Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Good Clinical Practice Inspection Program metrics report

July 2022 – December 2022

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Contents

Summary

This metrics report is the first annual report of the Good Clinical Practice (GCP) Inspection Program (GCPIP). It covers the period from implementation of the program on **1 July 2022 to 31 December 2022**. This report provides information about deficiencies that we identified to help clinical trial investigator sites improve their compliance and prepare for a Therapeutic Goods Administration (TGA) GCP inspection. While this report focuses on areas for improvement, the inspection program found a strong commitment to compliance with GCP, which provides confidence in the quality of Australian clinical trials. This report covers regulatory inspections carried out by the TGA in Australia. All information has been de-identified.

In GCPIP, we group observed deficiencies against five main categories, which include findings from 28 sub-categories. The main categories and sub-categories that are typically reviewed during an inspection are presented in Appendix I. We grade all findings as either minor, major or critical, consistent with the inspection programs of the European Medicines Agency (EMA) and other international regulators. A deficiency recorded for one of the five main categories may be comprised of a number of minor, major and critical findings. The grading recorded for the main category deficiency is set to the highest-level finding. For example, a site receives critical, major and minor findings across several sub-categories within the main category 'protection of participants'. This would be recorded as a critical grading for 'protection of participants'.

From 1 July 2022 to 31 December 2022, the TGA carried out a total of **five** routine GCP inspections.

Sites worked effectively to address identified deficiencies through the development of Corrective and Preventative Action (CAPA) plans. All deficiencies within this reporting period have been rectified. None of the critical findings warranted enforcement action and all were able to be addressed through the CAPA process.

The number and grading of deficiencies within each main category are described in table 1.

Table 1: Number and grading of deficiencies in 2022 routine GCP inspections by category

Main category	Critical	Major	Minor	Total by main category
Protection of participants	1	3	1	**5**
Protocol compliance	0	4	1	**5**
Documentation	1	0	4	**5**
Investigational Medicinal Product (IMP)	0	1	3	**4**
Trial management	1	0	2	**3**

Background

In April 2022, the TGA published the *GCP Inspection Program Guidance for GCP inspection of clinical trial sites for investigational biologicals and medicinal products*, marking the commencement of the routine GCPIP in Australia.

Following the publication of the GCPIP Guidance, the TGA held several educational webinars between May and July 2022 and published Frequently Asked Questions. The first routine inspection under the GCPIP was carried out in August 2022.

The GCPIP aims to strengthen the TGA's monitoring activities and protect the safety and wellbeing of clinical trials participants. GCP inspections allow the TGA to:

- verify compliance of the clinical trial sites with Australian legislation and guidelines
- provide education and work with sites to ensure there are effective procedures and systems in place to conduct clinical trials that meet all the relevant requirements
- if appropriate, inform the reviewing Human Research Ethics Committee (HREC) and/or the approving authority of identified deficiencies. Refer to Australian Clinical Trial Handbook to learn more about the approving authority and HREC.

Scope

All Australian investigator sites involved in clinical trials of medicines and biologicals regulated through the clinical trial notification and approval schemes (CTN and CTA) are subject to the GCP inspection program.

Inspections examine the sites compliance with the applicable Australian legislation and guidelines, including:

- *Therapeutic Goods Act 1989* (the Act)
- *Therapeutic Goods Regulations 1990* (the Regulations)
- Integrated Addendum to the ICH E6(R1): Guidance on Good Clinical Practice ICH E6(R2), annotated with the TGA comments (ICH GCP E6(R2))
- The National Statement on Ethical Conduct in Human Research (2007) Updated 2018 (the National Statement)
- The National Standard operating procedure (SOP) for Clinical Trials, including Teletrials, in Australia (The National SOP)
- The trial-specific protocol and amendments, approved by the relevant HREC.

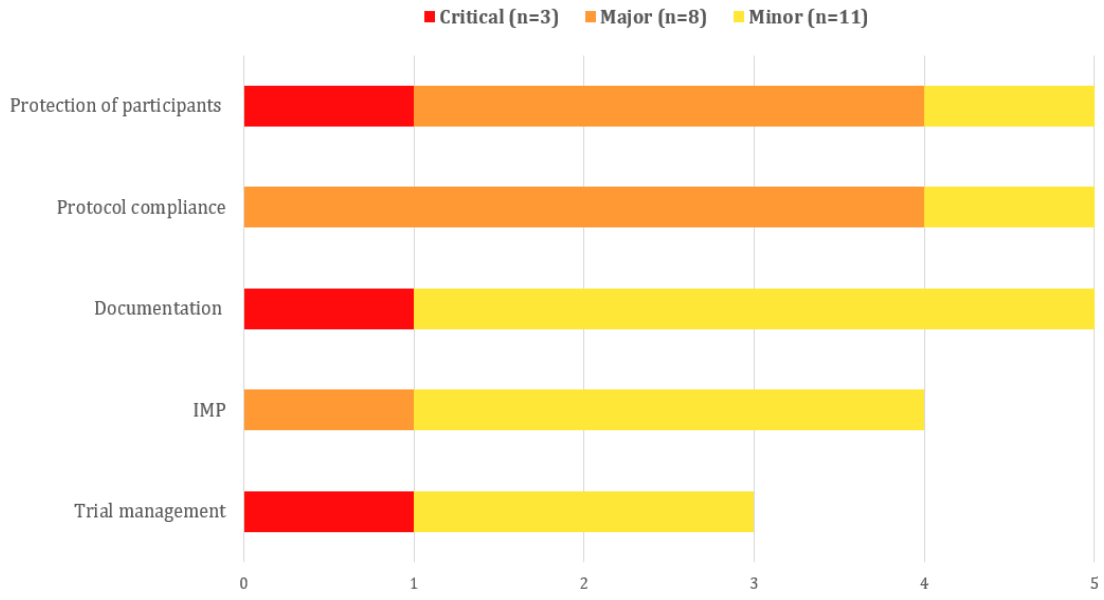
Inspections conducted

The TGA carried out five GCP inspections of Australian clinical trial sites from **1 July 2022 to 31 December 2022**. All inspections were routine announced inspections (see Appendix II for types of inspections). Three inspections were delivered face to face, with all inspectors onsite, and two inspections were delivered in a hybrid format with some inspectors onsite and others attending virtually.

A diverse range of sites were inspected during 2022, including public and private sites located in New South Wales, Victoria and South Australia. The inspected clinical trials ranged from phase 1 to phase 3 trials (see Appendix III for definitions of clinical trial phases). Clinical trials were either ongoing or had been completed at the time of inspection. The inspected trials were locally sponsored by either pharmaceutical companies, contract research organisations (CRO) or were investigator-initiated trials (IIT).

Deficiencies were identified in all five inspections across three or more main categories for each inspection. Deficiencies identified during the inspections were graded as critical, major or minor (see Appendix IV for definitions of inspection gradings). A summary of identified deficiencies is presented in figure 1.

Figure 1: Summary of main category deficiencies (1 July 2022 to 31 December 2022)



Inspection findings

For the purposes of this metrics report the term 'ICH GCP E6(R2)' is used to reference the current version of the ICH document adopted by us with annotations. Only selected ICH GCP E6(R2) sections are quoted in this report, refer to the full version of ICH GCP E6R(2) the for wording of the sections referred to only by a number in this report.

This section of the report provides details on the inspection findings within each main category. We have highlighted the most relevant sections of the ICH GCP E6(R2) in grey boxes throughout. All observed findings are presented in figure 2 at the sub-category level. A summary of sub-category findings with their grading can be found in Appendix VI.

Critical deficiencies were only identified in the categories of 'protection of trial participants', 'documentation' and 'trial management'. The highest number of major findings at the main category level was identified in 'protocol compliance' and 'protection of trial participants'. The highest number of minor findings at the main category level was identified in 'documentation' and 'IMP'.

Documentation was a key area of non-compliance that cut across all categories. It is critical for sites to have documented evidence of processes, events and decision making. The inspectors undertake interviews to help understand processes. However, if there is no supporting documented evidence then this will lead to deficiencies being recorded.

Figure 2: Summary of sub-category findings (1 July 2022 to 31 December 2022)

1. Protection of trial participants

According to ICH GCP E6(R2) section 1.28 *Informed Consent is a process by which a subject voluntarily confirms their willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.*

Clinical trials are often conducted using unapproved therapeutic goods with an unknown safety profile. All parties are responsible for the protection of trial participants when conducting and overseeing a clinical trial. Informed consent is a main element of participant protection.

Informed consent is obtained following a discussion between the participant and the medically qualified site staff and is documented by the signing of the consent form by both parties.

The Participant Information and Consent Form (PICF) must be reviewed and approved by the HREC before the start of the study. If updates to the PICF are required throughout the study, a new version must be re-submitted to the HREC for approval before implementation. To ensure compliance with this requirement it is expected that sites either develop robust SOPs on the consenting process and managing the submission of all participant-facing materials to the HREC or follow the National SOP and consider study-specific requirements.

We verify the consenting process at each GCP inspection. We review the PICFs signed by the trial participants, the content of the PICF, the source records documenting the consenting process, and the HREC and Research Governance Office (RGO) [referred to as the 'approving authority' in the Australian Clinical Trials handbook] approval of all versions of the PICFs used in the trial. The signed PICF also documents participants' consent for regulatory authorities to review their medical records and trial documents recording their participation in the clinical trial.

A deficiency in the protection of trial participants was identified in every inspection carried out during the reporting period.

Findings were made against the following criteria:
• ICH GCP E6 (R2) sections 2.11, 3.1.4, 4.2.4, 4.3.1, 4.4.1, 4.4.2, 4.4.3, 4.5.1, 4.8.1, 4.8.2, 4.8.5, 4.8.6, 4.8.7, 4.8.8, 4.8.10, 4.8.11, 4.9.0, 4.9.4, 4.10.1, 4.10.2, 4.12.1
• The National SOP sections 9.3, 9.5

Examples of findings include:

1.1 Informed consent - presence of informed consent

Major/minor

- It was not possible to verify if some participants provided valid consent as the PICF signature page and the original PICF were missing.

1.2 Informed consent process

Critical

- The PICF was signed by the participants, but not signed by the investigators.
- The PICF signed by the participants was a modified version of that approved by the HREC. The modified version was not submitted to the HREC before it was implemented at the site.
- Trial participants signed the forms electronically in a system that was not validated. This system did not allow for identification of the signatory – that is, the participants' signatures could not be verified as a legal equivalent of their handwritten signature.

Major/minor

- Documentation of the consenting discussion was missing, incomplete or incorrect.
- Non-English speaking participants consented to the study without an interpreter and/or impartial witness present.
- The PICF did not include the interpreter's signature when an interpreter was present during consenting discussion of a non-English speaking participant.
- Sub-investigators consented participants before being delegated the task of informed consent by the Principal Investigator (PI).

It is important for sites to ensure that there are quality assurance processes in place and documented, for example, confirmation that the PICF is completed in full, without any errors before a copy is provided to the participant.

Complete and accurate documentation of the informed consent process is essential to demonstrate compliance with protection of participants. We expect sites to follow documented informed consent procedures. At a minimum, documentation should include details of the explanation provided by the site personnel, questions asked by potential participants, and other relevant information covered during the discussion.

1.3 Informed consent form content

Major/minor

- The local PICF did not reference Australian-specific authorities.
- Adverse events (AEs) listed in the PICF were inconsistent with the trial protocol and the safety monitoring plan.

Compliance with the PICF content is a critical step in ensuring that participants have access to complete and accurate information when they are deciding whether to take part in a clinical trial. It is therefore important for the sites to have processes to ensure quality of the PICF content and its compliance with the ICH GCP E6(R2) section 4.8.10.

1.4 HREC/Approving authority - favourable opinion

Major/minor

- Participant-facing documents and advertising materials used in the study were not submitted to HREC and were therefore used without approval.
- Delays in the submission of investigator's brochures (IBs) and annual progress reports to HRECs and/or the RGO.

To demonstrate compliance with the HREC requirements it is important to ensure the timely submission of applicable documents for HREC and/or RGO review.

1.5 HREC/Approving authority - opinion, amendments, notifications

Major/minor

- Significant information about the study was not included in the annual progress report submitted to the HREC.

HRECs perform an important role in review of clinical trials in Australia. It is essential that the site provides complete and accurate information in submissions to the HREC so they can make an informed decision about whether their view of the study remains favourable.

1.6 HREC/Approving authority - composition, functions, operations

Observations for all sites met ICH GCP E6(R2) requirements for this sub-category.

It is important for sites to be familiar with HREC/approving authority requirements, to be aware of the reviewing HREC and approving authority's composition and to document any actual or perceived conflicts of interest, e.g. if a delegated site staff also has HREC responsibilities.

1.7 Participant protection – personal data protection

Critical

- Personal information of prospective participants who had never signed a PICF was retained. Data included full name, home addresses, email addresses, date of birth and medical history of potential participants.

Personal data in clinical trials setting can only be collected after the participant provides consent, and this information needs to be secure. It is important for sites to ensure that there are documented procedures to differentiate between the pre-screening, screening, consenting, and enrolling of patients. These procedures need to clearly define what information is considered to be private and confidential, and what information is not considered to be confidential if any.

1.8 Participant protection - safeguarding safety and well-being

Critical

- Healthcare staff consenting participants did not have medical qualifications or explicit HREC approval for participants to be consented by non-medically qualified personnel. There were no records to confirm that medically qualified personnel assessed the eligibility of the participants enrolled in the study.

Major/minor

- The safety monitoring and observation period post study-related procedure was not followed per protocol.
- There was no evidence to confirm whether safety updates included in the updated IB were discussed with the trial participant as they had not re-consented using the corresponding updated PICF.

According to ICH GCP E6(R2) section 2.3 *the rights, safety, and well-being or the trial subjects are the most important considerations and should prevail over interests of science and society*. It is therefore important for sites to ensure that there are quality assurance processes in place to safeguard participants' safety and well-being. For example, documented clear processes to ensure consenting, assessment of eligibility criteria and other relevant assessments are carried out by medically qualified staff.

2. Protocol compliance

ICH GCP E6 (R2) section 1.44 defines protocol as *a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial.*

ICH GCP E6 (R2) section 2.6 states that *a trial should be conducted in compliance with the protocol that has received prior ethics committee approval.*

ICH GCP E6 (R2) section 4.5 outlines the requirements of trial conduct in compliance with the protocol.

ICH GCP E6 (R2) section 4.9.1 states that *the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.*

ICH GCP E6 (R2) section 4.9.2 requires that the data reported on the CRF *are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.*

Protocol compliance is expected from all parties involved in the trial conduct, and it is verified at multiple levels via clinical trial monitoring, quality management, quality assurance (e.g. audits) and regulatory inspections. Trials with multiple deviations from the approved protocol and procedures pose risks to the participants and may jeopardise the quality of the data generated in a trial.

A deficiency in protocol compliance was identified in every inspection carried out during the reporting period.

Findings were made against the following criteria:
• ICH GCP E6 (R2) sections 2.3, 2.7, 2.13, 4.3.2, 4.5.1, 4.5.2, 4.9.0, 4.9.1, 4.9.2, 4.11.1

Examples of findings include:

2.1 Eligibility criteria

Major/minor

- The participants' records did not include sufficient evidence to verify that they met all eligibility criteria.
- An ineligible participant, meeting exclusion criteria, was enrolled based on a waiver granted by the study sponsor.

Complete and accurate documentation of eligibility is essential to demonstrate that only eligible participants are enrolled. The documentation of eligibility needs to be all-inclusive as per protocol inclusion/exclusion criteria and needs to be self-explanatory. It is essential for sites to have established processes to prevent enrolling ineligible participants.

Enrolment of an ineligible participant would usually be considered a critical deficiency. However, this finding was graded as major because the issue had already been addressed by the site, including escalation by the study team and informing the HREC. We expect that sites do not seek permission from the study sponsor to 'waive' eligibility requirements or action such 'waivers' if they are provided to the sites. A 'waiver' is a direct deviation from any of the applicable eligibility criteria and is different from a protocol deviation.

The correct process would be to carefully consider the protocol wording for eligibility criteria before the site activation and raise queries with the study sponsor if any of the criteria may be challenging for recruitment. When a sponsor agrees to change the eligibility criteria based on a site's comments, it is expected that the protocol and PICFs are updated, re-submitted to HREC and are only made effective at sites following full approval of the updated documents.

2.2 Assessment of efficacy

Observations for all sites met ICH GCP E6(R2) requirements for this sub-category.

Efficacy assessment is defined in the protocol. To demonstrate compliance the efficacy assessment needs to be performed and documented.

2.3 Safety reporting

Major/minor

- AEs were reported late, were discrepant/inconsistent in the source documentation or the documentation was incomplete.
- There were delays in assessing hospital admission and reviewing laboratory results for clinical significance.
- The PI of a commercially sponsored trial chaired the Dose Escalation Committee (DEC) meetings, which was a conflict of interest. The data sets used by the DEC were not recorded and there was no quality check of the data sets used to inform decisions of the DEC.
- No process for collecting reported/potential safety information from social media (approved for use by the HREC for this study), and no site standard operating procedures (SOPs) on safety reporting/management and dose escalation.

Reporting of safety information including AEs and serious AEs identified at sites is essential. Sponsors need access to a complete and accurate database of the safety events to inform decisions and take appropriate action. It is essential for sites to communicate the safety events and assess the seriousness of these events as per pre-agreed study requirements, as updated information about AEs may need to be included in the IB which is distributed across all relevant sites and studies. To ensure compliance with the safety reporting requirements it is expected that sites either develop robust SOPs or follow the National SOP and consider study-specific requirements.

2.4 Non-compliance with safety reporting to HREC/RGO/TGA

Major/minor

- Significant decisions related to participant safety and safety-related protocol deviations were not submitted to the HREC.

Accurate safety reporting is important to ensure that the regulator and approving bodies are informed of safety updates within required timeframes and can take prompt action to protect participants' safety if necessary. Robust processes of maintaining safety-related documentation, including decision making not to report a safety event (if applicable) is required to demonstrate compliance with safety reporting.

2.5 Reporting in case report form (CRF) /diary as specified in the protocol.

Major/minor

- Non-compliance with electronic CRF (eCRF) completion guidelines.
- Discrepancies between the eCRF and source documents.
- Missing eCRF entries and data not verifiable based on available source documents.

The CRF is one of the essential clinical trial documents. According to ICH GCP E6(R2) section 1.11 the CRF is *designed to record all of the protocol required information to be reported to the sponsor on each trial subject*. Each CRF entry is required to be verifiable as per source documentation without discrepancies. To facilitate compliance with this requirement, a record of the location(s) of source documents, also referred to as a source data agreement (SDA), is required to be maintained at the site as per ICH GCP E6(R2) addendum to section 8.1. The SDA is a document that confirms which data point in the source documentation is used to enter data into specific eCRF data field. The SDA is required to be updated every time there is a change either in source documentation processes or in the data required to be captured in eCRF. Keeping the SDA up-to-date and following the pre-agreed source data location as well as the eCRF completion guidelines are important steps to ensure quality of the generated data that will be used by the sponsor for analysis.

2.6 Other protocol non-compliance not listed above

Major/minor

- Protocol deviations were not identified by the site and therefore were not adequately reported in the study records.

The protocol is an essential document that requires HREC approval before it can be implemented. It is important to follow the approved version of the protocol, and to have proactive oversight of any deviations at site level, e.g. recorded in a form of a protocol deviation log. This active oversight will ensure the sites have a process to promptly detect any deviations to the protocol, perform a root cause analysis and implement a CAPA to avoid re-occurrence of protocol deviations. These steps support protocol compliance at the site. To ensure compliance with the protocol requirements we expect that sites either develop robust SOPs or follow the National SOP and consider study-specific requirements.

3. Documentation

Clinical trial conduct is documented in multiple records defined by the trial sponsor and the site. The records may include source documentation such as participants' medical records, signed forms, laboratory and imaging results, logs, study files and other records. The trial documentation describes the details of the trial conduct at the site. It is maintained throughout the trial and archived for at least 15 years following the completion of a clinical trial in line with the TGA annotations to ICH GCP E6(R2).

The documentation allows for reconstruction of the trial conduct while it is ongoing and after its completion when the site personnel may no longer be available to answer any questions. The quality, integrity and reliability of clinical trial data is critical to the acceptability of the clinical trial outcome by regulatory authorities.

Electronic systems used in clinical trials need to be validated to ensure that appropriate data integrity controls are in place. ICH GCP E6(R2) section 1.65 defines validation as *a process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.*

Computer system validation needs to be demonstrated for any electronic system.

According to ICH GCP E6 (R2) section 4.9.0 *the investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).*

A deficiency in documentation was identified in every inspection carried out during the reporting period.

Findings were made against the following criteria:

- ICH GCP E6 (R2) sections 2.1, 2.7, 2.8, 2.10, 2.13, 4.1.1, 4.1.3, 4.1.5, 4.2.3, 4.2.4, 4.9.0, 4.9.4, 5.5.3 (a, b), 8.3.18

Examples of findings include:

3.1 Essential documents

Major/minor

- Essential documents were missing from the investigator site files (ISF) for ongoing and archived studies.
- Laboratory sample handling and processing records were missing key information.

According to ICH GCP E6(R2) section 8.1 *essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with all applicable regulatory requirements*. Therefore compliance cannot be fully verified when some essential documents are missing. To facilitate compliance with this requirement, a record of the location(s) of files in the ISF is required to be maintained at the site as per ICH GCP E6(R2) addendum to section 8.1. This record can be in any format, e.g. a table of contents with an index to clarify what is filed electronically and what is filed in hard copy. Where an electronic system is used for filing, it is important to ensure that it complies with the requirements for validation as per the ICH GCP definition.

3.2 Source documentation

Critical

- There was no evidence as to whether the electronic medical records (EMR) which served both as the source documents and electronic case report forms (eCRF) had been validated for this purpose to fulfill the requirements of the ICH GCP E6(R2).
- There were no supporting documents to verify participant identity, confirm eligibility, medical history and IMP compliance of clinical trial participants.
- Site staff were able to amend information entered by the participants directly into the EMR.
- There was no robust process to ensure that electronic versions of the study documents were identical to the HREC-approved hard copy versions. There was more than one version of some approved documents and no mechanism to detect inadvertent human error.

Major/minor

- There were multiple conflicting source records with different data points and incomplete source data to support protocol compliance.
- The nursing notes were not available as part of source documents for a study.
- It was not possible to verify whether participants of an early phase study were made aware of the location of the closest emergency department or were provided with the protocol-required patient and emergency cards.
- The raw data for the study-specific test results were not filed in the archived documents although these were the primary source of information for clinical trial endpoints.

Documentation at a site should be complete. The documentation should be consistent and clear to allow for clinical trials activities to be repeatable. Following the ICH GCP E6(R2) requirements for documentation is essential to demonstrate compliance in this category.

To eliminate potential bias and establish the independence and reliability of data, participant-generated information should not be routinely subject to amendments.

Like the requirement to certify hard copies of the source documentation, it is important for sites to ensure that quality checks are performed in case of digitalising participant-facing study documents to ensure that the hard copy and e-version are identical.

The TGA has adopted the International scientific guideline: FDA: Use of electronic health record data in clinical investigations - Guidance for industry on 27 February 2023. This document may be used as another tool to perform self-evaluation of the electronic systems used in clinical trials.

3.3 Qualification and training

Major/minor

- Site staff were trained with a significant delay or not trained on relevant study-related documents.
- Site staff were not trained in the Australian clinical trial requirements outlined in the Australian Clinical Trial Handbook.
- Site personnel with delegated responsibilities in the study were also involved in the review of the study, as representatives of the HREC or RGO. There was no documentation of processes to manage potential or perceived conflicts of interest.

According to ICH GCP E6(R2) section 2.8 *each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)*. We expect that training is completed before performing study-related tasks, and any gaps in training are explained, e.g. in a site's SOP. It is important for sites to also establish processes to ensure staff are trained before conducting study tasks.

The National Statement section 5.4 states that *a conflict of interest in the context of research exists where:*

- *a person's individual interests or responsibilities have the potential to influence the carrying out of his or her institutional role or professional obligations in research; or*
- *an institution's interests or responsibilities have the potential to influence the carrying out of its research obligations.*

We expect that clinical trial site staff take proactive approach to identifying and managing perceived and real conflict of interest. Documentation related to any perceived and real conflicts of interest is required to demonstrate compliance with this requirement.

3.4 Standard operating procedures (SOPs)

Major/minor

- SOPs were outdated, had incorrect version control and content did not always match the title.
- SOPs referenced overseas authorities.

Having documented processes in the form of an SOP is an important quality assurance tool. To ensure compliance with this requirement we expect that sites either develop robust SOPs or follow the National SOP and consider study-specific requirements.

3.5 Organisation and personnel

Major/minor

- There were no available records to provide evidence of PI oversight of a very large study team including junior medical staff performing safety assessment of study-related AEs.
- The delegation log was not accurate/up-to-date, for example:
    - trial procedures were carried out by site personnel who were not authorised in the delegation log at time of performing the tasks.
    - site personnel in charge of the HREC submission were not listed in the delegation log.
    - backdating of the delegation log.
- The pharmacists did not have access to current/all versions of the Pharmacy Manuals applicable for the site.

It is a requirement of ICH GCP E6(R2) for the PI to demonstrate their oversight of all applicable aspects of a clinical trial.

3.6 Facilities and equipment

Major/minor

- A selection of expected laboratory samples could not be located at the site.
- Expired laboratory kits were stored with the laboratory kits within expiry dates.

It is a requirement of ICH GCP E6(R2) section 4.2.3 for the PI to ensure adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely. To ensure compliance with the protocol requirements we expect that sites either develop robust SOPs or follow the National SOP and consider study-specific requirements.

3.7 Randomization, blinding and codes of study drug

Observations for all sites met ICH GCP E6(R2) requirements for this sub-category.

It is important for sites to maintain documentation related to this sub-category when applicable, e.g. for a blinded randomised control trial.

3.8 Direct access to data

Observations for all sites met ICH GCP E6(R2) requirements for this sub-category.

To demonstrate compliance with this sub-category it is important to ensure that all relevant stakeholders including clinical trial monitors, auditors and inspectors have direct access to clinical trial data.

3.9 Contracts and agreements, including PI oversight of contractors/site-hired third-party vendors

Observations for all sites met ICH GCP E6(R2) requirements for this sub-category.

It is important for sites to ensure compliance with the contracts and agreements, and to maintain active oversight of any site-managed external vendors, if applicable.

4. Investigational Medicinal Product (IMP)

Clinical trials often involve use of the unapproved therapeutic goods, which have not been registered for use in Australia or other countries and for which we have limited information. IMP-related actions from IMP receipt to return/destruction are expected to be documented in relevant records, including shipping records, scripts, IMP accountability logs, IMP return records or destruction certificates. Management of the IMP at the site must follow strict procedures to mitigate the risks and to ensure compliance with ICH GCP E6(R2)

ICH GCP E6 (R2) section 4.6 outlines the site's responsibilities relating to the management of IMP from receipt, through prescription, dispensing, accountability, treatment compliance, to return to sponsor and destruction.

A deficiency in category 'IMP' was identified in four out of five inspections carried out during the reporting period.

Findings were made against the following criteria:
• ICH GCP E6 (R2) sections 4.5.2, 4.6.1, 4.6.5, 4.6.6, 4.7, 5.14.4b, 8

Examples of findings include:

4.1 IMP accountability at site

Major/minor

- There was no documented process to outline the management of an IMP by responsible parties at the site.

A documented process is an important quality assurance tool to demonstrate the site's ability to comply with ICH GCP E6R(2) requirements for management of the IMP at the site.

4.2 Supplying, storage, retrieving and destruction

Major/minor

- There was no documented process established for IMP delivery, temperature control during transit, return and destruction of the IMP within a decentralised trial.

According to ICH GCP E6R(2) section 4.6.3 *the investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor*. According to ICH GCP E6R(2) section 4.6.4 the IMP *should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s)*. To comply with these requirements, risk management and quality control are especially important in case of direct delivery of IMP to participants' homes.

If delivery methods are used that that are not monitored (for example, for temperature or receipt of the IMP) this needs to be carefully justified and documented. For example, undertaking a test run with a temperature monitoring before initiating the study may be appropriate to make an evidence-based decision on IMP delivery methods. The risk of not delivering IMP to the participant or loosing participants' IMP returns due to disruptions of the post provider should also be an important consideration in decision-making on IMP management.

4.3 Prescription, administration and compliance

Major/minor

- The IMP dose was calculated based on an incorrect weight measurement, which was obtained inconsistently from the method detailed in the protocol.
- The IMP was prescribed with incorrect dosing information resulting in the incorrect dose being administered to a trial participant.

According to ICH GCP E6R(2) section 4.6.5 *the investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol*. In order to comply with these requirements sites are expected to have robust processes in place to ensure correct weight-based dose calculations, e.g. to be aware at all times whether the participants are required to take their shoes off on scales, or if they are required to be weighed within a certain time prior to dosing.

According to ICH GCP E6R(2) section 4.6.6 *the investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly*. In order to comply with these requirements, sites are expected to have robust processes to ensure the IMP is only dispensed based on written confirmation that the dose was prescribed according to the protocol. The sites are also expected to have processes in place to ensure that the staff involved in dosing the participant are promptly informed of any changes in assigned doses to prevent incorrect dosing. This is especially important for sites without automatic IMP dispensing systems and for sites where standard practice is to prescribe the IMP ahead of the visit.

5. Trial Management

The main category 'trial management' verifies compliance with the ICH GCP E6(R2) and the Australian clinical trial regulatory requirements. Clinical trial management is an important aspect of clinical trial conduct. Trial management includes careful planning of clinical trial sites' participation in a clinical trial to ensure compliance with the requirements, including proactive identification, assessment and monitoring of the risks associated with trial conduct. Compliance with GCP should be integrated into the site's processes – it is not a standalone function. Additional responsibilities are assumed by the investigator when they take a role of sponsor-investigators. It is important to take time to proactively understand the TGA requirements and guidance on clinical trial conduct before initiating a clinical trial at your site.

The site's responsibilities relating to the trial management are outlined in the Australian Clinical Trian Handbook and in the NHMRC Australian Code of Conduct for Responsible Conduct of Research.

For investigator-initiated trials, the responsibilities of sponsor-investigator are defined in the ICH GCP E6 (R2) section 5 in addition to the section 4 responsibilities.

A deficiency in trial management was identified in four out of five inspections carried out during the reporting period.

Findings were made against the following criteria:
• The Australian clinical trials handbook
• ICH GCP E6 (R2) section 5 (IIT only)

Examples of findings include:

5.1 Non-compliance with local regulatory requirements (other than safety reporting)

Major/minor

- Although an approving authority had been notified to the TGA under the Clinical Trials Notification (CTN) scheme, there was no RGO or equivalent established at the site.
- Trial details notified to the TGA via CTN did not match the trial details maintained in the ISF.

We note that it is the local sponsor's responsibility to notify the TGA of the trial through a CTN submission; however, it is the site's responsibility to ensure that they provide accurate details of their site to the sponsor for the purpose of CTN submission.

It is also the site's responsibility to establish and follow the process at the site to ensure regulatory compliance of additional unapproved goods used at the site, e.g. this process should include ensuring that every medicine is listed in the CTN correctly and that all devices not listed on the Australian Register of Therapeutic Goods (ARTG) are notified to the TGA under the CTN prior to use of the unapproved goods at the site.

5.2 Sponsor-investigator responsibilities

Critical

- No risk management plan and/or risk management process was developed for the trial.
- No study-specific monitoring process had been implemented.
- The study documentation available for the inspected site did not adequately reflect or explain the distribution of responsibilities between the coordinating Sponsor-Investigator and PIs of the other sites for a fully decentralised trial.

The Australian Clinical Trial Handbook (p.25) states that when planning a clinical trial, trial sponsors should have processes in place to ensure the risks associated with its conduct are identified and assessed. Adequate trial monitoring and management plans are then developed to mitigate risk that may adversely impact participant safety or quality of data. To ensure compliance with trial management, training of the Sponsor-Investigator needs to cover the sponsor's responsibilities as outlined in the ICH GCP E6(R2) in addition to the GCP training on investigator's responsibilities.

We expect that clinical trial sites familiarise themselves with the local clinical trial sponsor's responsibilities for any type of a clinical trial.

Appendix I: Main categories and sub-categories reviewed during inspection

Main category	No.	Sub-category
Protection of participants	1.1	Informed consent - Presence of informed consent
	1.2	Informed consent - Informed consent process
	1.3	Informed consent - Informed consent form content
	1.4	HREC/Approving authority - Favourable opinion
	1.5	HREC/Approving authority - Opinion, amendments, notifications
	1.6	HREC/Approving authority - Composition, functions, operations
	1.7	Participant protection - Personal data protection
	1.8	Participant protection - Safeguarding safety and well-being
Protocol compliance	2.1	Eligibility criteria
	2.2	Assessment of efficacy
	2.3	Safety reporting
	2.4	Non-compliance with safety reporting to HREC/RGO/TGA
	2.5	Reporting in case report form/diary as specified in the protocol
	2.6	Other protocol non-compliance not listed above
Documentation	3.1	Essential documents
	3.2	Source documentation
	3.3	Qualification and training
	3.4	Standard operating procedures
	3.5	Organisation and personnel
	3.6	Facilities and equipment
	3.7	Randomization, blinding and codes of study drug
	3.8	Direct access to data
	3.9	Contracts and agreements, including PI oversight of contractors/site-hired third-party vendors
Investigational Medicinal Product	4.1	Investigational Medicinal Product (IMP) accountability at site
	4.2	Supplying, storage, retrieving and destruction
	4.3	Prescription, administration and compliance
Trial management	5.1	Non-compliance with local regulatory requirements (other than safety reporting)
	5.2	Sponsor-investigator responsibilities

Appendix II: Types of inspections

Excerpt from pages 9-10 of the Good Clinical Practice (GCP) Inspection Program Guidance for GCP inspection of clinical trial sites for investigational biologicals and medicinal products. Please note the TGA is referred to as 'we' or 'us', and clinical trial investigator sites as 'you'.

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).

Re-inspections

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.

Appendix III: Clinical trial phases for medicines and biologicals

Excerpt from pages 43-44 of the Australian Clinical Trial Handbook.

Phase	Indicative number of participants	Objectives
Phase 0: Human pharmacology (micro-dosing)	10-15 Involves dosing a limited number of humans with a limited range of doses for a limited period of time	**Assess pharmacokinetics** Gather preliminary data on pharmacokinetics and bioavailability to determine if the drug behaves as expected from preclinical studies 'Micro-dosing' studies
Phase I: Human pharmacology	10-100 May involve the first administration to humans, usually to small numbers of healthy volunteers or to patients	**Safety and tolerance** Define or describe pharmacokinetics and pharmacodynamics Determine dosing Explore drug metabolism and drug interactions Identify preferred routes of administration Phase Ia: Single ascending dose Phase Ib: Multiple ascending dose
Phase II: Therapeutic exploratory	100-300 May be undertaken in a larger group of human patients (several hundred)	**Efficacy and safety** Phase IIa: Demonstrate clinical efficacy or biological activity through pilot studies Explore therapeutic dose range Phase IIb: Determine optimum therapeutic dose and regimen (with efficacy as primary endpoint) Resolve uncertainties regarding the design and conduct of subsequent trials
Phase III: Therapeutic confirmatory	300-3000 Usually involve a large group of patients (from several hundred to several thousand)	**Safety, efficacy or effectiveness** Phase IIIa: Determine the therapeutic effect in patient populations for which the drug is eventually intended Provide a definitive assessment of risk-benefit balance (to support drug registration or change in clinical practice) Phase IIIb: Increase patient exposure and support marketing claims or publication
Phase IV: Therapeutic use	1000's	**Post marketing surveillance or resolution of treatment uncertainties** Monitor safety in real world populations To refine knowledge of the risk-benefit balance, detect rare or long-term adverse effects, drug interactions Pharmacoeconomics to gather data in support of the use Comparative effectiveness and community based research (sometimes described as Phase V trials) Trial combinations with existing products

Appendix IV: Inspection deficiency gradings

Excerpt from page 16 of the Good Clinical Practice (GCP) Inspection Program Guidance for GCP inspection of clinical trial sites for investigational biologicals and medicinal products.

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.

Appendix V: Acronyms

The following acronyms were used in this report:

AE	Adverse Event
ARTG	Australian Register of Therapeutic Goods
CAPA	Corrective and Preventative Action Plan
CTA	Clinical Trial Approval
CTN	Clinical Trial Notification
CRO	Contract Research Organisation
DEC	Drug Escalation Committee
eCRF	Electronic Case Report Forms
EMA	European Medicines Agency
EMR	Electronic Medical Records
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCPIP	GCP Inspection Program
GP	General Practitioner
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH GCP	International Conference of Harmonisation on Good Clinical Practice
ICH GCP E6(R2)	Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice
IIT	Investigator-Initiated Trial
IMP	Investigational Medicinal Product
ISF	Investigator Site Files
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
PICF	Participant Informed Consent Form
RGO	Research Governance Office
SDA	Source Data Agreement
TGA	Therapeutic Goods Administration

Appendix VI: Summary of sub-category findings

Main category	No	Sub-category	No of critical sub-category findings	No of major sub-category findings	No of minor sub-category findings	Total
Protection of participants	1.1	Informed consent - Presence of informed consent	0	3	0	**3**
	1.2	Informed consent - Informed consent process	3	12	1	**16**
	1.3	Informed consent - Informed consent form content	0	2	0	**2**
	1.4	HREC/Approving authority - Favourable opinion	0	4	0	**4**
	1.5	HREC/Approving authority - Opinion, amendments, notifications	0	7	2	**9**
	1.6	HREC/Approving authority - Composition, functions, operations	0	0	0	**0**
	1.7	Participant protection - Personal data protection	1	0	0	**1**
	1.8	Participant protection - Safeguarding safety and well-being	2	1	1	**4**
Protocol compliance	2.1	Eligibility criteria	0	6	0	**6**
	2.2	Assessment of efficacy	0	0	0	**0**
	2.3	Safety reporting	0	26	1	**27**
	2.4	Non-compliance with safety reporting to HREC/RGO/TGA	0	1	0	**1**
	2.5	Reporting in case report form/diary as specified in the protocol	0	5	3	**8**
	2.6	Other protocol non-compliance not listed above	0	7	0	**7**
Documentation	3.1	Essential documents	0	0	8	**8**
	3.2	Source documentation	4	0	27	**31**
	3.3	Qualification and training	0	2	18	**20**
	3.4	Standard operating procedures	0	0	3	**3**
	3.5	Organisation and personnel	0	0	10	**10**
	3.6	Facilities and equipment	0	0	4	**4**
	3.7	Randomization, blinding and codes of study drug	0	0	0	**0**
	3.8	Direct access to data	0	0	0	**0**
	3.9	Contracts and agreements, including PI oversight of	0	0	0	**0**

		contractors/site-hired third-party vendors				
Investigational Medicinal Product	4.1	IMP accountability at site	0	0	1	**1**
	4.2	Supplying, storage, retrieving and destruction	0	2	0	**2**
	4.3	Prescription, administration and compliance	0	0	7	**7**
Trial management	5.1	Non-compliance with local regulatory requirements (other than safety reporting)	0	0	11	**11**
	5.2	Sponsor-investigator responsibilities	3	0	0	**3**
Total			**13**	**78**	**97**	**188**

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