MELBOURNE CHILDREN’S TRIALS CENTRE (MCTC)

Guidance document title: Developing, amending and adhering to research protocols

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Document History

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3. Developing, amending and adhering to research protocols
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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 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, as well as for any subsequent modifications to the protocol. The current approved version of the protocol must be adhered to throughout the study.

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 which is designed to answer a specific question. The plan must be carefully designed to ensure it will answer the question of interest and to safeguard the health, safety and rights of the participants. In particular, the protocol should describe: the rationale for the study and the precise details of the study to be carried out,
including the target population; the study design; the schedule of tests, procedures, medications and dosages; the statistical analysis plan; and the length of the study. 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-centre study), to carry out the study in exactly the same way, to ensure that the data can be combined across participants and centres. The protocol also gives the study administrator(s) and local researchers a common reference document for the researchers' responsibilities during the study.

The protocol must be approved by a HREC and receive site specific authorisation prior to starting the study. The protocol needs to be well-managed throughout the life of the study. If any changes (modifications) need to be made to the protocol during the running of the study, these must be scientifically and ethically sound, and must be approved by a HREC and receive site specific authorisation before being implemented.

### 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
- Background and rationale
- Objectives
- Study design
- Population – selection & withdrawal
- Participant recruitment procedures
- Consent procedures
- Intervention(s) (where applicable)
- Randomisation and blinding (where applicable)
- Assessment of efficacy (where applicable)
- Assessment of safety (where applicable)
- Details of all study procedures
- Statistics – sample size justification & statistical analysis plan
- Outcomes
- Source documents
- Quality control/assurance
- Study oversight
- Ethics
- Data management

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 the Melbourne Children’s.
4.3. 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 that wish 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 the Melbourne Children’s 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 the Melbourne Children’s. CEBU should be contacted early in the protocol development stage as they ensure an appropriate and feasible research question is being asked, and that the study design and data analysis are appropriate. There can be varying levels of CEBU involvement in research projects from consultation to the statistician being named as an investigator on the study – speak to CEBU about what is the most appropriate for your research project.

Line manager of the Principal Investigator
The PIs 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 PIs 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 study, 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 research question posed. The full list of support and services the MCTC offers can be found on their 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 endorsement process are here.

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 the 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 needs to be made to the RCH Research Governance manager and site specific authorisation must be granted before the project can commence on Campus. The HREC and governance office also continues to provide ethical oversight, monitoring and advice 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. Where there is no external sponsor for a project (such as a commercial entity or collaborative group) the MCRI will be the sponsor.

### 4.4. 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, and other members of staff who will be responsible for the set-up and running of the study, and stakeholders mentioned above as appropriate. This 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 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. 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?
• Are there enough potential participants 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 detailed to ensure that the study will have fruitful 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 (where participants, their family or their treating clinician decides what treatment or intervention participants receives, and the investigators simply observe). 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 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 running 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, including for studies approved by a HREC other than The Royal Children’s Hospital HREC. 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. Modifications to the protocol
The PI or their delegate are required to:

- Submit any changes to the protocol for HREC and governance (site specific) review and seek documented approval and authorisation prior to implementing the changes (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.

4.5. 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 4.6), the protocol should also be signed by the sponsor.
- Document as appropriate any deviation from the protocol.

4.6. 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 the Melbourne Children’s (the PI), and by other members of staff who will be involved in the study on campus. 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 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

**RCT**: Randomised Controlled Trial

**SOP**: Standard Operating Procedure

7. **REFERENCES**

**CEBU website**
- For consultation and education

**CRDO website**
- For protocol templates, consultation and education

**REG website**
- For peer reviewer guidelines, investigator responsibilities, HREC and governance application details

**Research Launching Pad**
- For links to all Campus policies, procedures, templates and toolkits required for clinical research

**Note for guidance on Good Clinical Practice**

**Australian Code for the Responsible Conduct of Research**

**National Statement on the Ethical Conduct of Human Research**

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