

2019

HEALTH+MEDICAL RESEARCH

Managing and reporting safety events

Standard Operating Procedure



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SHPN: (OHMR) 190585-7

Document details

Document ID:	SITE SOP-TC-04
Version:	1.0
Effective date:	01/10/2019
Review date:	01/10/2020

Document approval

Name	Position	Signature	Date
Dr Antonio Penna	Executive Director, Office for Health and Medical Research		01/10/2019

Document history

Version number	Effective date	Details of editions
1.0	1 October 2019	New

1. Purpose

To describe the capture, management, and reporting of safety events at a trial site. To ensure that sites conducting clinical trials take appropriate account of the Guidelines for Good Clinical Practice based on sponsor requirements¹.

2. Scope

All clinical trials (except Teletrials)² conducted at NSW Public Health Organisations involving therapeutic goods: investigational medicinal products (IMPs), investigational biologicals (IBs), investigational medical devices (IMDs).

Other trials where safety issues may occur (e.g. surgical, psychotherapy, radiotherapy trials).

3. Applicable to

The Principal Investigator (PI) and all other individuals capturing, managing, and reporting safety events in clinical trials conducted within the organisation.

4. Definitions

Refer to SOP-G-01: Glossary of terms.

5. Background

NSW Health Policy Directive: *Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations* (PD2017_039) requires safety reporting for therapeutic goods trials to comply with NHMRC Guidelines for Safety Monitoring and Reporting. This policy directive also provides equivalent guidance for non-therapeutic goods trials. This SOP outlines aspects of the policy relevant to site staff.

ICH GCP (E6 R2) requires site to report Adverse Events (AEs) to the sponsor. In order for sites to ensure appropriate reporting, the PI (or their delegate) should ask participants at each visit (or as required by the protocol) if they have experienced any AEs and record all AEs reported to them*. All AEs should then be assessed for seriousness, for causality and for expectedness.

** For some trials, the protocol may describe reduced levels of safety data collection and reporting. For example, sponsors conducting trials involving interventions whose safety profiles have been well characterised, may specify in their protocol that only a*

limited range of safety data need to be captured and reported.

Assessing seriousness

All adverse events should be assessed for 'seriousness' against the definition of a Serious Adverse Event (SAE).

Assessing causality

For investigational product trials, all adverse events judged by the reporting investigator as having a reasonable causal relationship with the investigational product would qualify as an adverse reaction, or in the case of a medical device, an adverse device effect. The expression 'reasonable causal relationship' means to convey, **that there is evidence or argument** to suggest a causal relationship. A similar principle applies to trials involving non-therapeutic goods. Any adverse event that is judged as having a reasonable causal relationship with the intervention being tested would qualify as a 'related adverse event'.

For medicinal product/biological trials, the following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed (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 the investigational product) that indicates those events occur more frequently in the investigational product treatment group than in a concurrent or historical control group.

Assessing expectedness

Sponsors and sites also assess an event's 'expectedness' to determine whether any *Suspected Unexpected Serious Adverse Events (SUSARs)* or the device/intervention equivalent, has occurred. This

¹ All trials must comply with the principles of GCP (Section 2 of ICH GCP (E6 R2) or Clause 4 of ISO 14155) however sponsors submitting data to regulatory authorities will normally require full compliance with ICH GCP (E6 R2) or ISO 14155 GCP Guidelines.

² NSW Health have published an annotated version of these SOPs for sites utilising a Teletrials model.

assessment should be performed using the Reference Safety Information chosen for the trial. This would be the Investigator's Brochure/Product Information for therapeutic good trials or the protocol for non-therapeutic good trials.

Significant safety issues

Significant Safety Issues (SSIs) are safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. SSIs are unplanned events (not already managed by the protocol) and as such, result in an action, such as a protocol amendment or the temporary or permanent halt in the trial. SSIs may arise from the sponsor's analysis of aggregate data (e.g. a Data Safety Monitoring Board, finds an increase in frequency or severity of an adverse event) or may arise from a single case event such as a SUSAR*.

Some SSIs may need to be implemented as an Urgent Safety Measure (USM). A USM is defined as a measure required to eliminate an immediate hazard to the participant's health or safety (e.g. an occurrence of toxic epidermal necrolysis or hepatic failure). The PI should ensure the sponsor is made aware of a USM within 72 hours of its occurrence at the site**.

** Individual SUSARs (or their device/intervention equivalents) are no longer required to be sent to sites. If these events have any bearing on patient safety/trial conduct, they would meet the definition of a Significant Safety Issue and should be expedited to sites. Where there is no bearing on patient safety/trial conduct, sites should confirm receipt but are not required to print, review or file these reports.*

***Sponsor have responsibility for reporting SSIs and USMs to the HREC and all sites with specified timeframes, although they may delegate this activity to a third party (e.g., the Coordinating Principal Investigator).*

Pregnancies

Any pregnancies (of trial participants or their partners) during the course of a therapeutic goods trial should be notified to the sponsor as specified in the protocol. Any pregnancy should be followed up until its outcome as this ensures the detection and reporting of any congenital anomalies or birth defects.

6. Procedure

Principal Investigator (PI)

Supervise all individuals involved in safety reporting.

Ensure safety events are captured, managed, and reported in accordance with NSW Policy and the trial protocol.

Ensure all medical assessments (e.g. the causality assessment for adverse events and the assessment of the significance of laboratory abnormalities) are conducted/signed-off by medically qualified staff.

Ensure that any adverse events that meet the definition of a clinical incident are reported in accordance with the Organisation's internal clinical incident reporting policy and the NSW Policy Directive PD2014_004.

PI or delegate

Capture and manage all AEs (and device deficiencies for IMD trials) that occur at the site, in accordance with the protocol.

Report to the sponsor:

- All SAEs and device deficiencies (except those SAEs that are identified in the protocol as not needing immediate reporting) within 24 hours
- Any safety-critical events in accordance with the protocol.
- Any Urgent Safety Measure arising at the site within 24 hours.
- Any occurrences of congenital anomaly/birth defect arising from a pregnancy of a participant (or partner) in accordance with the protocol.

Report to the Research Office within 72 hours:

- Any SUSARs (or device/intervention equivalent) occurring at the site
- Any SSIs sent to the PI by the sponsor.

7. References

[ICH GCP \(E6 R2\): Good Clinical Practice Guidelines – Annotated by the TGA](#)

[NSW Health Policy Directive: Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Public Health Organisations \(PD2017_039\)](#)

[NHMRC Guidelines for Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods](#)

[NSW Policy Directive PD2019_034: Incident Management Policy](#)

[NHMRC Guidance: Risk-based Management and Monitoring of Clinical Trials Involving Therapeutic Goods](#)

[FDA: Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Post-approval Clinical Investigations Guidance for Industry](#)

8. Associated documents

Assessment of safety events flowchart – available in the Standard Operating Procedures templates [zip file](#)