



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration



Consultation Paper

Proposed clinical trial regulatory arrangements under the Australia New Zealand Therapeutic Products Authority (ANZTPA)

February 2007

HOW TO MAKE A SUBMISSION

You are invited to provide written comment on this consultation paper. Submissions can be sent by post or e-mail and, where possible, should be cross-referenced to the specific sections set out in this consultation paper.

Content of submissions

Your submission should include:

- your name and full contact details including: address, telephone number, and if applicable, facsimile and e-mail address;
- the particular issue being addressed;
- relevant evidence and/or examples to support the views expressed; and
- in the case of organisations, the level at which the submission was authorised.

Confidentiality of submissions

If you wish any information contained in a submission to be treated as confidential, please clearly identify the information and outline the reasons you wish it to be treated as confidential.

Address for submissions

Electronic submissions should be e-mailed to: consultation@anztpa.org

Hardcopy submissions should be addressed to either of the addresses below:

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Therapeutic Goods Administration
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WODEN ACT 2606
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WELLINGTON
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Questions relating to submissions

Any questions relating to submissions should be directed to the Clinical Trials Project Officer, by e-mail at: consultation@anztpa.org

Deadline for submissions

The deadline for receipt of submissions is **18 April 2007**.

PROPOSED CLINICAL TRIAL REGULATORY ARRANGEMENTS UNDER THE AUSTRALIA NEW ZEALAND THERAPEUTIC PRODUCTS AUTHORITY (ANZTPA)

1. Background

Clinical trials are conducted at a time when, for the particular therapeutic product(s) under development, there either does not exist sufficient information with respect to quality, safety, and/or efficacy of the product(s) to allow the product(s) to be granted a full marketing approval, or there are further questions about a product's place in therapy or its safety.

A clinical trial is a way of generating information about the safety and efficacy of a medicine, medical device or biological product. This information may be used to support further development of the product, as supporting information for an application to the ANZTPA for a product licence to allow the product to be marketed, or to increase an understanding of its safety. It may also be used to develop treatment guidelines. The ANZTPA is mainly concerned with trials addressing the former.

As use of a therapeutic product in a clinical trial exposes the participants in the trial to potentially increased levels of risk or harm compared with marketed products, international guidelines for Good Clinical Practice (GCP) have been created to ensure that clinical trials are designed and conducted to the highest scientific and ethical standards. Guidelines on GCP provide a framework for minimum standards of clinical research with respect to trial design, conduct, and analysis. This ensures that the rights, safety and well being of participants are protected, while providing for the collection of high-quality data that are recognised as such in all major regulatory jurisdictions worldwide.

An appropriate evaluation of the risks and benefits of any investigational product, device or procedure cannot be made without credible statistical design, data recording, analysis and interpretation. It is unethical to enlist the cooperation of human participants in clinical trials that are not adequately designed and conducted or which would not result in robust data that can be fully interpreted.

The personal integrity and welfare of the participants in a clinical trial are the ultimate responsibility of the investigator(s). Independent assurance that these matters have been considered is provided by a review of the trial proposal by an accredited ethics committee and by the requirement for the participants to make an informed choice and give freely obtained informed consent before participating in a clinical trial.

Currently the Australian and New Zealand regulatory agencies adhere to International standards of Good Clinical Practice (GCP). While both countries use the same foundation standards, the approval processes applied in each country differ somewhat in approach. These differences reflect the underlying legislation and the ethical review systems in each country, and are accommodated under the ANZTPA common scheme. Clinical trials approved under the proposed ANZTPA regulatory scheme will therefore seek separate ethical approval via the review system in each country in which it is proposed that the study will take place.

The proposed model for clinical trial regulation in this document is based on the same risk-managed principles that are proposed to apply to the regulation of medicines, medical devices and biologicals within the ANZTPA.

The draft Medicines and Medical Devices Rules (the Rules) set out the arrangements for the risk-managed scheme, to allow lawful supply of therapeutic products in clinical trials. The Rules propose two routes of approval: the Clinical Trial Assessment (CTA) for studies that pose a high risk to the participant and which require review by the ANZTPA, and Clinical Trial Certification (CTC) for all other clinical trials of therapeutic products.

These two trial approval avenues balance the need to protect the public health with the intention to foster clinical research, and the ANZTPA's intent to provide timely access to therapeutic products that are considered of sufficient quality, safety and effectiveness by international standards, in both countries.

As with the current Australian and New Zealand schemes for clinical trials, the proposed ANZTPA CTA and CTC schemes will continue to require all clinical trials conducted in either country to adhere to relevant ethical standards, as well as meet international standards of GCP defined in the ICH Note for Guidance on Good Clinical Practice CPMP/ICH/135/95, and for medical devices the ISO Standard 14155: 2003 Clinical investigation of medical devices for human subjects - Parts 1 & 2.

2. Clinical Trial Assessment (CTA) Scheme

A Clinical Trial Assessment will involve a determination that the therapeutic product proposed for use in clinical trials may pose a high-risk of harm to the trial participant, either through the toxicity, or nature of the product, or the phase or type of the trial. Determination of the high-risk nature of a trial may be made by the ANZTPA, the sponsor/investigator, or on the advice of a Human Research Ethics Committee (HREC) amongst others.

In addition, it is proposed that clinical trials that fit the following criteria will follow the CTA route:

- Trials in Australia or New Zealand involving the first administration in humans of:
 - a “new” substance(s);
 - a novel Active Implantable (or organ support) Medical Device ;
 - a hybrid medicine/biological device.
- *Trials using gene therapy products;
- *Trials with Class 4 human cells or tissues;
- *Trials involving xenotransplantation.

*Sponsors of trials involving gene therapy, xenotransplantation, or Class 4 human cells or tissues may proceed via the CTC route if the trial has been deemed by the relevant authorities (e.g. the relevant HREC(s) in Australia and the Health Research Council (HRC) in New Zealand) as meeting a lower risk profile. Australian HRECs must seek advice from appropriate external experts for such trials, such as the Gene and Related Therapies Technical Advisory Panel (GTRAP) of the National Health and

Medical Research Council (NHRMC) in the case of trials involving gene therapy, in reaching a decision about whether such trials may proceed via the CTC route. In addition, some trials with genetically modified organisms (GMOs) including recombinant viral vectors or vaccines, may require authorisation from the Office of the Gene Technology Regulator (OGTR) in Australia. It should be noted that currently Australia has a moratorium on approval of clinical trials involving xenotransplantation.

The ANZTPA may also review trials via the CTA route where an HREC, or any of the above named advisory bodies, has reviewed the trial essential documents and determined that the trial should proceed via a CTA. Reasons for requesting a CTA application be lodged may include a perceived lack of specialisation of the HREC in the particular therapeutic area; a trial that involves significant risk to participants, or; a trial that is found on review to fit the CTA criteria.

All CTA applications include a review by the ANZTPA and any trials commenced subsequent to a CTA approval require evidence of endorsement by an HREC before the trial can commence. An application will involve a review of the quality, safety and efficacy of information specific to the substance proposed, for use in subsequent clinical trials. The application will be in a prescribed format, set out in guidelines, and will be accompanied by the fee for the assessment of the application.

The CTA application will include:

1. A data package detailing:
 - pre-clinical and toxicological data exploring the safety of the therapeutic product, for example, biochemical and engineering information for medical devices;
 - summary quality control data relating to the manufacture of the product at that point in time;
 - data relating to any relevant clinical experience;
 - the sponsor's proposed guidelines for the use of the product in any subsequent clinical trials, should the application be approved;
 - a justification for the use of the product in the trial;
 - a description of how the safety of the participant is protected within the trial protocol given the limited data on the safety of the product in humans; and
2. Certification that the trial will be conducted in compliance with standard requirements; and
3. Evidence that the therapeutic product intended for use in the clinical trial meets an appropriate standard of Good Manufacturing Practice (GMP) as set out in the ANZTPA GMP Code for medicines; or for medical devices, that it complies with the essential principles addressing a quality system. (NB. it is proposed that other than trials involving first administration in humans, all trials of medicines and biological products will require the product to be manufactured in a licensed facility that meets the GMP requirements for clinical trial products).

The ANZTPA shall assess the application and make a decision about whether or not to grant an approval to allow clinical trials to proceed in the context of the sponsor's proposed usage guidelines. The ANZTPA may raise questions with the trial sponsor, including requesting additional data, during the evaluation process. The ANZTPA will make a decision within 45 working days of receipt of the CTA application from the trial sponsor.

Should a CTA be approved, subsequent clinical trials that are consistent with the approved usage guidelines may proceed via the CTC route (and the requirements therein) in either country.

When a CTA data package as described above is lodged with the ANZTPA for review, individual trial proposals that fall within the usage guidelines submitted as part of the CTA may be presented in parallel to HRECs for their consideration and approval. This decision to submit in parallel or after receiving an ANZTPA decision rests with the sponsor of the proposed trial(s). Such trials may not go ahead if the ANZTPA rejects the CTA, however there is no impediment to sponsors receiving an HREC endorsement in anticipation of ANZTPA approval of usage guidelines if they wish. Any conditions of approval or consequential changes to trial protocols as a result of an ANZTPA decision would have to be subsequently notified to the HREC(s) involved by the trial sponsor.

As with all applications to conduct clinical trials, the relevant HREC application will involve review of the trial protocol, investigator's brochure, and trial "essential documents" (defined under GCP guidelines), such as the patient information and consent forms.

3. Clinical Trial Certification (CTC) Scheme

Sponsors of clinical trials of therapeutic products that do not meet the criteria for CTA (above) may apply for an approval for supply through the CTC scheme. The risk-managed approach utilised by the ANZTPA for the CTC Scheme is based on a mixed model of assessment and self-certification by the trial sponsor.

The CTC scheme is intended for trials of therapeutic products that pose a lower-risk of harm to participants and the applications for a CTC approval will not routinely involve a full scientific review of the trial product(s) and their proposed usage by the ANZTPA.

Study proposals must be submitted to an HREC for review as required by the system for ethical review in each country before seeking a CTC approval. A trial proposed for both nations will need ethics approval in each country before an application can be made to ANZTPA under the CTC scheme.

All clinical trial certifications will be required to provide evidence by way of self-certification that the study complies with the following requirements:

- The trial protocol and proposal has undergone a scientific and ethical review by either an ethics committee in New Zealand*, and/or a Human Research Ethics Committee (HREC) in Australia; and

- The name of the ethics committee that has approved the study and the signature of its Chair confirming the committee's acceptance of the trial; and
- Evidence that the therapeutic product proposed for use in the study is manufactured in a GMP licensed facility or is manufactured in compliance with the essential principles addressing a quality system; and
- An undertaking by chief investigators and sponsors of the proposed trial; that the study complies with the requirements of GCP as set out in ANZTPA Guidelines; and
- An undertaking from the trial site(s) and HREC to allow officers of the ANZTPA to inspect the site(s) for compliance with GCP if deemed appropriate.

*Where an ethics committee in New Zealand requires assistance with the clinical or technical content of an application it is proposed that the committee refer the application to the Standing Committee on Therapeutic Trials (SCOTT) for advice, before making its decision.

In addition, clinical trials in New Zealand or Australia involving:

- The first use of a therapeutic product:
 - In a new patient group, or;
 - For a new indication, or;
 - Via a substantially different route of administration.
- Gene therapy, xenotransplantation or use of class IV human cells or tissues that have previously been determined by the HRC in New Zealand or the relevant HREC(s) in Australia as meeting a lower risk profile to allow the CTC route of approval,

will also be required to submit to ANZTPA basic trial documentation, such as the Investigator's brochure, protocol and (unless contained in the protocol) the patient information and consent documents, in addition to the self-certification of compliance with ethical and scientific guidelines.

As GCP guidelines require all trials to have such documentation the information required above does not place an increased compliance cost on the trial sponsor. The CTC scheme shall require "approval" by the ANZTPA, however it is proposed that the turnaround time for such an approval under the CTC scheme, where all documentation is correctly provided, will be five working days.

4. Audit for Compliance with GCP

The ANZTPA will have the right, at any time, to seek additional information about a particular trial, and may also inspect any trial site(s) to ensure compliance with GCP principles. Powers to request information and inspect clinical trials will include the power to seek information from any party involved in the conduct, review or governance of the trial; to inspect premises, and record and share such information that is obtained with relevant public health authorities in order to protect the public health.

Sponsors of clinical trials shall be required to submit to the ANZTPA a copy of the annual report of trial activity that is currently sent to the approving HREC(s).

5. Right to revoke an approval

The ANZTPA will have the power to revoke an approval granted to a sponsor in relation to a clinical trial if at any time it becomes aware that the ongoing conduct of the trial is not in the public interest.

6. Ethical review

The ANZTPA CTA and CTC schemes only grant approval for supply of an unlicensed therapeutic product in the context of a clinical trial, without the need to apply for and be granted a product licence.

Clinical trials granted approval for supply of unlicensed therapeutic products will still be required to obtain approval from appropriate accredited ethics committees in each country.

7. Cost Recovery

Government policy is that the ANZTPA will operate on a cost-recovery basis. A separate discussion paper on fees and charges has been issued.