Regulation of Clinical Trials in Australia

(DRAFT)

This document is open for comment until July 26th 2002.

Comments, with the subject clearly identified as Clinical Trials DRAFT Document, should be mailed to:

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### GLOSSARY

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<th>Abbreviation</th>
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<tr>
<td>ADI</td>
<td>ADVERSE DEVICE INCIDENT</td>
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<tr>
<td>ADR</td>
<td>ADVERSE DRUG REACTION</td>
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<td>ADRU</td>
<td>ADVERSE DRUG REACTIONS UNIT, TGA</td>
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<td>ADRAC</td>
<td>ADVERSE DRUG REACTIONS ADVISORY COMMITTEE</td>
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<td>AHEC</td>
<td>AUSTRALIAN HEALTH ETHICS COMMITTEE</td>
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<td>CAB</td>
<td>CONFORMITY ASSESSMENT BRANCH, TGA</td>
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<td>CTN</td>
<td>CLINICAL TRIAL NOTIFICATION (SCHEME)</td>
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<td>CTX</td>
<td>CLINICAL TRIAL EXEMPTION (SCHEME)</td>
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<td>DRUG SAFETY AND EVALUATION BRANCH, TGA</td>
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<td>EXPERIMENTAL DRUGS SECTION, TGA</td>
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<td>GMAC</td>
<td>GENE MANIPULATION ADVISORY COMMITTEE</td>
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<td>GTRAP</td>
<td>GENE AND RELATED THERAPIES RESEARCH ADVISORY PANEL</td>
</tr>
<tr>
<td>HREC</td>
<td>HUMAN RESEARCH ETHICS COMMITTEE</td>
</tr>
<tr>
<td>IRIS</td>
<td>INCIDENT REPORTING AND INVESTIGATION SCHEME (for Medical Devices)</td>
</tr>
<tr>
<td>NHMRC</td>
<td>NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL</td>
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Attachments:

A. Excerpt from Schedule 5A of the *Therapeutic Goods Regulations 1990.*
B. Flow chart of Clinical Trials and Associated Monitoring by the TGA.
1. The Current Australian Clinical Trial Arrangements

Clinical trials of medical products and devices are regulated via the CTN/CTX arrangements. Currently CTX applications would number less than 5 per year, including both medicines and medical devices. The overwhelming majority of clinical trials (around 450 per annum across all therapeutic goods) are notified via the CTN Scheme.

Administrative details for the CTX and CTN schemes are as follows:

1.1 CTX Submissions

The CTX Scheme entails sponsors submitting an application to the TGA for evaluation and comment prior to commencing a clinical trial. The CTX Scheme can be particularly useful in the case of a therapeutic good in the early stages of development.

In the case of clinical trials of medicines, the TGA reviews the information about the product provided by the sponsor, including the overseas status of the medicine, proposed Usage Guidelines, a pharmaceutical data sheet, and summaries of the preclinical and clinical data.

In the case of a medical device, the TGA examines design specifications and clinical data.

CTX applications for medicines are submitted in a set format and consist of:

Part 1: Administrative information and information complementary to the summaries of scientific information.

Part 2: A summary of chemical, pharmaceutical and biological documentation

Part 3: A summary of pharmaco-toxicological documentation

Part 4: A summary of clinical documentation

Part 5: Documentation on all fatal or life-threatening adverse events that have been associated with the use of the medicine prior to the date of the application.

Part 6: “Information for Human Research Ethics Committees”

The TGA delegate either objects or does not object to the proposed usage guidelines. For standard CTX applications for medicinal products, a 50 working day evaluation period applies. The TGA may evaluate data relating to chemical, pharmaceutical, biological, pharmaco-toxicological and clinical aspects of the medicinal product.

Timeframes commence from the date of acceptance of the application, or the date of receipt of the appropriate fee, whichever is the later.
If objections are raised, trials may not proceed until objection(s) have been addressed to the delegate’s satisfaction. If objections are not raised, the delegate still provides comments on the summary information provided, which the sponsor is then required to submit to the HREC(s) with jurisdiction at proposed clinical trial site(s).

Any number of trials may then be conducted without further assessment, provided the use of the product falls within the original usage guidelines. Each trial still requires approval by an HREC, and approving authority endorsements. In fact, the “Notification of the conduct of a trial under the CTX Scheme” form requires the same evidence of endorsements as described below for the CTN form. However, once these approvals are obtained, the trial can commence on the condition that the sponsor notifies the TGA within 28 days of commencing supply of the therapeutic goods.

Once a medicine is approved for use in clinical trials under the CTX Scheme, significant changes to that medicinal product should not be made while it is being used in clinical trials without the prior approval of the TGA. If such changes are proposed, an abbreviated application should be submitted, which qualifies for a 30 working day review period if the application does not need to be supported by further clinical or toxicological data.

1.2 CTN Scheme

To commence a clinical trial via the CTN arrangements, a sponsor is required to provide some general details about the trial, and certain evidence of endorsement by relevant authorities (see below). The clinical trial is “notified” to the TGA with the appropriate “notification fee”. This is all that is required to give the sponsor the exemption from Part III of the Act required to commence supply of the trial medication.

All new clinical trial notifications to the Experimental Drugs Section must contain the following signatures of appropriately authorised persons, as evidence of:

- **Endorsement by a member of a Human Research Ethics Committee, operating in accordance with NH&MRC guidelines, that has notified its existence to the Australian Health Ethics Committee, and gives the undertaking that the HREC has approved the clinical trial protocol and assumed responsibility for monitoring the conduct of the trial. The HREC also agrees to comply with requests by an authorised person, and allow an authorised officer to do the things mentioned in regulation 12AC and 12AB of the *Therapeutic Goods Regulations 1990*.**

- **Endorsement by the principal investigator of the study, who agrees formally to personally supervise the trial at the relevant site(s) and in accordance with the relevant protocol(s). They agree to promptly report all unanticipated problems to the HREC and will not make any changes to the trial without HREC and sponsor approval except where necessary to eliminate immediate hazards to subject safety. They further agree to comply with the Guidelines for Good Clinical Practice set out in regulation 12AB(2)(a) of the *Therapeutic Goods Regulations 1990* and the *National Statement of Ethical Conduct in Research Involving Humans*, as described in regulation 12AD(c) of the *Therapeutic Goods Regulations 1990*. It is accepted that information concerning the use of**
unregistered therapeutic good(s) may be released to State and/or Territory regulatory authorities.

- An endorsement by the sponsor of the trial (that must be an Australian entity), giving the assurances that they accept overall responsibility for the trial, that they will meet all Human Research Ethic Committee conditions of approval and that all serious and unexpected adverse events associated with the trial will be reported to the Therapeutic Goods Administration. They agree to conduct the trial in accordance with the ICH and NH&MRC guidelines, and comply with requests by an authorised officer and allow an authorised officer to do the things mentioned in regulations 12AC and 12AB of the *Therapeutic Goods Regulations 1990*. They also accept the possibility of release of information to State and Territory authorities.

- Endorsements by relevant “approving authorities”. It is pivotal in the authorisation of inspection of specific trial sites that someone with authorisation to represent the body, organisation or institution at each site where the trial will be conducted undertakes to comply with requests by an authorised person, and allow an authorised officer to do the things mentioned in regulations 12AC and 12AB of the *Therapeutic Goods Regulations 1990*. They further give the assurance that all use of the drug will comply with relevant Commonwealth and State or Territory legislation.

2. Clinical Trial Monitoring activities undertaken by the Therapeutic Goods Administration

2.1. Medical Device Trials

Clinical trial monitoring for devices is essentially similar to that for medicines. Often, the protocol is sent in by the sponsor/chief investigator(s) with the CTN notification form, and in such instances comments are provided on the document by the medical advisory staff. CTX applications for medical devices are rare. CTN notifications are checked for appropriate endorsements, and occasionally the product brochure for a medical device is requested for review. Otherwise, monitoring activities are the same.

2.2. Medicinal Product Trials

(i) CTX Scheme

The TGA assesses the data provided and any objections raised must be addressed before the supply of the investigational product can commence.

(ii) On receipt of CTN Form

Administrative staff check the form for completeness and if necessary liase with the chief investigators to correct any insufficiency, ie. missing endorsement. At this point, administrative staff may involve the professional staff of the EDS if required. For example, queries regarding approving authorities are often dealt with by professional staff. Details of the trial are entered into a database and the trial is assigned to a prescription medicine clinical unit, determined by the indication given for the
therapeutic good. These data are checked by a member of the EDS professional staff for data accuracy and any obvious concerns, for example, use of a clearly inappropriate product in humans.

Administrative staff generate a letter to the sponsor acknowledging receipt of the CTN form. Although not required by the legislation to do so, the TGA understands most clinical investigators wait for the acknowledgement letter sent by EDS staff on receipt of the notification form prior to commencing the trial. However, all that is required for a clinical trial to be deemed notified, is completion of the CTN form and the forwarding of this along with the relevant fee to the TGA.

All new clinical trial notifications are reviewed on a weekly basis by the relevant clinical unit head (as determined by the particular indication for the trial drug), and discussed at a meeting with all clinical unit heads. Should the trial raise any degree of concern, clinical unit heads may request additional information they consider necessary. This often includes Investigator’s brochure or trial protocol. Other information, such as sample copies of patient consent forms, may also be obtained at this point for review. The specific reasons for requesting additional information are discussed in section 3 of this document.

2.3 During and After the Clinical Trial

2.3.1 Monitoring activities:

(i) Adverse Drug Reactions (ADRs) and Adverse Device Incidents (ADIs)

Sponsors are required (as detailed in the clinical trial guidance document) to report serious and unexpected adverse drug and adverse device incidents to the TGA via the ADRAC blue card (medicines) or IRIS form (medical devices). For fatal or life-threatening ADRs or adverse device incidents, the initial report must be within 7 calendar days, followed by a complete report within 8 further calendar days. For all other serious and unexpected ADRs and adverse device incidents, a full report no later than 15 days after first knowledge of the incident must be submitted. Sponsors are instructed to tabulate other ADRs and ADIs and produce this data on request by the TGA. Clinical investigators are instructed to report ADRs/events to the HREC as determined by the individual HREC, and to the sponsor of the trial as per the study protocol.

Reports of ADRs and device incidents are reviewed by professional officers, who may seek further information concerning individual reports, or patterns of reporting.

(ii) Other Monitoring

The TGA has the legislative power to seek further information regarding any aspect of a clinical trial. This can include further information about an adverse drug reaction report, clarification about the safety profile of a specific therapeutic good, or details of problems/complaints the TGA has been informed of by a third party.
The TGA has the power to inspect clinical trial sites and search, examine, measure, record or document any information with respect to the trial, as described in Regulation 12AC of the *Therapeutic Goods Regulations 1990* with respect to CTX applications. For CTN trials, the endorsements outlined in the CTN form provide for the same powers that the Regulations specify for trials related to CTX applications. The principal investigator is required to comply with requests and any questions authorised officers may have.

3. **When the TGA may seek information or take further action**

3.1 **Triggers for requesting clarification about a clinical trial in the first instance**

Triggers for requesting further clarification can relate to patient safety concerns in general, or risks to subjects in relation to the quality, toxicity potential, or proposed use of the medicinal product. Specifically, the triggers may be:

- When trial information received to date raises any questions of unacceptable risk to participants (often clarified by protocol review).
- A perceived unusual use of a certain class of drug or a certain type of medical device for the stated indication.
- Use of a drug or medical device in a population of concern, ie. children, the elderly or those with comorbidities.
- Use of a medical device that is particularly invasive, ie. implantable heart valves.
- A trial using a drug which has a known significant side-effect profile.
- A trial with a new chemical entity or novel therapy.
- A drug or device that has received significant media exposure both in Australia and overseas.
- The receipt by the TGA of serious adverse and unexpected drug reactions or device incidents.
- A trial involving a medicinal product for treatment of a particularly serious disease, for which little other therapy currently exists.
- A trial with a medicinal product for which the TGA has minimal information regarding its safety or appropriate use.
- Receipt by the TGA of information (from whatever source) which raises safety or ethical concerns regarding the conduct of a clinical trial.
- The sponsor of a trial requesting TGA inquire into the conduct of the investigators
- Concerns from whatever source regarding the integrity of data recording and reporting.
3.2 Requesting Further Information

Receipt of initial information may trigger the seeking of further information. These circumstances would include:

- New information is required as a result of that provided under 3.1.
- Slow responses to initial enquiries
- Inadequate responses to initial enquiries
- Conflicting information from several sources that cannot be reasonably reconciled
- New information/concerns are raised from whatever source unrelated to initial queries

3.3 Performing a clinical trial audit

Triggers for performing an audit may bypass 3.2 above if serious or urgent safety concerns are revealed. An audit of a clinical trial can be useful for obtaining specific information with regard to the safe conduct of the trial. This is essentially done by inspecting compliance with guidance documents required by legislation to be followed, particularly in relation to protection of the interests of subjects, adequacy of safety monitoring, informed consent, and the balance between risk of a product’s toxicity and the reasonable expected benefits from treatment.

An audit may target a specific area of trial conduct about which concerns have been raised, and/or verify numerous procedures which assesses overall adherence to the principles of Good Clinical Practice and National and International guidance documents.

Audits are not expected to occur frequently. It is expected that most issues will be resolved via other actions outlined in 3.1, 3.2 and 3.4. An audit would usually be a last resort, to obtain information that was refused or not provided via other avenues, and was necessary for an assessment of subject safety. The trigger for an audit would be the receipt by the TGA of serious, valid safety or ethical concerns (from whatever source) of a nature that could only be addressed by an audit. Examples would be the need to validate whether or not the conduct of an investigative procedure was safe and carried out according to protocol, or the need to check dispensing records of a medicine to ensure safe usage.

3.3.1 Future Good Clinical Practice Inspection Activities

Future measures for Good Clinical Practice inspection will be developed to bring Australian GCP inspection standards into line with those of comparable regulatory agencies.

3.4 Further Action

Once data from monitoring of a clinical trial is assessed, as outlined in 3.1, 3.2 and 3.3, and issues of concern are identified, there are several methods by which the TGA may proceed. These methods, with some likely triggers, are as follows:
1. Liaison with sponsors, and/or chief investigators, and/or institutional authorities.

When:

- At any time

Why:

- To clarify specific information or specific comment about an issue pertaining to information received via 3.1 or 3.2 above.
- To discuss concerns with sponsors and investigators and request amendments to the trial process.

2. Liaison with the Human Research Ethics Committee, on matters related to the approval and ongoing monitoring of the clinical trial.

When:

- When issues related to the HREC’s endorsement need clarification.
- When there are concerns regarding the level of monitoring, to clarify that adequate procedures are in place.

Why:

- To request intervention if the TGA believe the approved protocol is not being followed and jeopardising subject safety or the trial’s ethical conduct.
- To inform the HREC of issues of concern for the TGA or reported to the TGA by other parties, not necessarily related to the use of therapeutic goods or under the jurisdiction of the TGA.
- To fully inform HRECs, in association with the AHEC, of their responsibilities and powers with respect to the endorsement of clinical trials.

3. The TGA may provide certain information to State and Territory authorities, including medical boards.

When:

- Concerns are raised in relation to violation of State or Territory law.
- Concerns are raised in relation to appropriateness of practice of a health professional.
- Public health issues come to light that require the knowledge and/or intervention by State and Territory health authorities.
- Concerns are raised in relation to trial practices at a State or Territory controlled institution.
Why:

- To clarify appropriate professional conduct has taken place.
- State and Territory governments require information to safeguard public health and safety.
- The TGA has information that State or Territory laws are not being followed, and this is impacting on the safety of trial participants.

4. The TGA may consult with, and provide information to, other Commonwealth authorities, including AHEC and GTRAP.

When:

- At any time when expert advice is needed by the TGA.
- When intervention by the AHEC in relation to a clinical trial is needed.

Why:

- As a result of concerns over the actions or constitution of a local HREC.
- To seek advice from GTRAP regarding trials involving genetically modified products, genetically modified organisms, or xenotransplantation.
- To seek advice from the AHEC on a particular issue, for example interpretation of guideline documents such as the *National Statement on Ethical Conduct in Research Involving Humans*.

5. The TGA has the power to stop a clinical trial on public safety grounds. The legislative basis for this is different for trials commenced via CTN notification and those that are a result of CTX application:

(i) **CTN**

Supply of unregistered goods via CTN notification is provided for in Section 18(1) of the *Therapeutic Goods Act 1989*, and Regulation 12 and Schedule 5A, item 3 of the *Therapeutic Goods Regulations 1990*. Schedule 5A provides conditional exemption for the experimental product from Part III of the Act, and the condition under item 3(e) states:

(e) the Secretary must not, at any time:

(i) have become aware that to conduct or continue the trial would be contrary to the public interest; and

(ii) have directed that the trial not be conducted, or be stopped
(ii) **CTX**

Supply of unregistered goods via CTX application is provided for in Section 19(1)(b) of the *Therapeutic Goods Act 1989*, and subject to the conditions specified in Regulations 12AB and 12AD, or any other conditions imposed by the Secretary when granting approval under Section 19(1)(b).

This action by the TGA would occur:

- To preserve public safety.
- When there is an immediate danger to trial subjects.
- When all other avenues for satisfactory resolution have not addressed the TGA’s concerns.
Item: 3

**Therapeutic Goods:**

Therapeutic goods used solely for experimental purposes in humans

**Conditions:**

(a) before starting to use the goods, the sponsor must notify the Secretary:

   (i) in a form approved by the Secretary; and
   (ii) in accordance with the requirements (if any) determined by the Secretary for
        the form of notification;

    that the sponsor intends to sponsor a clinical trial using specific goods; and

(b) the notification must be accompanied by the relevant notification fee referred to in
    item 14 or 14A of Schedule 9; and

(c) the approval of the goods for this purpose must be given by the sponsor (if the
    sponsor is conducting the trial), or by the body or organisation conducting the trial for
    the sponsor, having regard to the advice of the ethics committee that has, or will
    assume, responsibility for monitoring the conduct of the trial; and

(d) the terms of the approval by the sponsor, body or organisation referred to in
    paragraph (c) must be no less restrictive than the terms advised by the ethics
    committee; and

(e) the Secretary must not, at any time:

   (i) have become aware that to conduct or
       continue the trial would be contrary to
       the public interest; and
   (ii) have directed that the trial not be
       conducted, or be stopped; and

(f) the sponsor (if the sponsor is conducting the trial), or the body or organisation
    conducting the trial for the sponsor, must not receive, or have received, advice from
    the ethics committee that is inconsistent with the continuation of the trial; and

(g) the conditions set out in regulation 12AD must be complied with, as if that
    regulation applied to a person using therapeutic goods under this item.
Attachment B

Clinical Trial Monitoring Flowchart

- Triggers for further info initiated by:
  - clinical unit
  - CAB
  - EDS
  - 3rd party
  - HREC
  - Sponsor
  - AHEC

- Request(s) for further info by TGA, (s31A, s31B) typically from Chief Investigators

- Issues not resolved/Concerns increased or substantiated

- Further TGA Action
  - Local HREC
  - AHEC/GTRAP
  - Sponsor
  - State/Territory authorities
  - Audit
  - Investigators

- Issues resolved

- Satisfactory Outcome?
  - YES
  - NO

- Have all relevant avenues for resolution been exhausted?
  - YES
  - NO

- TGA ceases trial in the public interest

- CTN notification + CTX application

- Clinical Trial Conducted

- Evaluation of CTX application by DSEB
  - Unsatisfactory
    - Sponsor
  - Satisfactory
    - Notification of intention to conduct trial
    - Notification of serious and unexpected adverse drug events or adverse device incidents. Notification of information significantly impacting the safety profile of the investigational product

- Completion of Clinical Trial

- Publication/marketing application

- Trial completion advice sent to TGA