The Conduct of Clinical Studies

Clinical Study Overview

1.1 General

A clinical study is a type of research involving human subjects designed to determine the effects of a particular intervention including a particular pharmaceutical product, a clinical procedure, other therapeutic procedures and devices, a preventative procedure or a diagnostic device or procedure[1].

Clinical studies involving the use of pharmaceutical products in humans may be conducted in Australia on:

- a pharmaceutical product for which the Therapeutic Goods Administration (**TGA**) has not granted marketing approval. That is, the product is not entered on the Australian Register of Therapeutic Goods (**ARTG**);

- the use of a pharmaceutical product outside the conditions for which the TGA has granted it marketing approval. For example, use of the pharmaceutical product in another formulation, dose form, for another indication or under other directions; and

- the use of a pharmaceutical product within the conditions for which the TGA granted it marketing approval. For example, post marketing studies to monitor a pharmaceutical product's side effects or compare its effectiveness with another pharmaceutical product with marketing approval etc.

If a drug is imported for use in a clinical study, additional restrictions may apply under the *Customs (Prohibited Imports) Regulations* and the *Quarantine Act 1908* and possibly the *Wildlife Protection (Regulation of Imports and Exports) Act 1982*. This is of particular importance in relation to the importation of biological products.

All clinical studies conducted in Australia on pharmaceutical products involving humans require review and approval of the proposed study by a Human Research and Ethics Committee (**HREC**) including approval of studies involving the use of a pharmaceutical product within the conditions for which the TGA has granted it marketing approval.

Clinical studies are subject to the privacy laws and as such must comply with relevant privacy considerations in respect of personal information. In particular, the sponsors of clinical studies and HREC's must ensure that appropriate consent is obtained from the clinical study participants to the collection, storage, analysis and disclosure of their health and personal information.

From a TGA perspective the **Sponsor** is the individual or entity that endorses the application form for the purposes of the CTN or CTX scheme (refer below). The **Principal Investigator** is the lead investigator, usually a specialist medical practitioner, who undertakes and oversees the conduct of the clinical study. The HREC is responsible for monitoring the progress and conduct of the study. Primary responsibility for the conduct (not the monitoring) of a clinical study rests with the Principal Investigator and the Sponsor.

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[1] National Statement on Ethical Conduct in Human Research 2007, Chapter 3.3. The National Statement on Ethical Conduct in Human Research 2007 was developed by the National Health and Medical Research Council, the Australian Research Council and the Australian Vice-Chancellor's Committee.

1.2 The Sponsor

The Sponsor typically initiates the clinical study, undertakes its initial organisation and establishes the legal agreements and is responsible for the financial arrangements between the Sponsor, the institution at which the study is conducted (**Institution**) and the investigator who conducts (or oversees) the study. Clinical studies may be sponsored by an individual, corporations or institutions (such as hospitals).

The Sponsor fulfils all the ethical requirements associated with the conduct of the clinical study, satisfies all regulatory requirements of the TGA and carries the medico-legal responsibility associated with the conduct of the study. The Sponsor is usually responsible for the supply of the pharmaceutical product for use in the clinical study (**Study Product**) and in this regard must comply with the legislation in the States and Territories in relation to the supply of pharmaceutical products.

1.3 Ethics Committee Approval & Good Clinical Practice

The HREC reviews and approves the proposed clinical study and associated study protocol. The HREC provides advice to the Sponsor, Principal Investigator and the Institution prior to the study's commencement and throughout the study. In this regard the HREC undertakes an ethical and scientific review of the clinical study and may supplement its review with external expert advice as required.

Most Institutions that conduct clinical studies have an established HREC.

Clinical studies must be conducted in accordance with the approved protocol, good clinical practice (**GCP**) and the National Statement on Ethical Conduct in Human Research (**National Statement**) published by the National Health and Medical Research Council (**NHMRC**).
Available at weblink: http://www.nhmrc.gov.au/guidelines/ethics/human_research/index.htm

The principles of GCP have their origin in the Declaration of Helsinki, which was first developed post WWII in the wake of the revelations that flowed from the Nuremberg Trials, to ensure that human subjects involved in clinical research would forever have their rights, safety and well-being placed above the priorities in any clinical research. The document was used as the basis for developing guidance for GCP in clinical studies by the International Conference on Harmonisation. Refer to weblink: http://www.ich.org/cache/compo/276-254-1.html

The GCP principles detail requirements for clinical study documentation and procedures including indemnity, provision of medical care for the person participating in the study (**Study Participant**), adverse drug reaction reporting requirements and protocol amendment. The National Statement builds on the principles outlined in GCP.

The National Statement provides guidance on a wide range of ethical issues that arise in clinical research involving humans and has a specific chapter relating to clinical studies, which details many of the issues that must be addressed by an HREC in determining whether to approve a clinical study.

The HREC must be satisfied the clinical study has a specific aim that seeks to answer a specific scientific or medical question(s) and that a scientifically valid hypothesis is being tested that offers a realistic possibility that the intervention being studied will be at least as beneficial overall as the standard treatment. In this regard the clinical study must be designed to collect appropriate data and information that provides the evidence to an appropriate statistical standard that will answer the question(s) posed.

Other potentially relevant ethical considerations comprise the following:

- The study must be designed to minimise the risks of harm or discomfort to Study Participants;
- If there are no likely benefits to Study Participants, any known risks to Study Participants should be lower than would be ethically acceptable where there are such likely benefits; and
- Any likely benefit of the research comprised in the study must justify any risks of harm or discomfort to the Study Participants. In this regard the likely benefit may be to the Study Participants, to the wider community or both.

1.4 TGA Approval

Notification to the Therapeutic Goods Administration (**TGA**) under the Clinical Trial Notification Scheme[2] (**CTN**) or application to the TGA under the Clinical Trial Exemption[3] (**CTX**) scheme is required for all clinical studies involving humans conducted in Australia and the use of:

- a pharmaceutical product for which the TGA has not granted marketing approval; and

- the use of a pharmaceutical product outside the conditions for which the TGA has granted it marketing approval. For example, use of the pharmaceutical product in another formulation, dose form, for another indication or under other directions. In other words just because a pharmaceutical product may be included on the ARTG does not mean the product's intended use in a clinical study does not require notification under the CTN or approval under the CTX scheme

The CTN and CTX schemes do not apply to clinical studies involving the use of a pharmaceutical product that comes within the conditions for which the TGA granted it marketing approval. The CTN and CTX scheme effectively provide an exemption to the requirement that a pharmaceutical product for use in humans in Australia must have marketing approval.

Both the CTN and CTX schemes require that the clinical study have an Australian Sponsor and that it obtain approval from the HREC of the Institution before the study may proceed. The HREC providing such approval must have notified its existence to the Australian Health Ethics Committee (**AHEC**) of the NHMRC and must operate in accordance with the National Statement.

The choice of which scheme to follow lies initially with the Sponsor of the clinical study but the HREC may also require that a particular scheme be utilised. The TGA does not provide directions on which scheme to use, rather the decision will be influenced by a number of factors including the size of the institution, the experience of the Principal Investigator, the HREC's experience and expertise and the nature of the pharmaceutical products involved. Fees are payable to the TGA in respect of both a notification under the CTN scheme and application under the CTX scheme.

☎🗁◑CTN Scheme

[2] Pharmaceutical products for use in a CTN Scheme clinical study are exempt goods under section 18 of the *Therapeutic Goods Act 1989* (Cwth) and Schedule 5A to regulation 12 of the *Therapeutic Goods Regulations 1990* (Cwth) and such use does not require approval provided certain conditions are satisfied.

[3] Pharmaceutical products for use in a CTX Scheme clinical study are exempt goods under section 19 of the *Therapeutic Goods Act 1989* (Cwth) provided approval is obtained from the TGA prior to use.

Under the CTN Scheme application is not made to the TGA and the TGA does not review data relating to the proposed clinical study prior to its commencement. Responsibility for such review lies with the HREC and the researcher (usually the Principal Investigator). The TGA is merely notified by the Sponsor following the clinical study receiving HREC approval that the study is to be conducted.

The Principal Investigator at the direction of the Sponsor submits all material relating to the proposed clinical study, including the study protocol directly to the HREC. The HREC is responsible for assessing the scientific validity of the study design, the safety and efficacy of the Study Product and the ethical acceptability of the study overall. The HREC must operate in accordance with the National Statement. The HREC is responsible for approving the clinical study protocol and the Institution provides the final approval for the study.

A clinical study to be conducted under the CTN scheme may not commence until approval is obtained from the HREC and the Institution and the study has been notified to the TGA and the appropriate fee paid.

☎🗎◑ CTX Scheme

Under the CTX Scheme the Sponsor makes application to conduct the clinical study to the TGA for the TGA's evaluation and comment on the study. The TGA has a direct role in reviewing the scientific data supporting the proposed clinical study, providing comments to the HREC and then deciding whether or not to object to the proposed usage guidelines for the Study Product. In this regard, the TGA evaluation focuses primarily on safety.

The TGA may seek clarification of issues during the initial review period and if any issues remain unresolved at the end of the initial review period the TGA may issue an objection notice[4]. If the TGA raises an objection then the clinical study may not proceed until it is addressed to the satisfaction of the TGA. Even if the TGA does not raise an objection it may nevertheless provide comments on the accuracy or the interpretation given to the data and information provided by the Sponsor in support of its CTX scheme application.

The TGA does not comment directly on the clinical study Protocol, the approval of which is the responsibility of the HREC. An explanation of the clinical study Protocol is provided in section 1.6 of this paper. The HREC is responsible for approving the proposed clinical study following a review of the study Protocol on the basis of summary information provided by the Sponsor and any comments provided by the TGA.

The Sponsor must not commence a CTX scheme clinical study until formally advised by the TGA and approval is obtained from the HREC and the Institution. Any objections raised by the HREC must be notified to the TGA. Following HREC approval the TGA is notified of the commencement of the study. The Sponsor may conduct additional clinical studies without further assessment by the TGA provided the use of the Study Product in the proposed new study comes within the originally approved usage guidelines for the Study Product and provided the TGA is notified of the new clinical study's commencement.

Clinical Study - Sequence of Events

The following is an overview of a fairly "typical" phase III clinical study on a pharmaceutical product and is intended to highlight various issues of importance in the design of clinical studies and issues that may arise during the conduct of the clinical study. The overview also

[4] The sponsor may respond within 30 working days of receipt of the objection notice. However, the application will lapse if a response to the objection notice is not received within that time.

includes observations as appropriate regarding the clinical study of which Biogenerics Australia Pty Ltd (**BGA**) is the Sponsor and is currently in progress (**BGA Clinical Study**).

A Phase III clinical study is usually undertaken following completion of Phase I and II studies that have established the Study Product in question has potential benefits that outweigh any identified hazards. Phase III studies are typically reasonably large with perhaps between 100 and 2,000 study participants. Phase I and II(a) and II(b) studies establish the basic safety of the pharmaceutical product, appropriate dosing ranges, and perhaps provide some preliminary efficacy results. Phase III clinical studies seek to confirm whether the Study Product confers clinical benefits in the particular health condition for which the Study Product is proposed to be used and whether the incidence and nature of any adverse events of the Study Product are acceptable[5].

The Phase III study will typically involve comparison of the new pharmaceutical product utilising a particular dosing regimen, with either a placebo, or the existing pharmaceutical product. The BGA Clinical Study is perhaps best thought of as similar to a Phase III study.

1.5 Study Design

The first step in conducting a clinical study is to consider the exact question the clinical study is intended to answer and then designing a clinical study to answer the question. This necessitates consideration of a number of issues and undertaking various activities including:

- consideration of the data and information that will be required for gaining marketing approval of the Study Product if a particular regulatory pathway is utilised. This step is particularly problematic in circumstances where a regulatory pathway for the class of pharmaceutical product to which the Study Product belongs is unclear or does not exist at the time the clinical study is developed. In these circumstances the study design seeks to address as many of the anticipated regulatory requirements as possible, which will typically lengthen the time taken to develop the study design. Such circumstances applied at the time the BGA Clinical Study was designed and they were the major factor in the time taken to complete the design.
- consultation with recognised specialist medical practitioners in the therapeutic field in which the pharmaceutical product will be used. Undertaking this activity assists in identifying potential Principal Investigators for the clinical study.
- consideration of the ethical issues that may arise with a particular clinical study design. As noted above the likely benefit of the research must justify any risk of harm or discomfort to Study Participants. The ethical issues can become complicated in circumstances where the Study Participant is unlikely to receive any benefit from participating in the clinical study. The BGA Clinical Study raised a number of ethical issues that had to be addressed to the HREC's satisfaction, which took BGA and the study designers a considerable amount of time.

1.6 Study Protocol and Investigator's Brochure

Having designed the clinical study, a Protocol and Investigator's Brochure are then developed for submission to the applicable HREC. The **Protocol** describes exactly what the study will consist of and how it will be conducted including its design, the number of Study Participants, statistical considerations, data to be recorded, study visits, inclusion and exclusion criteria, stoping rules, subject withdrawal, adverse event reporting, data gathering, record keeping, pharmaceutical product handling and storage, financing, insurance and provision for extension of the study.

[5] National Statement on Ethical Conduct in Human Research 2007, page 34.

The **Investigator's Brochure** is a compilation of the clinical and non-clinical data available on the Study Product. The clinical and non-clinical data on the Study Product for use in the BGA Clinical Study was supplied by the product's manufacturer which BGA then reviewed and compiled into a format suitable for submission to the HREC. During this process BGA also had to ensure that the data and information supplied was suitable and sufficient.

1.7 Principal Investigator and Institution Selection

Selection of the Principal Investigator and Institution involves undertaking due diligence on the proposed Principal Investigator(s) and the Institution's systems and procedures and patient types, which will likely also include interviewing the proposed Principal Investigator and other key personnel involved in the clinical study. Issues for consideration include:

- ensuring the Institution has sufficient resources and facilities;
- ensuring the proposed Principal Investigator has sufficient experience to undertake the proposed clinical study and assessing the Principal Investigator's reputation; and
- ascertaining the availability of potential Study Participants at the relevant Institution. In this regard it is necessary to ascertain the number of patients the Institution can expect to treat on an annual basis who have the particular health condition required for participation in the clinical study.

The actual level of Study Participant recruitment is very difficult to accurately predict, as the number of the Study Participants is dependent upon people continuing to present with the relevant health condition or indication at the same rate into the future as has occurred in the past. In addition, in the case of chronic or terminal health conditions potential Study Participants will invariably require more time to decide whether or not to participate in the clinical study particularly if the study procedure is extensive which they may perceive as an additional burden to their already intensive treatment regime and this in turn may add to the overall time taken to complete the study. Study Participant recruitment has perhaps the greatest impact on the time taken to complete a clinical study and a deal of analysis and planning is undertaken in this regard in the Institution selection process. BGA selected the Institution at which the BGA Clinical Study is currently being conducted primarily because it has access to a large pool of oncology inpatients drawn from a wide area of the State in which the Institution is located.

1.8 HREC Application and Approval

Application is made to the HREC of the Institution at which the clinical study will be conducted. Consideration in consultation with the HREC is given to whether or not to utilise the CTN or CTX scheme. The HREC reviews the application and will typically seek clarification from the Sponsor on some issues particularly issues relating to ethics and study design. The HREC may undertake interviews including interviewing the Principal Investigator and may also compile questions to be answered by the Sponsor in writing.

HREC's typically meet to consider clinical study applications on a monthly, bi-monthly or quarterly basis. A HREC secretariat is usually responsible for co-ordinating the HREC including scheduling meetings and compiling submission papers for provision to the HREC members. The secretariat will also set deadlines for initial clinical study applications and responses to HREC questions, which if missed can result in further delays in obtaining HREC approval as the matter will be held over until the next scheduled HREC meeting.

If the CTX scheme is utilised the HREC approval process will take longer as a consequence of the requirement for the TGA's evaluation and comment on the clinical study, and approval

may be delayed further if the TGA requires clarification or further information. The BGA Clinical Study utilised the CTN scheme.

The BGA Clinical Study type and design raised a number of complex ethical issues which were addressed to the HREC's satisfaction following considerable consultation between the HREC, the Principal Investigator and BGA and included modifications to the original study design and resulting study Protocol. As a consequence the HREC approval of the BGA Clinical Study took considerably longer than would typically be expected for a clinical study without the complex ethical issues.

Following HREC approval the TGA is notified in accordance with the requirements of the CTN or CTX scheme and the clinical study may then commence. Following TGA notification Study Participant recruitment may commence at the Institution. Most clinical studies include a set of inclusion and exclusion criteria for determining whether a potential Study Participant is eligible to participate in the clinical study. For example, the Study Participants must be of a particular age, have a particular condition, must not be on particular medication etc. These criteria must be followed to ensure the statistical integrity of the clinical study data. The criteria will impact Study Participant recruitment rates.

1.9 Study Participant Recruitment and Consent

Typically Study Participants are inducted into the clinical study by the Principal Investigator, another investigating medical practitioner or their treating medical practitioner at the Institution. A key part of the induction process is the Study Participant providing valid and informed consent to participation in the clinical study. This process involves a comprehensive exploration with the Study Participant of the risks associated with the clinical study, the clinical study's objective, and the requirements of participation, in terms of attendances etc. It is also made clear that the Study Participant is free to withdraw at any time. A withdrawn Study Participant may not be included in the required Study Participant numbers as their clinical results will be incomplete. However, depending on the time of withdrawal, a withdrawn Study Participant will become part of safety population (SP) for the purpose of safety analysis and may still become part of the intention to treat (ITT) efficacy analysis. A further Study Participant will need to be recruited in place of the withdrawn Study Participant.

BGA is continually monitoring Study Participant recruitment in the BGA Clinical Study and is developing contingencies to recruit Study Participants at other Institutions in the event BGA considers the recruitment levels at the first Institution insufficient to ensure completion of the study within a reasonable time period. In this regard there is the need to balance the cost in establishing another arm of the clinical study against the potential for overall time savings in gaining marketing approval for the Study Product.

1.10 Conduct of the Clinical Study

The Institution and Principal Investigator are responsible for the conduct and management of the clinical study at the local level including the administration of the Study Product and the relevant reporting activities including data collection. The Institution and Principal Investigator are responsible for conducting the clinical study in accordance with GCP requirements and local regulatory requirements.

The clinical study will typically be structured in such a way that neither the Study Participant, nor the person supervising the study, including the Principal Investigator, will know which particular pharmaceutical product the Study Participant is receiving. This is known as a double-blinded clinical study and is designed to avoid bias in the study results, all of which seek to preserve the statistical integrity of the resulting data. For similar reasons the

Sponsor remains separate from the Principal Investigator and the conduct of the clinical study.

To ensure that blinding of the Sponsor and Principal Investigator is not compromised but at the same time to ensure safety concerns regarding individual Study Participants are properly monitored, an Independent Data Safety Monitoring Board (**IDSMB**) is established. The IDSMB is an independent, multidisciplinary group typically consisting of at least one biostatistician and at least two medical practitioners, who collectively have experience in the management of patients with the health condition(s) or indication(s) the clinical study is seeking to address and who are free of conflicts of interest. Ideally all IDSMB members will have expertise in the conduct and monitoring of randomized clinical studies. The duration of IDSMB membership will cover the duration of the clinical study and the final analysis on a clean and locked database. An un-blinded IDSMB support team, comprised of an independent statistician, a programmer, and an administrative coordinator, not employed by the Sponsor and not directly involved with the conduct of the clinical study, will perform all IDSMB data and administrative coordinating activities. Guidelines for establishing an IDMSB may be found at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

In this regard the BGA Clinical Study has an appointed IDSMB. Contact between the Principal Investigator for the BGA Clinical Study and any member of the IDSMB and IDSMB support team on the one hand and BGA (as the Sponsor) and any person associated with BGA on the other is tightly controlled in an effort to maintain the statistical integrity of the resulting study data.

In the course of the clinical study often additional tests are carried out which are retained as part of the clinical study records.

Typically larger clinical studies will be conducted at a number of sites, commonly in a number of countries, primarily because the number of Study Participants required for the clinical study is such that no one site is anticipated to have the number of potential Study Participants required available in the time period required for completing the clinical study. For such clinical studies a contract research organisation (**CRO**) will likely be engaged and take responsibility for the entirety of the clinical study, while in some cases different CRO's may be appointed for that part of the clinical study undertaken in different countries.

1.11 Indemnity

Study Participants have the benefit of a right to compensation and indemnity. Typically, this is provided in accordance with the Medicines Australia Clinical Trial Compensation Guidelines and a Standard Form Indemnity which can be found at the Medicines Australia web site www.medicinesaustralia.com.au.

1.12 Clinical Study Results and Data

Data from the clinical study is collected at the local level, and typically aggregated and reported on at the national or international level. The aggregated data, are typically de-identified. That is, the data does not contain information that permits the identification of the particular Study Participant to whom it relates. However, the information would ordinarily be structured in such a way that the Study Participant could be identified if the need arose e.g. to validate some result or to follow up on a serious adverse event.

The Sponsor does not receive or have access to any data from the clinical study whilst the study is on-going. During this time the Sponsor will only know if something has gone wrong with the study, for example Study Participants have suffered adverse events and the clinical

study has had to cease. BGA has not been notified of any such adverse events or happenings in relation to the BGA Clinical Study which is on-going.

The ultimate objective of the clinical study is to provide data suitable to support an application for marketing approval for the pharmaceutical product. As such the aggregated de-identified data from the clinical study may be utilised to support applications for marketing approval in jurisdictions outside Australia.

The Protocol may be amended during the study for the purposes of the proposed Australian product marketing approval or marketing approvals outside Australia to facilitate improved data or additional data for other use indications. Any such change will typically require HREC approval and may require further notification to the TGA. BGA is constantly monitoring developments with the regulatory pathway for follow on biologics in Australia and overseas to determine whether or not any changes are required to the Clinical Study to address any additional requirements that may arise (Refer to document entitled "Regulatory Approval of Pharmaceutical Products" for further information).

Additional Information

Additional information is available at the following websites:

- Therapeutic Goods Administration – Clinical Trials: www.tga.gov.au/ct/index.htm
- National Health and Medical Research Council: www.nhmrc.gov.au/
- Medicines Australia: www.medicinesaustralia.com.au
- International Committee on Harmonisation: www.ich.org/cache/compo/276-254-1.html