Australian Government
Department of Health
Therapeutic Goods Administration

Good Clinical Practice (GCP) inspection program

Guidance for GCP inspection of clinical trial sites for investigational biologicals and medicinal products

Version 1.0, April 2022

TGA Health Safety Regulation

Contents

Introduction

Clinical trials are regulated under commonwealth and state and territory legislation in Australia. The clinical trial environment in Australia is broad and there are various responsibilities resting with the Therapeutic Good Administration (TGA), Human Research Ethics Committees (HRECs), trial sponsors, the approving authorities (institutions), investigators and Commonwealth and State and Territory governments.

Therapeutic goods are regulated in Australia under the *Therapeutic Goods Act 1989* (the Act) and the *Therapeutic Goods Regulations 1990* (the Regulations). Under the Act and the Regulations, the TGA is responsible for regulating access to unapproved medicines, biologicals and devices for use for experimental purposes in humans. Exemptions for use are managed under the Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) schemes. Therapeutic goods legislation applicable to clinical trials is described in the Australian clinical trial handbook.

Clinical trials of medicines and biologicals regulated under the CTN or CTA schemes are subject to the Good Clinical Practice (GCP) Inspection Program. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials. Compliance with GCP provides assurance that the rights, safety, and well-being of clinical trial participants are protected and that the trial data generated are credible. For investigational medicinal products and investigational biologicals, the TGA recognises the following internationally accepted GCP guideline: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice with TGA annotations.

The TGA has also endorsed National Standard Operating Procedures for Clinical Trials, including Teletrials, in Australia. The document is consistent with ICH Guideline for Good Clinical Practice and the National Statement on the Ethical Conduct in Human Research 2007 (updated 2018).

The TGA inspects Australian clinical trial investigator sites of clinical trials for medicines and biologicals to assess whether they are meeting their GCP responsibilities.

This guidance describes:

- how we prioritise and schedule GCP inspections
- the kinds of inspections we might conduct
- the inspection process, and
- how we report and follow-up on inspection.

In this guidance, we use ‘must’ or ‘required’ to describe something you are **legally obliged** to do. We use ‘should’ to **recommend** an action that will assist you to meet your legal requirements. We refer to the TGA as ‘we’ or ‘us’, and to clinical trial investigator sites as ‘you’.

Responsibilities

The Regulations specify that the use of medicines and biologicals in a regulated clinical trial (that is, a trial conducted through the CTN or CTA schemes) must be in accordance with the Guideline for Good Clinical Practice. The Regulations also specify that the use of medicines and biologicals in a clinical trial must be in accordance with the National Statement on Ethical Conduct in Human Research (2007) Updated 2018 (the National Statement).

Clinical trials are conducted by researchers as part of a broad group of stakeholders with varying responsibilities under various authoritative documents including the therapeutic goods legislation. These include trial sponsors, Human Research Ethics Committees (HRECs), approving authorities (institutions in which the trial is being conducted), investigators and the TGA. The key responsibilities for each of these stakeholder groups in the context of the CTN and CTA schemes are described below.

Role of trial sponsors

The trial sponsor is responsible for the initiation, management, and financing (or arranging the financing) of the trial and carries the medico-legal responsibility associated with its conduct. The therapeutic goods legislation specifies responsibilities of the trial sponsor under the CTN and CTA schemes. Under the CTN and CTA schemes the use of therapeutic goods in the trial must be in accordance with:

- the relevant Guideline for Good Clinical Practice
- the National Statement
- the protocol approved by the HREC responsible for monitoring the conduct of the trial.

The trial sponsor must also comply with the requirements of any other Commonwealth and/or state and territory legislation in relation to clinical trials and the supply of therapeutic goods.

The responsibilities of the trial sponsor are extensive. This guidance does not describe all sponsor responsibilities. Section 5 of the Guideline for Good Clinical Practice provides further information on sponsor responsibilities.

Role of Human Research Ethics Committees (HRECs)

The National Statement sets out requirements for HRECs under the CTN and CTA schemes. HRECs are responsible for approval of the trial protocol under both the CTN and CTA schemes, and, in approving a clinical trial under those schemes, the HREC accepts responsibility for the continuing review and oversight of the trial.

Role of approving authorities

Approving authorities (the institutions or organisations where trials are conducted) have specific responsibilities, which are outlined in the National Statement and the Guideline for Good Clinical Practice. Under the CTN and CTA schemes, the approving authority gives the final authorisation for the conduct of the trial at the site following approval by the reviewing HREC.

The National Statement sets out obligations relevant to monitoring for institutions. Approving authorities must be made aware of any issues that may impact on trial authorisation or institutional risk. The approving authority may withdraw authorisation if necessary, which must be communicated to the HREC and to the TGA. Where a HREC has withdrawn ethical approval, the approving authority is obliged to ensure that the principal investigator promptly suspends the research.

Role of Principal Investigator (PI)

The Principal Investigator (PI) is responsible for protecting the rights and safety of trial participants under their care. The principal investigator is the person responsible, individually or as a leader of the research team at a site, for the conduct of a clinical trial at that site. As such, the principal investigator is responsible for adequately supervising their research team. The principal investigator must conduct the clinical trial in accordance with the clinical trial

protocol. Any significant departures that impact on the safety of participants or the reliability of trial data that occur at their site must be reported to the trial sponsor, HREC, and approving authority (when applicable as per local requirements), in line with NHMRC guidance.

Role of the Therapeutic Goods Administration (TGA)

Under the Act and the Regulations, the TGA is responsible for regulating access to unapproved therapeutic goods for use for experimental purposes in humans. Exemptions for use solely for experimental purposes in humans are managed under the CTN and CTA schemes. Therapeutic goods legislation applicable to clinical trials is described in the Australian clinical trial handbook.

The TGA can request certain information or documents about therapeutic goods exempt under the CTN scheme or approved under the CTA scheme. This can include the investigator's brochure and protocol, further information about safety reports, clarification about the safety profile of a specific therapeutic good, or details of problems or complaints. The TGA can require the trial sponsor of the goods exempt under the CTN scheme or the person who is granted approval under the CTA scheme to provide this information or these documents.

The TGA has the authority to inspect clinical trial sites of medicines and biologicals for trials approved under the CTA scheme, and trials of goods exempt under the CTN scheme. In addition, the TGA may release the inspection report and associated documents prepared by inspectors to approving authorities and responsible ethics committees (see Compliance and Enforcement).

Your inspection-related responsibilities include, but are not limited to:

- ensuring your clinical trials are conducted in compliance with Australian regulations and the relevant GCP guideline(s)
- maintaining your readiness for inspection, as inspections may be unannounced
- providing the inspectors, within the given deadline, with any information or documentation they need to prepare or conduct the inspection
- ensuring staff involved in the clinical trial are available (in person or remotely) during the inspection for interview or to clarify issues
- preparation and implementation of appropriate and timely corrective and preventative action (CAPA) plans to address the inspection's findings and prioritise any critical or major deficiencies.

Our inspection-related responsibilities include, but are not limited to:

- coordinating the inspection and personnel—including scheduling dates, times, venues—and providing the agenda
- producing our identity card if requested
- conducting the inspection
- preparing the inspection report
- reviewing your CAPA plan(s) and finalising the inspection.

Objectives of the Good Clinical Practice (GCP) inspection program

The GCP inspection program aims to strengthen the TGA's monitoring activities and protect public health.

GCP inspections allow us to:

- verify you are compliant with the GCP standard and have met your clinical trial responsibilities
- provide education and work with you to ensure you have effective systems in place in alignment with Australian legislation and the relevant GCP guideline(s).
- if appropriate, provide information relating to the inspection findings to the approving authority and/or the approving HREC.

Scope of the GCP inspection program

All Australian investigator sites involved in regulated clinical trials of medicines and biologicals are subject to the GCP inspection program.

Inspections will examine your compliance with the applicable Australian legislation and guideline(s):

- *Therapeutic Goods Act 1989* (the Act)
- *Therapeutic Goods Regulations 1990* (the Regulations)
- the GCP guideline(s).

The procedures for the conduct of regulatory GCP inspections are aligned with internationally harmonised processes and have been modelled on those published by the European Medicines Agency (EMA). At a minimum (for routine inspections), we will review the following during an inspection:

- legal and administrative – examination of aspects related to the implementation, progress, and termination of the clinical trial, including evidence of communication with the HREC and regulatory authorities
- organisational – examination of the implementation of the trial at the site, including qualifications and experience of site personnel, delegation of authority, standard operating procedures, facilities and equipment, source of the investigational medicinal product, monitoring, and auditing records
- informed consent – determine whether clinical trial participants consent was obtained in accordance with GCP Guideline(s) and approving authority requirements
- trial participant data – review whether the trial was conducted according to the study protocol by source data verification (SDV), particularly inclusion/exclusion criteria
- management of the investigational medicinal product (IMP) used in the trial.

Outcome of a GCP inspection

The outcome of a GCP inspection is a close out letter describing your compliance with the applicable Australian legislation and guideline(s). You will not be issued with a compliance certificate or any form of clearance, registration, or accreditation.

Inspection process

Inspection prioritisation

The TGA's GCP inspection program has been designed to be harmonised with current international approaches, with a particular focus on early phase trials of new medicines or of combinations of medicines, or where there may be safety or other concerns. The TGA will not inspect every clinical trial notified to or approved by the TGA. Most international regulators select a small percentage (between 1 and 3%) of regulated clinical trials for inspection each year.

We take a risk-based approach to selecting sites for GCP inspections. Trials with higher risk are more likely to be inspected. The majority of GCP inspections will be trial specific, routine inspections of clinical trials that have been completed and reported. However, other types of inspections including random inspections as well as 'for cause' inspections may also occur. The selection of clinical trials for inspection is based on risk assessment proposed by the National Health and Medical Research Council (NHMRC) in Risk-based Management and Monitoring of Clinical Trials Involving Therapeutic Goods 2018

The risk criteria fall into 2 categories:

- investigational medicinal product (IMP)
- trial conduct, design, and methods.

In addition, we will consider other elements, including but not limited to the following:

- type of site i.e., located at large institution vs. small clinic
- geographic location i.e., sites selected throughout the region
- number of participants screened, enrolled, and withdrawn for the trials at the site
- compliance history of the investigator sites and sponsor, including findings from previous GCP inspections of investigator sites.

Sites to be inspected

We choose the type and number of sites to inspect to ensure we meet the key objectives within the scope of the inspection. In most cases, we limit inspections to Australian investigator sites.

In addition, any party or organisation contracted to carry out some or all clinical-trial-related activities in conjunction with, or on behalf of, the site may be inspected to confirm they are capable of supporting the site's compliance with Australian clinical trial obligations. Such inspections will generally be arranged through the clinical trial site as part of an overall clinical trial inspection.

Types of inspections

Routine inspections

Routine GCP inspections are scheduled as part of the inspection program. There is no specific trigger for these inspections, although we take a risk-based approach to prioritising them. These inspections are usually of a single investigator site of a specific clinical trial, but other sites may be selected to verify and provide practical evidence of compliance.

‘For cause’ inspections

‘For cause’ inspections are undertaken in response to specific triggers where a GCP inspection is the appropriate way to examine the issues. ‘For cause’ inspections generally focus on specific aspects of the clinical trial at a particular investigator site or examine identified compliance issues and their impact. However, we may also inspect other sites as a result of a trigger. Significant safety concerns or identified noncompliance are expected to be the most common triggers.

Announced and unannounced inspections

We anticipate the majority of inspections will be announced—that is, we will notify you of them in advance to ensure the relevant personnel will be available for the inspection. However, it may sometimes be appropriate to conduct unannounced inspections or to perform an inspection at short notice (for example, when an announcement could compromise the objectives of the inspection or when prompt inspection is required due to urgent safety concerns).

Reinspections

There is no reinspection planned for clinical trials inspected as part of our routine inspection program. We will prioritise all routine inspections based on risk. However, if a previous inspection of a clinical trial identified noncompliance this may increase the chance you will be inspected at some time in the future, for example:

- where we have identified significant noncompliance
- to evaluate your ongoing compliance with requirements and evaluate changes to your clinical trial management systems.

Follow-up inspections may be performed, particularly of ‘for cause’ inspections, to verify you have taken appropriate corrective and preventative action in response to address noncompliance.

Remote inspections

Sometimes we will perform GCP inspections remotely using video- or teleconferencing, for example, where access to the investigator sites or other sites is difficult. If a remote inspection reveals issues that require on-site inspection, or the inspection objectives could not be met remotely, we may visit the inspection site.

Inspection notification

We will normally give you advance notice of our intention to conduct a GCP inspection. However, we have the right to perform a GCP inspection at any time. In exceptional circumstances, we can perform an inspection without notice.

The period of notice served should be sufficient for you to make logistic arrangements, and ensure key personnel are available that have access to relevant data. As a guide, we consider four weeks’ notice to be sufficient for a routine inspection.

Notice of the inspection would include, for example, the GCP inspector’s name(s), the inspection’s objectives and nature, the inspection date and, the address(es) to be inspected. We may also request information about the clinical trial so we can plan the inspection.

We will notify you of the GCP inspection in writing unless an unannounced inspection is required. We will issue the inspection notification to the principal investigator (PI) or a representative of the site to be inspected. We will request confirmation of the site PI's availability, ask for the cooperation of all parties and to confirm in writing that the PI agrees to the inspection of all relevant sites and will make all required documents and databases directly accessible to our inspectors.

We may also request trial-related documents including, but not limited to, copies of the clinical trial protocol, investigator's brochure, monitoring letters, research governance standard operating procedures (SOPs), trial specific user manuals, or statistical analysis plans. We will give you clear advice on when and how to submit these.

How to prepare for inspection

If you have been notified of a GCP inspection, you should prepare for the inspection by:

- ensuring your authorising institution, trial sponsor and clinical team are advised of the inspection
- ensuring access for the inspectors to clinical trial records and source documents is arranged for the time of the inspection.

We will avoid duplicating inspections conducted as part of another country's GCP inspection program when feasible.

We will prepare an inspection plan, which will identify:

- the objectives and scope of the inspection
- our inspection team member(s) and their respective role(s)
- the inspection date and site(s) to be inspected
- the specific documents, electronic tools, and systems to be reviewed and which we require access to
- the expected time and duration of each major inspection activity.

We will share the inspection plan with you in advance to ensure the relevant personnel, meeting rooms, databases and/or documents are available.

We may also request specific electronic documents prior to the inspection to allow sufficient pre-inspection analysis and inspection planning and will specify a timeframe for their delivery. You may provide such documentation to the TGA by means that meet your data privacy processes, including via secure email, provision of access to secure file hosting service or provision of USB or CD or other means.

Conducting the inspection

The inspection will proceed according to the details set out in the inspection plan. This will be negotiated prior to the inspection and can be amended during the inspection to ensure we achieve the inspection objectives. Any amendment to the plan will be documented. The inspection will take place over several days, typically 3 consecutive days, depending on the complexity of the trial.

We may collect relevant information to support the inspection and verify compliance with the study protocol, the GCP guideline(s) and the National Statement by, for example:

- interviewing appropriate staff members regarding trial related activities
- reviewing applicable site policies and procedures regarding research governance activities
- examination or demonstration of computers, electronic systems, and databases, where required, to obtain clinical trial data
- reviewing adverse event case documentation
- reviewing internal and external communication relevant to HREC or site governance
- reviewing staff training records in relation trial related activities.

If you refuse us access to any relevant record or documentation that our inspectors have a legal right to access, this will be documented in the inspection report so we can determine further action and consequences.

Opening meeting

Our inspection team will have an opening meeting with the study site principal investigator, other site staff, and institution and sponsor representatives (by invitation) before the inspection begins. The lead inspector will chair the meeting.

The purpose of the opening meeting is to:

- introduce the inspection team
- explain the regulatory framework for conducting the inspection
- provide information about the inspection's scope and objectives
- clarify logistics, timeframes and other matters referred to in the inspection plan
- allow you to introduce your representatives attending the inspection
- allow you to present an overview of the conduct of the trial at your site
- clarify with you whether there are any anticipated difficulties relating to the conduct of the inspection.

Collecting and verifying information

GCP inspections examine your compliance with the relevant Australian legislation and guidelines. The scope of inspections includes, but is not limited to, the following elements as appropriate to the system being reviewed:

- legal and administrative – examination of aspects related to the implementation, progress, and termination of the clinical trial, including evidence of communication with the HREC and regulatory authorities
- organisational – examination of the implementation of the trial at the site, including qualifications and experience of site personnel, delegation of authority, standard operating procedures, facilities and equipment, source of the investigational medicinal product, monitoring, and auditing records
- informed consent – determine whether clinical trial participants consent was obtained in accordance with GCP Guideline(s) and approving authority requirements

- trial participant data – review whether the trial was conducted according to the study protocol by source data verification (SDV), particularly inclusion/exclusion criteria
- management of the investigational medicinal product (IMP) used in the trial.

Closing meeting

At the end of the inspection, our inspectors will conduct a closing meeting with the study site principal investigator, members of the study team, and by invitation representatives of the institution and study sponsor. The purpose of the meeting is to:

- summarise the list of observations identified during the inspection to ensure you clearly understand them
- explain the procedures and timelines for distribution of our inspection report, your response, and any follow-up measures
- provide you an opportunity to correct any misconceptions and misunderstandings in the observations.

If the inspection is prematurely terminated due to exceptional circumstances, we will document the reason for the early termination and any deviations from the inspection plan in the inspection report.

Inspection reports

Our inspection team will prepare an inspection report and associated close-out record for each GCP inspection.

Timing of the GCP inspection report

Our inspectors will usually issue you the GCP inspection report and cover letter within 30 days of completing the inspection.

If our inspection identifies deficiencies, we will ask you to prepare a corrective and preventative actions (CAPA) plan in the form of a close-out record on the template provided with the inspection report. You should provide the inspectors with the close-out record within 30 days of receiving the inspection report. When you submit the close-out record, you should also comment on any major factual errors in the inspection report. If we do not receive your response within the agreed time frame, this will be recorded in the inspection report.

Our inspectors will assess the close-out record. We will correct any major factual errors in the final inspection report. We will assess the impact of any comments on the inspection findings and the adequacy of the proposed CAPA and proposed time frames.

We will document our assessment of the CAPA in the close-out record. If we do not accept your proposed CAPA or timeframes for actions, additional follow-up will occur to reach an agreement.

We will close the inspection when we have agreed on an acceptable CAPA plan. The lead inspector will sign the final inspection report and associated close-out record and issue these to you.

Our inspectors may ask you for ongoing evidence of completion or updates on your CAPA activities.

Inspection report contents

The inspection report consists of five sections:

1. Inspection-related data, including
   - details of the inspected site(s) and the site contact(s)
   - inspection details including inspection type, scope, date and the names and roles of the inspectors.
2. Introduction to and summary of the inspection activities including the inspection's purpose, and background information on the clinical trial inspected.
3. Inspection observations and findings.
4. List of any deficiencies observed during the inspection.
5. Name and signature of the person authorising the report on behalf of the TGA.

Content of the close-out record

We issue a close-out record with the inspection report to incorporate your CAPA commitments and our assessment of your CAPA.

The close-out record documents:

- any deficiencies identified
- the root cause of the deficiencies
- the proposed corrective and preventative actions to the root cause
- corrections to observed examples (if relevant)
- objective evidence provided (if relevant)
- proposed completion dates of CAPAs
- any comments by the inspector
- the final response acceptance.

Inspection follow-up

If we identify non-compliance with the study protocol, the GCP guideline(s) or the National Statement, we will follow up with you until you complete a CAPA plan **that appropriately addresses the non-compliance.** We may undertake one or more of the following follow-up actions:

- meeting with you to discuss the deficiencies, their impact, and your action plans
- reviewing progress reports on the corrective actions
- re-inspecting to assess appropriate implementation of the CAPA plan
- asking you to provide us with data you have not yet submitted
- communicating the inspection findings to other regulatory authorities, where applicable under international agreements.

Compliance and enforcement

The Regulatory Compliance Framework sets out the TGA's overall approach to compliance.

Where the GCP inspection process identifies deficiencies we will generally, in the first instance, work with you to address the deficiencies, for example by providing you with guidance and examples of best practice where available.

If we identify significant or critical deviations where you fail to comply with GCP requirements we can:

- provide information relating to the inspection findings to the approving authority and/or the approving HREC.

Inspection findings, including inspection reports and other associated documents, can be released to the approving authority and/or approving HREC under the Therapeutic Goods (Clinical Trial Inspections) Specification 2020 (No.2) ("the Specification"). This information does not include any personal or sensitive information in relation to participants of the clinical trial.

Records management

You should ensure you have appropriate processes in place to allow for the identification, retrieval and management of all documentation relating to clinical-trial-related activities. Our inspectors may ask to evaluate this documentation during the inspection process.

You are required to record all clinical-trial-related information and ensure it is handled and stored in a way that allows the information to be accurately reported, interpreted and verified. This includes information related to regulatory inspections—particularly inspection reports, close-out records and records related to implementing CAPAs.

We record GCP inspection data, including inspection plans, finalised inspection reports and close-out records, as well as any evidence of confirmed deficiencies. We handle and store this information in a way that allows it to be accurately reported, interpreted and verified. Our records management system for documents related to GCP inspection planning and reporting ensures the documents can be retrieved, and that measures taken to investigate deviations from regulatory compliance or GCP concerns can be traced.

Publishing GCP inspection data

Reported information

We will publish de-identified information on completed GCP inspections on the TGA web page; the information published will not identify individual clinical trial sponsor or investigator or investigator site names. However, if an inspection leads to regulatory actions being taken under the Act, this information will be published in line with the TGA's compliance and enforcement procedures, which can include identification of the parties and offences for more serious contraventions of the Act and/or Regulations. The de-identified inspection information published on the TGA website may include, but is not limited to:

- the number of inspections conducted in the previous 12 months and how many were scheduled as part routine or 'for cause' inspections
- aggregate information on
  - critical deficiencies and whether they have been resolved
  - major deficiencies and whether they have been resolved

- minor deficiencies and whether they have been resolved

We may include a short summary of conclusions based on the information above, particularly comparisons over time.

Reporting frequency

Reporting on our website will generally occur annually, commencing 12 months after the implementation of our GCP Inspection Program.

Grading deficiencies

Critical deficiency

A deficiency in clinical trial systems, practices or processes that adversely affects the rights, safety or well-being of clinical trial participants, or the quality or integrity of data, or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a party is observed to have engaged in fraud, misrepresentation, or falsification of data.

Major deficiency

A deficiency in clinical trial systems, practices or processes that could adversely affect the rights, safety or well-being of clinical trial participants, the quality or integrity of data, or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency

A deficiency in clinical trial systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of clinical trial participants, or the quality or integrity of data.

Comment

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of the investigational product. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.

Version history

Version	Description of change	Author	Effective date
V1.0	New guidance	Pharmacovigilance Branch	April 2022

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #