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CLINICAL TRIALS HANDBOOK Asia Pacific



AUSTRALIA

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Australia

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Introduction

Australia has a strong research community and is viewed as a country of choice for conducting clinical research, particularly for early stage trials, given that it has quality medical professionals, modern hospitals, a strong regulator and good safety practices.

The federal Therapeutic Goods Administration (**TGA**) is the Australian regulatory agency regulating the import and supply of therapeutic goods, including in the context of a clinical trial setting. "Therapeutic goods" includes goods such as medicines, medical devices and biologicals.

In order for therapeutic goods to be imported and supplied for clinical trial purposes, the TGA requires all clinical trials to be reviewed and monitored by an independent Human Research Ethics Committee (**HREC**), which is established either by the research organization conducting the trial or by a third-party organization. HRECs must be registered with the National Health and Medical Research Council (**NHMRC**).

The NHMRC is Australia's peak federal body for advising and supporting health and medical research. The NHMRC oversees the work undertaken by HRECs.

Regulatory framework

Key legislation and regulatory requirements

The principal legislation relevant to the conduct of clinical trials in Australia is the *Therapeutic Goods Act 1989* (Cth). Clinical trials must be conducted in accordance with international standards of good clinical practice.

The TGA has in principle adopted the European Union version of the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) ("**ICH GCP guidelines**"), an internationally accepted standard for designing, conducting, recording and reporting clinical trials, subject to Australian legal requirements that override some elements of the guidelines.

Clinical trials must also comply with the National Statement on Ethical Conduct in Human Research ("**National Statement**") prescribed by the NHMRC.

The National Statement describes the relevant principles of ethical conduct in research in general and also provides specific instructions for the formation and operation of HRECs. The National Statement is particularly important in the Australian context as HRECs in Australia have the primary role of assessing and approving trial proposals, as well as undertaking the ongoing monitoring of trials against good clinical practice standards. In some instances (for example, in relation to informed consent of trial subjects), the requirements of the National Statement override or supplement those of the ICH GCP guidelines. The use of the ICH GCP guidelines and the National Statement provide the basis for a standardized approach to clinical research in Australia that equates to a level of research rigor comparable with that of any other jurisdiction.

HREC review

The HREC reviews both the scientific and ethical aspects of the clinical trial proposal, which may be supplemented by external expert advice. An HREC is responsible for reviewing at a minimum the trial protocol, investigator's brochure, informed consent forms, patient information documents, procedures for subject recruitment, any planned payment

or compensation initiatives for the proposed trial, and the qualifications of the investigator(s). There are special ethical considerations that apply to particular types of research (e.g., qualitative, quantitative) and to certain types of participants (e.g., children, persons with impaired mental capacity, persons in dependent or unequal relationships, indigenous people).

Each state has its own system for ethical and scientific review, and both public and private HRECs operate in Australia. Several states have developed streamlined processes for single ethical review for multi-center studies conducted within the public health system.

The NHMRC has also established a National Approach to Single Ethical Review of Multi-Centre Research ("**National Approach**") to enable the recognition of a single ethical and scientific review of multi-center human research within and/or across Australian jurisdictions.

The National Approach provides institutions in a State or Territory with the ability to accept a single ethical review by an HREC certified by the NHMRC, irrespective of whether that HREC is located in the same or another State or Territory. The NHMRC certifies HRECs that meet particular criteria, which are in part based on the National Statement.

The Australian Capital Territory, New South Wales, Victoria, Queensland, South Australia, and Western Australia public health departments have signed up to a National Mutual Acceptance (**NMA**) Scheme, agreeing to approve single ethical reviews where the HREC is certified under both the NHMRC National Certification Scheme and under the NMA Scheme (but note that for Victoria and Queensland, certain central allocation systems may need to be used in applying for review).

The NHMRC's website contains resources for navigating the National Approach, including a National Certification Scheme Handbook, forms and HREC letter templates and indemnity and insurance Q&A.

Other regulatory requirements

The Australian Code for the Responsible Conduct of Research ("**Research Code**"), developed by the NHMRC, the Australian Research Council and Universities Australia, also applies in respect of research conducted by universities and other public sector research institutions. The Research Code is a principles-based document that articulates the broad principles and responsibilities that underpin the conduct of Australian research. Compliance with the Research Code is a prerequisite for NHMRC funding.

In addition to the general regulatory requirements for clinical trials, research involving gene technology and genetically modified organisms and research involving human embryos and stem cells are subject to additional regulatory requirements under the National Statement.

Medical device clinical trials must also meet the standards for clinical evidence set out in ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice).

The CTN and CTX schemes

In Australia, clinical trials of therapeutic goods may be conducted under either the Clinical Trial Notification (**CTN**) scheme or the Clinical Trial Exemption (**CTX**) scheme.

The **CTN scheme** is a notification scheme and as such, the TGA does not review or evaluate any data relating to clinical trials under this scheme at the time of submission. Under this scheme, the sponsor and the principal investigator submit clinical trial information (including clinical data and trial protocol) to an HREC. The HREC reviews the information in light of scientific, safety and ethical soundness. After the review, the HREC must advise the proposed institution whether it approves of the trial. Acting on this advice, the trial site grants final approval for the trial. Once approved, the clinical trial must be notified to the TGA using the online CTN form.

The **CTX scheme** is an evaluation process. Under this scheme, the sponsor submits the relevant information regarding the clinical trial, including scientific data for TGA evaluation and comment. The TGA can object to the sponsor's usage guidelines for the product, which may have to be addressed before the sponsor can move forward with the application. TGA approval of the trial is subject to HREC approval. Once the HREC and the trial site approves the trial, the trial can proceed.

The CTN scheme typically covers the conduct of Phase III and IV trials, and bioavailability/ bioequivalency studies (although Phase I and II trials may also fall within the scope of the CTN scheme if sufficient preclinical data is available). Clinical studies for drugs in earlier stages of development and for medical devices that introduce new technology, new material or a new treatment concept are generally conducted under the CTX scheme.

The majority of trials conducted in Australia obtain regulatory approval via the CTN scheme. The legislative requirements that need to be satisfied under the CTN scheme are simpler and less onerous than those under the CTX scheme. The choice of which scheme to follow lies first with the sponsor and then with the HREC that reviews the protocol. Clinical trials in which registered or listed medicines are used within the conditions of their marketing approval are not subject to CTN or CTX requirements but still need to be approved by an HREC.

Separate from CTX/CTN notifications and approvals, clinical trials may be registered on a public clinical trial database (e.g., the Australian and New Zealand Clinical Trials Registry). This is not required by the TGA but is contemplated in the National Statement, and HRECs may stipulate registration as a prerequisite for ethical approval.

Sponsors

The sponsor of a clinical trial, which must be an Australian entity, is that person, body, organization or institution that takes overall responsibility for the conduct of the trial. The sponsor usually initiates, organizes and supports the clinical study and carries the medico-legal responsibility associated with the conduct of the trial. Clinical research organizations, as well as pharmaceutical companies, are common sponsors.

The sponsor is responsible for ensuring that the study is conducted in accordance with all relevant regulatory requirements and the terms of any approval or notification from the TGA or HREC. In particular, the sponsor is responsible for the following:

- Trial design and trial management
- Selection of the appropriate investigator(s) and institution(s) to conduct and complete the trial and allocation of trial-related duties and responsibilities to staff
- Ensuring that quality assurance and quality control systems are in place so that trials are conducted and data is gathered and subsequently reported in compliance with the ICH GCP guidelines, the trial protocol and any TGA requirements
- Ensuring that medical expertise is on hand for trial-related medical queries or patient care
- Notifications and submissions to the regulatory authorities
- Manufacturing, packaging, labeling/coding and distribution to trial sites of all investigational products
- Provision of appropriate insurances and indemnities for the trial and trial-related staff, as well as measures for subject compensation for trial-related injury
- Ongoing safety evaluation and reporting of adverse drug reactions

- Ensuring compliance with monitoring/audit/inspection requirements
- Completion of the clinical study report

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a contract research organization (see "Clinical Trial Research Agreements" below), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

Investigators

The investigator is the person responsible for the conduct of the clinical trial at the trial site. Investigators are medical professionals and will be trained on the clinical trial protocol, procedural issues associated with the conduct of the clinical trial, and their key responsibilities as investigators under the ICH GCP guidelines. The investigator will often be employed by the institution that hosts the clinical trial. The key responsibilities of an investigator are the following:

- Have appropriate qualifications for the trial being carried out
- Declare any conflicts of interest, payments, etc., from other parties
- Maintain a list of any delegated duties with respect to the trial and the persons and qualifications of those persons to whom the duties are assigned
- Demonstrate that adequate subject recruitment is likely, with necessary time available to conduct the study with adequate facilities and trial staff
- Obtain the HREC's favorable endorsement of the trial protocol, patient information and consent documents, recruitment procedures, consent form updates and any other information given to subjects
- Conduct the trial according to the approved protocol and document any deviation from the protocol
- Submit necessary CTN/CTX forms for any new trial site subsequently added
- Be accountable for the investigational product at the trial site
- Ensure that subjects have provided fully informed written consent, with all trial risks and procedures adequately explained
- Provide any medical care to trial participants necessary as a result of any trial-related adverse events experienced during or following the trial
- Provide annually a trial report to the HREC, or more frequently if the HREC requires

Adverse event and drug reaction reporting

Sponsors and other parties involved in clinical trials must satisfy reporting requirements imposed by the TGA and the ICH GCP guidelines, including in relation to adverse events associated with the use of therapeutic goods. Detailed requirements are set out in the *ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, which have been adopted by the TGA in principle, as supplemented by TGA requirements and the NHMRC's guidance *Safety monitoring and reporting in clinical trials involving therapeutic goods*.

In summary, the key requirements are as follows:

- All fatal or life-threatening Suspected Unexpected Serious Adverse Reactions must immediately be reported by the investigator to the sponsor (unless the trial documentation provides otherwise), with a follow-up detailed report when this information is not contained in the initial report; the sponsor must report the event to the TGA immediately, but no later than seven calendar days after being made aware of the event, with any follow up information submitted to the TGA within a further eight calendar days.
- All other Suspected Unexpected Serious Adverse Reactions should be reported by the sponsor to the TGA no later than 15 calendar days after being made aware of the event.
- All Unanticipated Serious Adverse Device Effects must also be reported by the sponsor to the TGA under similar timeframes.
- Significant safety issues (**SSIs**) requiring implementation of urgent safety measures (**USMs**) should be reported by the sponsor to the TGA within 24 hours (where possible) and in any case, no later than 72 hours of the measure being taken. SSIs that arise from analysis of overseas reports (relating to a clinical trial in Australia) should be reported to the TGA under the same timeframe.
- Action with respect to safety that has been taken by an overseas regulatory authority (relevant to an ongoing clinical trial in Australia) must be reported to the TGA by the sponsor without undue delay and no later than 72 hours of the sponsor becoming aware of the action.
- All other SSIs (e.g., suspension of the trial, early termination of trial for safety reasons) must be reported by the sponsor to the TGA without undue delay and no later than 15 calendar days of the sponsor becoming aware of the issue or suspension or early termination.
- Investigators are also required to report other adverse events and reactions in accordance with the trial protocol and as required by the HREC.

Clinical Trial Research Agreements (CTRAs)

The sponsor is responsible for establishing legal and financial agreements between the sponsor, investigators and participating institutions/organizations (which should address issues such as indemnity of the parties involved in the trial and compensation and treatment of trial participants in the case of injury or death).

There are five CTRAs that have been developed by Medicines Australia (an industry body representing the manufacturers of prescription medicines in Australia) with the New South Wales, Queensland, Victoria, South Australia and Tasmania Health Departments:

- The Standard CTRA, which has become an industry standard for commercially sponsored clinical trial research
- The CTRA for Contract Research Organisations acting as the Local Sponsor (CRO Sponsored CTRA), which has been developed for use where a contract research organization acts as, and assumes all the responsibilities of, a local sponsor
- The Collaborative or Cooperative Research Groups CTRA, which has been developed for an academic and/or non-commercial collaborative research group responsible for sponsoring, initiating, managing, developing and coordinating the study
- The Phase IV Clinical Trial for Medicines CTRA

- The Phase IV Clinical Trial for Medicines CTRA for Contract Research Organisations as the Local Sponsor.

Other important requirements

Compensation for injury

The National Statement requires appropriate arrangements to ensure adequate compensation to participants for any injury suffered as a result of participation in a clinical trial. An HREC must be satisfied, before approving a clinical trial, that such arrangements exist. The sponsor must have, before the trial formally starts, an insurance statement that documents the compensation that will be available to participants for trial-related injuries. Further, the sponsor will usually be responsible for maintaining insurance coverage under a CTRA.

The Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a company-sponsored clinical trial are an industry standard that most sponsors in Australia abide by when conducting clinical trials. The guidelines provide that the “amount of compensation paid should be appropriate to the nature, severity and persistence of the injury” and set out a procedure for determining this. Medicines Australia recommends that member companies sponsoring a clinical trial provide a written assurance to the investigator and the HREC that the guidelines will be adhered to in the event of injury to a subject.

Record-keeping

Trial master files should be established at the commencement of a trial and must contain all essential documentation, such as an up-to-date investigator’s brochure, the trial protocol, a copy of the CTRA, patient consents, the insurance statement, and the approval from the HREC, as it is a mandatory requirement of all CTN and CTX trials that clinical trial documentation be maintained in compliance with good clinical practice standards.

The trial sponsor’s record keeping obligations are outlined in section 5.5 of the Guideline for Good Clinical Practice and section 7.4 of ISO 14155. Sponsors may in any event need to retain records longer, in anticipation of future potential product liability issues.

Consent requirements

Subject to a limited number of exceptions, each participant in a clinical trial must consent to their enrolment and continued involvement in a clinical trial. Such requirements are not expressly included in particular Australian legislation. However, one of the factors that the HREC must consider in determining whether to grant approval for the conduct of a clinical trial is compliance with the National Statement. The National Statement provides that, before commencing any research, the consent of any participants who will be involved in such research must be obtained.

A participant’s consent must be informed, voluntarily given and clearly established (preferably by a signed document). Participants must be free to withdraw their consent to further involvement in the clinical trial at any time, and if any consequences may arise from such a withdrawal, they must be advised about those consequences before consent to their involvement in the trial is obtained.

Clinical trial medicines will often be provided at no cost to participants. Any proposed payments to clinical trial participants will need to be reviewed and approved by an independent HREC. Under the National Statement, any payment disproportionate to the time involved, or any other inducement that is likely to encourage participants to take risks, is ethically unacceptable. The HREC will consider, on a case-by-case basis, whether a proposed payment or

incentive will pressure individuals to consent to participate. The HREC must also be satisfied that participants have been adequately informed of research funding arrangements and that it has been made clear to participants whether they will have continued access after the trial to treatments they have received during the trial, and on what terms.

Study results and privacy obligations

Sponsors and others involved in the conduct of clinical trials in Australia must also comply with obligations under applicable privacy legislation in the conduct of the trials.

In Australia, the collection, use, disclosure and transfer of participants' personal information in clinical trials will be subject to the Commonwealth *Privacy Act 1988* and/or relevant State and Territory legislation. The *Privacy Act 1988* applies to Commonwealth government agencies and many private sector organizations, including all private sector health service providers. In the Australian Capital Territory, Victoria and New South Wales, specific health privacy legislation applies to all health service providers (private and public sector) and organizations that collect, hold or use health information. Other States and Territories have legislation that only applies to their public sector bodies.

The legislation that applies will depend on the identity of the various bodies and organizations involved with the clinical trial.

Intellectual property

The allocation of rights in any background or foreground intellectual property will be a matter for negotiation between the relevant parties.

As a general rule, ownership of background intellectual property will usually remain with the party contributing such intellectual property.

The sponsor will usually require that any intellectual property developed or created in the course of the clinical trial be assigned to it. This is the approach taken in the Medicines Australia CTAs for commercially sponsored trials.



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