

Guideline For Developing a Standard Operating Procedure for an External Audit of a NSW Clinical Trial Site

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Clinical Trials and Data Platform

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Contents

Glossary 3

Introduction 4

The purpose of this guideline *4*

Key reference documents for creating an SOP and hosting an audit *4*

Disclaimer *4*

Section 1. Standard Operating Procedures and clinical trial audits 5

Defining Standard Operating Procedures *5*

The usual requirements in an SOP *5*

SOP templates that can be used for health procedures and research *6*

Organisational requirements to sign off on an SOP *6*

SOP Training and compliance *6*

Definition of a clinical trial audit *7*

The purpose of a clinical trial audit *7*

Who Initiates an external clinical trial audit? *8*

Section 2. High-level overview about procedures and responsible roles that need to be detailed in the SOP 9

What activities are covered in a clinical trials audit? *9*

Delegated duties and responsibilities *10*

Pre audit and preparation for audit *10*

Site inspection *11*

Post audit findings and follow up *12*

Remote audits *12*

Section 3. Audit outcomes and corrective and preventative actions 12

Corrective and Preventative Actions (CAPA) *13*

References 14

Appendix 14

Glossary

CAPA	Corrective and Preventive Action
CRF	Case Report Forms
CTC	Clinical Trial Coordinator
eCRF	Electronic Case Report Forms
eTMF	Electronic Trial Management Folder
GCP	Good Clinical Practice
HREC	Human Research Ethics Office
ICH	International Code of Harmonization
NHMRC	National Health and Medical Research Council
OHMR	Office of Health and Medical Research
PI	Principal Investigator
RGO	Research Governance Office
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
TMF	Trial Management Folder

Introduction

This guideline was developed by Maridulu Budyari Gumal SPHERE, NSW Regional Health Partners and Sydney Health Partners for use by their partner organisations.

It is designed to introduce clinical trial site personnel to key concepts related to hosting an external audit of a NSW based clinical trial and developing the Standard Operating Procedures that describe that process.

It is supported by three companion tools (see Appendix for links):

- Clinical Trial Documentation Audit Checklist
- Applying GCP to Audits of Clinical Trials Presentation
- Clinical Trials in Focus Podcast | Episode 1: Being Audit Ready

The purpose of this guideline

1. To describe what Standard Operating Procedures (SOP) and clinical trials audits are;
2. To provide a high-level overview about procedures and responsible roles that need to be detailed in the SOP; and
3. To introduce the requirements relating to audit outcomes, implementing corrective and preventative actions, and the need for revision and updating of SOPs.

This document acknowledges the guidance provided under the National Clinical Trials Governance Framework and User Guide. Those documents outline the requirements related to quality standards in clinical trials.

Key reference documents for creating an SOP and hosting an audit

- ICH Guideline for Good Clinical Practice E6(R3) – Sections 2.12 Records; 2.13 Reports; 3.16.4 Record Access

Disclaimer

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Section 1. Standard Operating Procedures and clinical trial audits

Defining Standard Operating Procedures

"Standard operating procedures (SOP) provide an ability to define the steps and processes required to undertake a given activity. This can be critical in setting team expectations and to identify the requirements – such as training or coaching – needed to complete the SOP." – Australian Government, Department of Health
https://www.health.gov.au/resources/publications/standard-operating-procedure-template

An SOP is a step-by-step set of instructions to guide team members to perform tasks in a consistent manner. SOPs are particularly important for complex tasks that must conform to regulatory standards. SOPs are also critical to ensuring efficiencies with little variation and high-quality output.

The usual requirements in an SOP

1. Identification, versioning and control
   - Procedure title and number Version number
   - Effective date Review date
   - Author name, job title, signature and date
   - SOP approver name, job title, signature and date
2. Background to the SOP
   - Introduction
   - Objective
   - Scope
   - Glossary or definitions
3. Details of the procedures and activities the SOP covers and responsible roles
4. Review and updating information
5. References
6. Amendment history

SOP templates that can be used for health procedures and research

Before developing a new SOP, check with individual Research Offices as they may already have approved audit Standard Operating Procedures/guidelines; and/or templates to use when creating a new SOP.

If you need to create a new SOP it may be easiest to adapt a standard template. Example SOP templates are available in the National Standard Operating Procedures for Clinical Trials, in Australia.

Organisational requirements to sign off on an SOP

When initiating a new SOP or amending an existing SOP, users should be invited to review the draft SOP. Create a formal review process that includes:

- Determining who has the final approval authority for the SOP
- Quality Assurance should ensure that implementation of the SOP is made effective and located in a central location within the organisation. Will everyone have access to a paper copy? Or will you be providing access to the procedures via an electronic document management system?

SOP training and compliance

- SOP training should be given by appropriately trained personnel to all staff.
- SOP training should be provided to all current employees when a new procedure is to be implemented or when an existing SOP has been amended.
- All new employees should receive training in the SOP.
- Training may need to be tailored to the different roles of employees.
- For quality and compliance, a record of SOP training should be retained and identify:
    - who has completed the training
    - acknowledgment that they have read and understood the SOP content and procedure
    - when the training was completed.
    - acknowledgment that they have read and understood the SOP content and procedure
    - when the training was completed.

Definition of a clinical trial audit

"An Audit is 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 SOPs, GCP, and the applicable regulatory requirements." - A Comprehensive and Practical Guide to Clinical Trials, *Chapter 17 Audits and Inspections, 2017.*

The purpose of a clinical trial audit

1. To demonstrate compliance with approved documentation;
2. To ensure that sites undertaking clinical trial activity follow applicable guidelines for Good Clinical Practice based on regulatory requirements, including the TGA Preparing for Good Clinical Practice Inspections and the National Clinical Trials Governance Framework; and
3. To identify opportunities for improvement.



Who Initiates an external clinical trial audit?

Sponsors frequently audit investigational sites to inspect for protocol compliance and adherence to ICH/GCP, during or after the completion of a trial.

A **Human Research Ethics Committee** (HREC) or **Research Governance Office** (RGO) which has approved a clinical trial, or other regulatory body- such as the therapeutic goods administration- may inspect investigational sites at any time during a clinical trial to ensure participant safety and compliance with ethical guidelines.

Site audits are likely to be conducted if:

- There is high enrolment of trial participants.
- Problems or concerns with the site have been reported by the monitor or other responsible personnel.
- The trial is one of extreme importance.
- The investigator's workload includes several studies with the same sponsor.
- The geographic location of the site coincides with other sites being audited.
- As part of hospital accreditation processes.



Section 2. High-level overview about procedures and responsible roles that need to be detailed in the SOP

In order to develop an SOP for an external audit of a clinical trial at a particular site, it is necessary to understand:

1. which staff roles will have responsibilities pre audit, during the audit/site visit and post audit;
2. how the site inspection will be managed, including what trial records will be accessed and how; and
3. how follow up and findings will be managed.

The following sections summarise these issues. The details of the requirements for each site will need to be determined.

What activities are covered in a clinical trials audit?

An audit may include the following activities:

- An opening meeting to confirm the purpose of the audit, provide introductions and information on how the audit proceedings will occur
- Development of a plan to conduct the audit. This plan may be revised as the audit proceeds
- Individual meetings with trials staff
- Review of trial related documents
- Tour of facilities
- A closing meeting
- Follow up actions may include: (see Corrective and Preventive Action)
    - a narrative of what happened
    - planned actions
    - responsible person/s for ensuring that the actions are taken
    - timelines for completion
    - documentation

Delegated duties and responsibilities

The audit inspection, and therefore the SOP, will apply to all personnel involved in the development, implementation and coordination of the trial(s).

This includes:

- Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, sub-investigator(s), CTCs and designated site personnel including Health Professionals. i.e., pharmacy, radiology, information technology, dieticians, and pathology.
- Associated governance staff such as those in the Research Office with site responsibilities and ethics and integrity staff and committee members associated with approving the clinical trial.

Responsibility for actions described in the SOP should be assigned to the appropriate personnel, noting them by job title.

Pre audit and preparation for audit

The clinical trial personnel who first receive notification of the proposed audit should inform the PI, lead Clinical Trial Coordinator (CTC) and/or trials manager. The SOP should state whether the process includes informing the Research Office about the proposed audit.

The PI appoints a lead team member to coordinate the audit. The lead team member and the PI review the scope of the audit and confirm a date that allows sufficient time to:

a) prepare for the audit and

b) all relevant staff to attend site visits and meetings as required.

The PI should review all documentation prior to the audit to check for completeness.

The PI will meet with the auditor(s):

a) prior to the audit for a brief introduction to the proposed audit and

b) at the conclusion of the audit to discuss findings and follow up.

The lead team member:

- Communicates directly with the auditor prior to the audit, if possible, to make certain that all required records are obtained, and necessary meetings are scheduled.
- Coordinates and prepares for the audit according to the instructions provided by the Sponsor, external auditor or other regulatory body.
- Ensures the Trial Management Folder (TMF) or Electronic Trial Management Folder (eTMF) is current and complete prior to the audit.
- Obtains and consolidates all trial-related records and/or identifies where and how they can be accessed. This will include Case Report Forms (CRF), including Electronic Case Report Forms (eCRF), source documents and investigator regulatory files. See Appendix for link to Clinical Trial Documentation Audit Checklist.
- Organises a suitable workspace for the auditor/s, with internet access and photocopying facilities.

If the Research Office will be involved:

- Meets with the PI and lead team member to prepare for the audit.
- Reviews trial related internal standard operating procedures, policies and work instructions to ensure they are GCP and regulatory compliant.

Site inspection

All trial team members should co-operate with requests for information needed to conduct the audit.

PI and/or lead team member:

- Assists the auditor(s) as needed.
- Greets the auditor(s) and verifies identification and site authorisation.
- Hosts an introductory meeting for all key staff.
- Ensures all related trial documents are available or provides them on request of the auditor. Ensures any related hard copy documents provided are de-identified and marked confidential. Lists all related documents provided on a document log.
- Accompanies the auditor/s during tours of the facility and any interviews.
- Ensures the minutes of meetings, discussions and queries are taken.
- Ensures key staff attend the final meeting for verbal feedback, questions, or final clarification.
- Attends to any other ad-hoc requests relating to the trial.
- Arranges for follow-up if required.

Post audit findings and follow up

Lead team member:

- Follows up on findings – includes relevant trials team members to facilitate Corrective and Preventative Actions (CAPA) from findings as required (see below))
- Coordinates responses, drafts formal response, seeks review from key staff and PI
- Responds to audit findings in the specified timeframe
- Liaises with appropriate staff on any required changes to documentation and/or procedures

Where the Research Office staff will be involved:

- Reviews and provides advice on CAPA
- Distributes audit findings to staff
- Uses key findings to evaluate and develop research practices and assist staff training across the organisation

Remote audits

In response to the COVID-19 Pandemic remote regulatory assessments and audits were necessary. At the time of updating this guideline, the TGA was engaged in a sector-wide consultation following a proposed minor amendment to the Therapeutic Goods Regulations 1990 and the Therapeutic Goods (Medical Devices) Regulations 2002. The proposed changes aim to clarify the legislation, ensure it continues to serve its intended purpose, and introduce provisions that allow for remote or hybrid Good Clinical Practice (GCP) inspections of clinical trial sites under regulations 12AC and 7.4, respectively.

This amendment aligns with the broader goals of the TGA's GCP Inspection Program, which supports a mix of on-site, remote, and hybrid inspection approaches. Sponsors and other organisations may also adopt this blended model to suit their operational needs.

Remote inspections offer several benefits, including reduced delays associated with on-site visits, minimised travel, and less disruption for trial sponsors, participants, and TGA personnel. However, we acknowledge that not all organisations currently have the capability to facilitate remote audits.

For the most up-to-date guidance on remote regulatory assessments and audits, please consult the current approved versions of the Regulations.

Section 3. Audit outcomes and corrective and preventative actions

Errors identified in an audit must be managed to ensure continuous improvement. An audit report should be provided to the organisation, along with sponsor feedback on any site deficiencies. The PI is responsible for ensuring the correction of deficiencies, the prevention of further deficiencies through the identification of the root cause and the implementation of a CAPA as required.

Changes to processes will also need to be reflected in revised versions of the SOP(s) that relate to how the clinical trial is conducted and perhaps also the clinical trial audit SOP. Importantly, any changes need to be communicated with the site personnel and, if necessary, training implemented.

Corrective and Preventative Actions (CAPA)

One of the key outcomes of an audit is to address any issues of non-compliance with GCP or protocol requirements and/or identified concerns regarding patient safety or data reliability.

CAPA are long term solutions to address the causes of non-compliance. The TGA ICH Guidance for Good Clinical Practice, the NHMRC Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods, and the supplementary guidance on Reporting of Serious Breaches of Good Clinical Practice or the Protocol for Trials Involving therapeutic Goods, require the Sponsor-Investigator to perform a root cause analysis and implement an appropriate CAPA if a serious breach occurs

A CAPA process can help address three possible outcomes of concern in a clinical trial:

1. A patient's safety, rights, or wellbeing is put at risk.
2. The trial data are compromised or incomplete.
3. There are findings that result in a warning letter from a regulatory inspection.

In a clinical trial, a problem resulting in any of the above has the potential to increase in severity or become more widespread if it is related to an internal process. This is when a CAPA process is especially valuable. CAPA is a risk-based tool to ensure continuous improvement and trial compliance. A clinical trial site may have a CAPA Standard Operating Procedure that should be referred to. Alternatively, a CAPA SOP could be developed alongside the Audit SOP.

Additional References

- SOCRA | Resolving and Preventing Repetitive Problems in Clinical Trials
- NSW Health and Medical Research | Clinical Trial Toolkit
- Therapeutic Goods Regulations 1990 | See Part 3, sections 12AB and 12AC
- VCCC | Corrective and Preventive Action
- NHMRC Australian Code for the Responsible Conduct of Research
- A Comprehensive and Practical Guide to Clinical Trials 2017 | Chapter 17 - Audits and Inspections
- FAO Soils Bulletin - 74 | Standard Operating Procedures

Appendix

The referenced audit companion tools are available on your partner organisation's website:

- NSW Regional Health Partners (NSWRHP)
- Sydney Health Partners (SHP)
- Maridulu Budyari Gumal, the Sydney Partnership for Health, Education, Research and Enterprise (SPHERE)