Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Good Clinical Practice (GCP) Inspection Program 2023 – 2024

A report on Therapeutic Goods Administration (TGA) clinical trial compliance activities

Version 1.0, March 2025

Contents

Background

The Good Clinical Practice Inspection Program (GCPIP) aims to strengthen the TGA's monitoring activities and protect the safety and wellbeing of clinical trial participants. The GCPIP commenced inspecting trials of medicines and biologicals in 2022. The program was expanded to include medical device trials in November 2023.

GCP inspectors assess whether Australian clinical trial sites are meeting their GCP responsibilities. We can inspect all Australian clinical trial sites involved in clinical trials conducted under the Clinical Trial Notification (CTN) and Clinical Trial Approval (CTA) schemes. Inspectors verify compliance with the applicable Australian therapeutic goods legislation and guidelines, including:

- Therapeutic Goods Act 1989
- Therapeutic Goods Regulations 1990
- Therapeutic Goods (Medical Devices) Regulations 2002
- The National Statement on Ethical Conduct in Human Research (the National Statement)
- Integrated Addendum to the ICH E6(R1): Guidance on Good Clinical Practice ICH E6(R2), annotated with the TGA comments (ICH GCP E6(R2)
- International Organisation for Standardisation (ISO) 14155 - Clinical Investigation of Medical Devices for Human Subjects - Good Clinical practice (ISO 14155:2011 and ISO 14155:2020)
- The trial-specific protocol and amendments, approved by the relevant Human Research Ethics Committees (HREC).

We have published a GCP Inspection Guidance document, which describes the type of inspections, who we inspect, how we prioritise and schedule inspections, how to prepare for an inspection and the inspection process. Definitions for terms frequently used in this report are provided in the GCP Inspection Guidance document.

We are working towards increasing the number of inspections as we mature the inspection program.

- We refer to the TGA as 'we' or 'our'.
- We use 'must' or 'required' to describe something you are legally obliged to do. We use 'should' to recommend an action that will support you to meet your legal requirements.

Purpose

The purpose of this report is to provide summaries of GCPIP compliance activities in 2023 – 2024, including:

- an overview of education activities
- areas of compliance and non-compliance with GCP standards
- examples of critical and major deficiencies identified in GCP inspections.

This report aims to support:

- GCP inspection readiness
- clinical trial sites to meet the Therapeutic Goods legislation and GCP guideline(s) requirements
- high quality clinical trials in Australia.

This report should be read in conjunction with:

- GCP Inspection Guidance
- Australian Clinical Trial Handbook
- Roles and responsibilities for clinical trial safety reporting of significant safety issues and urgent safety measures

The 2022 version of the TGA GCPIP metrics report is available on our webpage.

Scope

This report covers the period of **1 January 2023** to **31 December 2024**.

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. At the time of this report, all sites had either resolved the identified issues through a corrective and preventative action (CAPA) process or were in the process of addressing them.

All data has been **de-identified** and does not reveal the identities of individual clinical trial sites, investigators, sponsors, Human Research Ethics Committees (HRECs), local approving authorities (AAs) or any other relevant stakeholders. Refer to the TGA Privacy webpage to learn about how we handle personal information.

Note: This report references the National Statement on Ethical Conduct in Human Research (2023), which came into effect on 1 January 2024. The 2018 version has been superseded but was applicable for some inspections.

Proactive monitoring of high-risk medical device trials

In November 2023, legislative amendments expanded the TGA's capacity to gather more detailed information about certain high risk medical devices used in clinical trials. Access to this information helps us to identify any safety concerns.

Enhanced screening of medical device CTN submissions commenced on 4 April 2024, marking a key step in improving oversight and patient safety. The TGA's monitoring has focused on first-in-human trials of 8 categories of high risk devices (those implanted in the heart, great vessels and brain), which risk major consequences in the event of device failure. Monitoring efforts for these high-risk trials were significantly improved through the new CTN form. The business processes and stakeholder communications that have evolved have now become incorporated into business-as-usual work for the TGA. A 12-month review will occur during 2025, supported by further stakeholder consultation as required.

The reforms also meant that medical device trials were incorporated into the GCPIP. Therefore, the assurances around managing harms associated with how high risk medical devices are designed and made, achieved through enhanced CTN screening, are coupled to the broader GCPIP that safeguards how trials are conducted.

Stakeholder engagement and education

Our education initiatives aim to inform, engage and consult with our stakeholders and provide up-to-date, clear, and accessible guidance and information to assist regulated entities with compliance.

The education outreach activities delivered in 2023 – 2024 included:

- direct education to clinical trial sites before, during and after inspections to promote compliance and understanding of the relevant Australian legislation and guidelines
- updating the GCP Inspection Guidance to include medical devices and improve readability
- 3 live public webinars to educate on program changes, offering opportunities to ask questions and engage with inspectors and TGA staff
- 8 conferences and other external events to share updates on the regulation of clinical trials including the GCPIP.

A total of 2900 delegates/attendees interacted with the TGA representatives across all the educational outreach activities.

The topics covered in these events included raising general awareness about the GCPIP and compliance expectations, as well as addressing broader TGA reforms, such as updates to the safety reporting form and proactive monitoring of highest-risk medical device clinical trials.

Conducted inspections

A total of 13 GCP inspections were conducted over 2023 – 2024 (6 routine inspections in each year and one 'for cause'). We inspected a variety of clinical trial sites/trials as presented in Figure 1: GCP inspections conducted by the TGA in 2023 – 2024.

Figure 1: GCP inspections conducted by the TGA in 2023 – 2024

Types of GCP inspections

- 12 routine announced inspections
- 1 'for cause' announced inspection*****
- In-person and hybrid

Types of inspected sites

- Private and public
- Different geographical locations (ACT, NSW, QLD, SA, VIC)
- Different types of trials:
  - commercially sponsored
  - non-commercially sponsored clinical trials, including investigator-initiated trials (IITs)

Types of inspected trials

- Phases 1-3
- Ongoing and completed
- Different therapeutic goods / investigational products:
  - medicines
  - biologicals
  - medical devices
- 11 therapeutic areas

***** The 'for cause' inspection covered multiple clinical trials.

Summary of deficiencies

During the inspections, we reviewed compliance under five main categories: 'Protection of participants', 'Protocol compliance', 'Documentation', 'Therapeutic good / Investigational product', and 'Trial management'. Deficiencies found during the inspections are graded at three levels: minor, major and critical (see Appendix A for definitions of inspection gradings).

- At least one deficiency was identified in all inspections
- Critical deficiencies were identified in 'Protocol compliance', 'Trial management' and 'Therapeutic Good / Investigational Product' in both years
- No critical deficiencies were identified in commercially sponsored clinical trials
- Full compliance in one or more categories was observed in several inspections
- The highest level of compliance was observed in 'Therapeutic Good / Investigational Product'.

Figure 2: Summary of main category deficiencies in 2023 inspections

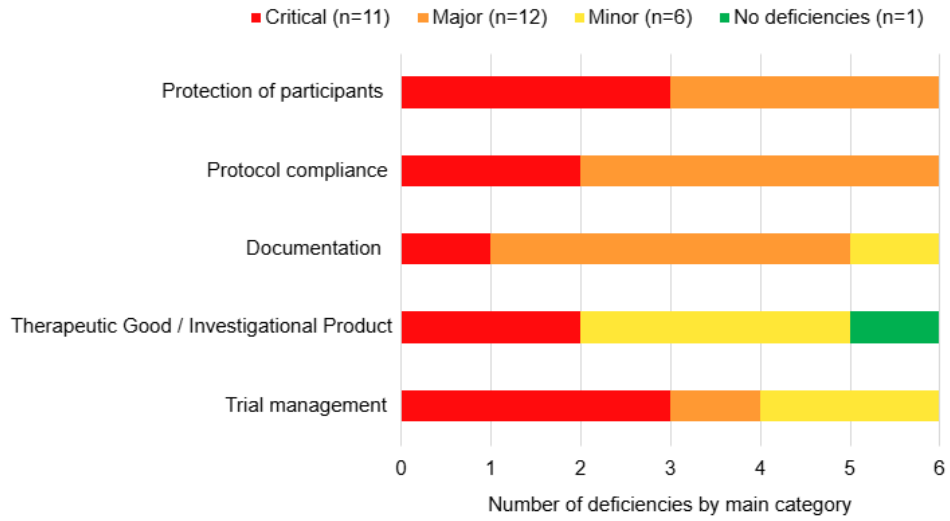
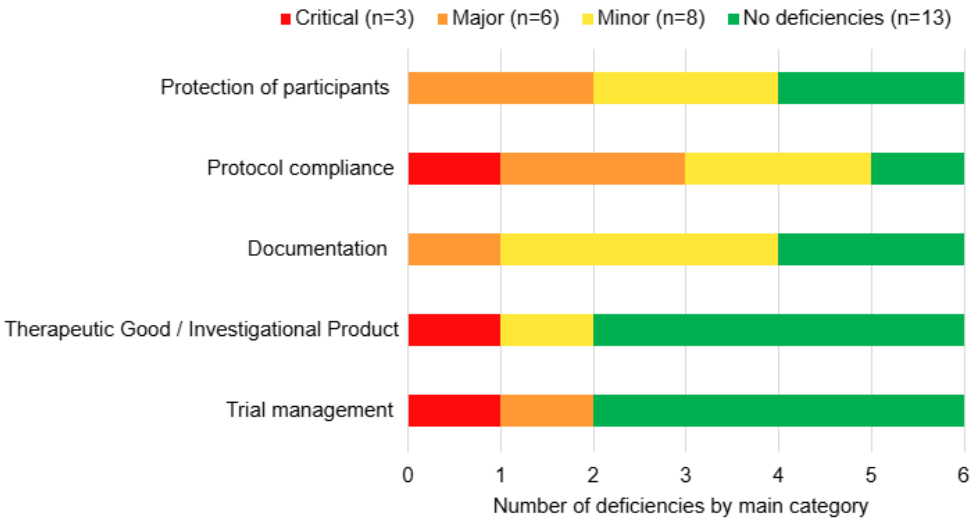


Figure 3: Summary of main category deficiencies in 2024 inspections



In these main categories, there are multiple sub-categories against which we verify compliance (further details are found in our GCPIP Inspection Guidance).

Direct comparisons across the reporting periods and trend analysis are not provided because of the small number of inspections conducted to date.

Examples of deficiencies

De-identified examples of deficiencies from both routine and 'for cause' inspections are provided below:

- These examples do not cover all findings in this period – only examples of major and critical deficiencies are included
- For a report on the number of all deficiencies at sub-category level (including minor), see Appendix B: Summary of deficiencies in 2023 and Appendix C: Summary of deficiencies in 2024.

Protection of participants

Deficiencies in 'Protection of participants' were identified in 10 out of 12 routine inspections. Most non-compliance was identified in the 'Informed consent process'. We observed high levels of compliance in the 'HREC/AA - Favourable opinion' sub-category.

Deficiencies in 'Protection of participants' were made against the following criteria:

Compliance requirements	Deficiencies against the following sections
The National Statement 2007 (updated 2018) *	2.2.1, 2.2.6(a), 2.2.9, 5.2.4, 5.2.11, 5.2.12, 5.2.25, 5.4, 5.4.1, 5.7.1
ICH GCP E6 (R2) with TGA annotations	2.1, 2.3, 2.7, 2.9, 2.11, 2.13, 3.2.5, 4.1.2, 4.1.3, 4.1.5, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.3.1, 4.3.2, 4.4.1, 4.4.2, 4.4.3, 4.5.1, 4.5.2, 4.7, 4.8.1, 4.8.2, 4.8.4, 4.8.5, 4.8.7, 4.8.8, 4.8.10, 4.8.11, 4.9.0, 4.9.4, 4.10.1, 4.10.2, 8.3.12
ISO14155:2011	4.5.2, 4.5.4, 4.7, 9.7
ISO14155:2020	4(g), 5.8.1, 5.8.2, 5.8.4, 7.7, 10.4, 10.5, 10.6, 10.7

* Equivalent sections from the National Statement 2023 are included in the below examples.

Examples of deficiencies include:

- ICH GCP E6(R2) section 4.8.10 requirements that the written informed consent, the informed consent discussion and any other written information to be provided to subjects should include specific explanations was not fully met. Examples of non-compliance included:

– information about the trial and alternative treatments was incomplete or missing from the participant informed consent form (PICF)

– documentation of the informed consent discussion was incomplete or missing.

- ICH GCP E6(R2) section 4.8.5 requirement that the investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the trial were not fully met. Examples of non-compliance included:

– participants were not informed about all pertinent aspects of the trial, including procedures that were conducted as part of the trial

– consent was obtained by personnel not designated by the investigator.

- ICH GCP E6(R2) section 4.8.8 requirement that prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the participant or

their legally acceptable representative, and by the person who conducted the informed consent discussion, was not met in several instances. Examples of non-compliance included:

– original signed PICFs were incomplete or missing

– participant's or the site staff's signatures and/or dates were missing from the PICFs

– procedures commenced prior to consent.

- ICH GCP E6(R2) section 4.8.2 requirements, including that any revised written PICF, and written information, should receive the HREC approval/favourable opinion in advance of use and that participants should be informed in a timely manner of new information that may be relevant to their willingness to continue participation in the trial were not fully met. Examples of non-compliance included:

– participants were not informed, or not informed in a timely manner of new information included in revised PICF

– participants were consented to a superseded PICF when a subsequent PICF had already been approved by the reviewing HREC.

- The National Statement 2023 section 2.2.9 requirement to include a person as a participant only if their consent is voluntary was not fully met. The PI's relationship with some participants could have been perceived as a position of power, and this was not addressed.

- The National Statement 2023 section 5.3.11 requirement that a researcher must disclose to the review body any interests that may constitute an actual or potential conflict of interest, including any financial or other interest or affiliation that bears on the research, was not fully met. Examples of non-compliance included clinical trial investigators and/or delegated site staff who were also members of the reviewing HREC did not disclose this potential conflict of interest.

- Multiple requirements for the investigator to communicate with the HREC before initiating a trial and implementing all subsequent amendments and updates (ICH GCP E6(R2) sections 4.4.1, 4.4.2, 4.4.3, 4.10.1 and ISO 14155:2020 section 10.4 (c)). These require the investigator to have written and dated approval/favourable opinion from the HREC, to provide trial-related documents to the HREC and provide reports at least annually. Examples of non-compliance included:

– written and dated approval letters for initial trial protocol and protocol amendments were missing

– participant recruitment procedures were followed without evidence of HREC approval

– Investigator's Brochure (or equivalent) was not provided to the reviewing HREC

– delayed submission of annual progress reports

– annual report did not include information regarding non-compliance with the conditions of the initial HREC approval

– trial extended beyond the initial HREC approval period without being reported to the reviewing HREC.

- Multiple requirements related to medical care and medical decisions in a clinical trial (ICH GCP E6(R2) section 2.7, 4.3.1, 4.3.2 and ISO 14155:2020 sections 4 (g), 10.7 (a)). The requirements that a qualified physician/healthcare professional be responsible for medical care and medical decisions were not fully met.

Examples of medical decisions made by a non-medical /qualified healthcare staff included:

– consent obtained by non-medically qualified staff without HREC approval

– a decision to enrol participants in an interventional trial involving an ‘unapproved’ therapeutic good was made by non-medically qualified staff

– a decision to prescribe and administer an ‘unapproved’ therapeutic good was made by staff without evidence of their qualification to perform this task.

- Examples of medical care provided by a non-medical staff/qualified healthcare staff included:

– participants informed of the nature and possible cause of any experienced adverse events by non-medically qualified staff

– participants provided with instructions on use and handling of ‘unapproved’ therapeutic goods by non-medical staff/qualified healthcare staff

– participants’ response to intervention and subsequent recommendations on future treatment were made by non-medically qualified staff.

Protocol compliance

Deficiencies in ‘Protocol compliance’ were identified in 11 out of 12 routine inspections. Most of the individual deficiencies were identified in the ‘Safety reporting’ sub-category. The least number of deficiencies were identified in ‘Non-compliance with safety reporting to HREC/AA/TGA’ sub-category.

Deficiencies in ‘Protocol compliance’ were made against the following criteria:

Compliance requirements	**Deficiencies against the following sections**
Therapeutic Goods Regulations 1990	12AD(b)
ICH GCP E6 (R2) with TGA annotations	2.3, 2.7, 2.9, 2.13, 4.2.4, 4.2.6, 4.3.1, 4.3.2, 4.3.4, 4.5.1, 4.5.2, 4.5.3, 4.6.5, 4.9.0, 4.9.1, 4.9.2, 4.11.1
ISO14155:2011	6.4, 9.6, 9.8
ISO14155:2020	6.4, 7.4, 7.10, 10.2, 10.6, 10.8

Examples of deficiencies include:

- The Therapeutic Goods Regulations 1990 section 12AD(b) and ICH GCP E6(R2) section 4.5.1 requirement that the investigator should conduct the trial in compliance with the HREC approved protocol was not fully met. Examples of non-compliance included:

– participants who did not meet all eligibility criteria were enrolled

– records of some participants’ eligibility did not cover all inclusion and exclusion criteria specified in the protocol

– records were insufficient to demonstrate that all requirements of the protocol were complied with

– participants’ visits or procedures were not conducted in compliance with the protocol.

- ICH GCP E6(R2) section 4.5.2 requires that the investigator should not implement any deviation from, or changes of the protocol without prior review and documented approval/favourable opinion from the HREC of an amendment. Examples of non-compliance included investigators knowingly deviating from the protocol without obtaining prior HREC approval when:

– omitting required procedures

– conducting participants' visits and procedures

– not collecting, documenting and reporting information required for safety and efficacy assessment.

- ICH GCP E6(R2) section 4.5.3 requirement that the investigator or person designated by the investigator, should document and explain any deviation from the approved protocol was not fully met because protocol deviations were not documented and explained by the site staff.
- ICH GCP E6(R2) section 4.11.1 requirement that all serious adverse events (SAEs) should be reported immediately to the sponsor was not fully met as events meeting the SAE definition were not reported or were reported with a delay.
- ICH GCP E6(R2) sections 4.9.1 and 4.9.2 requirements that the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the Case Report Forms (CRFs) and in all required reports and that data that are derived from source documents, should be consistent with the source documents or the discrepancies explained were not fully met. Information reported in CRFs was inaccurate, incomplete, not provided in a timely manner and did not have any source to support the data entry.

Documentation

Deficiencies in 'Documentation' were identified in 10 out of 12 routine inspections. Individual deficiencies in sub-categories 'Essential documents' and 'Source documentation' were reported almost twice as often as in any other sub-categories. We observed high level of compliance in 'Contracts and agreements, including PI oversight of contractors/site-hired third-party vendors' sub-category. Most deficiencies in 'Documentation' were due to non-compliance with the ALCOA-C principles explained below.

ALCOA-C DATA INTEGRITY PRINCIPLES
Documentation should meet the ALCOA-C principles to ensure data integrity at a clinical trial site:

Attributable	Is it obvious who wrote/did it/made a change and when?
Legible	Can the data be read easily?
Contemporaneous	Are the data recorded in real time? Are signatures dated?
Original	Is it a primary source? Is the original available? Is the original protected against premature destruction?
Accurate	Is the information error free? Is there a quality control/assurance process? Are conflicting data recorded elsewhere?
Complete	Has the information been recorded in its entirety?

Deficiencies in 'Documentation' were made against the following criteria:

Compliance requirements	Deficiencies against the following sections
The National Statement 2007 (updated 2018)	2.2.9, 5.2.6, 5.2.11, 5.2.12, 5.4
The National Statement 2023	5.3.11, 5.3.12, 5.6
ICH GCP E6 (R2) with TGA annotations	1.63, 1.65, 2.8, 2.10, 2.13, 4.1.1, 4.1.3, 4.1.5, 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.7, 4.5.1, 4.7, 4.9.0, 4.9.1, 4.9.2, 4.9.4, 4.9.6, 4.9.7 5.5.11, 5.5.3, 5.13.4, 6.4.9, Addendum to 8, 8.1, 8.2, 8.3
ISO14155:2011	5.9, 6.6, 6.8, E.1
ISO14155:2020	7.8, 7.8.1, 7.9, 7.10, 10.1-10.3, 10.6, 10.7 (f), A.12, E.1

Examples of deficiencies include:

- ICH GCP E6(R2) section 4.9.4 requirements that the investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and should take measures to prevent accidental or premature destruction of these documents were not fully met. Examples of missing or incomplete essential documents/records included:

– source documents were destroyed prematurely

– participant screening/enrolment and identification logs were not created

– the record of the locations of essential documents was not maintained or was incomplete.

- ICH GCP E6(R2) section 4.9.0 requirements that the investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants, that source data should be ALCOA-C and 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) were not fully met. This was evident in multiple forms of source data including paper records, electronic medical records and source data worksheets.

- ICH GCP E6(R2) section 4.1.5 requirement that the investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties was not fully met as delegation lists or equivalent documentation were not maintained.

- ICH GCP E6(R2) section 4.2.3 requirement that the investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely was not fully met. Examples of non-compliance included:

– staff were not appropriately qualified

– an onsite laboratory without certification, accreditation, established quality control and external quality assessment or other validation was used

– storage facility calibration or maintenance were not current.

- ICH GCP E6(R2) section 4.2.4 requirement that the investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational products, and their trial-related duties and functions was not fully met because site staff performed trial duties before being trained.

- ICH GCP E6(R2) section 2.13 requirements that systems with procedures that assure the quality of every aspect of the trial should be implemented, and that aspects of the trial that are

essential to ensure human participant protection and reliability of trial results should be the focus of such systems, were not fully met. Examples of non-compliance included:

- inconsistencies between written policies and associated procedures
- procedures not documented/implemented
- procedures not being up to date.

- ICH GCP E6(R2) section 4.7 requirements that the investigator should follow the trial's randomisation procedures and should promptly document and explain to the sponsor any premature unblinding were not fully met. Examples of non-compliance included:

- randomisation was not completed according to the protocol requirements
- date of unblinding and informing participants of their intervention allocation was not documented
- blinded staff had direct unmonitored access to unblinded data during trial conduct.

Therapeutic good (TG) / Investigational product (IP)

This main category was formerly reported as ‘Investigational Medicinal Product (IMP)’ but has been updated to reflect all types of therapeutic goods in scope of the GCPIP.

Deficiencies in ‘TG/IP’ were identified in 7 out of 12 routine inspections. Most of the individual deficiencies were identified in the ‘Supplying, storage, retrieving and destruction’ and ‘Prescription, administration and compliance’ sub-categories. We observed high levels of compliance in the ‘TG/IP accountability at site’ sub-category.

What are 'therapeutic goods'?

'Therapeutic goods' are defined in Section 3 of the *Therapeutic Goods Act 1989*.

Australian Register of Therapeutic Goods (ARTG) is the public database of therapeutic goods approved for supply in Australia.

‘Unapproved’ therapeutic goods include:

- any medicine not included in the ARTG, such as any new formulation, strength or size, dosage form, name, indications, directions for use or type of container of a medicine already in the ARTG
- any medical device (including an *in vitro* diagnostic device (IVD)) not included in the ARTG, such as any new sponsor, manufacturer, device nomenclature system code, classification or unique product identifier (for certain classes of medical devices only) of a medical device already in the ARTG
- any in-house IVD medical device, used for the purpose of a clinical trial, where the laboratory providing the in-house IVD is unable to comply with the regulatory requirements for in-house IVDs (a laboratory developed test used for research purposes where results of such testing are not being used in patient diagnosis, treatment or management decisions would not be considered an in-house IVD)
- any biological not included in the ARTG such as:

– any new applicable standards, intended clinical use or principal manufacturer of a Class 1 or 2 biological already in the ARTG

– any new product name, dosage form, formulation or composition, therapeutic indication, type of container or principal manufacturer of a Class 3 or 4 biological already in the ARTG

– therapeutic goods already included in the ARTG to be used in a manner not covered by the existing entry in the ARTG.

Deficiencies in ‘TG / IP’ were made against the following criteria:

Compliance requirements	Deficiencies against the following sections
ICH GCP E6 (R2) with TGA annotations	2.12, 4.1.2, 4.5.2, 4.6.1, 4.6.2, 4.6.3, 4.6.4, 4.6.5, 4.6.6, 4.7, 5.13.1, 5.13.2, 5.14.2, 5.14.3, 5.14.4
ISO14155:2011	5.10, 6.9, 9.6
ISO14155:2020	6.10, 7.9, 10.6
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (jointly known as the PIC/S) Guide to Good Manufacturing Practice for Medicinal Products	Annex 13

Examples of deficiencies include:

- Multiple sections in GCP cover responsibilities of the investigator related to the IP documentation (ICH GCP E6(R2) sections 4.6.1, 4.6.3, 4.6.6 and ISO 14155:2020 section 7.9). Examples of non-compliance with requirements relating to IP accountability and maintaining IP records included:

– accountability records were incomplete, inconsistent or missing

– no documentation of who and when it was decided that a participant would receive a particular intervention

– records were not maintained to demonstrate that participants were provided doses specified by the protocol and / or that participants followed instructions properly

– protocol-required pre-medication records were missing batch numbers without documented justification and HREC approval.

- Multiple sections in GCP require that the IP is manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP) (ICH GCP E6(R2) sections 2.12, 4.6.4, 4.6.5 and ISO 14155:2020 section 6.10). Examples of non-compliance included:

– IP manufacturing batch records did not demonstrate compliance with GMP

– IP manufacturing batch records allowed data modification without traceability

– medicinal IPs were not labelled as required by GMP (PIC/S Guide to GMP, Annex 13 clause 6.6)

– IP was not stored and used in accordance with the protocol

– evidence was not available to demonstrate the IP was within its expiry date at time of administration.

Trial management

- Deficiencies in ’Trial management’ were identified in 8 out of 12 routine inspections. The majority of individual deficiencies were identified in the ‘Sponsor-investigator responsibilities’. We also observed non-compliance with ‘Local regulatory requirements (other than safety reporting)’. These two categories cover different types of responsibilities, with sponsor-investigator responsibilities only applicable to IITs.

Deficiencies in 'Trial management' were made against the following criteria:

Compliance requirements	Deficiencies against the following sections
Therapeutic Goods Regulations 1990	12AD, Schedule 5A Item 3
Therapeutic Goods (Medical Devices) Regulations 2002	7.3, Schedule 4 Part 2 Item 2.3
ICH GCP E6 (R2) with TGA annotations	1.54, 1.65, 2.1, 2.2, 4.1.3, 4.2.2, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.1, 5.5.3, 5.12.2, 5.16.1, 5.18.2, 5.18.3, 5.18.4, 5.18.5, 5.18.6, 5.18.7, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, 6.16, 7.1, 7.2, 7.3, 7.4, 7.5
ISO14155:2011	5.1, 5.2, 5.3, 5.4, 8.1, 8.2, 8.3, 8.4, Annex A, Annex B
ISO14155:2020	5.4, 6.1, 6.2, 6.3, 6.4, 6.5, 6.7, 7.1, 7.2, 7.3, 9.1, 9.2, 9.3, 9.4, Annex A, Annex B

Examples of deficiencies include:

- The Therapeutic Goods Regulations 1990 Schedule 5A Item 3 and the Therapeutic Goods (Medical Devices) Regulations 2002 Schedule 4 Part 2 Item 2.3 requirements that the Secretary must be notified about the trial and the therapeutic goods covered by the trial before they begin to be used in the trial [also see ICH GCP E6(R2) section 4.1.3 and ISO 14155:2020 section 7.1]. Example of non-compliance included:

– supply of 'unapproved' therapeutic goods commenced prior to notification to the TGA

– CTN form did not contain all 'unapproved' therapeutic goods used in the trial

– CTN form specified an approving authority for a clinical trial site although there was none.

We acknowledge that the sponsor is responsible for the CTN/CTA form however, the investigator is required to be aware of and comply with the regulatory requirements. We expect that the site staff review the information provided to them on the current version of a CTN/CTA and will notify the sponsor of any updates required to ensure the CTN/CTA remains complete and accurate.

- Multiple sections in GCP cover sponsor-investigator responsibilities in investigator-initiated trials (IITs). Examples of non-compliance include:

– ICH GCP E6(R2) section 5.18.3 (and consequently sections 5.18.2, 5.18.4-5.18.7) and ISO 14155:2020 sections 6.7 and 7.3 requirements related to clinical trial monitoring were not met because the sponsor-investigator did not monitor the trial.

– ISO 14155:2020 section 7.2 requirements that an initiation visit shall be conducted for each participating site and documented was not met because a clinical trial commenced without a site initiation visit.

– ICH GCP E6(R2) section 5.5.3 requirement that electronic trial data handling systems should be validated were not met because these systems were used without validation.

– ICH GCP E6(R2) section 5.0 requirements related to critical process and data identification, evaluation, control, communication, review and reporting, and ISO 14155:2020 section 6.2 requirements related to risk management, were not fully met because a system to manage quality throughout all stages of the trial process was not implemented and the risk management process was incomplete and not documented.

- ICH GCP E6(R2) section 6 and ISO 14155:2020 sections 6.3, 6.4 and Annex A requirements for protocol/clinical investigation plan (CIP) design were not fully met because several sections of the protocol/CIP were missing or incomplete without justification.
- ICH GCP E6(R2) section 7 and ISO 14155:2020 section 6.5 and Annex B requirements for Investigator's Brochure were not met because there was no Investigator's Brochure (or equivalent) for the therapeutic goods supplied in the inspected trial.
- ICH GCP E6(R2) section 2.1 and ISO 14155:2020 section 5.4 requires a clinical trial to be conducted in accordance with the Declaration of Helsinki (DoH). DoH section 35 requirement that medical research involving human participants must be registered in a publicly accessible database before recruitment of the first participant was not fully met because the information in the publicly available Australian New Zealand Clinical Trials Registry (ANZCTR) website and site files did not match.

Appendix A: Inspection deficiency gradings

We group observed deficiencies against 5 main categories, which include individual deficiencies reported at sub-category level:

- Protection of participants
- Protocol compliance
- Documentation
- Therapeutic Good / Investigational Product
- Trial Management.

We grade all individual deficiencies as either minor, major or critical. A deficiency recorded for one of the 5 main categories may be comprised of a number of minor, major and critical deficiencies. Refer to the GCPIP Guidance document for a list of 28 sub-categories.

The grading recorded for the main category deficiency is set to the highest-level finding. A maximum of one deficiency can be identified in each main category, regardless of the number of individual deficiencies identified in the sub-categories. This reporting practice ensures that the inspected site is not penalised more than once in each category. For example, if we identify critical, major and minor deficiencies across several sub-categories within the main category 'Protection of participants' during an inspection we will report this as a critical grading for 'Protection of participants'. Individual deficiencies with a lower grade that were explicitly reported as such in the reports, e.g. as 'major/minor' under critical deficiency, are reported under the major grading in Appendix B: Summary of deficiencies in 2023 and Appendix C: Summary of deficiencies in 2024.

Critical deficiency

- A 'critical deficiency' is an issue in clinical trial systems, practices or processes that:
  - adversely affects the rights, safety or well-being of clinical trial participants; or
  - adversely affects the quality or integrity of data; or
  - 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.
- In some circumstances an otherwise major deficiency may be categorised as critical. For example, a deficiency reported after a previous inspection and not corrected may be given higher classification.

Major deficiency

- A 'major deficiency' is an issue in clinical trial systems, practices or processes that:
  - could adversely affect the rights, safety or well-being of clinical trial participants,
  - could adversely affects the quality or integrity of data; or

  - represents a violation of applicable legislation and guidelines.
- Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency

- A 'minor deficiency' is an issue 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
  - quality or integrity of data.

Appendix B: Summary of deficiencies in 2023

Main category	No	Sub-category	No of critical	No of major	No of minor	Total
Protection of participants	1.1	Informed consent - Presence of informed consent	4	7	0	**11**
	1.2	Informed consent - Informed consent process	6	17	0	**23**
	1.3	Informed consent - Informed consent form content	3	6	0	**9**
	1.4	HREC/AA - Favourable opinion	2	0	0	**2**
	1.5	HREC/AA - Opinion, amendments, notifications	0	17	0	**17**
	1.6	HREC/AA - Composition, functions, operations	0	5	0	**5**
	1.7	Participant protection - Personal data protection	1	5	0	**6**
	1.8	Participant protection - Safeguarding safety and well-being	4	9	0	**13**
Protocol compliance	2.1	Eligibility criteria	3	13	0	**16**
	2.2	Assessment of efficacy	1	3	0	**4**
	2.3	Safety reporting	3	25	0	**28**
	2.4	Non-compliance with safety reporting to HREC/AA/TGA	0	2	0	**2**
	2.5	Reporting in CRF/diary as specified in the protocol	0	21	0	**21**
	2.6	Other protocol non-compliance not listed above	1	9	0	**10**
Documenta-tion	3.1	Essential documents	0	26	2	**28**
	3.2	Source documentation	1	23	4	**28**
	3.3	Qualification and training	0	7	1	**8**
	3.4	Standard operating procedures	0	10	0	**10**
	3.5	Organisation and personnel	0	9	0	**9**
	3.6	Facilities and equipment	1	7	0	**8**
	3.7	Randomization, blinding and codes of study drug	0	2	0	**2**
	3.8	Direct access to data	0	6	0	**6**
	3.9	Contracts and agreements, including PI oversight of contractors/site-hired third-party vendors	0	1	0	**1**
TG/IP	4.1	TG/IP accountability at site	1	2	0	**3**
	4.2	Supplying, storage, retrieving and destruction	2	6	5	**13**
	4.3	Prescription, administration and compliance	1	3	5	**9**
Trial management	5.1	Non-compliance with local regulatory requirements (other than safety reporting)	3	6	3	**12**
	5.2	Sponsor-investigator responsibilities	9	2	0	**11**
Total			**46**	**249**	**20**	**315**

Appendix C: Summary of deficiencies in 2024

Main category	No	Sub-category	No of critical	No of major	No of minor	Total
Protection of participants	1.1	Informed consent - Presence of informed consent	0	2	0	**2**
	1.2	Informed consent - Informed consent process	0	9	2	**11**
	1.3	Informed consent - Informed consent form content	0	2	1	**3**
	1.4	HREC/AA - Favourable opinion	0	2	0	**2**
	1.5	HREC/AA - Opinion, amendments, notifications	0	2	2	**4**
	1.6	HREC/AA - Composition, functions, operations	0	0	0	**0**
	1.7	Participant protection - Personal data protection	0	0	1	**1**
	1.8	Participant protection - Safeguarding safety and well-being	0	1	0	**1**
Protocol compliance	2.1	Eligibility criteria	2	2	0	**4**
	2.2	Assessment of efficacy	0	0	0	**0**
	2.3	Safety reporting	0	4	0	**4**
	2.4	Non-compliance with safety reporting to HREC/AA/TGA	0	1	0	**1**
	2.5	Reporting in CRF/diary as specified in the protocol	0	6	0	**6**
	2.6	Other protocol non-compliance not listed above	0	5	2	**7**
Documenta-tion	3.1	Essential documents	0	1	2	**3**
	3.2	Source documentation	0	3	6	**9**
	3.3	Qualification and training	0	2	2	**4**
	3.4	Standard operating procedures	0	2	1	**3**
	3.5	Organisation and personnel	0	1	0	**1**
	3.6	Facilities and equipment	0	1	1	**2**
	3.7	Randomization, blinding and codes of study drug	0	2	0	**2**
	3.8	Direct access to data	0	0	0	**0**
	3.9	Contracts and agreements, including PI oversight of contractors/site-hired third-party vendors	0	0	0	**0**
TG/IP	4.1	TG/IP accountability at site	0	3*	1	**4**
	4.2	Supplying, storage, retrieving and destruction	3	0	0	**3**
	4.3	Prescription, administration and compliance	1	4*	1	**6**
Trial management	5.1	Non-compliance with local regulatory requirements (other than safety reporting)	0	3	0	**3**
	5.2	Sponsor-investigator responsibilities	4	3	1*	**8**
Total			**10**	**61**	**23**	**94**

*These individual deficiencies were reported under main category deficiency with a higher grading as explained in Appendix A: Inspection deficiency gradings.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Pharmacovigilance Branch	March 2025

Therapeutic Goods Administration

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

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