

MELBOURNE CHILDREN'S TRIALS CENTRE (MCTC)

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The author is signing to confirm the technical content of this document

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1. PURPOSE

The purpose of this document is to define the requirements for developing, amending and adhering to a clinical research protocol.

2. RESPONSIBILITY AND SCOPE

All staff at the Melbourne Children’s campus who undertake a research project – irrespective of their level of involvement in the study, or the study design - have a responsibility to ensure that the study has a protocol that contains all of the details about the study, including the justification, the design and the procedures of the study. The protocol must be approved by a Human Research Ethics Committee (HREC) and have received site specific authorisation prior to the commencement of the study, and this applies also to any subsequent modifications to the protocol. The current approved version of the protocol must be adhered to.

3. APPLICABILITY

The Principal Investigator (PI), sub-investigator(s), research coordinators and other staff delegated research-related activities by the PI.

4. PROCEDURE

4.1. Introduction and background

A protocol is the document that outlines the plan for a research project; the research project is designed to answer a specific question. The plan must be carefully designed to ensure it will answer the question of interest and will safeguard the health, safety and rights of the participants. In particular, the protocol should describe the rationale for the study, the research question and full

details of the proposed research including: the target population (inclusion and exclusion criteria); the study design (including aims, methods, objectives and how the objectives will be measured); the schedule of tests and procedures; the key elements of the statistical analysis plan; and the length of the study. For clinical trials, additional information is required (e.g. full details of the intervention and associated risks, how the different participant groups will be assigned, how efficacy and safety will be assessed, plans for oversight of the trial). The International Conference on Harmonisation Good Clinical Practice (ICH GCP) gives the following definition for a protocol: *a document that describes the objective(s), design, methodology, statistical considerations, and organisation of a clinical research study.*

A protocol allows research staff, whether at the same location or at multiple locations (in the case of a multi-site study), to carry out the study in exactly the same way (i.e. standardised), so that the data can be combined across participants and sites. The protocol also provides the study administrator(s) and local researchers a common reference document for the researchers' responsibilities during the study.

Prior to starting the study, the protocol (and other documents) must receive ethical approval from an HREC (note that an HREC can approve the study at more than one study site) and receive institutional authorisation (known as site specific authorisation). If any changes (amendments) need to be made to the protocol during the study, these must be scientifically and ethically sound; before implementation, the amendments must be approved by the HREC(s) and receive site specific authorisation.

4.2. Protocol content and design

The specific content of the protocol will vary depending on the research question, but there are common areas that must be addressed in all protocols:

- Administrative information - study title, details of authors of the protocol
- Background and rationale
- Research question
- Objectives
- Study design
- Population – selection (inclusion and exclusion criteria) & withdrawal
- Participant recruitment procedures
- Consent procedures
- Details of all study procedures
- Statistics – sample size justification & key elements of the statistical analysis plan (if needed a detailed analysis plan may be prepared separately)
- Outcomes
- Source documents
- Quality control/assurance
- Study oversight
- Ethics
- Data management

For clinical trials, additional information must be addressed and includes:

- Details of the intervention(s) (e.g. investigational drug, device or procedure) along with details of the comparators or controls
- Randomisation and blinding (where applicable)
- Assessment of safety
- Assessment of efficacy (this may not be required in very early phase clinical trials of investigational drugs or devices)
- Arrangements for trial oversight, including safety monitoring and reporting
- Quality assurance plans

See section 4.4c below for information about the protocol templates available to assist in developing protocols to ensure that each of the above sections are considered. These templates reflect the standard of protocols expected at Melbourne Children's.

Stakeholders and support

Although the protocol should be written by the study investigators and their delegates, development and final approval of a protocol involves a number of stakeholders. There is also a lot of support to be found on campus during the protocol development phase.

Supporting departments

Studies wishing to utilise the support of departments other than their own for the running of their study (e.g. pathology, pharmacy, etc.) should seek input from the relevant staff in these departments to ensure the study is feasible, and that they are willing to support the planned study. This may also involve the discussion of funding for the support required. Staff within the supporting departments at Melbourne Children's campus have significant experience in conducting research and can offer useful information for the protocol.

Statistician

Good clinical research makes extensive use of professional statistical advice. In this regard, the Clinical Epidemiology and Biostatistics Unit ([CEBU](#)) is available to provide advice and support in research design and analysis to researchers at Melbourne Children's. CEBU should be contacted early in the protocol development stage to ensure that the research question is appropriate, the study design is feasible and the proposed data analysis is appropriate. There can be varying levels of CEBU involvement in research projects, from just consultation through to the statistician being an investigator on the study – speak to CEBU about what is the most appropriate for your research project.

The Principal Investigator's line manager

The PI's line manager should be consulted prior to a protocol being written to ensure the research question aligns with the departments strategic and research priorities, and that there are sufficient resources within the department to conduct the study. Approval from the PI's line manager indicates that the department/theme can resource the study and support the study to adhere to good research practices.

Melbourne Children's Trials Centre (if the study is a clinical trial)

It is good practice to engage with the Melbourne Children's Trials Centre (MCTC) in the early stages of planning a clinical trial, ideally during the discussion of the research question. This will allow the MCTC to staff to work with you, in consultation with CEBU, to define your research question and ensure your protocol is appropriate to answer the proposed research question. The full list of support and services the MCTC offers can be found on the [MCTC](#) website. Your protocol may be endorsed by the MCTC which indicates that the senior members of the trials centre support the research project and the study design. Endorsement is looked on favourably by the RCH HREC and the RCH Foundation. Details regarding the MCTC endorsement process can be located on the [MCTC](#) website under 'Processes'.

Peer reviewer

Peer review is a key indicator of quality assurance in research and is an essential process to ensure that relevant and scientifically sound research is undertaken at Melbourne Children's. The primary purpose of the peer review is to identify technical flaws which can render the project scientifically invalid and therefore unethical. The reviewer should be independent of the project, but this person may be internal to the Melbourne Children's and may be a member of the same department. Peer reviewers cannot be co-investigators or members of the research team. Any researcher or member of staff who is asked to undertake peer review must declare any conflicts of interest relating to the project. Peer review must occur before HREC submission.

Human Research Ethics Committee (HREC)

The HREC provide independent, competent and timely review of research projects involving humans in respect of their ethical acceptability. The HREC prescribes the principles and procedures to govern research projects involving human participants, human tissue and/or personal records. All research projects require HREC approval and site specific authorisation before being conducted. See the RCH [Research Ethics and Governance](#) website for details on how to apply for this. If ethical approval is granted by a HREC other than RCH HREC, a site specific application still needs to be made to the RCH Research Governance manager and site specific authorisation must be granted before the research can commence on this campus. The RCH HREC (where it is the approving HREC) continues to provide ethical oversight during the conduct of the study; the RCH Research Ethics and Governance office provides governance oversight during the conduct of the study.

Murdoch Childrens Research Institute (MCRI)

The institution where the study is being conducted is responsible for the provision of good research governance and management practices to ensure a safe research environment. This includes having policies and processes in place to review and approve appropriate research protocols. For investigator-initiated research where there is no external sponsor for a project (such as a commercial entity or collaborative group), MCRI will act as the sponsor.

4.3. Operating Instructions

The PI, who is generally the main driver of the research project, should lead the development of the protocol based on the current literature and his/her experience, although the protocol writing may be delegated to another member of the investigator team with PI oversight. The development of the protocol should also include input from the rest of the investigator team, other members of staff

who will be responsible for the set-up and running of the study, and relevant stakeholders (which should include the study statistician or someone qualified to take on responsibility for the statistical aspects of the study). The final protocol should be approved by all members of the investigator team prior to submission to the HREC.

No study-specific procedures can begin until HREC approval and site specific authorisation have been granted for the protocol. Following authorisation, the protocol becomes the legally binding, definitive document for study conduct, evaluation and reporting. Once a protocol is approved and authorised, it is essential that the study is carried out in accordance with the details in the protocol, as the investigators have authorisation to do only the research as described in the protocol.

a. Before starting to write

The first and most essential part of writing a study protocol is to ensure that there is a clearly defined research question. This should include details of: the population under study, the exposures or intervention(s) under investigation and the main outcome(s) that will be measured, including the time at which they will be measured.

A good study question should be feasible, interesting to researchers and clinicians, novel, ethical and relevant (i.e. required). Think ahead about potential challenges (scientific, regulatory, cultural, and logistical) and consider key questions of feasibility such as:

- Is there clinical equipoise regarding the research question?
- Can enough potential participants be recruited to answer the research question?
- Are the patients and families to be involved in this study likely to find the study acceptable?

b. Writing the protocol

A protocol is a recipe that should enable anyone knowledgeable in research to conduct the study. Importantly it should be specific and sufficiently detailed to ensure that the study will be able to provide results. The first step in writing a protocol is to decide on the study design. Figure 1 outlines a range of different study designs that can be used in a research study. Clinical research is either experimental (where the investigator controls what treatment or intervention participants receive) or observational (no intervention is involved). It is often assumed that observational studies, particularly those that are retrospective (i.e. use data that are collected in the past) are not complicated and do not require a protocol. This is not the case.



Figure 1: Hierarchy of study designs. Those at the top are considered to be stronger, more robust study designs

c. Protocol templates

The Clinical Research Development Office ([CRDO](#)) website has, under the ‘Resources’ section, a range of protocol templates that provide clear instructions about what details need to be included in the various sections of a protocol, including example text. It is expected that protocols developed by staff at the Melbourne Children’s follow these templates.

The protocol templates are generic templates, hence some sub-sections and suggested text may not be appropriate for a specific study. If a section is not appropriate for your study it can be deleted.

d. HREC approval

HREC approval will only be granted to studies with protocols that are scientifically and ethically sound and include all of the relevant details regarding the conduct of the study.

A protocol that is considered inadequate will not be approved by the HREC, and queries and/or requests for changes will need to be addressed by the PI or their delegate before the study will be approved. This process can delay the commencement of the study, and can be avoided by submitting a high quality protocol in the first instance.

e. Governance/site specific authorisation

Site specific authorisation must also be sought for all studies. Site specific authorisation (also known as governance approval, or trial authorisation) is granted when the resources, study budget details, site-specific policies, and declarations from departments are deemed appropriate by the Research Governance Manager.

f. Amendments to the protocol

The PI or their delegate are required to:

- Submit any proposed amendments to the protocol to the approving HREC for approval and to the Research Governance Office for site specific authorisation. Documented approval and

authorisation must be obtained prior to implementing the amendments (except where immediate implementation is necessary to eliminate an immediate hazard to study participants).

- Inform the HREC and governance office as soon as possible of any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the study or may indicate the need for modifications to the study protocol.

4.4. Protocol compliance

The PI or their delegate are required to:

- Conduct the study in compliance with the approved and authorised protocol. Following HREC and governance approval, the protocol becomes the legally binding, definitive document for the study conduct, evaluation and reporting
- Sign the protocol, or an alternative contract, to confirm agreement with the protocol. Where there is an external sponsor for the study (see Section 4.5), the protocol should also be signed by the sponsor.
- Document any deviation from the protocol.

4.5. Externally sponsored studies

For externally sponsored studies, the protocol will generally be provided by the sponsor. It is however important that the protocol is reviewed by the person who will be responsible for the study at Melbourne Children's (the PI), and by other members of staff on campus who will be involved in the study. Prior to commencing the study, the PI should document his/her agreement with the protocol as described. As with investigator driven studies, the study should follow the approved and authorised version of the protocol at all times.

5. GLOSSARY

Good Clinical Practice (GCP): International Conference on Harmonisation: Good Clinical Practice (ICH-GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

International Conference on Harmonisation (ICH): International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigator: An individual responsible for the conduct of a clinical study at a study site and ensures that it complies with GCP guidelines. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the Principal Investigator. In this instance they may delegate tasks to other team members.

Investigator Team: The group of people responsible for the study. This will include the PI and should be a multi-disciplinary team ideally including members with clinical, research and statistical backgrounds.

National Health and Medical Research Council: (NHMRC). An independent statutory body within the portfolio of the Australian Minister for Health and Ageing responsible for allocating funding for, and directing, health and medical research, ethics and advice.

Principal Investigator (PI): The Principal Investigator is the person responsible for the overall conduct of the research project and is usually the person driving the study.

Melbourne Children's: Encompasses The Royal Children's Hospital, Murdoch Childrens Research Institute and The University of Melbourne Department of Paediatrics.

Research Governance Office/Manager: The Office or coordinated function within the Melbourne Children's which is responsible for assessing the site-specific aspects of research applications, make a recommendation to the CEO / delegate as to whether a research project should be granted authorisation at that site, and overseeing that authorised research at the site meets appropriate standards (research governance).

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Study Team: Refers to the extended group of people involved in a research study. This includes the investigator team and any additional members of staff who are involved in the set-up or conduct of the study e.g. research nurse, research assistants.

Sub / Associate investigator: Any individual member of the clinical study team designated and supervised by the investigator at a study site to perform study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows, clinical research coordinators). The PI will designate who will be nominated as Associate Investigators for that site.

Therapeutic Goods Administration (TGA): The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating therapeutic goods including medicines, medical devices, blood and blood products.

Trial: Any research project that prospectively assigns human subjects to an intervention, a concurrent comparison group or control group.

6. ACRONYMS

CEBU: Clinical Epidemiology and Biostatistics Unit

CRDO: Clinical Research Development Office

HREC: Human Research Ethics Committee

ICH-GCP: International Conference on Harmonisation: Good Clinical Practice

PI: Principal Investigator

RCH: Royal Children's Hospital, Melbourne

RCT: Randomised Controlled Trial

SOP: Standard Operating Procedure

7. REFERENCES

[CEBU](#) website for information, consultation and training

[CRDO](#) website for protocol templates and other tools, consultation and training

[MCTC](#) website for consultation, processes and facilities

[Research Ethics and Governance](#) website for investigator responsibilities, peer reviewer process, HREC and governance application details, policies and guidelines, useful internal and external links

[Research Launching Pad](#) for links to all Campus policies, procedures, templates and toolkits required for clinical research

Australian research guidelines

- National Statement on Ethical Conduct in Human Research (2007 and all updates)*
- Australian Code for the Responsible Conduct of Research (2007 and all updates)*
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) (2000) (Annotated with TGA comments)*
- NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (Nov 2016)*

* *Hyperlinks can be found on the CRDO and REG websites*