STANDARD OPERATING PROCEDURE (SOP)

Title: **Institutional Sponsorship Application and Approval for Sponsor-Investigator Initiated Trials (IITs).**

Document ID: MCTC037

Version: 2.1

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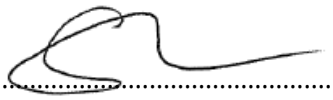
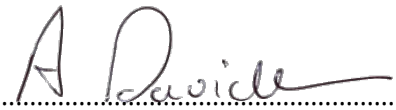
The author is signing to confirm the technical content of this document

Signature:  Date: 12th May 2022

Reviewed and Approval

Andrew Davidson Medical Director, Melbourne Children's Trial Centre

This signature confirms the reviewer agrees with the technical content of the document and that this document is approved for implementation at the Melbourne Children's.

Signature:  Date: 12th May 2022

This document is effective from the date of the last approval signature and will be reviewed in two years.

Document History

Revision	Modified by	Change No.	Description of Change
1.0	Katie Arkell	N/A	New Issue
2.0	Stephanie Firth	1	Updates to initial Submission requirements NEW section 5.3 Oversight of Sponsored Trials Clarifications throughout document
2.1	Stephanie Firth	.01	Section 5.1.3 - Applicants to the Sponsorship Committee are required to attend the meeting considering their trial

CONTENTS

1. PURPOSE

This Standard Operating Procedure (SOP) describes the activities undertaken by the Murdoch Children's Research Institute (MCRI) and the MCRI Sponsorship Committee (SC) to grant sponsorship, by MCRI, for Investigator Initiated Trials (IITs)

The SC's primary goal is to ensure MCRI-Sponsored trials are conducted appropriately and efficiently, and will be completed to a high quality and achieve maximum impact.

To ensure the trial's successful completion, the SC will review and approve MCRI's institutional risk with respect to Investigator-Initiated Trials (IITs) sponsored by MCRI, and in particular, the information provided in the Sponsorship Committee Application Risk Management Table. It does not primarily assess scientific quality, research merit or ethical acceptability of the trial design, as this is the responsibility of the reviewing HREC.

MCRI will not support individual members of staff to personally act as the sponsor of a clinical trial. As such, this SOP outlines the process Investigators need to follow to request that MCRI acts as the legal representative for a trial, thereby acting as the Sponsor. When MCRI agrees to act as the Sponsor of an IIT, MCRI will be the official name used on all relevant documents including contracts with third parties, Clinical Trial Notifications to the Therapeutic Good's Administration (TGA), and clinical trial registration.

All applicable SOPs produced by MCRI are to be used in conjunction with the relevant applicable NHMRC policies and procedures when conducting a MCRI sponsored IIT.

This SOP is consistent with the requirements set out in the National Statement on Ethical Conduct in Human Research 2007 (updated 2018) and the ICH Topic E6 (R2) Integrated addendum to ICH E6 (R1): Guideline for Good Clinical Practice (ICH E6 R2) with TGA annotations.

1.1. What are the risks attached to MCRI taking on the role of Sponsor?

A sponsor organisation is exposed to potential risks in a number of areas, including but not limited to the following.:

- Financial
- Legal ethical approval or contravention of pharmacovigilance requirements.
- Reputation

2. BACKGROUND

Good Clinical Practice (GCP) clearly outlines the responsibilities of a trial sponsor. The Therapeutic Goods Administration (TGA) discusses sponsor responsibilities in the handbook

(mentioned below) where they distinguish between the GCP definition of sponsor and the TGA's definition in the Therapeutic Goods Act. The MCRI Certificate of Sponsorship outlines the responsibilities for MCRI, the Sponsor-investigator and the participating sites, specific to each trial.

In these documents it states that the sponsor of a clinical trial assumes the overall responsibility for the initiating, managing (including ongoing oversight) and financing (or arranging the financing) of a trial, as well as the overall scientific integrity of the data derived, and results reported. Sponsors can delegate one or more elements of these sponsorship responsibilities to people within the sponsoring organisation.

For further details regarding the requirements of the sponsor please refer to TGA Guidance: Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australian using "unapproved" therapeutic goods, Version 2.4 August 2021.

3. SCOPE

All clinical trials opened in Australia, require a specifically named Australian entity as sponsor. Should an Investigator wish the MCRI to act as Sponsor, they must first seek documented approval. This will most commonly be:

a) MCRI IITs
b) International IITs seeking a local Australian Sponsor.

This document should be referred to by any staff member applying for sponsorship from MCRI, or when completing any steps of the sponsorship approval process.

Investigators requesting sponsorship for an IIT must be employees of, or have honorary appointments with, The Royal Children's Hospital and/or MCRI.

Any MCRI-sponsored IITs initiated on or after January 1, 2020, must receive formal sponsorship approval from the MCRI SC before commencing recruitment. Trials initiated prior to 2020 are not required to obtain retrospective sponsorship approval. In some circumstances, Investigators for trials commenced prior to January 1, 2020, may wish to/benefit from formal Sponsorship review.

Investigators must submit their IIT protocol and supporting documentation to the MCRI SC for review and approval before obtaining HREC approval and prior to commencement of the trial. Additional consideration is required by the SC for sponsorship of international sites.

The SC submission and review process does not duplicate the Research Ethics and Governance (REG) process for MCRI; it exists in parallel. It is strongly recommended that all IIT protocols be

reviewed by the SC prior to or at the same time as submission to RCH HREC to ensure that the SC approval process does not slow down the ethics approval and research governance authorisation process. RCH HREC will no longer approve any IITs without evidence of Sponsorship Committee approval by the MCRI or an external collaborative network, company or organisation.

This SOP does NOT Apply to:

- Observational studies
- Trials which have been designed by an organisation external to MCRI and have an external Australian commercial or collaborative group sponsor.

If Investigators are unsure if the sponsorship process applies to them – they are advised to contact the Director of the MCTC for clarification and guidance. For example, depending on the level of risk it may be unclear if a protocol for a "pilot study" requires SC review.

4. RESPONSIBILITY

This SOP applies to the following roles:

- **Principal Investigator:** An Investigator is an individual responsible for the conduct of a study, ensuring that the study complies with GCP guidelines. There are different terms used to distinguish the varying role of Investigators. 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 (PI). In this instance they may delegate tasks to other team members.
- **Co-ordinating Principal Investigator:** If a study is conducted at more than one study site, the Principal Investigator taking overall responsibility for the study and for the coordination across all sites is known as the Coordinating Principal Investigator (CPI); the Principal Investigator at each site will retain responsibility for the conduct of the study at their site.
- **Sponsor-Investigator:** Note that for Investigator-Initiated research, the PI or CPI leading the research takes on responsibilities of the Sponsor and the term "Sponsor-Investigator" should be adopted to highlight the dual sponsor and Investigator role.
- **MCTC Medical Director:** This could be the Director or Acting Director (or delegated person) representing the Melbourne Children's Trials Centre on the SC.
- **MCRI Sponsorship Committee:** The committee consists of representatives from the following departments:
  - Melbourne Children's Trials Centre
  - Research Ethics and Governance (REG)

- Office of Research
- Legal
- Finance
- Grants
- Current & Experienced Sponsor-Investigator(s) (at least one)

5. PROCEDURE

5.1. Submission Process for Sponsor-Investigators

For a visual representation (flowchart) of the process, refer to the Appendix 13.3 – Process Flow Diagram.

5.1.1. Submission

Prior to SC review, the Sponsor-Investigator needs to provide to the MCTC Medical Director (or Acting Director) (contact mctc@mcri.edu.au) at least one working week prior to the next SC meeting:

- A completed MCRI Sponsorship Committee Application Coversheet and Risk Management Table
- The current draft of the protocol with a version no and date.
- A current trial budget
- Evidence of the source of trial funding (e.g. Grant approval letter, email from department head, etc.)
- A Division of Responsibilities Matrix showing role of the international Sponsor and local Coordinating Principal Investigator – *Applicable to IITs sponsored by an overseas company/organisation/institution, where MCRI is acting as the local Sponsor only*

5.1.2. Initial Review

The MCTC Medical Director (or delegate) will review the submission to ensure all submission documents are satisfactory, and to assess whether or not the project:

a) Requires MCRI Sponsorship Approval (see 3.0 Scope)

b) Is of Negligible Risk (see 5.1.2.2 Negligible Risk)

c) Is of greater than negligible risk.

The MCTC Medical Director (or delegate) may request a meeting to discuss the details of the trial and request revisions.

Once the MCTC Medical Director (or delegate) is satisfied with the trial documents submitted and necessity for SC review, the trial be a will be added to the next SC meeting's agenda for consideration.

5.1.2.1. Conflict of Interest

Should the MCTC Medical Director have a conflict of interest, the Sponsorship Committee's Deputy Chair will perform the initial review in the place of the MCTC Medical Director.

5.1.2.2. Negligible Risk trials

Clinical trials deemed to be of negligible risk to MCRI can be approved by the MCTC Medical Director (or delegate) on behalf of the SC. The MCTC Medical Director (or delegate) will advise the committee of all Negligible Risk Trials which have been approved on behalf of the Committee at the next SC meeting.

5.1.3. SC Meetings

The trial documentation will be circulated to the SC one week prior to the meeting to ensure SC members can review the documents and send questions to the applicant for response prior to or at the SC meeting.

Meetings are held the first Monday of the month from February to December each year. The Sponsor-Investigator will attend the meeting considering their trial. At the meeting, the Sponsor-Investigator (or delegate) will be asked to provide an overview of their trial, highlight any risks they have identified in their Sponsorship Application and completed Risk Management Table and answer any questions from the SC.

Note: *The SC Chair may excuse the Sponsor-Investigator from attending the meeting in exceptional circumstances. In these cases, the SC will discuss the application and send any questions and/or recommended action to the Sponsor Investigator following the meeting. The Sponsor Investigator must provide a response prior to receiving Sponsorship Approval. This process may delay SC approval.*

During the meeting, the SC will determine:

- The overall risk rating of the trial
- The degree of SC (or delegate) oversight required
- Any further actions required for mitigating and/or monitoring the risks identified by the SC and Sponsor-Investigator (or delegates)
- If the Committee will require the Sponsor-Investigator to submit any of the following documents for further review:
  - Data Sharing Plan
  - Data Management Plan
  - Monitoring Plan

  If these documents are required, the committee will also determine a due date for their submission.

5.1.4. Response to SC Feedback

If any revisions/concerns are recommended by the SC, the Sponsor-Investigator needs to address these and re-submit the revised documents to the MCTC Medical Director (or delegate) for approval. The Sponsor-Investigator is required to address the concerns from the committee in writing and provide a management plan/solution to a level that satisfies the MCTC Medical Director.

5.1.5. Approval post SC Feedback

Providing the recommended changes are implemented, the trial does not need to go back to the full SC for review. The MCTC Medical Director may grant sponsorship approval and update the SC regarding the sponsorship status at the next scheduled meeting.

5.1.6. Issue of Certificate of Sponsorship

Once the recommended revisions (if any) have been addressed, the MCTC Medical Director (or delegate) will send a "Certificate of Sponsorship" to the Sponsor-Investigator to state that the trial will be sponsored by MCRI. This must be signed by both the MCTC Medical Director and Sponsor-Investigator prior to being submitted with the trial's ethics application. The Sponsor-Investigator may then proceed to complete their REG Application if not already done so.

Note: *The Certificate of Sponsorship is not the confirmation to commence recruitment. It is an approval document certifying MCRI is willing to sponsor the trial. RCH HREC will not approve an ethics application for MCRI Sponsored trials until the SC has issued a Certificate of Sponsorship.*

5.2. Protocol Amendments post SC approval

5.2.1. Assess impact on SC Risk assessment

If changes are made to the protocol or trial that substantially impact the sponsorship application risk assessment at any time after approval by the SC, then the SC should be notified at the same time as the reviewing HREC and RCH Research Ethics Governance Office (for trials where RCH/MCRI is a participating site), and the Risk Management Table should be updated and re-submitted.

Note: *While the Sponsor-Investigator holds the primary responsibility for determining whether a protocol amendment substantially increases the trial risks, REG staff reserve the right to reject an amendment without prior review by the SC where REG considers that the proposed amendment substantially changes the trial's risk.*

5.2.2. Re-issue of Certificate of Sponsorship

The "MCRI Certificate of Sponsorship" must be updated and re-signed by the MCTC Medical Director or delegate each time a significant change is made to the protocol/trial design (including protocol amendments); particularly if the changes will significantly impact the institution's decision to sponsor the trial.

5.2.3. RCH HREC and Governance approval

For studies that have received RCH HREC approval and RCH Research Governance authorisation, where the amendment is deemed to change the trial's risk, REG will provide approval only after receipt of the updated and signed Certificate of Sponsorship, demonstrating the changes to the trial/protocol amendment have been sighted, considered, and approved by the MCTC Medical Director and/or SC.

5.3. Oversight of MCRI Sponsored Trials

Apart from protocol amendments as detailed in section 5.2 Protocol Amendments post SC approval, the SC must be notified as soon as possible of any other events (internal or external) which may impact the risk assessment of the trial. The Risk Management Table must also be updated and re-submitted within one month of the Sponsor-Investigator becoming aware of the event.

5.3.1. Expedited Safety and non-compliance event reporting

The Sponsor-Investigator must report to the SC the same subset of safety and non-compliance events that must be reported to the reviewing HREC and local research governance office in real time. This includes:

- Serious Breach reports (Sponsor-level and Melbourne Children's site), within 7 calendar days of confirmation
- SSIs, within 72 hours of becoming aware of the event
- USMs, within 72 hours of becoming aware of the event
- SUSARs, within 72 hours of becoming aware of the event

For all serious breaches both at the Sponsor and Trial Site level, the Sponsor-Investigator must provide a Corrective and Preventive Action plan (CAPA) to both the reviewing HREC and the SC as soon as possible.

5.3.2. Periodic reviews

MCRI sponsored clinical trials will be reviewed by the MCTC Medical Director (or delegate) at regular intervals as determined by the SC, based on the risk and

recruitment status of the trial. This will typically be half-yearly for high risk clinical trials, and yearly for medium risk clinical trials. Low and negligible risk trials will typically not require review and only be required to submit a SC annual report, as detailed in section 5.3.3.

The aim of the periodic review is to ensure the trial is being conducted in a manner consistent with the most recently submitted Risk Assessment and Management Matrix.

The depth and breadth of the review will be determined by the risk profile. It will typically involve between one to three hours of review, including meetings between the SI and MCTC staff as appropriate. Depending on the risk profile, the following updated documents will be provided to the MCTC Medical Director (or delegate) one week prior to the first scheduled meeting:

- Sponsorship Risk Assessment, with 'Tracked Changes' since the last submitted Risk Assessment
- Current Protocol
- Trial budget

5.3.2.1. Periodic Review Fee

A Periodic Review Fee will be charged to the cost centre of Trials to be reviewed to cover MCTC staff time, as follows:

HIGH RISK TRIALS:.....$1,500 per review

MEDIUM RISK TRIALS:.....$750 per review

In order to ensure trials are able to incorporate this fee into their budget, the Periodic Review Fee will be applied to trials seeking MCRI Sponsorship which submit their Grant Application budget from July 1st 2022.

5.3.3. SC Annual Progress Report

5.3.3.1. Submission

The Sponsor-Investigator must annually submit for SC review:

- A Sponsorship Committee Annual Progress Report Form [MCTC 137]
- An updated Risk Management Table with 'tracked changes' since the last submitted risk assessment
- Central non-compliance log

- SAE / AE Line Listing (if applicable)
- Current Protocol
    - Data Management Plan (if updated since last review)
    - Data Sharing Plan (if updated since last review)
    - Monitoring Plan (if updated since last review)
- Current Trial Budget

5.3.3.2. Annual Progress Report Review

The MCTC Medical Director will delegate review of the Annual Progress Report to a member of the SC.

The SC member who reviews the submission will provide an overview of the trial's progress to the other SC members at the next meeting, along with recommendations for further action if required. An updated risk rating and/or review period will be determined.

5.3.3.3. SC Feedback

The Sponsor-Investigator will be provided with the Sponsorship Committee's assessment and recommendations within 7 days of the SC meeting's discussion of their submission. The Sponsor-Investigator must address feedback as per the process in section 5.1.6

5.3.3.4. Reissue of Certificate of Sponsorship

The Certificate of Sponsorship must be reissued as per the process detailed in section 5.2.2.

5.4. Submission Deadlines

Applications and updates submitted for MCRI sponsorship to the MCTC Medical Director must be made at least 7 working days prior to the next SC meeting. This is to ensure that any revisions and changes requested by the MCTC Medical Director can be made prior to the SC meeting.

If the submission deadline is missed the project will be reviewed at the next scheduled meeting. If an application is submitted on time but deemed to be invalid, the project will be discussed at the next meeting after the application is confirmed to be valid.

5.5. Decisions not to Sponsor a Trial

Should the SC determine that risks to the MCRI are inadequately addressed by the Sponsor-Investigator, the SC may decline to grant MCRI sponsorship. The reason for

rejecting an application will be provided to the Sponsor-Investigator in an email from the MCTC Medical Director.

As REG require evidence of Sponsorship prior to approving clinical trials, this may also prevent the trial from receiving HREC approval.

Where appropriate, the Sponsor-Investigator may discuss the decision with the MCTC Medical Director.

5.6. Termination of Sponsorship

Any trials that have been increased in its risk rating since starting as per the Risk Management Table must be re-assessed by the SC. The SC may decide to withdraw sponsorship, if needed, and will notify the reviewing HREC of this decision. This may then trigger the reviewing HREC to withdraw Ethical Approval and/or Governance Authorisation. The TGA may also need to be notified.

The Sponsor-Investigator will be given clear notice, in writing, to cease all trial activities other than those deemed necessary for participant safety. The SC, in consultation with REG and the approving HREC, will advise the Sponsor-Investigator if they need to cease administration of treatment for all participants and will discuss the requirements for advising participants about the closure of the study and the follow-up steps which need to be completed.

5.6.1. Appeals to reconsider Sponsorship

Any RCH or MCRI employee may write to the SC where they believe they have grounds to request that a trial not be sponsored by MCRI or have an existing sponsorship revoked. Each appeal will be considered by the committee, who may seek clarification from relevant sources. If the committee decides that there are legitimate grounds for revoking or withholding sponsorship, then the committee will prepare a recommendation for the MCRI director for approval and/or comment.

6. GLOSSARY

Clinical Monitoring Plan (CMP)

In accordance with the Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2) Section 5.18.7 (that was formerly adopted by the TGA with annotations on 8 February 2018), the Sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. This plan must describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use.

Clinical Research Development Office (CRDO)

CRDO provides education and training to facilitate and increase capacity for clinical and public health research across the Melbourne Children's campus. This includes the development and implementation of Standard Operating Procedures and templates to enable researchers to conduct high quality research.

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'.

Corrective and Preventive Action (CAPA) Plan

A Corrective and Preventive Action (CAPA) plan is a quality system plan and incorporates:

- Identifying the issue, including scope and impact
- Identifying the root cause of the issue – how/why it occurred
- Identifying actions to prevent recurrence of the issue (corrective action) or, identify actions to prevent an issue from occurring (preventive action)
- Documenting that the corrective actions/preventive actions were completed
- Documenting that the corrective/preventive action has resolved the problem

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.

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.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. There are three 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 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.

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 / Coordinating Principal Investigator (CPI)

In investigator-initiated and collaborative research group trials, the Principal Investigator taking overall responsibility for the study and for the coordination across all sites (if it is a multi-centre trial) is known as the Sponsor-Investigator or Coordinating Principal Investigator (CPI). In this case, the Sponsor will delegate many sponsor responsibilities to the Sponsor-Investigator/Sponsor-Investigator.

Investigator Initiated Trial (IIT)

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 Good Clinical Practice

(GCP) and regulatory requirements associated with both the management and conduct of the trial.

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.

Monitor

A person appointed by the Sponsor to undertake the role of monitoring for the trial. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.

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.

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.

Non-Compliance Report Form

Used by sites participating in MCRI-sponsored IITs to report non-compliance with protocol or GCP to the Sponsor-Investigator/CPI when their assessment suggests a serious breach has occurred.

Non-Compliance Review Form

Used by Sponsor-Investigator/CPI to review non-compliance report Forms submitted by participating sites. This form documents the review and assessment of whether the Sponsor-Investigator/CPI determines the non-compliance to meet the definition of a serious breach.

Protocol

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

Protocol Deviation

A protocol deviation is any breach, divergence or departure from the requirements of GCP or the clinical trial protocol.

Research Ethics and Governance Office (REG)

REG supports the HREC and institutional research governance processes at MCRI.

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).

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

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 and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. This can include diagnosis of cancer.

Serious Breach

A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial. Note: this guidance's definition of serious breach differs from the definition in the Australian Code for the Responsible Conduct of Research and is about deviations from the requirements of Good Clinical Practice or the clinical trials protocol.

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability of the trial.

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.

Suspected Breach

A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the Sponsor.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is a serious adverse event:

- Where there is at least a reasonable possibility of a causal relationship between an intervention and an adverse event (in other words the relationship of the SAE to the trial drug/device/other intervention cannot be ruled out)

  and
- That is unexpected, meaning that the nature or severity of the reaction is not consistent with the known scientific information (e.g. Investigator's Brochure for an unapproved investigational product or product information document or similar for an approved, marketed product)

The National Health and Medical Research Council (NHMRC)

NHMRC is Australia's leading expert body for: supporting health and medical research; developing health advice for the Australian community, health professionals and governments;

and providing advice on ethical behaviour in health care and in the conduct of health and medical research.

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. Third Party Suspected Breach Report Form

Form used by sites to directly notify the reviewing HREC of a suspected serious breach. This route is uncommon and used if the Sponsor disagrees with the site assessment that a serious breach has occurred.

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.

Urgent Safety Measure (USM)

A measure required to be taken to eliminate an immediate hazard to a participant's health or safety.

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

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

Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) annotated with TGA comments, available at https://www.tga.gov.au/sites/default/files/ich37795.pdf

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

Department of Health and Human Services Victoria, Coordinating Office for Clinical Trial Research

Information on requirements for trials can be found in "Research governance and Site specific assessment – process and practice" available at http://www.health.vic.gov.au/clinicaltrials/site-specific.htm

NHMRC

NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, Nov 2016, available at: https://nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods

8. APPENDICES

8.1. Appendix 1: Terms for Risk Assessment and Management

The objective for the institution is for each trial to run to completion, with adequate resources, and generate high quality evidence which will change clinical practice. The risk management plan is to ensure these objectives are met for all clinical trials conducted by MCRI.

RISK

A risk is defined as the effect of uncertainty on objectives. A risk is often assessed in terms of a combination of the consequences of an event and the associated likelihood of occurrence.

RISK IDENTIFICATION (SOURCE)

The purpose of risk identification is to find, recognise and describe risks that might prevent a trial achieving its objectives, and/or other risks eventuating for the institution that may emerge due to the trial activity. When identifying risks the following questions should be considered;

- What event(s) can happen that will have an adverse effect on the trial or the institution?
- How can it happen?

CONSEQUENCE

The impact identifies the significance of each risk (i.e. what are the effects to your trial if it risk does happen?). The impact may vary for each risk (for example the impact of funding shortfalls will vary depending on the magnitude of the shortfall)

RISK MITIGATION

Risk mitigation is an activity developed or planned to manage and/or reduce the risk.

LIKELIHOOD

Likelihood is the chance that something might happen. Likelihood is rated at: *Almost certain, Likely, Possible, Unlikely or Very unlikely*.

RISK MONITORING PLAN

This is the process whereby the risks would be identified when they materialise.

IMPACT LEVEL

The Committee or delegate (i.e. MCTC Medical Director (or Acting Director)) to complete what they believe is the impact level, based in the information provided and the type of risk and likelihood to occur. A rating of LOW, MED, HIGH for each risk will be assigned. The Sponsor–

Investigator needs to explain in significant detail the mitigation and management plan for risks considered Medium and High Impact.

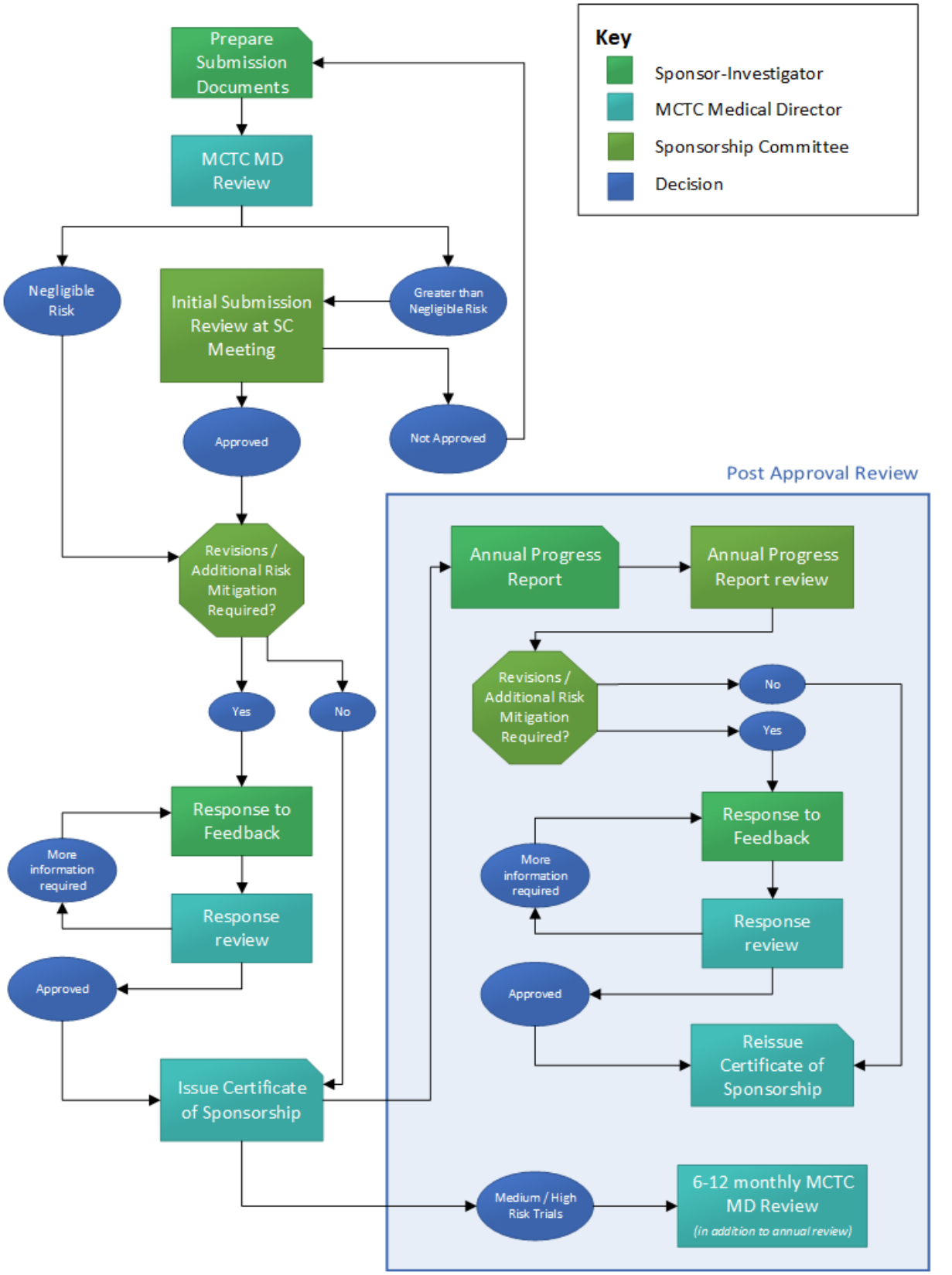
The number and type of risks with a HIGH impact level will determine the level of oversight required by the SC for each trial.

8.2. Appendix 2: Risk Management Table

The table below, "Table A: RISK IMPACT", helps the SC to make an Impact Level Assessment for each risk detailed for the trial. It is used to complete the last column of "MCTC006: Risk Assessment and Management Table". For example, a risk that has a possible likelihood of occurring and major consequences for the study outcome and/or for the organisation if it was to occur, is categorised as a HIGH (Red) RISK IMPACT.

Likelihood	Insignificant Consequences	Minor Consequences	Moderate Consequences	Major Consequences	Catastrophic Consequences
Almost Certain	Low	Medium	High	High	High
Likely	Low	Medium	High	High	High
Possible	Low	Medium	Medium	High	High
Unlikely	Low	Low	Medium	Medium	High
Rare	Low	Low	Medium	Medium	Medium

8.3. Appendix 3: Sponsorship Approval Process Flow



9. RELATED DOCUMENTS

- MCTC007 | Sponsorship Committee Application and Risk Matrix
- MCTC027 | Certificate of Sponsorship
- MCTC137 | Sponsorship Committee Progress update report
- MCTC005 | Safety Monitoring and Reporting Procedure for MCRI-sponsored investigator-Initiated Trials of Medicines/Medical Devices
- MCTC008 | Expedited Safety Report Form
- MCTC094 | Site PI Safety Reporting (IIT)
- MCTC095 | Sponsor Safety Reporting (IIT)
- MCTC123 | Management of non-compliance: Protocol Deviations and Serious Breaches
- MCTC061 | Continuous Improvement: A Corrective and Preventive Action (CAPA) Plan
- MCTC080 | Corrective and Preventive Action (CAPA) Plan template
- MCTC079 | Data sharing and access procedure for MCRI sponsored investigator-initiated clinical trials

DOCUMENT END