Standard Operating Procedure

Title: **Delegation of Sponsor Responsibilities in MCRI-Sponsored Investigator-Initiated Trials**

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CONTENTS

1. PURPOSE

Clinical trials should be managed and conducted in accordance with the approved protocol, sponsor Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and relevant jurisdictional regulations and guidelines.

The purpose of this document is to describe the standard operating procedure for the delegation of responsibilities within single-site and multi-site investigator-initiated trials.

1.1. Quality Improvement

This SOP safeguards the quality of clinical trials by ensuring that the delegation of any Sponsor responsibilities to third parties is appropriately documented. It also enables clear accountability of all delegated roles and responsibilities, providing Sponsor-Investigators/Coordinating Principal Investigators (CPIs) with a robust framework to oversee delegated third-party responsibilities, in line with the requirements of GCP.

1.2. Participant Safety

This SOP ensures the safety of participants by ensuring that the delegation of any sponsor responsibilities to third parties, in particular safety-related responsibilities, is appropriately documented.

2. BACKGROUND

GCP defines the Sponsor of a trial as either an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. Each institution will have its own policy regarding the sponsorship role.

For MCRI-sponsored investigator-initiated trials, MCRI will assume the role of the Sponsor, however, MCRI delegates many Sponsor responsibilities to the Sponsor-Investigator/CPI. In this case, the Sponsor-Investigator/CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Some sponsorship responsibilities are delegated to other organisations involved in the trial, for example where the Sponsor-Investigator/CPI or other investigators are based at other sites, or if there is a need to assign a Local Sponsor in a country outside of Australia in order to conduct the trial (or vice versa).

The need for clarity around roles and responsibilities is fundamental to the conduct of research. GCP clearly places the responsibility for clinical trials on the Sponsor, and states that "prior to initiating a trial the Sponsor should define, establish and allocate all trial-related duties and functions" (ICH E6 (R2); 5.17).

GCP also permits the Sponsor of a clinical trial to delegate any or all of its functions to any person, however, any such arrangement shall not affect the responsibility of the Sponsor. As such the Sponsor can delegate responsibilities but remains accountable for the trial. It is therefore critical that the Sponsor implements procedures to ensure oversight of all delegated roles and responsibilities at the level of organisations and the individual.

In addition, the UK Policy Framework for Health & Social Care Research also states that there should be clear designation of responsibility and accountability with clear lines of communication between all those involved in research. Communication pathways should be clear in terms of what, how, who, when and why, with documented roles and responsibilities. This is particularly important for trials being conducted within the UK and EU, whereby a Local Sponsor, Legal Representative or Collaborative group is delegated certain Sponsor responsibilities on behalf of MCRI as overall Sponsor.

3. SCOPE

This SOP applies to all clinical trials in the following situations:

When MCRI is the Sponsor of the IIT, however, is required to delegated certain Sponsor responsibilities to a third-party (external to MCRI)

- Where there is an external Sponsor (usually overseas), however, MCRI has been delegated certain Sponsor responsibilities to conduct the trial in Australia.

4. RESPONSIBILITY

This SOP applies to all staff involved in conducting trials MCRI-sponsored Investigator-Initiated clinical trials. All staff are directly responsible for implementing the procedures set out in this SOP within their study teams.

4.1. Sponsor Responsibilities

Sponsor (MCRI) responsibilities include:

- Providing a Roles and Responsibilities Matrix (MCTC168 | Template Roles & Responsibilities Matrix) for MCRI-sponsored IITs and agreeing on the onward delegation of Sponsor responsibilities on behalf of MCRI
- Agreeing, ensuring, and contracting with collaborators and sub-contractors their roles and responsibilities in MCRI-sponsored IITs, as required.

4.2. Sponsor-Investigator/CPI Responsibilities

The Sponsor-Investigator/CPI responsibilities include:

- Ensuring all delegated roles and responsibilities are appropriately delegated and recorded on the Roles and Responsibilities Matrix
- Ensuring that he/she has an appropriate study team assigned to support the conduct of the trial and maintain trial oversight
- Ensuring the matrix is included in any relevant Clinical Trial Research Agreement (CTRA) with any delegated party (as applicable)
- Ensuring all delegated Sponsor responsibilities are met as agreed within the Roles and Responsibilities Matrix
- Negotiating costs associated with engaging any third parties
- Reporting to the Sponsor any instances where agreed delegations and responsibilities have not been met by the delegated party.

5. PROCEDURE

5.1. Principles of Delegation

Whilst MCRI, as Sponsor, is legally responsible for the overall conduct of a trial, regulations allow for certain functions to be shared or delegated by written agreement.

Before a trial commences, individual trial related tasks must be defined, established, and documented. Hence, as part of any trial development phase, a Roles and Responsibilities Matrix must be established between the Sponsor (MCRI), the Sponsor-Investigator/CPI and any other applicable party/ies.

Examples of when a Roles & Responsibilities Matrix should be established include:

1. When MCRI is the Sponsor of an IIT, however, the CPI has engaged with collaborators (external to MCRI) to provide certain services or has delegated certain Sponsor responsibilities
2. When MCRI has been delegated certain Sponsor responsibilities to conduct the trial from an external Sponsor

5.2. Decisions to Delegate Responsibilities

Decisions to delegate accountability for specific functions/responsibilities will be made by the Sponsor-Investigator/CPI (or delegate) in collaboration with their Central Trial Coordinating Team and any other applicable party, depending on the requirements of the protocol and resources required to conduct the study.

The rationale for delegation and description of duties must be discussed with the Chair of the MCRI Sponsorship Committee or representative of the Melbourne Children's Trial Centre, MCRI Legal and others as needed for the trial. This must take place in advance of applying for any ethical and/or regulatory approvals.

5.3. Vendor Assessment

The Sponsor-Investigator/CPI (or delegate) will assess the capability and capacity of the other party to undertake the delegate functions/responsibilities. This will include a combination of the following:

- Confirming vendor/staff qualifications, clinical research experience, medical licences, CVs, and training records (as applicable), and other relevant documentation to assure suitability to undertake the delegated tasks
- Reviewing accreditation certificates (e.g. Phase1 unit accreditation, or applicable clinical trial unit experience/accreditation).
- Confirming capacity and capability to undertake the delegated tasks
- Confirming that their Quality Management System and/or SOPs, forms and templates are appropriate.
- Requesting any other applicable additional information or evidence of expertise
- Review of any associated services charges/costs, as applicable.

5.4. Completion of Roles and Responsibilities Matrix

Where the Sponsor-Investigator/CPI (or delegate) intends on delegating some of its responsibilities as Sponsor to another party, then these responsibilities will be agreed upon by both parties and documented on the MCTC168 Form | Roles and Responsibilities Matrix.

- Agreed functions/responsibilities must be documented in the MCTC168 Form | Roles and Responsibilities Matrix clearly indicating which responsibilities are being delegated to:
  - The sponsor, indicated by including a (✓) in the "Sponsor" column
  - The Sponsor-Investigator/CPI, indicated by including a (✓) in the "CPI" column
  - The Central Trial Coordinating Centre, indicated by including a (✓) in the "Central Trial Coordinating Centre" column
  - Legal Representative, indicated by including a (✓) in the "Legal Representative" column
  - Or any other party, indicated by including a (✓) in the "Other Relevant Party" column.
- Completed Roles and Responsibilities Matrices must be included in any relevant Clinical Trial Research Agreement (CTRA) with any delegated party (as applicable) and negotiated by the MCRI Legal Team
- As circumstances change, the Sponsor-Investigator/CPI (or delegate) must review, and update previously delegated responsibilities accordingly
- Completed Roles and Responsibilities Matrices must be filed within the Trial Master File (TMF).

5.5. Oversight of Delegation

For MCRI to retain oversight of the delegated function(s), the requirements below must be agreed to by the delegated party:

- To copy in the Sponsor-Investigator/CPI and Central Trial Coordinating Team on all correspondence related to the delegated task
- To provide status update reports at an agreed frequency
- To provide copies and assurance that SOPs, templates, forms which are to be used are compliant with the relevant regulations and policies
- To attend project team meetings (where applicable) upon request of the Sponsor-Investigator/CPI (or delegate)
- To provide copies of meeting minutes, and key correspondence, as applicable
- To permit Quality Assurance audit(s) by a MCRI representative
- To ensure a mechanism is in place to feed any deviations from assigned delegations or roles back to the Sponsor, as applicable
- To share, for Sponsor review and sign off, study documentation (e.g. Ethics submission packages, master consent forms, protocol addendums, monitoring visit reports, data management plans, statistical analysis plans, review of deviation logs, audit trails etc.).

6. GLOSSARY

Adverse Event

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product or other intervention. It does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Case Report Form (CRF)

Data collection tool used to record all the protocol required information to be reported to the sponsor on each research/trial participant. The CRF may be paper or electronic.

Central Trial Coordinating Team

A group of MCRI researchers organised to coordinate the planning, development, operations and conduct of an MCRI-sponsored IIT, multi-centre, clinical trial.

Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Clinical Trial

The World Health Organization (WHO) definition for a clinical trial is: 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.

Clinical Trial Research Agreement

An agreement between the Sponsor and a participating site that sets out the rights and obligations of each party in relation to the conduct of a clinical trial.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. Filing essential documents at the Sponsor site and participating trial sites also assists with the successful management of the trial.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Good Manufacturing Practice (GMP)

A set of principles and procedures that when followed helps ensure that therapeutic goods are of high quality.

A basic tenet of GMP is that:

- quality cannot be tested into a batch of product
- quality must be built into each batch of product during all stages of the manufacturing process.

Human Research Ethics Committee (HREC)

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

International Conference on Harmonisation (ICH)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when 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.

Investigational Medical Device (IMD)

A device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. There are four types of Investigator roles used to describe Investigators with different levels of responsibility for the conduct of clinical trials. These are described below.

Associate Investigator

Any individual member of the clinical trial team designated and supervised by the Principal investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). May also be referred to as sub-investigator.

Coordinating Principal Investigator (CPI)

If a study is conducted at more than one study site, the Principal Investigator taking the additional responsibility for coordination of the study across all sites in a region is known as the Coordinating Principal Investigator (CPI). This role applies to externally sponsored studies where the Sponsor may be a collaborative research group, commercial Sponsor or an institution. The Principal Investigator at each site will retain responsibility for the conduct of the study at their site.

Principal Investigator

The PI is the person responsible, individually or as a leader of the clinical trial team at a site, for the conduct of a clinical trial at that site. As such, the PI supports a culture of responsible clinical trial conduct in their health service organisation in their field of practice and, is responsible for adequately supervising his or her clinical trial team.

The PI must conduct the clinical trial in accordance with the approved clinical trial protocol and ensure adequate clinical cover is provided for the trial and ensure compliance with the trial protocol.

Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a participant. The term does not include any person other than an individual (eg, it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Investigator-Initiated Trials (IITs)

A clinical trial which is initiated and organised by an Investigator i.e. an individual rather than a collaborative group, company, or organisation. In these cases, the Investigator will take on the role of the trial sponsor and will then be responsible for the extensive GCP and regulatory requirements associated with both the management and conduct of the trial.

Investigator Site File (ISF)

Filing repository controlled by the site Principal Investigator. It is held at the trial site and contains all the essential documents necessary for the site trial team to conduct the trial as well as the essential documents that individually and collectively permit evaluation of the conduct of the trial at the site and the quality of the data produced.

Melbourne Children's
The campus encompassing all staff from The Royal Children's Hospital, Murdoch Children's Research Institute and Department of Paediatrics University of Melbourne who initiate or carry out research under one or more of these institutional affiliations.

Melbourne Children's Trials Centre (MCTC)
Melbourne Children's Trials Centre (MCTC) is a collaboration between the Royal Children's Hospital, The Murdoch Children's Research Institute, The Royal Children's Hospital Foundation and The University of Melbourne. This Centre brings together expertise in research, clinical practice, and education and incorporates anyone who initiates or carries out research under one or more of these institutional affiliations.

Murdoch Children's Research Institute (MCRI)
An Australian paediatric medical research institute located in Melbourne, Victoria, affiliated with the Royal Children's Hospital and the University of Melbourne. The institute has six research themes: cellular biology, clinical sciences, genetics, infection and immunity, population health, and data science.

Participant
A participant is a person that is the subject of the research.

Pharmacovigilance
Process of ongoing monitoring of the safety profile, combined with the ongoing assessment and evaluation of the risk-benefit of medicines. The process is important to identify adverse reactions/adverse device effects and changes in the known safety profile.

Protocol
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

Research Governance Office (RGO)
The Office or coordinated function within 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).

Royal Children's Hospital (RCH)
The Royal Children's Hospital is major specialist paediatric hospital in Victoria, the Royal Children's Hospital provides a full range of clinical services, tertiary care, as well as health promotion and prevention programs for children and young people. Its campus partners are the

Murdoch Children's Research Institute and The University of Melbourne Department of Paediatrics, which are based on site at the hospital.

Serious Adverse Event (SAE)

An adverse event is defined as serious if it:

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

Other important medical events will be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the research participant safety and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. This can include diagnosis of cancer.

Source Data

Source data is the original recording of an item of data. "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." (Section 1.51, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments).

Source Document

Source documents are documents which contain source data. When data is entered directly into your electronic Case Report Forms (data collection forms) or database, the Case Report Form/database becomes your source document for that information.

Sponsor

An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, MCRI or RCH will act as the Sponsor but delegate many sponsor responsibilities to the Coordinating Principal Investigator. In this case the CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Standard Operating Procedure (SOP)

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.

Therapeutic Good

In relation to the evaluation, assessment and monitoring done by the TGA, therapeutic goods are broadly defined as products for use in humans in connection with:

- preventing, diagnosing, curing, or alleviating a disease, ailment, defect, or injury
- influencing inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling, or preventing conception
- testing for pregnancy

This includes things that are:

- used as an ingredient or component in the manufacture of therapeutic goods
- used to replace or modify of parts of the anatomy

Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods.

Trial Coordinator

A Trial Coordinator has a significant role in the management of the clinical trial at the Sponsor level and provides leadership in clinical trial activities to ensure that the trial is completed within budget, on time and of the highest quality. A Trial Coordinator is responsible for managing the planning, implementation, and tracking of the clinical monitoring process, administration, and start-up of the clinical trial at the participating site and maintaining an overview of the conduct of the trial at sites. Some common roles and responsibilities performed by the Trial Coordinator include:

- Participate in protocol development, CRF design and clinical study report writing
- Guide in the creation and development of important study documents and manuals
- Conduct feasibility assessments
- Develop study budgets
- Oversee participant recruitment
- Oversee overall trial conduct
- Ensure compliance of site-staff with the trials Standard Operating Procedures
- Ensures compliance to all regulatory requirements both at a local and international level
- Ensures compliance to all data protection requirements both at a local and international level
- Ensures compliance to all safety reporting requirements both at a local and international level
- Conduct team meetings and site-staff training programs

- Overall responsibility of the trial
- Supervise in-house clinical trial staff

Trial Master File (TMF)

Filing repository controlled by the Sponsor/Sponsor-Investigator. It is the collection of essential documents that allows the Sponsor responsibilities for the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with Good Clinical Practice (GCP) to be evaluated.

Trial Management Group (TMG)

The TMG is a group of key people at the coordinating or principal site who oversee the day-to-day conduct and progress of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. For many investigator-initiated trials, the TMG performs the role of a TSC (see below) and/or the DSMB.

Trial Steering Committee (TSC)

Most commonly used in commercial trials and large international non-commercial trials, a TSC is appointed by the sponsor to provide independent expert oversight for the trial. The TSC may include investigators, other experts not otherwise involved in the trial and, usually, representatives of the sponsor. Although blinded, the TSC acts as a body that takes responsibility for the scientific integrity of the protocol and the assessment of study quality and conduct.

Quality Assurance (QA)

Covers all policies and systematic activities implemented within a quality system. QA ensures that data are recorded, analysed, and recoded in accordance with the protocol and GCP. The use of GCP guidelines ensures ethical and scientific quality standards for the design, conduct, recording, and reporting of HREC approved clinical trials that involve research participants.

7. REFERENCES

- The National Clinical Trials Governance Framework
- TGA Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (2) 2016 – Annotated with TGA comments available at https://www.tga.gov.au/publication/note-guidance-good-clinical-practice
- TGA Guidance: Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australian using "unapproved" therapeutic goods, Version 2.2 October 2018, available at https://www.tga.gov.au/publication/australian-clinical-trial-handbook
- https://www.hra.nhs.uk/planning-and-improving-research/research-planning/roles-andresponsibilities/
- UK Policy Framework for Health and Social Care Research - Health Research Authority (hra.nhs.uk)

- The University of Oxford CTRG Form 304c Division of Responsibilities template v5.0_01August 2018

8. COLLABORATORS

Name/Role	Department/Group	Affiliation
Kate Scarff / CRDO Lead	Clinical Research Development Office	MCRI
Iona Walton / Administrative Assistant	Melbourne Children's Trials Centre	MCRI

9. RELATED DOCUMENTS

MCTC168 | Form: Roles and Responsibilities Matrix
MCTC065 | SOP: Start-Up Clinical Trials
MCTC056 | Checklist: Trial Development and Study Start-Up
MCTC037b | SOP: Sponsorship Committee Process for IITs
MCTC182 | SOP: Sponsor-Investigator Responsibilities in MCRI-Sponsored IITs

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