

Title of procedure: **Investigators' Responsibilities in Research**

Key words: **research, responsibilities, investigator, researcher, clinical trial, HREC**

Alternative alphabetical listing: **Principal Investigators' Responsibilities, Researchers' Responsibilities**

1. Overview/procedure description

The purpose of this procedure is to outline the responsibilities of Principal Investigators conducting human research projects under approval of the Royal Children's Hospital (RCH) Human Research Ethics Committee (HREC).

The Principal Investigator (PI) of any human research project to which this procedure applies must comply with all the applicable responsibilities outlined in this document. The PI may delegate some of their responsibilities to other members of the research team, however the PI retains ultimate accountability for ensuring that their delegates are conducting these responsibilities in compliance with this procedure. Any member of the research team delegated responsibilities by the PI must be familiar with the relevant requirements outlined in this procedure and conduct their study related duties in compliance with them.

This procedure incorporates the requirements of National research guidelines (The National Statement and the Code of Conduct), the conditions of RCH HREC approval and the policies of the RCH Ethics and Research Department (ERD).

This procedure also forms a framework against which human research projects are audited by the RCH Research Governance Officer.

If a section of this procedure is not followed, the Principal Investigator should document the breach and the steps taken to resolve the issue and notify the ERD, their line manager and other people overseeing the study, as appropriate.

2. Related Policy

Research

3. Definition of Terms

Adverse Event (AE): Any untoward medical occurrence in a patient enrolled into a study regardless of its causal relationship to study treatment.

Clinical Trial: a form of human research designed to find out the effects of an intervention(s), involving allocation of participants to treatments. A clinical trial can involve testing a drug, a surgical procedure, other therapeutic procedures and devices, a preventive procedure, or a diagnostic device or procedure.

CTRA (Clinical Trial Research Agreement): an agreement between an Institution and an External Sponsor to define the terms, conditions and responsibilities associated with the conduct of a clinical trial. CTRAs must be completed on the VMIA/Medicines Australia templates.

ERD: Ethics and Research Department

External Sponsor: An individual, company, institution or organisation outside of RCH, MCRI and UoM, that takes responsibility for the initiation, management, monitoring, and/or financing of a research project. The external sponsor may be, for example, a collaborating group or a commercial entity. For projects with no external sponsor the RCH, MCRI or UoM take on the responsibility of the sponsor.

Human Research: research conducted with participants, or their data or tissue

HREC: Human Research Ethics Committee

Investigational Product (IP): a drug or device which is being tested or used as a reference in a clinical trial. This includes a product with TGA approval if it is being used or assembled (formulated or packaged) in a way different from the approved form; **or** when used for an unapproved indication; **or** when used to gain further information about an approved use.

Investigator: A researcher assigned 'Investigator' status by the Principal Investigator due to their senior role in the research project.

Line Manager: the person responsible for the PI. Line Managers have two main functions with respect to human research projects 1) promoting quality in project applications and 2) promoting accountability in researchers

MCRI: Murdoch Children's Research institute

NHMRC: National Health and Medical Research Council

Participant: a person that is the subject of the research

Principal Investigator (PI): The person primarily responsible for the conduct of the human research project. The Principal Investigator must be an RCH, MCRI or UoM employee, unless otherwise approved by the RCH HREC.

Serious Adverse Event (SAE): Adverse events (AE) are classified as serious or non-serious. Unless otherwise defined in the protocol, an SAE is defined as any AE that:

- results in death; or
- is immediately life threatening; or
- requires inpatient hospitalisation; or
- requires prolongation of existing hospitalisation; or
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs are defined as Internal & External:

External SAE: occurring in a participant under jurisdiction of another HREC

Internal SAE: occurring in a participant under the jurisdiction of the RCH HREC

Suspected Unexpected Serious Adverse Reaction (SUSAR): an SAE that is:

1) *Reaction:* meaning there is a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. That is, the relationship of the SAE to the study drug cannot be ruled out.

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

TGA: Therapeutic Goods Administration, the Australian regulatory authority (equivalent to the Food & Drug Administration (FDA) in the US)

VMIA: Victorian Managed Insurance Authority, the Insurance agency for the RCH & MCRI.

4. Procedure details

4.1 CONDUCT

It is the responsibility of the Principal Investigator (PI), or their delegate/s, to:

- 4.1.1 Comply with the *RCH Procedure: Informed Consent in Research*, if the project involves informed consent.
- 4.1.2 Ensure that each new project submitted to the RCH HREC has:
 - A finalised protocol
 - A complete application, and
 - Undergone peer review prior to submission.
- 4.1.3 Possess, prior to study commencement, a written HREC approval certificate endorsing the current study protocol as well as any patient or parent information and consent documents to be used in the study.
- 4.1.4 Have received HREC approval for all public advertising material and all other written information to be given to participants or potential participants, prior to the use or distribution of the material.
- 4.1.5 Disclose the existence of any financial interest and any other potential conflict of interest of any of the investigators to the ERD, in writing, in the initial application for project approval, and as conflicts of interest arise, as applicable.
- 4.1.6 Have mechanisms in place to deal adequately with any harms that may occur.
- 4.1.7 Submit an *Annual Report* to the ERD within one month of the anniversary of the original approval date for the study. Note: *Annual Reports* are not required for projects considered 'Negligible Risk'.
- 4.1.8 Submit an application for renewal of ethics approval to the HREC, if there is an intention to continue the project beyond the approval period granted. It is the responsibility of the Principal Investigator to ensure that ethics approval remains current for the entire duration of the research project; ethics approval must not lapse, even during periods of inactivity.
- 4.1.9 Notify the ERD of any changes to the study personnel, including the line manager. Note: If an investigator is added or removed from the study team, a completed *Change of Investigator Form* must be submitted to the ERD. If the study PI changes, the outgoing PI is required to sign the *Change of Investigator Form* in addition to the new PI. Any other study personnel changes may be notified via email.
- 4.1.10 Submit, for HREC review, an application for a proposed modification to an approved study, if any changes are to be made to the approved study. HREC approval must be obtained prior to the implementation of the change. Such changes may include, but are not limited to:
 - Changes to the protocol
 - Changes in recruitment strategies
 - Changes to Information Statements and Consent Forms
 - Changes to (or additional) letters, advertisements or questionnaires that will be read by participants or potential participants.

Note that if the only proposed change to the study is a change of investigator, an application for a proposed modification is not required. Instead, a *Change of Investigator Form* must be submitted (see 4.1.6).

4.1.11 Conduct the study according to the most recently approved version of the protocol. This includes (where applicable):

- Recruiting the number of participants as per the approved application (a modification should be submitted if this number changes)
- Ensuring all participants meet the eligibility criteria
- Following all procedures as outlined
- Projects must not run longer than specified without an extension of approval granted by HREC

Failure to conduct research according to a current ethically approved protocol risks researchers' legal indemnity, right to publication and opportunity to seek future funding.

4.1.12 Report to the ERD departures from the protocol that have any significant potential impact on one or more of the following:

- the ethical acceptability of the study;
- the integrity of the results;
- the safety of the participants.

4.1.13 Ensure that their research continues to be ethically acceptable. If, at any stage of the research a researcher judges that the level of risk in a research project is not justified by the benefits, they should submit an appropriate study modification for HREC approval if they wish to continue the project.

4.1.14 Report to the ERD, in a timely fashion, any incident associated with a study participant that may result in a claim against the hospital, within 72 hours of occurrence or investigators first knowledge. The report should be made in writing (email is acceptable) and must include a detailed description of what occurred and the steps taken to resolve/address the incident.

4.1.15 Report to the ERD in a timely fashion any adverse incidents occurring during the study that are considered by the investigator to:

- be serious and unexpected and possibly related to the procedures of the study; or
- Require a change in the consent form; or
- Require a change in the conduct of the study

4.1.16 Handle any complaints from participants in accordance with the *RCH Procedure: Research Complaints Management & Resolution*.

4.1.17 Manage the resources for the study in such a way that maximises the chances of the study being completed with the available funding.

4.1.18 Ensure that the results are analysed, written up and disseminated appropriately and in a timely fashion.

4.1.19 Disclose any financial interest and any other conflicts of interest of any of the investigators, when presenting relevant Research results at meetings, when submitting relevant articles for publication, and when applying to funding agencies to support their Projects.

4.1.20 Compile a *Final Report* and submit this to the HREC for review in a timely fashion following study completion and final data analysis, and prior to the expiry of the project approval.

4.1.21 Submit a final report to the HREC in a timely fashion if a decision is made to permanently discontinue the approved project.

4.1.22 Compile a letter of thanks, including a final lay summary of the project results and submit this to the HREC (no later than the final report submission) for approval to send to participants, unless alternative procedures have been approved by the HREC

4.2 PROJECT STAFF

It is the responsibility of the PI, or their delegate/s, to:

- 4.2.1 Ensure that all staff with involvement in the project are adequately informed about the protocol and understand their project related duties.
- 4.2.2 Maintain a running record of all staff delegated responsibilities in the project, specifying their responsibilities.
- 4.2.3 Ensure that all staff involved in the project have an appropriate level of education, training, qualification, experience and supervision to perform their delegated tasks.
- 4.2.4 Maintain adequate documentation demonstrating that project staff are appropriately trained and qualified (see 4.2.3).
- 4.2.5 Seek appropriate collaborators or training when the research involves procedures outside the experience and expertise of the project staff.
- 4.2.6 Ensure staff with involvement in the project are well supported in their project responsibilities.
- 4.2.7 Provide oversight of the performance of project responsibilities by delegated staff, including monitoring adherence to all the requirements outlined in this procedure.
- 4.2.8 Ensure that clear lines of communication are open between members of the project team.
- 4.2.9 Ensure appropriate insurance and indemnity cover is in place for all members of the project team who are not employees of RCH/MCRI/UoM, where necessary.
Please note: HREC Approval grants indemnity and insurance for the project protocol (from our insurers VMIA). However it does not provide insurance and indemnity to individuals. Individual insurance and indemnity is provided through employment at RCH/MCRI/UoM. As such if an external researcher is part of an RCH/MCRI/UoM project they must be working for an institution which provides indemnity and insurance to its employees as part of their employment or they must seek private cover if necessary.
- 4.2.10 Ensure that all members of the project team have documented their understanding and acceptance of the requirements of this procedure.
- 4.2.11 For projects which span more than one institution, researchers must establish an agreement on arrangements. This must be done prior to the commencement of the collaborative research project. The agreement should cover intellectual property, confidentiality and copyright issues, responsibility for ethics and safety clearances, and reporting to appropriate agencies, as applicable. It should address the procedures to be followed by the partners when disseminating research results, and the management of research materials and data.

4.3 DATA AND DOCUMENTATION

It is the responsibility of the PI, or their delegate/s, to:

- 4.3.1 Ensure that all electronic project documents are accessible only by authorised members of the project team.
- 4.3.2 Maintain security procedures for the protection of the privacy and confidentiality of all data collected from or about participants, including those contained in electronic records.
- 4.3.3 Only use only data and/or tissue samples for the project for which HREC approval has been granted, in accordance with the protocol.
- 4.3.4 Store all data, including electronic data, in a durable, indexed and retrievable form.
- 4.3.5 Securely store data and documents to prevent loss, including regularly backing up any electronic files.
- 4.3.6 Maintain accessible study documentation or files, which form a complete record of the study and collectively permit evaluation of the conduct of the study and the quality of the data produced. These documents include at minimum:
 - All significant correspondence with the ERD, including submissions and certificates of approval
 - All current and superseded HREC approved study documents, including the protocol and informed consent forms
 - A complete log of participant IDs listing the enrolment status of all those who were allocated a study ID
 - A list of participants' names and their corresponding study ID
 - Documentation of staff training and qualifications (see 4.2.4)
 - Significant correspondence (detailing a decision or important discussion or change regarding study conduct)
 - Delegation record (see 4.2.2)
- 4.3.7 Ensure all study data are recorded, handled and stored in a way that allows accurate reporting, interpretation and verification of the data.
- 4.3.8 Take reasonable steps to ensure that the data contained in the database and final report agrees with original observations.
- 4.3.9 Provide access to the requested documents, records and data if selected for audit by the Research Governance Officer and to cooperate during the auditing process and follow-up.
- 4.3.10 Ensure that the study documents and data are archived following the study. Provision must be made for the archived documents to be accessible in case the need arises at any point in the archival period to access the stored records.
- 4.3.11 Ensure that health information collected is retained in storage for 7 years following the study if all the participants are over 18 years old, and for 7 years following the 18th birthday of the youngest participant if the participants are not all over 18 years old.

4.4 OTHER POLICIES AND PROCEDURES

Unless alternative procedures have been approved by the HREC, it is the responsibility of the PI, or their delegate/s, to be familiar with and ensure compliance with the following, as applicable:

- 4.4.1 RCH Research Policy and related Procedures:
http://www.rch.org.au/policy_rch/index.cfm?doc_id=12653
- 4.4.2 NHMRC National Statement for Ethical Conduct in Human Research:
<http://www.nhmrc.gov.au/PUBLICATIONS/synopses/e72syn.htm>
- 4.4.3 Declaration of Helsinki
- 4.4.4 NHMRC Australian Code for the Responsible Conduct of Research:
<http://www.nhmrc.gov.au/publications/synopses/r39syn.htm>
- 4.4.5 Health Records Act 2001 (contains Health Privacy Principles (HPP)):
<http://www.health.vic.gov.au/healthrecords/>

4.5 CLINICAL TRIALS OF INVESTIGATIONAL PRODUCTS – ADDITIONAL RESPONSIBILITIES

Clinical Trials of Investigational Products are subject to additional requirements and therefore the Investigators conducting these trials must fulfil the following additional responsibilities.

Unless alternative procedures have been approved by the HREC, it is the responsibility of the Principal Investigator, or their delegate/s, to be familiar with the following requirements and ensure compliance with the following, as applicable:

- 4.5.1 The research must be designed and conducted in accordance with the parts of Good Clinical Practice relevant to the protocol, as listed in the TGA's *Note for guidance on good clinical practice (CPMP/ICH/135/95 - Annotated with TGA comments)*
- 4.5.2 The trial must be registered on a public register of clinical trials within 21 days of the first patient being recruited, and the ERD must be notified.
- 4.5.3 Assess whether the trial must be conducted under the Clinical Trial Exemption (CTX) Scheme or the Clinical Trial Notification (CTN) Scheme of the Therapeutic Goods Administration (TGA), and if so, to complete a CTN or CTX Form and submit this to the TGA in accordance with the instructions, prior to commencing the trial. A copy must be maintained on file at the research site. These schemes must be used for all clinical trials involving:
 - any product not entered on the Australian Register of Therapeutic Goods; or
 - use of a registered or listed product in a clinical trial beyond the conditions of its marketing approval.
- 4.5.4 All SAEs occurring in RCH participants, or participants that the PI is responsible for, must be reported to the RCH HREC (via the ERD) within 72 hours of occurrence.
- 4.5.5 External SAEs (occurring in participants at other sites) must be reported in a prompt manner if the information impacts the continued ethical acceptability of the trial. This includes cases where the information requires, or indicates the need for, a change in the trial protocol or information statement, including changed monitoring.
- 4.5.6 All other External SAEs (that do not fit the criteria in 4.1.5) need only be submitted if they meet the definition of a SUSAR and may be submitted as a periodic listing. A periodic listing of SUSARs must be submitted at least six monthly.

4.5.7 If the study is conducted under a CTN: Comply with the requirements of the CTN scheme, which include the following:

- All SUSARs reported to the Experimental Drugs Section, Drug Safety and Evaluation Branch of the TGA in an expedited fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe. All other ADRs and AEs are tabulated as per usual trial protocols and produced on request.
- All SUSARS in device trials are reported to the Devices Clinical Section, Office of Blood, Devices and Tissues of the TGA in an expedited fashion as described in the paragraph above. Other adverse device events to be tabulated and produced upon request.
- Archive records for a minimum of 15 years following the completion of the study.

4.5.8 If the study is conducted under a CTX: Comply with the requirements of the CTX scheme.

4.5.9 If there is an External Sponsor: There must be a written CTRA between the RCH/MCRI/UoM and the External Sponsor which sets out the responsibilities of each party. A copy of this agreement must be provided to HREC and maintained on file at the research site.

4.5.10 If there is an External Sponsor: Maintain current insurance and indemnity coverage that meets the requirements of the VMIA, and supply HREC with a copy of the current insurance certificate.

Note: Indemnity must be provided by an Australian corporate entity, even if the external sponsor is an overseas-based organisation.

5. References & Links

- The NHMRC National Statement for Ethical Conduct in Human Research (2007): <http://www.nhmrc.gov.au/PUBLICATIONS/synopses/e72syn.htm>
- NHMRC Australian Code for the Responsible Conduct of Research: <http://www.nhmrc.gov.au/publications/synopses/r39syn.htm>
- Health Records Act 2001: <http://www.health.vic.gov.au/healthrecords/>
- RCH Policies & Procedures: http://www.rch.org.au/policy_rch/index.cfm?doc_id=6097
- ICH GCP *Annotated with TGA comments*: <http://www.tga.gov.au/docs/html/ich13595.htm>
- ERD website: http://www.rch.org.au/ethics/index.cfm?doc_id=882
- VMIA website: <http://www.vmia.vic.gov.au/display.asp?entityid=3006>

6. Contacts

RCH Strategic goals	Excellence in Healthcare Focus on Quality and Safety Leadership in Research Education
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Authoriser	Policy & Procedure Committee
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