Title: Standard Operating Procedure (SOP) for Institutional Sponsorship Application and Approval for Sponsor-Investigator Initiated Trials (IITs).

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Andrew Davidson – Medical Director, Melbourne Children's Trial Centre (MCTC)

Signature:  **Date: 13Jan2020**

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Document History

Revision	Modified by	Change No.	Description of Change
1.0	Katie Arkell	N/A	New Issue

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).

An IIT is 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.

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. In the instance when MCRI agrees to act as the Sponsor of an IIT, MCRI will be the official name used on all relevant documents.

All applicable SOPs produced from 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 (updated May 2015) and the ICH Topic E6 (R2) Integrated addendum to ICH E6 (R1): Guideline for Good Clinical Practice (ICH E6 R2) with TGA annotations. Available from: https://www.tga.gov.au/publication/note-guidance-good-clinical-practice.

2. RESPONSIBILITY AND SCOPE

All trials conducted by MCRI require a specifically named 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.

When a trial has been designed by an organisation external to MCRI the trial is likely to have an external commercial or collaborative group sponsor. MCRI will not need to act as the sponsor in these instances.

The MCRI Sponsorship Committee (SC) will review and grant sponsorship for IITs conducted at sites within Australia. For sponsorship of international sites additional consideration is required by the SC.

MCRI will not support individual members of staff to personally act as the sponsor of a clinical trial. This requires Investigators to 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 project.

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, however, that any IIT in its early design stage be reviewed by the SC to ensure that the SC approval process does not slow down the Research Ethics and Governance process.

The SC does not primarily assess scientific quality, research merit or ethical acceptability of the trial design. The review by the SC will focus on the business risk for each trial and in particular, the information provided in the Risk Management Table (refer to Appendix 16.2 Table B).

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, it may be unclear if a protocol for a "pilot study" requires SC review.

3. 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 "Certificate of Sponsorship" outlines the responsibilities for MCRI, the investigator and the sites specific to each trial.

In these documents it states that the sponsor of a clinical trial assumes the overall responsibility for the initiation, management (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 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 2.2 October 2018, available at (https://www.tga.gov.au/publication/australian-clinical-trial-handbook).

4. APPLICABILITY

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)
  - ☐ Legal
  - ☐ Finance
  - ☐ Grants
  - ☐ Current & Experienced Principal Sponsor-Investigator(s) (at least one)

5. PROCESS FOR SPONSORSHIP

The SC will meet monthly (or more frequently if required) to review new trial applications for sponsorship.

The SC will identify any requirements for extra indemnity, insurance and contracts for a trial, on a case by case basis. The SC will advise Sponsor-Investigator (and REG where necessary) of these requirements for each trial reviewed.

The SC will review all sponsorship applications for new trials as of Q1 2020.

For a visual representation (flowchart) of the process, refer to the Process Flow Diagram (see section 16.4).

5.1. Submission Process for Sponsor-Investigators

For trials that require MCRI to be the sponsor, the protocol needs to be considered by the SC prior to submitting the protocol to the REG for review and approval. Sponsor-Investigators need to apply to the SC for approval by following the process outlined below (also summarized in Appendix 16 - Process Flow Diagram).

The Sponsor-Investigator needs to complete the

a) MCRI SPONSORSHIP COMMITTEE APPLICATION COVERSHEET and TABLE B: RISK MANAGEMENT TABLE (see Appendix 16) and provide it, along with the latest draft of the protocol, to the MCTC Medical Director (or Acting Director) (contact mctc@mcri.edu.au) for review. The protocol draft must provide a version date.

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

c) Once the MCTC Medical Director is satisfied with the documents, the trial documentation will be sent to the next SC meeting for approval.

d) The Sponsor-Investigator will need to attend the SC meeting to discuss the trial with the SC members.

   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 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.

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

e) The SC will discuss and decide at the meeting on the degree of oversight required and recommendations for monitoring.

f) Once the recommended revisions (if any) have been made 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 is called the "Certificate of Sponsorship"; note this certificate should be provided to the REG as part of the governance application.

Once the Sponsor-Investigator receives the "Certificate of Sponsorship" the Sponsor-Investigator should sign it, provide a signed copy to the MCTC Medical Director and proceed to complete their REG Application.

g) The Sponsor-Investigator must present the trial Risk Management Table for regular Review to the MCTC Medical Director. This review would usually be scheduled as an annual appointment but may be more frequent for high risk trials. The date of the annual review will be determined by the MCTC Medical Director. Any trials identified with an overall Risk Impact as "HIGH" or "RED" by the SC, may need to be added to the MCRI Risk Register.

5.2. Amendment Process Post Sponsorship Committee Approval

If changes are made to the protocol or trial that substantially impact the risk assessment *at any time* after approval by the SC, then the committee should be notified and the Risk Management Table should be updated and re-submitted.

Note that while the Sponsor-Investigator holds the primary responsibility for determining whether a protocol amendment substantially changes the risk of a trial, 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.

Where the amendment is deemed to change the trial's risk, REG will provide approval only after receipt of the updated "Certificate of Sponsorship" (i.e. the Certificate of Sponsorship is re-signed by the MCTC Medical Director, demonstrating the changes to the trial/protocol amendment have been sighted, considered and approved by the SC).

6. SUBMISSION DEADLINES

Applications for MCRI sponsorship to the MCTC Medical Director must be made at least 7 working days prior to the 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.

7. NOTIFICATION OF COMMITTEE DECISION TO NOT SPONSOR A TRIAL

For applications that have been rejected by the SC, the reasons for rejection will be provided to the Sponsor-Investigator in an email from the MCTC Medical Director. The Sponsor-Investigator may discuss the decision with the MCTC Medical Director, where appropriate.

8. OVERSIGHT OF SPONSORED TRIALS

The SC will advise the Sponsor-Investigator that they must present an updated Risk Management Table reflecting the current status of the trial on an annual basis (or more frequently, depending in the trial) to the

MCTC Medical Director. The date of review will be determined by the MCTC Medical Director (most likely 12 months from the date of the meeting).

It's important to note that this review is not "data monitoring" or an "audit".

9. WITHDRAWAL OF SPONSORSHIP APPROVAL MID-TRIAL

Any trials that have increased in any risk since starting must be re-assessed by the SC. The SC can then decide to withdraw sponsorship, if needed. This may then trigger the REG to withdraw Governance Authorisation (the TGA may need to be notified also).
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 Lead 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 what follow-up steps need to be completed.

10. SAFETY REPORTING CONSIDERATIONS

The 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 outlines the responsibilities of trial sponsors, Investigators, HRECs and institutions for safety reporting. It is the Sponsor-Investigator that is responsible for reporting safety events to the TGA and approving HREC.

Sponsor-Investigators must keep records of all adverse events (particularly serious adverse events (SAEs)) reported to them (for Interventional Investigational Medicinal Product or Investigational Medical Device trials) and are expected to maintain up-to-date tabulations of these events. This data needs to be readily available for the TGA, should they request to see it. This requirement is for the Sponsor-Investigator to easily conduct safety evaluations of the data on an ongoing basis (i.e. conduct Data Safety Monitoring Board (DSMB) Reviews at study milestones). Please note that not all clinical trials require a DSMB review. For guidance and information on establishing a Data Safety Monitoring Board Review, refer to the CRDO Guidance Document "Data and Safety Monitoring Boards" located on the CRDO web site.

If new safety information that meets the definition of a Significant Safety Issue (SSI) is discovered, and it requires an Urgent Safety Measure (USM) it should be reported to the TGA within 72hrs by the Sponsor-Investigator.

Data on 'other adverse events' should be recorded in tabular format. As a minimum, this table should include: Participant identification codes age, sex, name(s) of the therapeutic good(s) involved, dose and duration of treatment (including start and stop dates of treatment and dates SAEs occurred to help with causality assessment), nature of the reaction or event, condition being treated, potentially confounding factors and outcome.

For further information on this please refer to the CRDO SOP "Safety Monitoring and Reporting Procedure for MCRI-sponsored Investigator-Initiated Trials of Medicines/Medical Devices" and the associated process flow charts (all located on the CRDO web site).

11. IMPORTANT TO NOTE

The "Certificate of Sponsorship" is **not** the confirmation to commence recruitment. As mentioned previously, this is simply the notification to proceed with the Ethics and Governance Application for the trial.

RCH HREC will approve an ethics application for MCRI Sponsored trials until the SC has issued a "Certificate of Sponsorship".

12. 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.

13. GLOSSARY

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'.

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.

Governance Office/r
The Office or coordinated function within a Public Health Organisation which is responsible for assessing the site-specific aspects of research applications, make a recommendation to the District 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).

Delegate
A person delegated specific but appropriate QA tasks in relation to SOP generation

HREC
Human Research Ethics Committee

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 / Principal Investigator/ Coordinating Investigator/ Associate 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 as described below.

- 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.

- A senior member of the clinical trial team designated and supervised by the investigator at a trial site to perform trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows, clinical research coordinators may be called an Associate Investigator. The Principal Investigator will designate who will be nominated as Associate investigators for the site.

- 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.

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.

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 authorization 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.

MCRI
Murdoch Children's Research Institute

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.

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.

Research Ethics and Governance Office (REG)
REG supports the HREC and institutional research governance processes at MCRI.

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 jeopardize 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.

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.

Standard Operating Procedure (SOP)
Detailed, written instructions to achieve uniformity of the performance of a specific function.

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.

Sponsor-Investigator
For Investigator-Initiated Trials/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. For the purposes of this SOP, we simply have used the term "Investigator".

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)

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.

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.

Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors.

Urgent Safety Measure

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

14. 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

15. Certificate of Sponsorship

Please refer to supporting document "MCRI Certificate of Sponsorship" which is a separate document to this SOP. The "MCRI Certificate of Sponsorship" has both signatures from the MCTC Medical Director (representing the SC) and the Sponsor-Investigator and outlines the tasks each party is responsible for and is specific for each trial.

The ''MCRI Certificate of Sponsorship'' needs to be re-signed by the MCTC Medical Director or delegate each time a 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.

16. APPENDICES

16.1. Terms for Risk 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 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.

16.2. Application Coversheet

APPLICATION COVERSHEET MCRI SPONSORSHIP COMMITTEE

murdoch children's research institute

Project Reference Number: Please also refer to the guidance material on "How to get a project reference number."		
Project Title:		
Co-ordinating Principal Researcher	**Name**	
	Dept or Group	**Institution**
	Phone	**email**
Contact Person (if different from above)	**Name**	
	Dept or Group	**Institution**
	Phone	**email**
Do you wish MCRI to be the Sponsor of this trial?	☐ Yes	☐ No
Is the protocol attached?	☐ Yes	☐ No

Steps for researchers to complete:

1. Read "Standard Operating Procedure (SOP) for Institutional Sponsorship Application and Approval for Sponsor- Investigator Initiated Trials (IITs)" via this research link: https://www.rch.org.au/research/researchers
2. Complete "Table B: The Risk Management Table" for your project.
3. Contact the MCTC Medical Director (email crdo.info@mcri.edu.au) to arrange a review of the documents listed below:
    a. *This application coversheet*
    b. *Draft or Final Protocol*
    c. *Any relevant supporting documents for your protocol (i.e. Investigator Brochure (if you have one))*
    d. ***Completed*** *Table B: Risk Management Table*
4. Attend review meeting with MCTC Medical Director to discuss project prior to sponsorship committee review

Please list below all the institutions planning to conduct this research if different from above.

Please provide names of all participating sites, if there are more than 3, add an additional page to this application if needed

Name of Institution		
Name of Contact Person		
International	☐ **YES**	☐ **NO**
Name of Institution		
Name of Contact Person		
International	☐ **YES**	☐ **NO**
Name of Institution		
Name of Contact Person		
International	☐ **YES**	☐ **NO**

For MCRI Sponsorship Committee to Complete:

Original Submission	Date
Review by MCTC Director	Date
Review at Sponsorship Committee Meeting	Date

16.3. Risk Management Table A and B

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 Table B. 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 (see Table A).

Table B is prepopulated with 10 risk categories. Most would be applicable to all trials. Each category may have a number of distinct risks. The table has in italics some examples of risks in each category. These are examples which would be applicable to most trials. Sponsor- Investigators may delete those risks that are clearly not applicable and add other risks that are relevant to their trial. It would be expected that Sponsor- Investigators identify individual risks, beyond those given as examples. The table also includes examples in italics of possible impacts and mitigation strategies. Sponsor- Investigators should not just cut and paste these. Each should be considered carefully in the context of the trial and amended or added to as appropriate.

Table A: 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

Table B: RISK MANAGEMENT TABLE

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
1) INADEQUATE FUNDING					
1.1 FUNDING WILL RUN OUT PART-WAY THROUGH THE TRIAL	*Resources for managing and conducting trial will not be available, trial may not run to completion*	Choose an item.	*We have funding from the following sources and we plan to seek further funding form the following source*	*PI will review budget 6 monthly*	

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
2) RECRUITMENT FAILS TO MEET TARGET					
2.1 INNACURATE ESTIMATE OF PARTICIPANT AVAILABILITY	*Insuffiicent participant recruitment will mean the study will not have sufficient data to make a satisfactory conclusion regarding the end-point of the study*	Choose an item.	*Pilot data on availability of eligible participants has been collected* *Consent likely to be high due to low burden/low risk for participants*	*NA*	
2.2 SLOWER RECRUITMENT THAN EXPECTED	*Insuffiicent participant recruitment will mean the study will not have sufficient data to make a satisfactory conclusion regarding the end-point of the study. Costs may increase*	Choose an item.	*Extend study duration if needed* *Open new sites if needed* *Identify and increase recruitment efficiency at each site* *Alter inclusion criteria if needed*	*Recruitment rates will be reviewed quarterly by the trial steering committee or DSMB*	

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
			Mass media strategy to increase public awareness		
3) OUTCOMES NOT COLLECTED					
3.1 OUTCOME MEASURES NOT FEASIBLE	*Loss of primary outcome data*	Choose an item.	*Outcome is a widely recognised tool* *Outcomes have been assessed to be feasible in pilot studies* *Sponsor- Investigators and trial staff trained appropriately in outcome collection*	*DSMB will monitor primary outcome data*	

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
3.2 PARTICIPANT DROP OUT	*Loss of priary outcome*	*Choose an item.*	*Careful selection of participants based on…* *Retention of participant enthusiasm through…*	*DSMB will monitor primary outcome data*	
4) PROTCOL VIOLATION					
4.1 PROTOCOL DIFFICULT FOR PARTICIPANTS TO COMPLY WITH	*Loss of outcome data*	Choose an item.	*Protocol tested in feasibility studies* *Amendments will be made as required*	*Outcome data monitored by DSMB and Trial Steering Committee (TSC)*	
4.2 PROTOCOL DIFFICULT FOR FELLOW INVESTIGATORS/CLINICIANS TO FOLLOW	*Loss of outcome data*	Choose an item.	*Protocol is simple and does not vary substantially from standard of care* *Protocol tested in feasibility studies*	*Trial management team will review sites regularly to ensure protocol is being followed*	
5) DATA AND SAMPLES					

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
5.1 ERRORS IN DATA COLLECTION	*Loss of outcome data*	Choose an item.	*CRFs piloted and found to be easy to complete*	*Data cleaning will be performed in real time and errors reported to trial TSC*	
5.2 ERRORS IN DATA ENTRY	*Loss of outcome data*	Choose an item.	*Source data regularly checked as follows…* *Data will be double entered* *Checks placed in data base*		
5.3 LOSS OF DATA THROUGH THEFT, MALWARE ETC	*Loss of data*	Choose an item.	*Follow MCRI data husbandry policies* *Use recognised secure database maintained on and institute platform*		
5.4 LOSS OR DEGRADATION OF SAMPLES OR SPECIMENS	*Loss of data*	Choose an item.	*Follow MCRI policies* *Use of core lab to store specimens*		

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
			Use of appropriate refrigerators with appropriate alarms and backup power		
6) STAFF AND SKILLS					
6.1 LACK OF EXPERIENCE IN TRIAL CENTRAL MANAGEMENT	*Failure of trial goals*	Choose an item.	*Senior staff on trial team* *Mentorship from senior staff on team* *Experienced coordinator employed* *Mentorship from experienced coordinator*		
6.2 LACK OF TRIAL STATISTICS SKILLS	*Inapprorpiate analyses*	Choose an item.	*Trial statistician on study team* *Mentorship and supervision from experienced trial statistician*		

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
6.3 SITE COORDINATOR OR RA UNDER SKILLED	*Poor data collection and protocol adherence*	Choose an item.	*Site staff trained* *CVs maintained for all site staff* *Initiation visits to ensure site staff trained*	*Central coordinator will ensure site staff qualifications recorded and reviewed*	
7) TEAM COHESION					
7.1 OVERALL TEAM COHESION FAILS DURING THE TRIAL	*Poor recruitment and data collection*	Choose an item.	*Regular meetings across sites* *Regular trial meetings and updates at conferences* *Regular newsletters to all involved Sponsor-Investigator and central study coordinator regularly visits all sites*	*PI visits sites*	
8) CONTRACTS AND INDEMNITY					

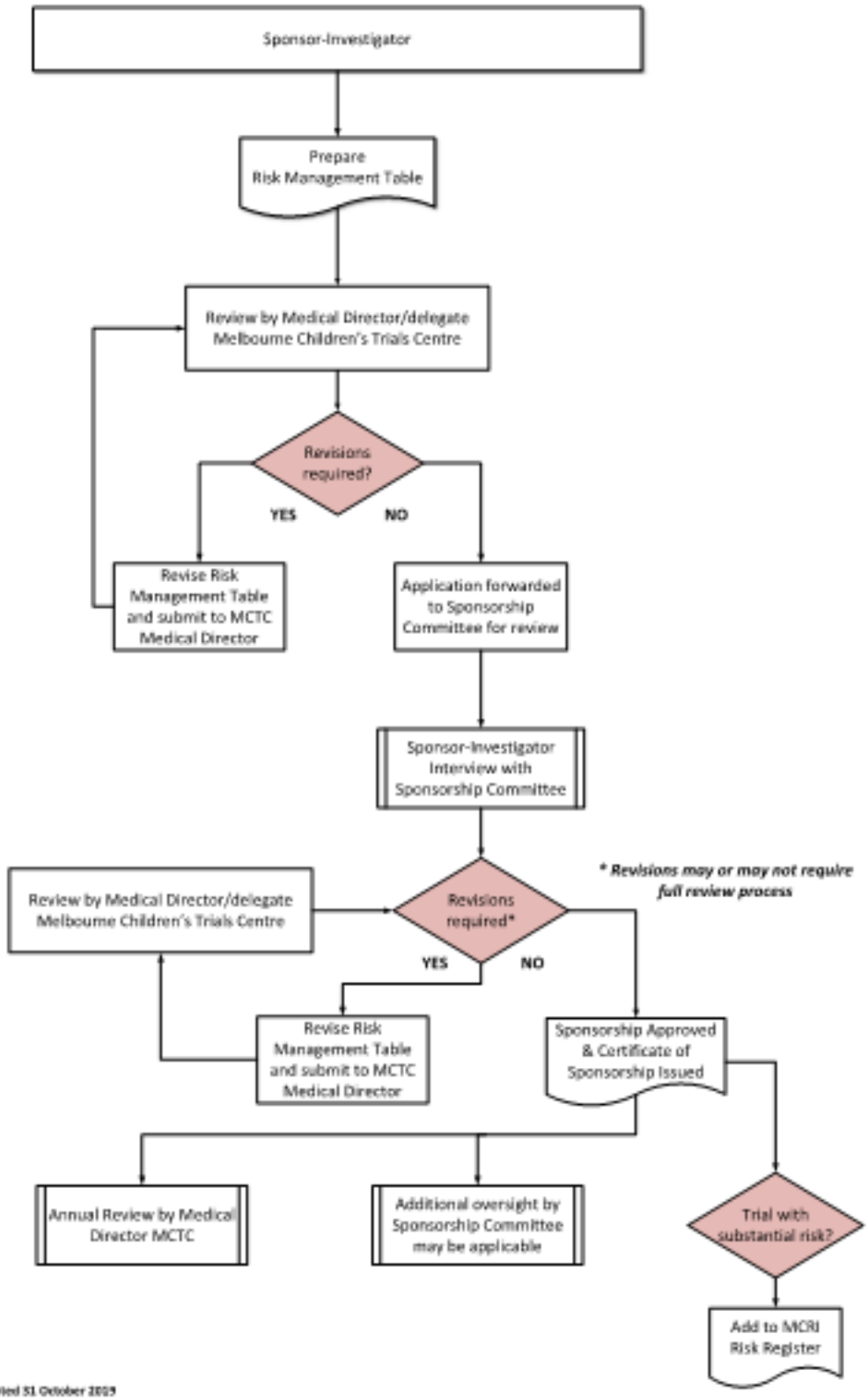
Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
8.1 CONTRACTS NOT IN PLACE	*Disputes lead to poor cohesion or failre to publish* *Delay in recruitment if not in place*	Choose an item.	*Ensure all appropriate contracts between sites are in place*	*PI ensures contracts in place before recruitment at each site*	
8.2 INDEMNITY NOT IN PLACE	*Sponsor-Investigators and institutions liable* *Delay in recruitment if not in place*	Choose an item.	*Ensure appropriate indemnity in place prior to recruitment at each site*		
9) IMPACT					
9.1 QUESTION IS IRRELEVANT TO PRACTICE	*Trial has limited impact*	Choose an item.	*Stakeholders are engaged before design finalised*		
9.2 QUESTION BECOMES IRRELEVANT DUE TO OTHER ADVANCES IN UNDERSTANDING OF THE	*Trial has limited impact* *Trial may be stopped as it is futile*	Choose an item.	*NA*	*Literature monitored by Sponsor-Investigator or DSMB*	

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
PROBLEM OR ANOTHER SIMILAR TRIAL IS PUBLISHED					
10) HARM TO PARTICIPANT					
10.1 INTERVENTION IS UNSAFE	*Patient harmed* *Trial suspended* *Sponsor-Investigators liable*	Choose an item.	*Protocol reviewed by HREC, CTX filed with TGA* *Intervention is similar to standard of care*	*DSMB monitors events*	
10.2 PROTOCOL IS INHERENTLY UNSAFE	*Patient harmed* *Trial suspended* *Sponsor-Investigators liable*	Choose an item.	*Protocol reviewed by TGA, via CTX and/or HREC*	*DSMB monitors events*	
10.3 ERROR IN FOLLOWING PROTOCOL	*Patient harmed* *Trail suspended*	Choose an item.	*Site staff trained*	*Chief coordinator reviews delegation log*	

Risk Identification ***What event(s) can happen and how it can happen***	**Consequence** ***What are the effects if the risk does occur***	**Likelihood** ***What are the chances that the risk will actually happen***	**Mitigation Strategy** ***What are you doing to prevent the risk from happening or manage the risk if it does happen***	**Risk Monitoring Plan** ***How will you monitor this risk?***	**Impact Level** ***Assigned by Committee from Table 16.1 asssessed on likelihood and consequence*** **LOW (Green)** **MED (Orange)** **HIGH (Red)**
			Delegation log kept to ensure only trained staff are involved in the trial	*Sites are audited* *DSMB monitors events*	

16.4. Process Flow Diagram

Investigator Initiated Trials – Process Flow for Sponsorship Approvals



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AUTHORISED BY
MCRI Sponsorship Committee

AUTHOR/CONTRIBUTORS
Katie Arkell – Snr Project Officer, MCRI

In Consultation With
CRDO and MCTC

REVIEW AND UPDATING
This SOP will be reviewed every whenever there are changes to legislation or working practices that impact upon the content of this document. This SOP may be merged with another SOP if appropriate or removed entirely if it becomes redundant.

DOCUMENT END