Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

The Australian Clinical Trial Handbook

A simple, practical guide to the conduct of clinical trials to International standards of Good Clinical Practice (GCP) in the Australian context

March 2006

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. The TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

Version history

Version	Description of change	Author	Effective date
V1.0	Initial publication	OPM	03/06
V1.1	Transferred to new template	OPSS	05/11
V1.2DRAFT	Update to language and developments no CT reform		

Foreword

Clinical Trials have enjoyed a steady and substantial increase in number from the inception of the Clinical Trial Notification (CTN) Scheme in Australia. From around 50 medicine trials before the commencement of this scheme, trials notified to the TGA now number over 700 annually, a testament, at least in part, to the reduction of charges on the part of the regulator in the process of initiating clinical trials.

Many more trials that do not require a CTN by virtue of the fact that they are not making use of unapproved therapeutic goods are also initiated every year. Hence Australia is viewed as a country of choice for conducting clinical research, both in terms of the logistics involved, as well as the standard of clinical conduct that exists in this country, which bestows confidence upon the scientific conclusions reached by these clinical trials.

Through the efforts of the International Conference on Harmonisation (ICH), standards of conduct for clinical trials have been determined that are now essentially uniform for all the major regulatory agencies world-wide, including Australia's Therapeutic Goods Administration (TGA). These comprise the so-called principles of "Good Clinical Practice" or GCP. Although the methods for implementing and enforcing these principles vary across regulatory agencies, the end result, it is hoped, are trials that collect high quality, credible data that contribute to the answering of specific scientific questions, while most importantly protecting the rights, safety and well-being of clinical trial participants. All these principles have their origin in the World Medical Association's Declaration of Helsinki.[1]

In the Australian context, the National Health and Medical Research Council (NHMRC) plays a major role in giving guidance and advice to Human Research Ethics Committees (HRECs), for the pivotal role they play in reviewing the scientific and ethical aspects of clinical trial proposals, and undertaking the chief role of ongoing monitoring of such research. This is crucial in delivering a number of the requirements of GCP-standard research, and highlights one way in which Australia differs from other regulatory agencies in the provision of GCP standards, with many other jurisdictions using the regulator for initial trial documentation review.

GCP standards exist to provide a benchmark of clinical research quality that can be relied upon throughout the world. Many extensive documents exist that describe in detail GCP principles, ethics, scientific assessment and other issues involved in clinical trials, such as adverse event reporting and production of study medication. This book is solely intended to be a practical quick-reference guide to the essentials of conducting clinical research in Australia to GCP standards. It is written from a "things to do", or "things to ensure" viewpoint, and provides key information relevant to all clinical trials, not simply those making use of an unapproved therapeutic good, or intended as part of a marketing submission to the TGA. Parts of key guidance documents are reproduced for ease of reference.

[1] WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: Ethical Principles for Medical Research Involving Human Subjects <http://www.wma.net/e/policy/b3.htm> (as at 19.12.2005)

Contents

Introduction

Clinical trials conducted using "unapproved therapeutic goods" in Australia, that is, goods which have not been evaluated by the TGA for quality, safety and efficacy and entered into the Australian Register of Therapeutic Goods (ARTG) for general marketing, are required to make use of the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes. This is because such products are considered experimental, and do not have general marketing approval. Such goods include medical devices. There are a number of avenues in the Therapeutic Goods Legislation[2] via which "unapproved" goods may lawfully be supplied. The CTN and CTX schemes provide two of these avenues for access.

It should be noted that, particularly in the case of prescription medicines, the definition of an unapproved good can encompass many aspects of a product. These include formulation, dose form, name, indications, directions for use and container. Hence simply because a product *is* entered onto the ARTG, this may not necessarily mean that the product intended for use in a clinical trial does not need an exemption via the CTN or CTX schemes in order to be lawfully supplied. The indication may be quite different, or dosage higher than that approved for marketing, or the product may be sourced from a foreign market, for example. It is also relevant to remember that *all* therapeutic goods used in an ***unapproved*** fashion in a clinical trial, not simply the main product of interest, are required to be noted on the CTN or CTX paperwork.

Clinical trials that do not make use of unapproved goods are not required to be processed via the CTN or CTX routes at the TGA, as these schemes, as previously explained, exist to bestow an exemption on the clinical trial product(s) concerned such that their supply in Australia in the context of a clinical trial is lawful. Thus it follows that trials which make no such use of unapproved products, such as trials comparing different surgical methods, or trials that use Australian registered products within their marketing approval (e.g. long-term safety studies) do not require such an exemption.

All clinical trials in Australia do, however, require review and approval of trial proposals by an ethics committee. In the case of the CTN and CTX schemes, such a committee must have notified its existence to the Australian Health Ethics Committee (AHEC) of the National Health and Medical Research Council (NHMRC) and provided assurances that it is operating within its guidelines. Ethics committees in Australia provide a combined ethical and scientific review process, which may be supplemented on an as-needed basis by external expert advice as the committee(s) concerned see fit. In the case of the CTX scheme, the TGA has a direct role in review of trial scientific data and must give an "approval" for the proposed trial programme to go ahead; however, ethics committee review is still required. For comprehensive information regarding the CTN and CTX scheme, the document "Access to Unapproved Therapeutic Goods – Clinical Trials in Australia"[3] should be consulted. Application for trial approval to an ethics committee is usually in a standardised format, with a number of essential elements, which will be discussed later in this handbook.

[2] The Therapeutic Goods Act 1989, the Therapeutic Goods Regulations 1990, and the Therapeutic Goods (Medical Devices) Regulations 2002. http://www.comlaw.gov.au
[3] http://www.tga.gov.au/hp/access.htm

Good Clinical Practice (GCP) in the Australian context

The principles of GCP, as mentioned previously, have their origin in the World Medical Association's Declaration of Helsinki. This document was first developed post-WWII as a result of the revelations of the Nuremberg trials, to ensure that human subjects involved in clinical research would, in future, forever have their rights, safety and well-being placed above all other priorities in clinical research. The document has been reviewed several times since it was first published, with the current revision dating from January 2004.

This document was used as a basis in developing guidance for GCP practices in clinical trials by the International Conference on Harmonisation. The TGA has adopted the European Union version of this guideline in Australia[4] with respect to Good Clinical Practice and clinical trial conduct in general. The guideline has a few specific comments from TGA officers relevant to the Australian context. Supplementing this are several other guideline documents detailing practices and providing helpful advice with respect to clinical trial issues in general[5], however worthy of particular mention is the Note for Guidance with respect to Clinical Safety Data Management, describing the reporting processes for expedited reporting of Adverse Drug Reactions (ADRs) in clinical trials.[6] Reporting procedures are also summarised in this handbook.

The GCP guideline document details the requirements for trial documentation, as well as many logistical requirements such as indemnity, provision of medical care for subjects, reporting lines for ADRs, protocol amendments, etc. These shall be discussed in greater depth later in this document.

Complementing these guidance documents is Australia's National Statement on Ethical Conduct in Research Involving Humans (the National Statement), published by the NHMRC.[7] The document provides guidance on a wide range of ethical issues in human research. It describes the principles of ethical conduct in general, but also provides specific instructions for the formation and operation of ethics committees, issues surrounding multi-centre research, and specific points to consider for ethics committees considering the approval of a study. Chapter 12 of this document relates to clinical trials and not surprisingly is highly relevant for ethics committees as well as those proposing clinical trials in that it details many issues that must be addressed in order for an ethics committee to consider approval of a clinical study. In some respects the National Statement is more stringent than the EU GCP guideline; for example, with respect to ethics committee membership requirements.

The National Statement is particularly important in the Australia context of GCP, as ethics committees in Australia have the primary role of assessing and approving trial proposals, as well as undertaking the ongoing monitoring of trial conduct to GCP standards. The assessment of initial trial documentation is a key milestone where all necessary documentation and logistical requirements of a trial are reviewed for compliance by the ethics committee(s) concerned. Hence, proper planning and the provision of comprehensive documentation are necessary to achieve approval.

The use of the GCP guideline and the ~~NHMRC~~ National Statement provide the basis for a standardised approach to clinical research in Australia that equates to a level of research rigor comparable with that of any other major regulatory sphere. The requirements are extensive and require significant resources on the part of the trial sponsor. However, they result in a standard of research that other countries as well as major regulatory agencies can have confidence in when the data form part of either a marketing submission to a regulatory body, or a submission to a peer-

[4] http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm
[5] http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinicalefficacy
[6] http://www.tga.gov.au/industry/clinical-trials-note-ich37795.htm
[7] http://www.nhmrc.gov.au/publications/synopses/e35syn.htm

reviewed journal. Most of all, they ensure that subjects have had their well-being considered paramount in the trial process, with mandatory fully-informed consent and ongoing medical care.

Getting started: Questions to be answered

Although ethics committees are well-practiced in pointing out a lot of issues to consider in the planning and conduct of a clinical trial, it is worth mentioning the following which, anecdotally, are often overlooked. Some of these issues fall into the trial governance arena, but all are a part of ensuring GCP compliance. These points are not intended to be comprehensive, but are a list of problems that sponsors or investigators involved in trials have encountered or overlooked when conducting clinical research in Australia:

- What is the exact question this clinical trial is intended to answer? What is the primary outcome variable? Is this readily measured? Is it a direct measure of outcome or do you intend to rely on surrogate endpoints? Are these outcomes those specified by guidance documents as the preferred measures for the outcome of interest? (The last is of particular relevance if you intend the trial to be part of a marketing submission – see TGA website: European Union Guidelines adopted in Australia[8]).
- Is the trial design appropriate? Are subject numbers etc. sufficient to give adequate statistical power to detect a difference in treatments should one exist, or demonstrate non-inferiority? i.e. *can* the trial answer the proposed research question or will the data be equivocal? This aspect of design is often overlooked, but represents a genuine ethical consideration undertaken by Human Research Ethics Committees (HRECs) and needs professional statistical consideration.
- Are your trial centre(s) likely to be able to provide an adequate number of subjects for the trial? Should the trial be extended to additional sites to ensure recruitment? (Dealing with this early on reduces the likelihood of additional CTNs being required later on. It also works towards adequate recruitment to satisfy statistical requirements.)
- Are adequate indemnity provisions in place for the trial itself as well as the staff involved? Some indemnity cover does not include clinical trial related activities or the use of experimental treatments.
- Have you considered the ongoing treatment of trial subjects should they respond to the unapproved medical product under investigation? Building in a trial extension provision into the original protocol design not only fulfils GCP requirements but also can allow such treatment to continue without having to put together another trial proposal after the initial trial ceases. Of course, this is not the only way to provide ongoing treatment post-trial, but is a point to consider in the planning process.
- Are the investigational products correctly labelled and packaged according to annex 13 of the Australian GMP code for experimental products?[9]
- Do patient consent documents contain a full description of the requirements of trial participation, in lay language, such that subjects can make an informed decision?

[8] http://www.tga.gov.au/industry/pm-euguidelines-adopted.htm
[9] http://www.tga.gov.au/industry/manuf-medicines-cgmp.htm

Trial Documentation: The Essentials

The essentials of trial documentation are detailed at item 8 in the EU Note for Guidance on GCP[10], however it is of value to describe some of them here. These documents allow the assessment of a clinical trial as to whether it complies with the standards of GCP, in terms of the conduct of the trial and the quality of data generated. Thus they are an objective means of verifying GCP, as well as an indispensable part of trial management, e.g. with respect to drug accountability, for example.

Trial Master Files should be established at the commencement of a trial at both the chief investigator's/institution's site and at the sponsor's place of business. At trial closeout, all the necessary documentation described here apart from perhaps source documents in the case of hospital records must be confirmed to be present on the Trial Master File.

A trial must have an up-to-date **Investigator's Brochure (IB).** This document is a compilation of the clinical and non-clinical data available on the experimental products intended for use in the clinical trial in question. It provides trial organisers and staff with an understanding of the rationale of the trial, in order to inform their compliance with the protocol requirements. The information enables a risk/benefit assessment of the appropriateness of the proposed trial, of vital importance to HREC considerations. In very rare cases where a product is **marketed**, *and* has a well-understood pharmacology, an extensive Investigator's Brochure may not be required, but can be substituted by a Product Information document (PI), for example, as long as current and reasonably comprehensive information about the product under study is available to the investigators. If a product is marketed, yet the proposed trial intends a new indication for the product, an IB should be collated with reference to this new indication.

The IB should remain up-to-date via *at least* annual revision, depending on the type of product and its stage of development. **The responsibility for this lies with the trial sponsor.** On occasion, information needs to be communicated immediately to investigators and regulatory authorities. More will be mentioned of this later in the handbook.

A minimally sufficient Investigator's Brochure is outlined in item 7.2 of the ICH GCP Guideline on GCP, and is reproduced below:

7.2 General Considerations

The IB should include:

7.2.1 *Title Page*

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the

[10] http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm

number and date of the edition it supersedes, be provided. An example is given in Appendix 1. (of the GCP guideline document)

7.2.2 *Confidentiality Statement*

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 *Table of Contents*

An example of the Table of Contents is given in Appendix 2 of the GCP guideline document.

7.3.2 *Summary*

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 *Introduction*

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 *Physical, Chemical, and Pharmaceutical Properties and Formulation*

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical

properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 *Nonclinical Studies*

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:

  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)

- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 *Effects in Humans*

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and
- absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible,
- and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies
- performed within clinical trial(s).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug

reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 *Summary of Data and Guidance for the Investigator*

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical,

chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

The other critical trial document is the trial **Protocol.** This document describes exactly what the trial will consist of, i.e. design, subjects, statistical considerations, data elements to be recorded, study visits, inclusion/exclusion criteria, stopping rules, subject withdrawal, product handling, data gathering procedures, adverse event reporting, record keeping, finance and insurance, trial extension, etc. Of paramount importance, **patient consent and information documents**, may form part of the protocol or be located separately. A detailed description of the requirements of a protocol document is also reproduced from the GCP guideline:

6. Clinical trial protocol and protocol amendment(s)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).
6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).
6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.
6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
6.2.6 Description of the population to be studied.
6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.
(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.
6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.
6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.
6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
6.9.3 The level of significance to be used.
6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.
6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)[11]

[11] http://www.tga.gov.au/pdf/euguide/ich013795en.pdf

Other Essential Documents of particular note ***in addition to the necessity of reviewing all at item 8 of the GCP Guideline*** include:

Before trial commencement

- Patient informed consent and any other information documents supplied
- Documentation of financial agreements between the sponsor and investigators
- Insurance statement – to ensure compensation for trial-related injury or misadventure.
- Signed and Dated approval from the HREC(s) concerned of protocol, investigator's brochure, consent forms, Case Report Forms (CRFs).
- Copy of CTN form or CTX approval where applicable.
- Curriculum Vitae of investigator(s) and sub-investigators.
- Certificates of Analyses and compliance with Good Manufacturing Practice (GMP) for investigational products (GMP certification not required for first experimental studies in human volunteers).
- Decoding procedures for blinded trials.
- Master Randomisation list.

During the trial

- Investigator brochure updates.
- Dated approvals for revisions of protocol, informed consent, advertisement, ongoing trial review, patient information documents.
- Curriculum vitae for new investigators.
- Monitoring visit reports.
- Signed informed consent forms.
- Notification to sponsor and HREC of serious AEs.
- Notification to TGA of serious and unexpected ADRs.
- Annual reports of study progress.
- Investigational Products accountability documents.

After trial completion

- Investigational product accountability.
- Subject identification code list.
- Final closeout trial monitoring report.
- Clinical study report.

The above documents are required for all clinical trials in order to be compliant with GCP standards. All CTN and CTX trials have this standard as a **mandatory** requirement. The endorsements on the CTN form or the CTX "Notification of the conduct of a trial under the CTX scheme" are legal undertakings on the part of the signatories that provide, among other things, agreement that the trial in question shall be conducted to these standards.

Human Research Ethics Committees

As mentioned previously, HRECs have a pivotal role in clinical research in Australia, by virtue of the fact that they undertake the key responsibilities of clinical trial approval and oversight in this country. HRECs that are operating under the auspices of the Australian Health Ethics Committee form the cornerstone of the practical operation of the CTN process, as well as reviewing all other research proposals involving human subjects in a clinical trial context.

An HREC is responsible under GCP for reviewing as a minimum the trial protocol, investigator's brochure, informed consent forms and patient information documents, procedures for subject recruitment, any planned payment or compensation initiatives for the proposed trial, and the investigator(s) qualifications. In addition, HRECs have the authority to request any additional documentation that they feel is necessary in the individual circumstance in order to discharge their responsibilities and review trial documentation fully. All this documentation must be presented to an HREC if a sponsor expects to have the trial considered for endorsement with a positive outcome.

Ongoing review of trials is required at intervals determined by the HREC to be applicable to the degree of subject risk, but in any event at a minimum of one year intervals.

Operations of an HREC should be documented with respect to membership, scheduling of meetings, conducting trial initial approval and ongoing review and monitoring of trials. Decisions should be made with a minimum of a quorum of members. Advice may be sought from persons who are not members of the committee, but only committee members may vote.

An HREC must receive from any investigator(s), in an expedited manner, any deviations from the trial protocol that were undertaken by investigators to prevent imminent harm to subjects; any change significantly affecting the risk/benefit of the trial; all adverse drug reactions that are serious or unexpected; and any new, significant safety information that comes to hand.

The National Statement provides more detailed requirements than the GCP guideline on the necessary composition of Australian HRECs.[12] Procedural requirements of the HREC in the National Statement are broadly similar to those of the GCP guideline, although the National Statement provides more detail in this regard, and should be considered the primary reference document when an inquiry about the administrative functioning of HRECs is sought.

The responsibilities and functions of HRECs in relation to clinical trials specifically is detailed in chapter 12 of the National Statement document. Essentially, an HREC must be satisfied of the following, (and hence, must be provided with adequate information by the sponsor and investigator(s)) prior to any endorsement of a proposed trial:

a. The trial is designed to answer a *specific* question or questions;

b. There is a scientifically reasonable hypothesis to be investigated which suggests any experimental treatment is at least as good as the current treatment available (including no treatment);

c. Where the research is intended to be therapeutic, there is an acceptable risk/benefit balance based on the known scientific information available;

d. The methodology is adequate to demonstrate selection rationale; recruitment method(s); appropriate informed consent; a clear description of the proposed intervention(s) and observation(s); and a sample size adequate to demonstrate clinically and statistically significant effects.

e. There is adequate expertise available to advise on the safety of the medicinal products or other interventions available;

[12] http://www.nhmrc.gov.au/publications/synopses/e35syn.htm (page 15)

f. The protocol conforms to the National Statement, the ICH Note for Guidance on GCP (CPMP/ICH/135/95), and any other Commonwealth, State or Territory law.

g. Any financial arrangement on the part of investigator(s) and sponsor(s) is disclosed;

h. Aspects of budget for the trial that impact on ethical acceptability have been addressed, including capitation fees, payments to researchers, institutions or organisations involved; current and consequential institutional or organisational costs and costs incurred by participants;

i. Adequate compensation is available to subjects in the event of any trial-related injury.

j. Procedures are in place for regular reporting of trial progress; serious or unexpected adverse event reporting; reporting of significant new information regarding the trial products; reporting of premature trial discontinuation, and in the case of medical devices, that a system is in place to track the recipient for the lifetime of the device.

Investigators

The following responsibilities must be fulfilled by the investigator(s), in terms of GCP requirements and TGA regulatory requirements:

- Appropriate qualifications for the trial being carried out.
- Declaration of any conflicts of interest, payments etc. from other parties.
- Must 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.
- Must be able to demonstrate that adequate subject recruitment is likely to be possible, with necessary time available to conduct the study to GCP requirements, and with adequate facilities and trial staff.
- Must provide medical care to trial participants that is necessary as a result of any adverse events experienced during or following the trial that are related to the trial.
- Must possess, prior to trial commencement, a favourable HREC endorsement of trial protocol, patient information and consent documents, recruitment procedures, consent form updates and any other information given to subjects.
- All trial related documents are subject to HREC review. A regular trial report is also mandatory for provision to the HREC (at least annually, more frequently if the HREC so desires).
- The trial MUST be conducted according to the approved protocol.
- Any deviation from the protocol must be documented for later review.
- No deviation from protocol may occur without HREC endorsement, unless it is required to prevent imminent harm to participants. If the protocol deviation results in the creation of a "separate and distinct" therapeutic good as defined in section 16 of the Therapeutic Goods Act 1989, a new notification is required for CTN or CTX trials.
- A new CTN is required, or in the case of CTX a new "notification of intent to conduct clinical trial" form, for any new trial site subsequently added.
- CTN forms notified must be **originals.** A copy should be kept in the Trial Master File.
- Accountability of the investigational product at the trial site(s).
- Ensuring subjects have made fully informed, written consent, with all trial procedures and risks adequately explained.

Sponsors

From a TGA perspective, the sponsor of a clinical trial is that individual who endorses the CTN or CTX form. A sponsor must be an "Australian Entity" for the purposes of the CTN or CTX.

The responsibilities of a trial sponsor with respect to GCP are extensive, and detailed in item 5 of the Note for Guidance on GCP.[13] In summary, the responsibilities include:

- Ensuring Quality Assurance and Quality Control systems are in place to ensure trials are conducted, data is gathered, and subsequently reported, in compliance with GCP, the trial protocol, and any TGA requirements.
- Ensuring medical expertise is on hand for trial-related medical queries or patient care.
- Trial design and appropriate analysis.
- Data handling, record keeping, and overall trial management.
- Selection of the appropriate investigator(s) and institution(s) to conduct and complete the trial according to GCP standards.
- Definitive, unambiguous allocation of trial-related duties and responsibilities to trial-related staff.
- Provision of appropriate insurance and indemnity for the trial and trial-related staff, as well as measures for subject compensation for trial-related injury.
- Ensuring the confirmation of endorsement from the relevant HREC(s) and notification of the approval etc. to the TGA.
- Ensuring appropriate manufacture, packaging, labelling/coding and distribution to trial sites of all investigational medicinal products.

Ongoing safety evaluation and AE/ADR reporting as described earlier in this document TGA: I would suggest a link here and delete the reproduction: YES / NO

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- Compliance with Monitoring/Audit/Inspection requirements.
- Notification of any premature termination of the trial in question.
- Completion of the Clinical Study Report.

[13] http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm

Clinical Trial Medicines – Manufacture, Import, Export and Documentation

"Unapproved" therapeutic goods in Australia, as previously mentioned, consist of goods that are not entered onto the Australian Register of Therapeutic Goods (ARTG), or the entry on the ARTG is such that the product entered is "separate and distinct" from a good proposed for use in a clinical trial. As explained previously, what makes a product "separate and distinct" involves a number of factors. Any product where the active ingredient may form part of a register entry may still be unapproved because the product's characteristics are different from the register entry version, i.e. a different indication, formulation, dose etc.

In essence, in terms of the Therapeutic Goods legislation, a product may not be manufactured, imported, exported or supplied in Australia unless it is either entered onto the ARTG, or is "exempt" from the requirement for such entry. The CTN and CTX schemes are two such avenues of "exemption" that allow unapproved goods to be supplied to members of the Australian public in specific circumstances, i.e. in the context of a clinical trial reviewed and endorsed by an HREC.

This "exemption" is solely in terms of the requirement for a register entry prior to supply of the product. The other requirements of the Therapeutic Goods legislation, such as manufacturing standards, still apply. The only exception to this is described in item 1 of Schedule 7 of the *Therapeutic Goods Regulations 1990,* and pertains to "goods prepared for the initial experimental studies in human volunteers". Hence, for ***all other clinical trial products, standards of Good Manufacturing Practice as outlined in Annex 13 of the Australian GMP code apply.***[14]

It follows that a CTN thus creates an exemption for the authority to supply the clinical trial products entered onto the CTN. It also follows that, if a protocol amendment alters these goods to the extent that they are rendered "separate and distinct", then supply of such goods is unlawful until a new, complete CTN is notified.

Clinical trial medicines and medical devices may be imported and held in secure premises by the Australian clinical trial sponsor pending CTN or CTX outcomes. They may not be ***supplied*** until such an exemption is in place. If a clinical trial product also happens to be a prohibited import under the *Customs (Prohibited Imports) Regulations*

1956[15], then an import permit will be necessary, obtained from the TGA, before the products can be brought into the country.

Export of unapproved clinical trial therapeutic goods can only occur via a permission granted by a TGA delegate under section 19 of the *Therapeutic Goods Act 1989.*[16] An individual wishing to export clinical trial drugs should contact the Experimental Drugs Section of the TGA, or the Devices Section of the Office of Blood, Devices and Tissues, to request an export permission. Typical supporting documentation includes a description of the goods and the amount or numbers involved; the name and address of the person to whom the goods are to be sent, and an assurance that any clinical trial use shall be in accordance with GCP standards.

It is a requirement of GCP that a written accounting of clinical trial products is kept throughout the duration of a clinical trial, and that unused product(s) is/are appropriately disposed of at the conclusion of the trial. Trial products should only be used in accordance with the trial protocol, and use outside this scope is not lawful unless another form of exemption is to be utilised.

[14] http://www.tga.gov.au/industry/manuf-medicines-cgmp.htm

[15] http://www.comlaw.gov.au/ComLaw/Legislation/LegislativeInstrumentCompilation1.nsf/current/bytitle/DD3A737E7F8A8221CA2570CE00028848?OpenDocument&mostrecent=1

[16] The *Therapeutic Goods Act 1989.* http://www.comlaw.gov.au

Managing Adverse Events and Adverse Drug Reactions

Requirements for the tabulation and reporting of adverse events and adverse drug reactions in clinical trials are detailed in several documents. Foremost for Australia in terms of regulatory reporting for the CTN and CTX schemes is the TGA's publication, "Access to Unapproved Therapeutic Goods – Clinical Trials in Australia".[17] The EU GCP guideline[18] as well as the European Union guideline on expedited reporting[19] also describe the required reporting of such adverse reactions and events.

The reporting of adverse events and adverse drug reactions is an area that regularly causes confusion. It is worthwhile to delineate exactly what is required in terms of clinical trial reporting.

Definitions (DRUGS):

Adverse Event (Drug)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product.

Adverse Drug Reaction (ADR)

For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered ADVERSE DRUG REACTIONS. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

For marketed medical products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

An Unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable scientific information (e.g. Investigator's Brochure for an unapproved investigational product or Product Information (PI) document or similar for an approved, marketed product).

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is:

Any untoward medical occurrence that at any dose:

· Results in death,

[17] http://www.tga.gov.au/hp/access.htm
[18] http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm
[19] http://www.tga.gov.au/industry/clinical-trials-note-ich37795.htm

- Is life-threatening, (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or;
- Is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Definitions (MEDICAL DEVICES):

Adverse Event (DEVICE)

Any undesirable clinical occurrence in a subject whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

Adverse Device Event

A clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of the device, or the performance of the device system.

The EU GCP guideline CPMP/ICH/135/95 states:

For the Investigator:

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names,

personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

For the Sponsor:

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

The NHMRC National Statement on Ethical Conduct in Research Involving Humans states:

12.8 An institution or organisation and its HREC must require the researcher:

d. to inform the HREC and the TGA of all serious or unexpected adverse events that occur during the trial and may affect the conduct of the trial or the safety of the participants or their willingness to continue participation in the trial;

e. to inform the HREC as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the trial or which may indicate the need for amendments to the trial protocol.

The regulatory requirements of the TGA for clinical trials require that:

All serious **AND** unexpected **ADVERSE DRUG REACTIONS** are reported to the Experimental Drugs Section, Drug Safety and Evaluation Branch of the TGA in an expedited fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life-threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe. All other ADRs and AEs are tabulated as per usual trial protocols and produced on request.

All serious **AND** unexpected **ADVERSE DEVICE EVENTS** are reported to the Devices Clinical Section, Office of Blood, Devices and Tissues of the TGA in an expedited fashion as described in the paragraph above. Other adverse device events to be tabulated and produced upon request.

For Post-Marketing Clinical Trials of Medicines used *within* marketing approval

Adverse event reporting should occur directly to the Adverse Drug Reaction Unit of the TGA, not the Experimental Drugs Section of the Drug Safety and Evaluation Branch.

Adverse events and adverse drug reactions that occur as part of an international arm of a trial being conducted in Australia are not required to be reported to the TGA. The TGA requires that such new information that comes to hand is evaluated by the trial sponsor and, should it significantly affect the risk/benefit profile of a drug or device, that the information be communicated to the TGA within 72 hours of first knowledge.

Summary of Clinical Trial Adverse Event (AE) and Adverse Drug Reaction (ADR) Reporting

All **Serious Adverse Events:**

- Report to sponsor from investigator immediately, with follow-up detailed reports when this information is not contained in the initial report.
- Report to the Human Research Ethics Committee(s) concerned.

All **Serious AND Unexpected Adverse Drug Reactions**

- These come to the sponsor as part of the serious events described above. ADRs that are both serious and unexpected are to be reported by the **sponsor** to all participating investigators (obviously not the one from whom the report originated), to the HREC(s) involved, and to the TGA.

Adverse Drug Reactions from the use of marketed drugs in clinical trials

The Adverse Drug Reaction Unit (ADRU) of the TGA advises that all drugs, when used in clinical trials, should have ADRs reported as per clinical trial reporting guidelines, whether used as "unapproved" goods or within their marketing authorisation, if applicable. For a purely post-marketing study with drug used within marketing approval, ADRs are to be reported directly to ADRU.

Clinical Trial Monitoring and Inspection

As previously mentioned, the endorsing HREC(s) involved in a clinical trial have the overall responsibility for the monitoring of that clinical trial. This involves regular reporting to the HREC(s) with a frequency to be determined on a case-by-case basis, however never greater than annually. In addition, as described in the Adverse Event and Adverse Drug Reaction reporting section of this document, the HREC receives serious adverse events for consideration as well. It may be in some cases that this information is initially reviewed by a Data Safety Monitoring Board (DSMB) or similar, however, the HREC(s) remain ultimately responsible for this monitoring and the DSMB(s) report to them.

The TGA also has a complimentary role in clinical trial monitoring involving those trials that are conducted as part of the CTN or CTX arrangements.

Medical Device Trials

Clinical trial monitoring for devices is essentially similar to that for medicines. Often, the protocol is sent in by the sponsor/principal 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 as for medicines.

Medicinal Product Trials

CTX Scheme

The TGA assesses the data provided and any objections raised must be addressed before the supply of the investigational product can commence. Monitoring activities subsequent to this are similar to that for a CTN trial.

On receipt of CTN Form

Administrative staff check the form for completeness and if necessary liaise with the trial coordinator or sponsor to correct any insufficiency, ie. a 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 Experimental Drugs Section (EDS) professional staff for data accuracy and any obvious concerns, for example, use of a clearly inappropriate/toxic product in humans.

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 varied.

Monitoring activities:

Adverse Drug Reactions and Adverse Device Incidents

Sponsors are required (as discussed earlier) to report serious AND unexpected adverse drug and adverse device incidents to the TGA.

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

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*[20] 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[21]. The principal investigator is required to comply with requests and answer any questions authorised officer(s) may have.

Further Action

Once data from monitoring of a clinical trial is assessed, and issues of concern, if any, are identified, there are several methods by which the TGA may proceed. These include liaison with sponsors, and/or principal investigator(s), and/or institutional authorities; liaison with the Human Research Ethics Committee, on matters related to the approval and ongoing monitoring of the clinical trial; liaison and provision of certain information to State and Territory authorities, including medical boards; and correspondence with, or provision of information to, other Commonwealth authorities, including AHEC and the Gene and Related Therapies Technical Advisory Panel (GTRAP) of the NHMRC. When any of these activities are carried out clearly depends on the nature of the concern the TGA may have.

As a last resort, the TGA has the legislative power to stop a clinical trial on public safety grounds. This might occur if all other avenues of resolution have been exhausted and concerns are still present, or might occur more quickly if it was considered that the danger to subjects was imminent if the trial in question was allowed to continue. In practice the use of this provision is extremely rare.

Potential triallists should be aware of the monitoring activities of the TGA as described above, and understand that the requesting of further information in the form of certain essential documents relating to the trial is a common practice.

[20] The *Therapeutic Goods Regulations 1990.* http://www.comlaw.gov.au
[21] http://www.tga.gov.au/industry/clinical-trials-guidelines.htm

Clinical Trial Databases

As a final noteworthy point, regular triallists would be aware that having their trial "registered" in an online database is now necessary for the publication of the trial in certain well-respected clinical journals. There are also considerable other benefits that registration of a clinical trial can bestow both individually and to the research community as a whole. This topic is discussed at length in the recent Bansemer Review of Access to Unapproved Therapeutic Goods.[22]

A clinical trial database has been set up at the University of Sydney via a Project Grant from the NHMRC. For further information, the reader is directed to the "Australian Clinical Trial Registry" website.[23]

[22] http://www.tga.gov.au/archive/review-clinical-trials-050405.htm
[23] http://www.actr.org.au/

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Reference/Publication #