

2019

HEALTH+MEDICAL RESEARCH

Reporting non-compliance and suspected breaches of GCP or the Protocol

Standard Operating Procedure



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SHPN: (OHMR) 190585-8

Document details

Document ID:	SITE SOP-TC-05
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 process for identifying and reporting non-compliance and suspected serious breaches of Good Clinical Practice (GCP) or the protocol that occur 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.

3. Applicable to

The Principal Investigator (PI) and all site staff involved in the conduct of a clinical trial involving therapeutic goods.

Research Office staff.

The reviewing Human Research Ethics Committee.

4. Definitions

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

5. Background

Poor compliance with the protocol or Good Clinical Practice (GCP) can lead to data being rejected by regulatory authorities, can compromise participant safety and can nullify a trials insurance/indemnity. ICH GCP requires that the PI (or delegate) document and explain any deviation from the protocol and requires that non-compliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) lead to prompt action to secure compliance.

In the majority of instances, non-compliances are deviations that do not result in harm to trial participants or significantly affect the scientific value of the reported results of the trial. Some of these deviations are unavoidable (e.g. a participant misses a visit) or permitted (e.g. a deviation from the protocol to protect a participant from an immediate hazard (known as an urgent safety measure)).

ICH GCP requires all non-compliances (both minor and major) to be reported to the trial sponsor. The NHMRC Guideline: Reporting of Serious Breaches of GCP or the Protocol for Trials Involving Therapeutic Goods, categorises certain instances of non-compliances as a serious breach, defined as:

A breach that is likely to affect to a significant degree:

- (a) The safety or rights of the trial participant.
- (b) The reliability and robustness of the data generated in the clinical trial.

Examples of serious breaches

Deviations that may (depending on their nature) meet the definition of a serious breach include:

- Intentional or accidental loss of blinding of study medication.
- Failure to control investigational medicinal product(s) such that participants are put at significant risk or the scientific value of the trial is compromised.
- Deviations from eligibility criteria related to the diagnosis of patients.
- Non-compliance relating to evaluation of important efficacy endpoints.
- Missing source data which are extensive or which concern diagnosis, primary efficacy assessments, and important safety information.
- Persistent or systematic non-compliance with GCP or protocol that has a significant impact (e.g. systematic underreporting of serious adverse events leading to an inappropriate dose escalation in a phase I study).
- Proof of fraud relating to clinical trial records or data.

Confirmation of a serious breach

Suspected breaches* occurring at the site may be identified by anyone involved in the conduct, management or monitoring of a trial. However, the sponsor should normally make the decision on whether a breach meets the definition of a *serious breach* as they are best placed to understand the impact of the breach on overall contribution of the data to key analysis parameters, and the impact of excluding the data from the analysis. For breaches affecting participant safety or rights, sponsors can discuss the potential significance of a breach with the HREC. Where a sponsor decides not to report a breach, they are required to keep records of these decisions and be prepared to justify them during an audit or regulatory inspection.

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.

**Suspected breaches are defined in the NHMRC Guidance as; 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.*

Where site staff believe that the sponsor has committed a serious breach, the PI should discuss the case with the sponsor who would then be responsible for sending a serious breach notification to the HREC. Exceptionally, where the sponsor and site disagree on the outcome of the sponsor's assessment, the site may report the suspected breach directly to the HREC.

Implementing processes for continuous improvement

To minimise the risk of a serious breach occurring at site, deficiencies relating to trial conduct identified at a site should be actively managed to ensure continuous improvement. Such deficiencies may be identified by site staff or through internal/external audit or inspection. When deficiencies are made known to the Organisation, consideration should be given to both correction of specific deficiency, and also identification and correction of the root cause of the deficiency. Actions should address immediate corrective actions and future preventative actions (CAPA).

6. Procedure

Principal Investigator (PI)

Ensure that the trial team is aware of the process for reporting non-compliances and suspected serious breaches.

Ensure all non-compliances (minor and major) are reported to the sponsor in accordance with sponsor requirements.

Ensure all suspected breaches are reported to the sponsor within 72 hours of the site becoming aware of the breach.

PI or delegate

Follow any process outlined by the sponsor to report non-compliances.

Where a non-compliance has been assessed by the PI as possibly meeting the definition of a serious breach (i.e. a suspected breach has occurred), report it to the sponsor within 72 hours of becoming aware of the breach.

Liaise with the sponsor to determine the outcome of the sponsor's assessment of all suspected breaches reported. If the sponsor confirms that a serious breach has occurred, inform the local Research Office within 72 hours of this confirmation.

Research Office

Facilitate any CAPA that are implemented by the sponsor.

Assess each reported serious breach to determine whether its occurrence impacts on other trials conducted by the institution/investigator. If applicable, facilitate any appropriate CAPA.

Where departures from the principles and responsibilities of the code by researcher staff has contributed to the occurrence of a serious breach, determine whether the application of the Australian Code for the Responsible Conduct of Research is required.

7. List of appendices

None

8. References

[NHMRC: Reporting of Serious Breaches of GCP or the Protocol for Trials Involving Therapeutic Goods](#)

[NHMRC: Guide to Managing and Investigating Potential Breaches of the Australian Code for the Responsible Conduct of Research](#)

9. Associated documents

None