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Non Compliance

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Date	23 February 2024	23 February 2024	23 February 2024
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1.0 Introduction / Background

Non-compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) or regulatory requirements can compromise participant's rights, safety and well-being and can invalidate a clinical trials contractual obligations, insurance/ indemnity. ICH GCP explains the role of the Sponsor, Human Research Ethics Committee (HREC) and Principal Investigator (PI) in non-compliance. Events of non-compliance are generally identified by the Sponsor of the clinical trial during a site monitoring visits, an internal or external audit or during a Regulatory inspection.

In the majority of instances, non-compliances do not result in harm to clinical trial participants or significantly affect the scientific value of the reported results of the clinical trial. Some 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 clinical trial sponsor within specific timeframes as outlined by the Sponsor and within the NHMRC Guideline: Reporting of Serious Breaches of GCP or the Protocol for Trials Involving Therapeutic Goods.

The NHMRC Guideline also categorise certain instances of non-compliance as a serious breach. This term refers to a serious and/or persistent breach of GCP and/or clinical trial-related procedures that have an impact on participant safety, may substantially alter risks to participants, may have an effect on the integrity of the trial data, and/or the ethics of the trial (e.g. failure to perform a required safety assessment, written informed consent not appropriately obtained before initiation of trial-related procedures).

If non-compliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

The Human Research Ethics Committee (HREC) assesses compliance under the Clinical Trial Notification Scheme (CTN) and will make a decision whether incidence of non-compliance should be reported to the Therapeutic Goods Administration (TGA). Under the Clinical Trial Approval Scheme (CTA) non-compliance must be reported directly to the TGA.

The Sponsor, HREC or Regulatory Authority may terminate the PI or Institutes participation in a clinical trial if the monitoring and/or auditing identifies serious and/or persistent non-compliance. If this occurs the Regulatory Authority(ies) will be promptly notified.

The National Clinical Trial Governance Framework released by the Australian Commission on Safety and Quality in Health Care documents that the Institution meets its compliance obligations and this includes identifying and addressing non-compliance.

2.0 Objective

To describe the process for identifying and reporting non-compliance and suspected serious breaches of ICH GCP or the protocol that occur at a clinical trial site.

3.0 Scope

This Standard Operating Procedure (SOP) applies to all staff involved in clinical trials at South Western Sydney Local Health District (SWSLHD) and the Ingham Institute.

4.0 Ownership and Responsibility

The PI and Sponsor are responsible for the recording, reviewing and reporting of clinical trial non-compliance. The task may be delegated to another suitably trained individual but the responsibility remains with the PI and clinical trial Sponsor. Corrective action plans must be put in place to mitigate the risk to the clinical trial participants.

The HREC is responsible for reviewing non-compliance and making decisions on serious breach actions in accordance with the NHMRC guidelines.

The Institution is responsible for ensuring that compliance is maintained for clinical trials.

5.0 Associate Documents

SOP_CTSU_01 Risk Assessment for Clinical trials

SOP_CTSU_02 Investigator responsibilities

SOP_CTSU_03 Communication with Human Research Ethics Committee, Trial Sponsor and Insurer

SOP_CTSU_22 Managing Corrective and Preventative Actions (CAPAs)

SOP_CTSU_23 Sponsor Audits and Regulatory Inspections

FM_018 Corrective and Preventative Action Plan

FM_027 Non-compliance Log

6.0 Procedure

In the case where a non-compliance event has been identified the following processes are essential. Significant non-compliance (serious breach) must be reported to the Clinical Trial Support Unit by the PI and a risk assessment implemented to ensure participant safety and data integrity are maintained.

6.1 PI and Clinical Trials Team

The PI should not implement any deviation from or changes of the protocol without agreement from the Sponsor and documented approval/favourable opinion of the HREC. An exception is when it is necessary to eliminate an immediate hazard to trial participants.

When non-compliance is identified within the clinical trials team it should be brought to the attention of the PI and Sponsor as soon as possible. The PI should assess the non-compliance to determine whether it significantly affects or has the potential to significantly affect human subject protection or reliability of clinical trial results and perform a root cause analysis and implement appropriate corrective and preventive actions.

The site PI and delegated clinical trials team are required to follow any process outlined by the sponsor to report non-compliances. Please refer to SOP_CTSU_03_Communication with Human Research Ethics Committee, Trial Sponsor and Insurer. The Sponsor will assess whether the non-compliance meets the definition for a serious breach.

Where a non-compliance has been identified by the PI as possibly meeting the definition of a serious breach, the PI must report the event to the sponsor within 72 hours.

There are provisions in the NHMRC Guidelines for a third party to report a serious breach if they feel the Sponsor has not reported this to the HREC. If this situation occurs please contact the Clinical Trials Unit or the Director of Research to discuss further.

Any non-compliance that does not meet the definition of a serious breach will be documented on FM_027 Non-Compliance Log and filed in the ISF/eISF. Additionally, an accurate description of the event is required to be documented in the source notes and CRF. All non- compliance events of this nature are reported to the approving HREC at the next annual progress report.

The PI will work with the Sponsor to determine that whether a Corrective and Preventive Action (CAPA) plan is required to accompany the non-compliance event. A CAPA can also be implemented by the site PI/ delegate as a proactive response to risk mitigation and improved quality processes. Review SOP_CTSU_22_Managing Corrective and Preventative Actions (CAPAs) Plans for more information.

The PI should make an ongoing assessment of the non-compliance reports to identify any quality improvement activities. The Institution will also review and support quality improvement processes and implement changes accordingly.

6.2 Reporting to the HREC and RGO

Any documentation relating to non-compliance is required to be submitted to the approving HREC and RGO. If the noncompliance has not identified as a serious breach by the Sponsor or Delegate and SWSLHD is the approving HREC, complete the annual report via REGIS providing details.

If the noncompliance is identified as a serious breach by the Sponsor or Delegate and SWSLHD is not the approving HREC, Sponsor and the Institute must follow the approving HREC instructions for reporting. The SWSLHD RGO guidelines must be followed for reporting and this is documented on the website https://www.swslhd.health.nsw.gov.au/ethics/.

7.0 References

ICH GCP (E6 R2): Good Clinical Practice Guidelines – Annotated by

TGA National Statement on Ethical Conduct in Human Research(2023)

Australian Code for the Responsible Conduct of Research (2018)

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

NHMRC: Guide to Managing and Investigating Potential Breaches of the Australian Code for the Responsible Conduct of Research (2018)

8.0 Amendment History

Version	Date	Amended by	Details of Amendment
2.0	23-Feb-2024	Erfan Jaberiyanfar	• 1.0 – Update to indicate CTA scheme • Updated list of associated documents. • 6.2 – Updated to indicate Sponsor and Institution responsibilities. • Grammatical changes. • Update of reference links.

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