance staff should:

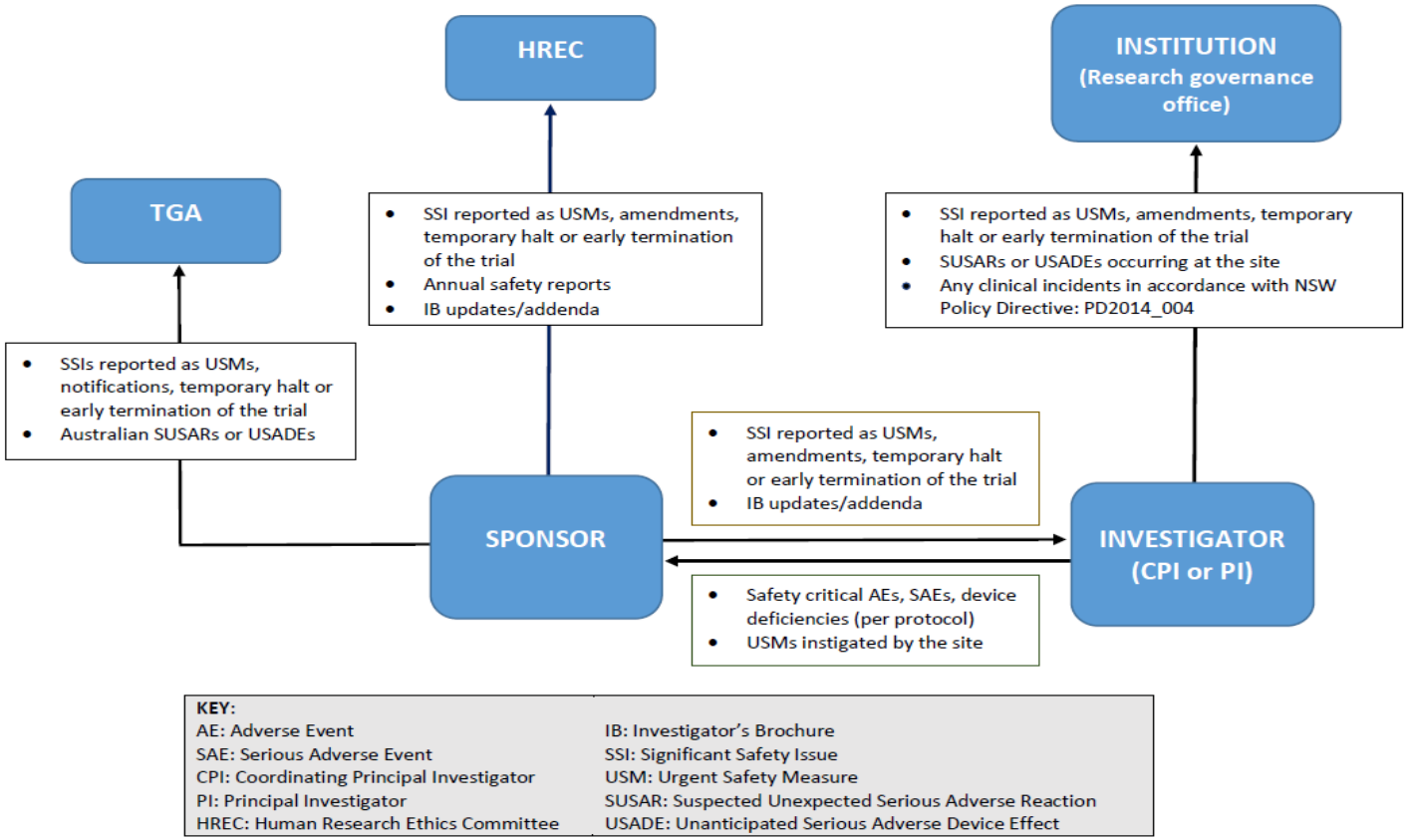
a) Assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation[9] and, where applicable, facilitate the implementation of corrective and preventative action.

b) Develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document(s) should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator-initiated or collaborative group trials.

c) Acknowledge receipt of any safety-related communication.

[8] Adapted from Part 1 Section C4 of the NHMRC Guidelines.
[9] If applicable, following discussion with the reviewing HREC and/or the PI.

2.4 Figure 1: Reporting Pathway for Therapeutic Goods Trials[10] [11]



[10] This flowchart uses terminology for IMP trials. An equivalent flowchart for IMD trials can be found on p 22 for the NHMRC Guidance

[11] As illustrated, sponsors may report directly to NSW HRECs; however, they must ensure that all communications sent to the HREC adequately identify the trial and provide context in relation to the HREC's role (e.g. whether there is any impact on patient safety, trial conduct or trial documentation).

2.5 Table 1: Summary of Notifications to the HREC and RGO (Therapeutic Goods Trials)

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is both serious and unexpected.

Unanticipated Serious Adverse Device Effects (USADEs)
A serious adverse device effect 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).

Urgent Safety Measure (USM)
A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

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.

Type of Event	Who Reports	To Whom	When	How
Significant Safety Issue (SSI) implemented as an Urgent Safety Measure (USM)	Sponsor	The reviewing HREC (and all investigators participating in the study)	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	*SSI Notification Form*[1] or sponsor's template
Significant Safety Issue (SSI) **not** implemented as an Urgent Safety Measure (USM)	Sponsor	The reviewing HREC (and all investigators participating in the study)	Within 15 days of the sponsor becoming aware of the SSI	*SSI Notification Form* or sponsor's template
All Significant Safety Issues (SSIs)	Principal Investigator	The RGO for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	*SSI Notification Form* or sponsor's template
Suspected Unexpected Serious Adverse Events (SUSARs) and Unanticipated Serious Adverse Device Effects (USADEs) occurring	Principal Investigator	The RGO for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	SUSAR/USADE/URSAE *Notification Form*
Investigator's Brochure Updates/Addenda	Sponsor	The reviewing HREC	As and when updates are generated	Submitted with a cover sheet or as part of an annual progress/annual safety report
Annual Safety Report	Coordinating Principal Investigator or sponsor	The reviewing HREC	Within annual progress report sent to the HREC or aligned with the safety reporting cycles of global companies	Annual progress report or sponsor's template

[1] The SSI Notification Form (Attachment 1) should be adopted by all PHO-sponsors.

3. SAFETY MONITORING AND REPORTING FOR NON-THERAPEUTIC GOOD TRIALS

For clinical trials involving interventions other than therapeutic goods (e.g. surgery, radiotherapy, psychotherapy) this section describes a safety monitoring and reporting framework (i.e. definitions, responsibilities and reporting pathways) that align, as far as possible, with the requirements for therapeutic goods trials.

3.1 Key Definitions

Definitions for all clinical trials	
(Clinical) Incident[12]	Any unplanned event resulting in, or with the potential for, injury, damage or other loss. This includes a near miss.
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.
Coordinating Principal Investigator (CPI)	The Coordinating Principal Investigator is; a) In relation to a clinical trial conducted at a single trial site, the investigator for 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.
CTN/CTX Scheme	The principal schemes that provide access to unapproved therapeutic goods for clinical trials conducted in Australia (see TGA website).
Data Safety Monitoring Board (DSMB)	A committee that reviews the accumulating data in a trial and recommends to the sponsor (either directly or indirectly) whether to continue, modify, or stop a trial for either safety or ethical reasons.
Good Clinical Practice (GCP)	An international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials.
Near Miss	Any event that could have had adverse consequences but did not. An arrested or interrupted sequence where the incident was intercepted before causing harm e.g. an incorrect medication added to an infusion but not administered.
Non-Therapeutic Goods Trials	Trials other than therapeutic goods trials.
Principal Investigator (PI)	The Principal Investigator is the person responsible, individually, or a leader of the researchers at a site, for the conduct of a trial at that site. In a single centre trial, may also be the Coordinating Principal Investigator.
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.
Sponsor	An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.
Therapeutic Goods Trial	Trials investigating the safety and/or efficacy/effectiveness of medicines, biologicals or medical devices (therapeutic goods).
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

[12] PD2014_004

Definitions Specific to Non-Therapeutic Goods Trials	
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant receiving a trial intervention that does not necessarily have a causal relationship with this intervention.
Related Adverse Event	An adverse event that is judged as having a reasonable causal relationship with the trial intervention. **Note:** The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	Any adverse event that: • results in death; • is life-threatening; • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; • consists of a congenital anomaly or birth defect; or • is otherwise considered medically significant by the investigator
Unexpected and Related Serious Adverse Event (URSAE)	An adverse event that is: • Serious – meets the definition of a serious adverse event • Related – resulted from administration of the trial intervention • Unexpected – the event is not described in the protocol as an expected occurrence.

3.2 Assessment of Adverse Events

Each adverse event must be evaluated for:

- **Seriousness:** An assessment of whether the adverse event meets the definition of a Serious Adverse Event (SAE)[13].
- **Causality:** A clinical assessment of whether there is a reasonable causal relationship between the adverse event and the trial intervention.
- **Expectedness:** An assessment against the SAEs listed in the protocol as expected occurrences (considering the nature and frequency of the event).

3.3 Responsibilities

3.3.1 Sponsor Responsibilities

Clinical trial sponsors should have documented processes to manage the ongoing safety evaluation of their trials. Sponsors should ensure that the nature and extent of safety monitoring is determined through a risk assessment so that safety monitoring plans developed are proportionate to risk. The trial protocol (or other document)

[13] The term 'severe' is often used to describe the intensity (clinical severity) of a specific event. This is not the same as 'serious', which is based on patient/event outcome or action criteria.

should clearly demonstrate that appropriate measures to monitor the safety of participants are in place.

When the sponsor is a NSW PHO, it may delegate some or all sponsor functions to the Coordinating Principal Investigator (CPI) or other third party (e.g. a coordinating centre). When CPIs are delegated sponsor functions, they would undertake both the investigator and sponsor responsibilities described in this document.

As part of the sponsor's oversight of clinical trials, proportionate levels of monitoring and audit should be implemented.

Sponsors should:

a) Ensure that all sponsor responsibilities are allocated or delegated appropriately and any third parties that are delegated sponsor functions (e.g. the CPI) are aware of their responsibilities.

b) Ensure that the protocol (or alternative document) describes the assessment and management of risk[14] and where relevant, includes/references any safety reporting definitions, procedures, responsibilities and reporting timelines.

c) Ensure the protocol lists the expected occurrence of SAEs and where applicable, details of the nature and frequency of those events.

d) Maintain records of all adverse events.

e) Provide a summary of the trial's evolving safety profile in an annual safety report[15] including, where applicable, a description of any safety issues that have arisen and the steps taken to mitigate any new risks to participants.

f) Notify in writing, any significant safety issues (SSIs), to the HREC and participating investigators. SSIs that meet the definition of an urgent safety measure (USM) should be notified within 72 hours, and all other SSIs should be notified within 15 calendar days of the sponsor becoming aware of the issue.

3.3.2 Investigator Responsibilities

Investigators must have the necessary training and experience to undertake their GCP responsibilities for safety monitoring and reporting. The investigator is responsible for supervising any individual or party to whom they have delegated safety monitoring or reporting duties or functions and must ensure that any members of their trial team are appropriately qualified and trained to undertake those activities.

[14] Including details of any oversight committees conducting ongoing safety monitoring.
[15] Provided within the trial's annual progress report.

Investigators should:

a) Capture and assess all adverse events that occur at the site, in accordance with the protocol.

b) Report SAEs to the sponsor **within 24 hours**, except those SAEs that are identified in the protocol as not needing immediate reporting.

c) Report any urgent safety measures (USMs) to the sponsor **within 24 hours.**

d) Act on all verbal or written reports of SSIs from the sponsor to ensure any implications for trial participants are managed appropriately.

e) Report to the RGO as soon as possible, and in any case no later than **72 hours:**

- All SSIs; and
- URSAEs[16] arising from the local site.

f) Ensure that any research-related events that meet the definition of *an incident* are processed in keeping with any organisation-wide reporting of incidents relating to patient safety, in accordance with the Incident Management Policy (PD2014_004).

3.3.3 Human Research Ethics Committee (HREC) Responsibilities

HRECs must assess whether the sponsor's safety monitoring plans are acceptable and whether any changes to the risk-benefit ratio reported as the trial progresses are compatible with continued ethics approval.

HRECs should:

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 DSMB, any 'stopping rules' and/or criteria for withdrawing individual participants from the trial.

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

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

[16] Reported when, in the investigator's judgement, a URSAE has occurred. In a blinded trial, the investigator should not unblind the event for the purposes of reporting to their institution.

e) Advise investigators and their institutions of any decision to withdraw approval.

f) Acknowledge receipt of any safety-related communication.

3.3.4 Research Governance Office (RGO) Responsibilities

Research governance staff must act on any information received during the course of a trial that may impact on the institution's duty of care to patients and other clinical trial participants.

Research governance staff should:

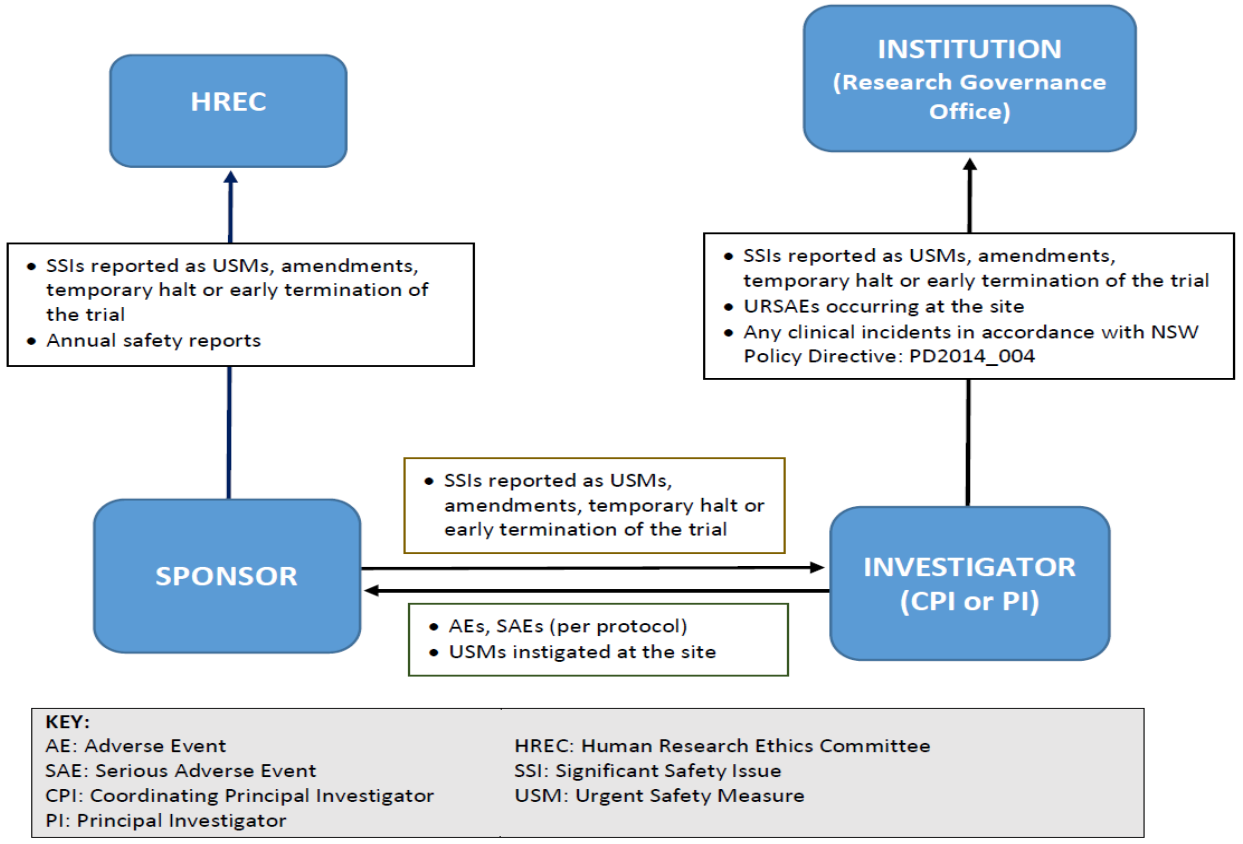
a. Assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation[17] and, where applicable, facilitate the implementation of corrective and preventative action.

b. Develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials. This document(s) should cover the requirements for both externally sponsored clinical trials and, if applicable, internally sponsored investigator-initiated or collaborative group trials.

c. Acknowledge receipt of any safety-related communication.

[17] If applicable, following discussion with the reviewing HREC and/or the PI.

3.4 Figure 2: Reporting Pathway for Non-Therapeutic Goods Trials[18]



[18] As illustrated, sponsors may report directly to NSW HRECs; however, they must ensure that all communications sent to the HREC adequately identify the trial and provide context in relation to the HREC's role (e.g. whether there is any impact on patient safety, trial conduct or trial documentation).

3.5 Table 2: Summary of Notifications to the HREC and RGO (Non-Therapeutic Goods Trials)

Unexpected & Related SAEs (URSAE)
An adverse event that is:

- *Serious – meets the definition of a serious adverse event*
- *Related – resulted from administration of the trial intervention*
- *Unexpected – the event is not described in the protocol as an expected occurrence.*

Urgent Safety Measure (USM)
A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

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.

Type of Report	Who Reports	To Whom	When	How
Significant Safety Issue (SSI) implemented as an Urgent Safety Measure (USM)	Sponsor	The reviewing HREC (and all investigators participating in the study)	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	*SSI Notification Form*[19] or sponsor's template
Significant Safety Issue (SSI**) <u>not</u>** implemented as an Urgent Safety Measure (USM)	Sponsor	The reviewing HREC (and all investigators participating in the study)	Within 15 days of the sponsor becoming aware of the SSI	*SSI Notification Form* or sponsor's template
All Significant Safety Issues (SSIs)	Principal Investigator	The RGO for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	*SSI Notification Form* (or sponsor's template
Unexpected & Related Serious Adverse Event (URSAEs) occurring at the site	Principal Investigator	The RGO for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	*SUSAR/USADE/URSAE Notification Form*
Annual Safety Report	Coordinating Principal Investigator or Sponsor	The reviewing HREC	Annually (within the annual progress report)	*Annual Progress Report*

[19]The SSI Notification Form (Attachment 1) should be adopted by all PHO-sponsors.

4. LIST OF ATTACHMENTS

1. Significant Safety Issue Notification Form
2. Local SUSAR/USADE/URSAE Notification Form

4.1 Attachment 1: Significant Safety Issue Notification Form

SIGNIFICANT SAFETY ISSUE NOTIFICATION FORM[20]			
HREC:		**HREC Ref. No:**	
Project Title:			
Coordinating Principal Investigator (CPI):			
Sponsor Name:			
Contact details of the person making this report (sponsor or sponsor's delegate) **Name:** **E-mail:**			
Date Significant Safety Issue occurred:			
Please complete either Section 1 or Section 2 deleting the section that is not applicable			
SECTION 1: TO BE COMPLETED IF THE SIGNIFICANT SAFETY ISSUE (SSI) WAS IMPLEMENTED AS AN URGENT SAFETY MEASURE The form should be completed by the trial sponsor (or delegate) and sent to: 1) The reviewing HREC, 2) All investigators*, 3) The Therapeutic Goods Administration (CTX/CTN trials only). Notification should be made within **72 hours** of the sponsor becoming aware of the SSI. *Investigators should: 1) Act on all verbal or written communication from the sponsor in relation to the site's management of the SSI. 2) Forward this notification to their Research Governance Office within **72 hours** of receipt and if applicable, include any additional detail on how the SSI was/is being managed at the site. 3) Consider whether the SSI should be reported locally as an incident (NSW PD2014_004).*			
A. Details of the significant safety issue			
B. Actions taken/further actions planned. Delete rows that do not apply.			
☐ ***Notification of an amendment:*** *Please indicate any actions taken to protect participants from the immediate hazard and details of any resulting amendment (e.g. revised trial documentation) and the likely timeframe for submission of the amendment to the reviewing HREC, if not provided with this notification.*			
☐ ***Temporary halt of the trial for safety reasons:*** *Please describe the scope of the halt - e.g. suspension of recruitment or cessation/interruption of trial treatment/intervention. Please provide details of the number of participants still receiving treatment in Australia at the time of the temporary halt and their proposed management.* *If you are not ready to submit complete details with this application, please provide this information in letter format no later than 15 days from the date of the temporary halt.*			

[20] This form may be amended from time to time. New versions will be published on the NSW Health website.

☐ ***Early termination of the trial:*** *Please provide details of the number of participants still receiving treatment in Australia at the time of early termination and their proposed management. Please also comment on the consequences of early termination for the evaluation of the results.*
If you are not ready to submit complete details with this application, please provide this information in letter format no later than 15 days from the date of the early termination.

SECTION 2: TO BE COMPLETED IF THE SIGNIFICANT SAFETY ISSUE WAS NOT IMPLEMENTED AS AN URGENT SAFETY MEASURE

The form should be completed by the trial sponsor (or delegate) and sent to:
1) The reviewing HREC, 2) All investigators*, 3) The Therapeutic Goods Administration (CTX/CTN trials only)
Notification should be made within **15 days** of the sponsor becoming aware of the SSI.

Investigators should: 1) Act on all verbal or written communication from the sponsor in relation to the site's management of the SSI. 2) Forward this notification to their Research Governance Office within **72 hours of receipt and if applicable, include any additional details on how the SSI was/is being managed at the site. 3) Consider whether the SSI should be reported locally as an incident (NSW PD2014_004).*

A. Details of the significant safety issue

B. Actions planned. Delete rows that do not apply.

☐ ***Notification of an amendment:*** *Please indicate the likely nature of the amendment (e.g. revised trial documentation) and the likely timeframe for submission of the amendment to the reviewing HREC if not provided with this notification.*

☐ ***Temporary halt of the trial for safety reasons:*** *Please describe the scope of the halt - e.g. suspension of recruitment or cessation/interruption of trial treatment/intervention. Please also provide details of the number of participants still receiving treatment in Australia at the time of the temporary halt and their proposed management.*
If you are not ready to submit complete details with this application, please provide this information in letter format no later than 15 days from the date of the temporary halt.

☐ ***Early termination of the trial:*** *Please provide details of the number of participants still receiving treatment in Australia at the time of early termination and their proposed management. Please also comment on the consequences of early termination for the evaluation of the results.*
If you are not ready to submit complete details with this application, please provide this information in letter format no later than 15 days from the date of the early termination.

SPONSOR OR DELEGATE: I declare that the information provided above is true and accurate.			
Name of Reporter:			
Signature:		Date:	

Acknowledgement of receipt by HREC (please insert name): The [ ] HREC acknowledges receipt of the above.

Signed:	Date:
Name:	Position:

4.2 Attachment 2: Local SUSAR/USADE/URSAE Notification Form

LOCAL SUSAR/USADE/URSAE NOTIFICATION FORM[21]

To be completed for all clinical trials (therapeutic goods and non-therapeutic goods)

This form should be completed by the Principal Investigator (or delegate) as notification to their local Research Governance Office (RGO) when, in the opinion of the investigator[22] one of the following events has occurred at the site:

- A *Suspected Unexpected Serious Adverse Event* (SUSAR) in a medicines or biologicals trial
- An *Unanticipated Serious Adverse Device Effect* (USADE) in a medical devices trial
- An *Unexpected and Related Serious Adverse Event* (URSAE) in any other interventional trial

This form should be sent to the RGO within 72 hours of the site becoming aware of the event.

The investigator should also consider whether the event should be reported locally as an incident (in accordance with PD2014_004.)

HREC:		**HREC Ref. No:**	
Project Title:			
Principal Investigator:		**Department:**	
Sponsor Name:			

DETAILS OF THE EVENT			
Date event occurred:	`	Location where the event occurred:	
Provide details of the event or attach a copy of the SAE report form. In the investigator's opinion, will the event have any implication for the site that fall outside the management of events in accordance with the protocol?			

PRINCIPAL INVESTIGATOR OR DELEGATE

I declare that the information provided above is true and accurate.

Name of Reporter:		Contact Number:
Signature:		Date:

Acknowledgement of receipt

Signed:	Date:
Name:	Position:

[21] This form may be amended from time to time. New versions will be published on the NSW Health website.
[22] For blinded trials, the investigator should not unblind the event for the purposes of reporting to their RGO unless unblinding is necessary for the safety and medical management of the participant.