BOOKLET 13

Griffith University Research Ethics Manual

The ethical design and conduct of clinical trials

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Contents

1.0 About this booklet

This booklet is one of four booklets relating to clinical research. This booklet covers the ethical standards and the regulatory guidance for clinical trials. Researchers who are planning, or about to seek, ethics approval for, or conducting a clinical trial should read this booklet in conjunction with Booklet 12 (Clinical research: Ethical and governance considerations).

Material already covered by Booklet 12 is not repeated here, unless to highlight where different standards/expectations apply for clinical trials.

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2.0 National and international guidance material

As was noted in Booklet 12 of the Griffith University-HREM the Australian national reference point for human research ethics is the National Statement on Ethical Conduct in Human Research (2007 updated 2018). Chapter 3.1 of the National Statement contains guidance for clinical research, therapies, interventions and clinical trials.

The Australian governance approach to clinical trials and related matters is articulated in guidance, policy and resource materials issued by the National Health and Medical Research Council (NHMRC), the Therapeutic Goods Administration (TGA) and the Australian Commission on Safety and Quality in HealthCare (ACSQHC).

An important guideline for the conduct of clinical trials involving unapproved therapeutic agents is the International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use (ICH) Integrated Addendum to ICH (E6)(R1): Guideline for Good Clinical Practice E6(R2) Current step 4 version dated 9 November 2016 (Guideline for GCP). It is important to note that compliance with the Guideline for GCP is a legislated requirement under Regulation 12AD of the Therapeutic Goods Regulations 1990. The TGA also recognises that ISO 14155 is the equivalent to the Guideline for GCP for medical devices. The TGA has published the Australian Clinical Trial Handbook to provide more specific guidance about its requirements and the use of the Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) schemes. Notwithstanding the requirement to follow the Guideline for GCP the TGA state *"If requirements specified in the National Statement appear to differ from those specified in the Guideline for Good Clinical Practice, the TGA recommends compliance with the National Statement."* It is also important to note that trials that do not use unapproved therapeutic goods are not subject to the requirements of the Guideline for GCP, although its requirements are highly relevant to all trials.

Commentary Inset 1 – Trial with an unapproved pharmaceutical agent or device

As per the TGA Act, research that involves the supply/trialling or other in-human testing with a pharmaceutical agent or medical device, requires an approval under either the CTN or CTA schemes unless the agent or device appears in the ARTG.

As noted at 3.0 the use of a registered agent or device outside conditions of its marketing approval requires approval via ether the CTN or CTA schemes.

In practice this means that the use of a registered agent or a device in a manner outside of what is listed in the ARTG (e.g. at a different dosage, for a different medical condition) is highly likely to be considered a breach of the Act

Griffith University's approach to clinical trials is our implementation of the Australian arrangements and the international guidance on the good conduct of clinical trials.

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3.0 Regulated clinical trials

The TGA has established approval arrangements for clinical trials. Those arrangements involve an interaction between the relevant institution's research ethics review mechanisms and the TGA's CTN and CTA schemes. These are codified in the *Therapeutic Goods Act, 1989* (the Act) and the Therapeutic Goods Regulations 1990.

Experimentation with therapeutic goods (whether a pharmaceutical agent or device) that are not yet registered, listed or entered on the Australian Register of Therapeutic Goods (ARTG) are subject to the Therapeutic Goods Administration's clinical trial arrangements. Without submitting a notification or receiving an exemption from the TGA (see 4.1 and 4.2) any medical research use of an unapproved pharmaceutical agent or device is illegal.

Commentary Inset 2 – About the TGA

The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating therapeutic goods including clinical trials.

The TGA administers the ARTG and administers the exemption schemes for the approved use of unregistered products.

The role of the TGA with regards to the research use of unregistered pharmacological agent or medical device is articulated by the TGA Act, regulations and associated arrangements.

Clinical trials in which registered/listed pharmaceutical agents or medical devices are used within the conditions of their marketing approval are not subject to notification or exemption by the TGA. However, the principles related to Good Clinical Practice are relevant to all Clinical Trial activities and Griffith strongly encourages researchers to make themselves familiar and, wherever possible, align the conduct of their research with them.

More specific details related to regulatory requirements are provided in Booklet 14 Pharmacological clinical trials, Booklet 15 Medical device clinical trials and Booklet 16 Complementary medicine and other clinical trials and are not repeated here.

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4.0 Use of the terms 'Sponsor' and 'Trial Sponsor'

The term 'sponsor' often creates confusion as it can mean different things depending on the context it is used in. The TGA uses the term 'sponsor' to define the person who imports or manufactures therapeutic goods for use in Australia or arranges for another person to do this. The TGA uses the term 'trial sponsor' to refer to the Australian entity that "is responsible for the initiation, management and financing (or arranging the financing) of the trial and carries the medico-legal responsibility associated with its conduct." However, the GCP guideline refers to the 'trial sponsor' as just the 'sponsor'. The Australian Clinical Trials website developed by the NHMRC and Department of Industry, Innovation and Science provides additional background to the term "sponsorship" and uses 'sponsor' as synonymous with 'trial sponsor'. Care must therefore be taken when using the term in the specific context of the Australian regulations and it is better to interpret 'trial sponsor' wherever GCP refers to 'sponsor' rather than 'sponsor' as defined by the TGA.

Commentary Inset 3 – Matters considered by the TGA

When reviewing an application to use an unapproved product in a clinical trial (ie. an application under the CTX scheme), the TGA considers a number of factors:

The approval status of the pharmaceutical agent/device overseas (e.g. has it been approved for use in the US?).

The proposed usage sheet (e.g. in terms of dosage, duration of use, screening of participants, strategies to mitigate risk, and the monitoring arrangements).

(In the case of a pharmaceutical agent) The pharmaceutical data sheet.

(In the case of a medical device) The specifications of the device.

A summary of the preclinical and clinical data.

The above information is provided to the TGA by the sponsor of the proposed trial.

All CTN and CTA trials must have an Australian legal entity as the trial sponsor and it is that entity who is responsible for submitting the CTN or CTA to the TGA. Non-regulated trials do not legally have to have a trial sponsor as defined by the TGA but it is important to define the organisation that has overall responsibility for the trial as the 'trial sponsor' for insurance and governance purposes. There are significant responsibilities placed upon 'trial sponsors' for both regulated and non-regulated trials and it is vital that researchers establish whether or not they and Griffith University more broadly can fulfil these. Establishing whether the roles and responsibilities for 'trial sponsorship' are met is at the core of Research Governance review and approval. Researchers should plan how they are going to meet these obligations by discussing their intentions as early as possible with the Research Ethics and Integrity team in the Office for Research. In clinical trials the 'sponsor' is responsible for all aspects of monitoring and evaluation of the trial. . Griffith University is usually considered the sponsor for grant-funded clinical trials.

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5.0 Insurance

The *National Statement (paragraph 5.1.38-39)* and the TGA guidance provide direction with regards to minimal institutional insurance/indemnification for individual trials.

The institutional requirement for the indemnification of clinical trials **does not** include negligence on the part of an investigator. In addition to the insurance expectations for a clinical trial paragraph 5.1.39 of the

National Statement specifies that institutions **must** have insurance for negligence by a researcher during the conduct of research.

When a clinical trial is externally sponsored (e.g. as in the case of trials sponsored and funded by a pharmaceutical company), the Medicines Australia Form of Indemnity and Guidelines for Compensation is the basis for agreements with sponsors with respect to the participants only.

Griffith University's insurance and indemnification arrangements comply with the Australian and international standards. It is however an absolute requirement that the details of a planned trial be submitted for approval by the University's insurer (see Griffith University Clinical Trials) **but only after** the trial has received HREC approval.

Contact details for the University's Risk Management and Insurances Advisor, and other information about these matters can be found in Booklet 10 of the Griffith University-HREM.

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Commentary Inset 4 – Continued access to treatment after the end of a trial

Internationally there has been considerable debate as to whether participants in a clinical trial should continue to have access to the trialled agent after the completion of the trial. This is often referred to as expanded access.

In part this debate was prompted by the trialling in developing countries of pharmaceutical agents, where the trials resulted in medicines that are outside the financial reach, or otherwise unavailable to the participants – i.e. the resulting medicines primarily benefit the residents of developed world countries. Essentially this is an ethical question with regards to the ethical principles of justice and beneficence (i.e. the flow of the longer term benefits not going to the participants, or indeed the participant community).

The WMO's Declaration of Helsinki indicates that trialled therapeutic goods should, in most circumstances, be made available to participants of a trial after the completion of that trial. This standard is reflected in the Guidelines for Good Clinical Practice (CPMP/ICH/135/95).

In its adoption of the international guidelines, the TGA and the NHMRC have elected to direct only that participants must be informed whether they will have continued access to the trialled agent, not that continued access is a requirement.

Even though it is not a requirement for Australian clinical trials, Griffith University researchers are urged to consider making an agent available to participants after the completion of a trial. This should be considered an aspirational standard, as it is accepted that such a provision may simply be cost prohibitive.

Furthermore there are a number of ethical and regulatory requirements with regards to the continued supply:

i) does the team still possess the expertise, and access to the necessary resources, to continue to offer the intervention;

ii) is there a strong justification for the belief that the continued access to the agent is in the best interests of the participant(s);

ii) if the recipients need to be monitored (e.g. for an adverse reaction that might emerge later) are there are appropriate persons/resources available;

iii) approval for the continued supply must be obtained (e.g. TGA Special Access Scheme or Authorised Prescriber scheme); and

iv) how any costs associated with the above will be met

6.0 Human research ethics review

In addition to Griffith University's standard research ethics review arrangements (which are described in) and additional arrangements for clinical research (see 5 of Booklet 12 of this Manual), additional standards apply for the research ethics review of clinical trials

The role of HRECs in the research ethics review of proposed clinical trials is outlined by the TGA Act and arrangements and is described in the Australian clinical trial handbook. The role of HRECs applies to CTN and CTA situations. In summary, the role of HRECs includes:

1. (For trials being reviewed under the CTN scheme) The reviewing HREC considers scientific validity of the trial design and the safety and efficacy of the medicine or device as well as the ethical acceptability of the trial process.

2. (For trials being reviewed under the CTA scheme) The TGA reviews summary data about the therapeutic good. The TGA then provides comment to the HREC about the product. The TGA will indicate the minimum information which must be provided to the reviewing HREC.

a. The HREC in each host institution/organisation is responsible for approving the proposed trial protocol. The committee(s) must review the summary information from the sponsor and the investigator as well as any additional comments from the TGA. The HREC is also able to request any additional information they believe is necessary to undertake review of the proposed trial.

3. In addition to the TGA requirements and guidelines, the *National Statement* must be the basis of a HREC's review of a proposed trial.

4. The HREC also needs to be aware of any relevant State and Territory laws that pertain to the supply of therapeutic goods or to issues otherwise relating to a clinical trial proposal.

5. An issue to be considered during the review of a proposed trial is what mechanisms are proposed for the continued access to treatments which have been found to be effective and where long-term therapy would be appropriate following completion of the trial.

6. In the event the GUHREC believes itself unable to review the proposed trial, the Committee may recommend that review be conducted by an HREC that has been certified to review clinical trials.

Commentary Inset 6 – Sufficient resources/expertise

It is often the case when the Griffith University HREC reviews and clears a clinical trial that the ethics clearance was based very much upon the experience of specific members of the research team, access to specific resources and facilities, and there being sufficient funds to conduct the trial as described in the submitted documentation.

These factors can sometimes change in one of the below ways:

i) a key member of the research team leaves the trial, has other commitments that mean they can no longer be directly involved in the active elements of the trial, or they move to a more distant location;

ii) some of the resources, equipment or facilities described in the approved protocol are no longer available or at least not readily available; or

iii) the expected funds are no longer available, perhaps placing pressure on the team to abridge some elements of the trial.

As per 9.0 such changes may warrant the research team suspending the project and consulting with the Research Ethics Office.

Hopefully in its review decision the Griffith University HREC will have indicated whether the clearance was particularly dependent upon the three matters discussed above (expertise, resources and funds).

Even if the Griffith University HREC did not alert the team to such a condition on its ethics clearance and/or the team believe the trial can still be conducted, the Griffith University researchers must alert the Research Ethics Office of any change and provide a response to the following:

i) despite the changes do the researchers believe that the trial still be conducted as per the approved protocol;

ii) what changes need to be made to the ethics clearance to reflect the changes to personnel/resources/funds;

iii) do the changes introduce any new, or compound any existing, risks or ethical sensitivities associated with the trial; and

iv) is there any reason to believe that the trial will no longer successfully, safely and appropriate reach the approved objectives/end points of the trial?

The Research Ethics Office will advise whether the trial needs to be suspended while the Griffith University HREC is consulted. ***If there are significant concerns about the impacts of the changes the applicants may be asked to submit the updated trial for a new research ethics review.***

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7.0 Clinical trials and the principles of ethical conduct

The *National Statement* describes the four principles of ethical conduct in human research: merit and integrity; justice; beneficence; and respect for persons. These principles are the basis on which the design, conduct and reporting of a human research project should be judged.

Booklet 1 of the Griffith University-HREM introduces Griffith University's approach to these principles. Subsequent booklets provide more detailed guidance on the principles and their application to specific methodologies, participants and contexts.

Chapter 3.1 of the *National Statement* contains references to the considerations for the four principles with regards to clinical trials. In summary, it provides the following guidance:

7.1 Research merit and integrity

Provisions 3.1.4 to 3.1.6 of the *National Statement* expand upon the general ethical principle of 'research merit and integrity'. At 7.0 of Booklet 12, the Griffith University-HREM discusses all the expectations for clinical research (including clinical trials).

There are several international standards in use for guiding the development of clinical trial protocols including but not limited to the SPIRIT Statement. The reviewing HREC will need to be confident the team for a proposed HREC includes researchers with all the relevant expertise/training (where the University is the trial sponsor).

When planning a trial, the sponsor must ensure there is sufficient safety and efficacy data (e.g. from non-clinical studies, previous clinical studies) to justify specifics of the trial protocol (e.g. the dosage of the pharmaceutical agent under investigation). Such documentation will almost certainly be important for the research ethics review of the proposed trial. This requirement can be found in both Australian and international guidance material (e.g. see part 5.12.1 of the *Guideline for GCP*).

Commentary Inset 7 – Describing risks compared to their current/usual treatment

To best inform the decision made by potential participants, the risks of the trial should be presented relative to either their current treatment (if any) or the usual treatment for their medical circumstance.

As much as possible this must be presented in lay terms or where technical language is required, the technical terms must be explained.

A similar approach must be taken in the application for ethics clearance, though because of their technical role, the language used in the investigator brochure and clinical trial protocol is unlikely to be in lay terms

The Investigator Brochure is a key document for the design, research ethics review, conduct (of both the clinical and research dimensions of the work) and sometimes the reporting of a clinical trial. Considerable guidance on the objectives, role, language, structure and content of investigator brochures are available (see part 7 of the *Guideline for GCP*). **The GUHREC will not review a proposed trial unless the investigator brochure is provided with the application for research ethics review.**

The investigators must provide the ethics reviewers with full details about all the financial arrangements for the trial (including funding received/sought, payments to the investigators, any limitations on the publication of the results, how any perceived conflicts of interest will be addressed, and what information about these arrangements will be shared with potential participants, etc.).

7.2 Justice

Provisions 3.1.13 – 3.1.16 of the *National Statement* expand upon the general ethical principle of 'justice'. At 9.0 of Booklet 12, the Griffith University-HREM discusses the justice expectations (specifically relating to inclusion and exclusion of potential participants) for clinical research (including clinical trials).

7.3 Beneficence

Provision 3.1.38 of the *National Statement* expands upon the general ethical principle of 'beneficence'. At 11.0 of Booklet 12, the Griffith University-HREM discusses the expectations for clinical research (including clinical trials).

In addition, sections 3.1.4 (c) and (d) of the *National Statement* indicate:

> (c) where patient care is combined with intent to contribute to knowledge, that any risks of participation should be justified by potential benefits to which the participants attach significance. The prospect of benefit from research participation should not be exaggerated, either to justify to the reviewing body a higher risk than that involved in the participant's current treatment or to persuade a participant to accept that higher risk;
>
> (d) whether the intervention or other research procedures are without likely benefit to participants. For such research to be ethically acceptable, any known or emerging risks to the participants must not be greater than the risks that would be associated with the health condition and its usual care.

Commentary Inset 8 – Follow up testing

The risk management strategies for a trial can sometimes involve periodic review and testing of participants.

For example – Every two weeks during the trial participants will attend the clinic for blood to be drawn and a general health review to be conducted. These visits have the dual purpose of evaluating the response of the participants to the therapeutic agent and also to check for known/new side effects. After the completion of the trial the participants will be reviewed every six weeks for the next eight months.

Potential participants need to be forewarned of the need for and nature of monitoring, the frequency and location of the monitoring, and the time commitment required. This should be explained in the consent materials and in the discussion between the potential participants and the research team.

In addition to any burden on the time and discomfort associated with the monitoring, there may also be costs (e.g. travel costs and parking). Any testing itself may have costs. The research team must carefully consider how these costs will be covered and what out-of-pocket expenses the participants themselves will bear.

It is worth noting that the parking cost at some hospitals is very high and the frequency of visits can represent a not insignificant cost for participants.

It is understood that any tests for research purposes should not be billed to Medicare and the cost otherwise covered (e.g. by the sponsor).

Once again potential participants must be forewarned of whether costs will be met and whether there are any costs they will be expected to cover.

When describing the use of placebo in clinical trials, section 3.1.5 states:

Where current and available treatments are known or widely believed to be effective and/or there is known risk of significant harm in the absence of treatment, placebo or non-treatment groups are not ethically acceptable. Non-treatment (including placebo alone) groups may only be used:

> (a) where the existing standard of care comprises or includes the absence of treatment (of the type being evaluated); or
>
> (b) where there is evidence that the harms and/or burdens of an existing standard treatment exceed the benefits of the treatment.

See Booklet 9 of the Griffith University-HREM for more about benefits, risks and beneficence in human research.

7.4 Respect for persons

Provisions 3.1.17, 3.1.21, 3.1.22 and 3.1.23 – 3.1.39 of the *National Statement* expand upon the general ethical principle of 'respect for persons'. As with any research project the current version of the consent material must be provided to the reviewing HREC, with dated and version-numbered copies provided for

any proposed variation to the clinical trial protocol and/or ethics approval. Refer to 14.0 of Booklet 22 of the Griffith University-HREM for more about the required features of consent materials and Booklet 6 of the Griffith University-HREM for more about variations. A copy of the signed and dated consent form must be provided back to each participant (or legal representative), as well as any subsequent update to the materials.

A matter for important consent materials/processes for clinical trials is ensuring that participants understand:

- whether after the completion of their involvement in the trial they will continue to receive the drug, use of the device, or access to the other interventions being trialled;
- if there will need to be follow up tests or monitoring after the completion of their involvement in the trial (including when, where and how the monitoring will occur and who will pay for the follow up) ; and
- whether there could be any side effects or other negative consequences if they discontinue their involvement in the trial early.

At 11.0 of Booklet 12, the Griffith University-HREM discusses all the expectations for clinical research (including clinical trials).

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Commentary Inset 9 – Implications of withdrawal

The standard expectation for human research is that participant should be able to withdraw their consent at any time "without comment or penalty".

In practice withdrawal from a clinical trial can sometimes be more complicated.

Issue one: *Sometimes immediately ceasing taking a pharmaceutical agent/the removal of a medical device could be the source of symptoms or risks. Consequently, there may need to a phased or gradual withdrawal from the trial.*

Issue two: *Further to the above, the risks and implications of withdrawal are so serious that participants simply cannot cease their involvement*

Issue three: *It can some times be the case that withdrawal from the trial could require a medical procedure (e.g. to remove the device) or shifting over to the ordinary treatment.*

Issue four: *It may be necessary to monitor persons who withdraw for some time to identify and treat any negative reactions to the withdrawal.*

Any of the above matters that apply to a trial must be discussed in the consent material and discussed with an individual who advises they wish to withdraw from a trial.

8.0 Documents and record keeping

The *National Statement* and the Guideline for GCP indicate the required documentation for clinical trials and the records that must be retained for each trial. The specific requirements for record retention are described in the Clinical Trial Standard Operating Procedures (SOPs) of Griffith University and all Health Services are required to have these as part of compliance with the National Clinical Trials Governance Framework.

In accordance with section 3.1.45 of the *National Statement* researchers must develop a data management plan for the durable, safe, secure and appropriate storage of trial data. For some trials this may require the storage of materials that are derived from biological matter. Where there is some uncertainty with regards to the long-term effect of a therapeutic good, appropriate contact details should be maintained in case there is a matter or diagnostic, clinical or other therapeutic significance to participants (whether individually or as a group). In most cases this possibility should be discussed with potential participants (e.g. as an element of the trial's consent materials) and the view of participants should be sought as to whether they wish to be contacted in the future about such matters.

In instances where a clinical trial will be utilising electronic records, as per part 5.5.3 of the *Guideline for GCP* the sponsor of the trial must establish appropriate standard operating procedures, processes and systems to: validate access, track changes, uniquely identify records that relate to an individual trial subject and to prevent unauthorised changes to those records.

Part 5.5 of the *Guideline for GCP* also specifies the responsibilities and necessary actions for sponsors with regards to trial records (e.g. retention after a sponsor ends their involvement in a trial, and notification if an investigator is removed from a trial for some reason).

When requested, the investigators/institution, as well as the sponsor, must make a full and up to date copy of the documentation available to the GUHREC and other trial site HRECs (as appropriate), as well as to the monitor, auditor and regulatory board must be able to request and access a full copy of all the trial documentation. For this reason, the consent materials provided to potential participants must anticipate the identified records may be accessed for quality assurance, audit or other regulatory purposes.

Commentary Inset 11 – Who pays for the monitoring after the cessation of a trial?

If a trial has been terminated early, and it has been determined that the monitoring of at least some of the participants is required (see Commentary Inset 10), the important question of who pays for this monitoring must be determined.

The consultations, testing and response to any identified problems could be expensive and extend over a period of time.

Generally, the sponsor should provide resources to enable the monitoring to occur.

This question may come down to a technical interpretation of the clinical trial contract/agreement and also involve matters of law. If it appears a clinical trial will be terminated early, the chief investigator should consult with Griffith Enterprise or the Research Ethics Office (as relevant to the funding arrangements for the trial).

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9.0 Clinical trial registration

Clinical trial registers play an extremely important role in the governance and excellence in conduct of clinical trials. They are a public listing of current and previous clinical trials, listing the scientific and safety data about individual trials.

Since 2005 many medical journals require that, before accepting an article about a clinical trial, that trial must have been included in a World Health Organisation recognised clinical trial register. Paragraph 3.1.7 of the *National Statement* specifies that before commencing the clinical phase of a trial the researchers must ensure that the trial appears in a publicly accessible registry. In most cases the sponsor will register the trial (especially when it is a multisite trial). Further commentary about the role and value of clinical trial registers can be found at the Australian Clinical Trials website.

Commentary Inset 12 – Referring participants to sources of support following the early cessation of a trial

If a trial has been terminated early the research team should make a participant-by-participant assessment of whether any individuals need to be referred to specific sources of care/advice/support.

This assessment should be based upon such matters as the needs of individual participants, their location, cost and urgency.

If the team cannot formally refer the individuals to the source of care/advice/support they may still wish to urge participants to consult the identified provider. The team may also need to prepare information for the provider to enable them to better assist the participant.

Where the participant may encounter costs associated with consulting the identified provider these may need to be factored into the matters discussed at Commentary Inset 11.

Even if the decision is made that individual participants, or the entire participant cohort, does not need to be referred to a source of care/advice/support the research team should consider whether to produce a letter about the trial for the individual participants to provide when they later consult with a health professional.

Covering trials for Australia and New Zealand (or conducted by investigators from those countries), the ANZCTR is a publicly owned register that is operated by a non-government and not-for-profit body. The ANZCTR is free to use, funded by the NHMRC and located at http://www.anzctr.org.au/Default.aspx.

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10.0 Multisite clinical trials

Some clinical trials require recruitment from two or more sites to be able to meet their objectives. This can involve including sites across many jurisdictions – including locations outside of Australia.

For the most part Griffith University will only be involved in multisite clinical trials with one of four sets of circumstances:

1. Griffith University is the lead institution (trial sponsor) and its staff are conducting the trial procedures at each of the sites;

2. Griffith University is the lead institution (trial sponsor), but other investigators will be conducting the trial procedures at the other sites under a Clinical Trial Research Agreement (CTRA);

3. Griffith University researchers are conducting the trial at one site, but another institution is the trial sponsor (and there may also be multiple other sites); or

4. Griffith University is conducting only one element of the trial (e.g. the analysis of samples), another institution is the trial sponsor (and there may also be multiple other sites).

Commentary Inset 13 – Correspondence to participants following the early cessation of a trial

Having decided that a trial should be terminated early, and having consulted the Griffith University HREC, the team must determine the arrangements with regards to:

Continued access to the trial agent/intervention (Commentary 4)

The monitoring of participants (Commentary 10)

The arrangements with regards to covering the costs (Commentary 11)

Whether participants need to be referred to a source of care/advice/support (Commentary 12)

Participants must then be sent correspondence detailing the arrangements with regards to the above.

This correspondence should outline the reasons for the early cessation of the trial.

If some participants are being referred to a source of care/advice/support different correspondence and attachments may need to be sent to those participants. Similarly, if all participants are being urged to consult a health professional an advisory letter for the professional may have to be included.

The correspondence should also provide details for a telephone contact point for the participant to discuss/arrange a meeting to discuss their personal situation and the implications of the early cessation of the trial and what arrangements that have been made.

In recent decades there has been considerable commentary in the academic, clinical and popular press about the poor experience of investigators and sponsors in their treatment by the research ethics review and governance for multisite trials. This has pointed to delays, lost opportunities, inefficiencies and frustrations when the same trial is reviewed numerous times with sometimes very different, and even conflicting, review feedback.

Although the 1999 version of the National Statement expressly permitted single ethics review for multicentre research, Chapter 5.3 of the *National Statement* (2007) made it more clear that institutions should not duplicate ethics review . In 2011, the Harmonisation of Multisite Research Ethics Review (HoMER) program was formally launched, which resulted in the *National Approach* to research (especially clinical trials) that are conducted across multiple sites. This has seen the certification of a subset

(about 40) of experienced HRECs that are to conduct the lead review for multisite clinical research with the other sites accepting that lead review and only conducting a governance review for their component of the project.

More recently, the National Mutual Acceptance scheme has seen most Australian states and territories agree to a memorandum of understanding that provides for single ethics review of multisite and multi-jurisdictional clinical trials. Current information about the operation of this scheme is at NMA. The Griffith University HREC was not recognised as an NMA-certified HREC (as of September 2021). For clinical trials that are going to be conducted as multicentre studies it is strongly advised that an NMA HREC be used for the human ethics review and not the Griffith University HREC.

For more about Griffith University's approach to multisite clinical trials refer to Booklet 8 of the Griffith University-HREM.

11.0 Griffith University as a clinical trial site

Griffith University clinical trials are conducted (a) in a Griffith University facility; (b) at another site (e.g. a hospital); or (c) where only an element of a trial will be conducted at Griffith University (e.g. exercise testing of trial participants at a University lab).

At 13.0 of Booklet 12, the Griffith University-HREM discusses common ethical issues in clinical research. Most of these are especially relevant to clinical trials where Griffith University is a site (e.g. Screening – Necessary Expertise).

When Griffith University is a site for a trial, or indeed if only some testing will occur at a University facility, we have increased responsibilities with regards to the safe, ethical and appropriate conduct of the trial. The University also has a direct duty of care to the trial participants.

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Commentary Inset 14 – Wait-listed participants and the early cessation of a trial

The design of some clinical trials can have a comparative component. Some examples include:

i) the first trialled intervention is being compared to another trialled intervention;

ii) the trialled component is to be compared to the standard treatment;

iii) the trialled component will be compared to placebo.

As was noted in parts 14 and 15 of Booklet 12 of the Griffith University-REM, special ethical guidelines and considerations can apply to such research designs.

A common strategy for research involving such comparisons is to wait-list those participants who have not received the trialled intervention.

For example – A trial involves a comparison between the standard treatment for a muscular injury and a new treatment protocol. Participants are randomly assigned to either the standard treatment or the new treatment. After the 'control' participants have received the standard intervention, and the trialled intervention is deemed superior, those participants will later receive the trialled intervention. Whilst not always possible, such wait-listing ensures that a group of participants are not denied an important benefit of the trial.

Even though such a design is valid, and in many cases ethically important to ensure 'control participants' are not penalised, this can introduce additional complications if a trial is terminated early.

Depending upon when a trial ceases, it may be that the control participants have not yet been offered the trial intervention but the results indicate that the trial intervention is preferable to the standard treatment.

There are obviously a large range of variables, combinations and considerations in this situation, ranging from:

i) the trial is being terminated because the trialled intervention is clearly better than the standard treatment; through to; and

ii) the trial cannot be continued because the researchers with the necessary expertise/necessary resources are no longer available.

When it is feasible, safe and appropriate, it may be possible to continue to conduct the trial until the wait-list group receive the trialled intervention (see Commentary 4). In other cases where this is not possible those participants may need to be referred to other sources of treatment (see Commentary 12).

The researchers must consult with the Griffith University HREC with regards to the approach that will be taken for the wait-listed participants.

Following their consultation with the ethics committee the team may need to advise/consult with the sponsor of the trial and the regulator.

The researcher must then advise the wait-listed participants of if, when and how they are to be offered access to the trialled intervention. Those participants may consider it a breach of faith if they are not offered access to the trialled intervention

12.0 Monitoring of clinical trials

The *National Statement (Chapter 5.5)* discusses the monitoring requirements for all human research (including clinical trials). The University's implementation of these requirements can be found in Booklet 5 of the Griffith University-HREM. In addition to the standards articulated by the *National Statement* the NHMRC provides further direction with regards to the monitoring of clinical trials.

The responsibilities of the trial sponsor are extensive, and they should ensure that a trial is appropriately monitored for safety and for data integrity in accordance with the National Statement and Guideline for GCP. Before initiating a trial, the trial sponsor should ensure that quality management systems are in place and that these systems are robust enough to fulfil all GCP and regulatory requirements, including relevant state and territory legislation. For example, when designing a trial, the Guideline for GCP requires trial sponsors to use a multi-disciplinary team of qualified individuals (for example, biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and case report forms to analysing and preparing interim and final clinical trial reports.

When planning a clinical trial, trial sponsors should have processes in place to ensure the risks associated with its conduct are identified and assessed so that adequate trial monitoring and management plans can be developed to mitigate risk that may adversely impact on trial quality or participant safety. The NHMRC guidance on Risk based Management and Monitoring of Clinical Trials Involving Therapeutic Goods provides further information on the implementation of risk based management and monitoring plans.

To ensure there is appropriate safety oversight, trial sponsors should generally use an independent committee or independent individuals. A Data Safety Monitoring Board (DSMB) may be convened based on the potential risks and benefits to participants associated with the trial and the trial design. The NHMRC guidance on Data Safety Monitoring Boards (DSMBs) provides advice on the use of DSMBs. Processes for the monitoring and reporting of adverse events in clinical trials involving therapeutic goods is described in the NHMRC Guidance on Safety monitoring and reporting in clinical trials involving therapeutic goods. Trials not involving therapeutic goods should still refer to these guidelines. Regulators have recognised the need to take approaches to monitoring that adjust for the potential risks involved. The European Union has published Risk proportionate approaches in clinical trials and the NHMRC provides specific guidance on Risk-based Management and Monitoring of Clinical Trials involving Therapeutic Goods. All proposed monitoring processes must be approved by the reviewing HREC.

12.1 Serious Adverse Events (SAEs)

On 25 February 2022 Griffith University introduced a Standard Operating Procedure for the timely reporting and the governance of SAEs in clinical trials. This applies to all trials conducted under the aruspices of Griffith University.

Following the approval of the SAE Standard Operating Procedures, on 30 June 2021, Griffith University introduced a standard operating procedure on the reporting of SAEs to Human Research Ethics Committees, particularly the HREC that conducted the lead review of a trial.

12.2 Expected side effects/harms

Clinical trials often involve people who have existing health problems and in settings in which the existing standards of care result in side effects. Where trials involving comparisons are added to existing therapies it is important to understand how this will create additional risk of harmful side effects. Where treatments have undergone extensive testing through pre-clinical means or through prior use there will be knowledge about the likelihood of any potentially harmful side-effects. All of these should be described in the protocol and a clear plan of how to provide the information to potential participants provided as well as how the risks will be managed. The protocol should outline the expected frequency and severity of any of these

expected side effects and outline how these will be evaluated by the DSMB to ensure that the trial is not observing a higher frequency or severity of any of the expected side effects. A plan for early termination of the trial or adjustment of the intervention should be clearly outlined.

12.3 Unexpected side effects/harms

If unexpected side effects/harms arise during the conduct of a trial these should be evaluated by the DSMB or relevant body approved by the HREC and a determination made as to whether or not the trial should be suspended, at least temporarily. If this occurs the trial may resume when appropriate strategies are in place to address the side effects/harms. The clinical trial protocol and ethics approval may need to be varied to incorporate the new strategies.

Refer to Booklet 6 of the Griffith University-HREM for further information about variations and Booklet 9 for more about risks in human research.

12.4 Worse than existing/standard/validated treatment

An important researcher responsibility during the conduct of a trial is to continue to make comparison between the intervention/agent/device being tested and the existing, standard or validated treatment available. This is ideally performed by an independent DSMB working on pre-specified parameters. There should be a clear plan for early termination if there is clear futility of the intervention. The details of how this is to be managed must be outlined in the protocol and be approved by the HREC.

Refer to Booklet 3 of the Griffith University-HREM for more about the responsibilities of researchers.

12.5 Logistical change

In nearly all cases, the ethics approval for a trial will be very much based upon the expertise of members of the research team, access to correctly calibrated equipment and/or other logistical matters. If there is a change to any of these factors the research team must place the progress of the project on hold while they consult with HREC. Sometimes a project may need to be abandoned, or at least suspended for a period, while appropriate new arrangements can be made (e.g. the appointment of new specialist investigators).

Refer to Booklet 6 of the Griffith University-HREM for more about variations to active projects.

12.6 Significant Deviations

In the event the GUHREC or another review body of a project becomes aware that the conduct of a project has deviated from the approved clinical protocol the ethics approval for the project may be suspended or revoked. Such a finding may be considered research misconduct with potentially serious consequences. Refer to Booklet 7 of the Griffith University-HREM for more about the review of alleged breaches of ethics approvals.

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13.0 Cessation of trials

Clinical trials can be discontinued for several reasons (see below). The guidance material issued by the TGA outline the steps that must be followed/issues to consider if a trial is discontinued.

Typical reasons for the discontinuation of a trial include, but are not limited to the following:

1. the trial is complete, having collected the required data/answered the research questions/achieved the approved objectives of the work;

2. there have been, or will be significant deviations from the approved trial protocol;

3. unexpected side effects/harms have arisen, or expected side effects/harms are occurring more often or at greater severity than was expected;

4. as the trial progresses it appears that the treatment/intervention being tested is much worse than existing/standard/validated treatment;

5. as the trial progresses it appears that the treatment/intervention being tested is much better/much worse than one of the others being tested; and

6. a change in the availability of a key investigator, equipment or some other logistical change means that it is no longer possible to conduct the trial.

Whenever a trial ends/is ceased, or is suspended for any length of time, the trial investigators should consider:

1. whether it is possible to continue to make available an intervention, pharmacological agent, device after the trial;

2. whether it is necessary to continue to monitor participants (e.g. for adverse reactions) beyond the cessation of the trial;

3. if there are any costs associated with the two points above, how will these costs be managed, and

4. whether it is necessary to refer participants, or encourage participants to consult, a health professional for care/advice/support.

In accordance with the Declaration of Helsinki "*sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.*" (*Post-Trial Provisions* 34). This would normally be done as an open label extension study (described within the original clinical trial protocol) as a separate trial (with its own CTN number) or under the Special Access Scheme (see 4.3 of this Booklet).

The researchers must consult with the GUHREC with regards to their plans with regards to the above. Once a strategy with regards to these matters has been finalised, correspondence about the arrangements should be sent to all current participants (including former participants who are currently being monitored). If a trial includes a wait-list component special consideration will need to be given to the implications of the early cessation of the trial to any participants that are currently in the wait-list cohort .

The trial data, records and documents must be retained as per the retention schedule appended to the Griffith University Schedule of Retention Periods for Research Data and Primary Materials.

13.1 Trial complete

The researcher(s) may consider a trial to be complete when sufficient data has been collected, the end points described in the trial have been reached or the approved research questions/objectives have been reached. In most cases this is likely to occur at the originally stated completion date. There can however be cases where a trial is completed sooner than anticipated (e.g. because participants who met the inclusionary criteria for the research were recruited much faster than expected).

There may be compelling reasons for every effort to be made to complete the trial as soon as possible (e.g. the potential for serious harms means that as soon as the required data has been collected the trial should be concluded, even if this happens earlier than anticipated).

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14.0 Reporting of results

Arguably a clinical trial (or indeed any human research) is not truly complete until the result of the work has been published. This contribution to the body of academic and clinical knowledge is important because it can inform the conduct of further research and clinical practice (e.g. with regards to the efficacy and safety of a therapeutic agent).

For this reason, Griffith University researchers are urged to publish the results of a trial, even if those results are not what was anticipated/positive. Despite the above, it is acknowledged that a sponsor/funding body of a clinical trial can have a valid commercial or other stake in the timing and the nature of the reporting of a trial. Those interests should not ordinarily dictate whether results are published or the conclusions that the publication draws from the trial.

When negotiating an agreement/contract for a clinical trial, Griffith University researchers should endeavour to retain academic freedom with regards to publications arising from the work. When publishing the results of a trial there should be a clear statement of whether the work was commercially funded.

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Commentary Inset 15 – The ethical and responsible reporting of a trial

One of the key societal benefits of a clinical trial is when the results are added to the body of scientific and clinical trial, where the understanding of the efficacy and safety of an intervention is made available to other researchers, clinicians and other health professionals, and to wider members of society.

Related to this is the degree to which, once published, researchers are aware whether a planned trial has been conducted before elsewhere, the experience with regards to matters such as risks and benefits, and whether there is a justifiable need for a new trial.

This is why academic freedom in the publication of results is so important, even if the results do not reflect favourably on a trialled intervention (indeed arguably the publication of negative results is incredibly important).

Commentary in recent years (see at Hudson & Collins, Sharing the results of Clinical trials suggested that a large proportion of the published results of commercially funded clinically trials report favourable results and very few reflect poorly on the trialled intervention.

For the reasons stated above, this situation is not considered optimal.

This why Griffith University researchers, when negotiating the contract/agreement for a commercially sponsored clinical trial, are urged to pursue publication/reporting provisions that do not preclude the reporting of results that might not reflect positively upon the trialled intervention.

15.0 Glossary

ANZCTR – Australia and New Zealand Clinical Trial Register is a WMA approved, free to use, publicly accessible clinical trial register which is operated by a not-for-profit and non-government organisation.

ARTG – The Australia Register of Therapeutic Goods is a list of therapeutic goods (pharmaceutical agents and medical devices) approved for use in Australia. Goods that are not approved for therapeutic use can only be used if one of the exemptions described in the *Therapeutic Goods Act* 1989 is obtained.

CTN – Clinical Trial Notification scheme

CTA – Clinical Trial Exemption scheme

Investigator – The TGA guidance material, and the international material on which they are based, use the term investigator rather than researcher (which is the term used in the *National Statement* and Griffith University-HREM). It is considered that this distinction is just a case of preference, rather than indicating a slight difference in meaning.

Investigator Brochure – An important document for each clinical trial that is produced by the trial sponsor. It contains a description of the therapeutic agent for the trial, risks and safety information, and other technical information about the trial.

TGA – The Therapeutic Goods Administration is the Australian statutory body with responsibility for the governance of Australian clinical trials.

Trial Protocol – Another important document that describes in detail matters such as: the intended participant pool; recruitment procedure including any screening procedures and exclusionary criteria; the actual testing/clinical/data collection procedures; the strategies for the negation/minimisation/management of risks; and the trial end points, including criteria for the early cessation of the participation of individuals.

Sponsor – The sponsor is the individual, group, company, institution or body that takes overall responsibility for the conduct of the clinical trial. For commercially funded trials this will typically be the pharmaceutical company that has commissioned the trial. The sponsor is usually responsible for arranging the relevant regulatory requirements, coordinating between sites for multisite trials, and carries the medico-legal responsibility associated with the conduct of the trial. In instances where a Griffith University researcher initiates and organises a trial (eg. For grant-funded trials), Griffith University is defined as the sponsor of the trial and will be responsible for the sponsor's functions (i.e. it is the researcher, rather than Griffith University, who is the sponsor). This may also include circumstances where another party (usually a pharmaceutical company) provides the medicinal product used in the clinical trial but where that third party has no other involvement in the design or conduct of the trial.

WMA – The World Medical Association is the international body that released and updates the Declaration of Helsinki.

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16.0 Further reading

Throughout this Manual are references to the clinical research policies and resources produced or required by the TGA. These are important reference point for clinical trials. Researchers are also urged to consult the booklets of the Griffith University-HREM that are relevant to their needs. Researchers must be aware of the relevant legislation that applies in the jurisdiction where the trial will be conducted.

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Contacts

There are a number of resources available to assist researchers formulate an appropriate response to a question or challenge about the design and/or conduct of a project. This includes the Griffith University Research Ethics Manual and the Human Research Ethics Information Sheet Series. These documents are available from the URL below.

Research students – The first point of contact for research students for advice on any research ethics matter is always your supervisors.

REAs – All academic elements of the University have been asked to appoint at least one member of academic staff as a Research Ethics Advisor. REAs are a local contact for advice, information and suggestions. The contact details of all the current REAs can be found on the URL below.

Office for Research – Staff in the Office for Research (see below) are available to advise with the process of lodging an application or other administrative matters, procedural or policy questions. However, you will be asked what advice you have sought or received already (e.g. consultation with the REA for your area).

Manager, Research Ethics and Integrity

Tel: (07) 373 54375
research-ethics@griffith.edu.au

Policy Officer, Research Ethics and Integrity

Tel: (07) 373 58043

Research Ethics Systems and Support Officer

Tel: (07) 373 5 2069

On the ethics web site you will find:

https://www.griffith.edu.au/research/research-services/research-ethics-integrity/human

- The other booklets of the *Griffith University Research Ethics Manual*
- The *Griffith University Human Research Ethics Information Sheet Series*
- Either downloadable copies of, or links to, the various application forms
- Contact information for the Research Ethics Advisers (REA) and other contacts
- Educational and other resource material
- Useful external links

Griffith University is commercialising the GUREM through licenses to other universities and research institutions. Consequently, Griffith University staff are asked not to send copies of any booklet to persons external to Griffith. For further information please contact the Office for Research (see above)