Melbourne Children's clinical trial (drug or device intervention) protocol template: Notes to users

Protocol template version	DRUG OR DEVICE INTERVENTION PROTOCOL TEMPLATE Version dated 29 November 2019 This template has been developed by Murdoch Children's Research Institute's (MCRI) Clinical Research Development Office (CRDO) and the Clinical Epidemiology & Biostatistics Unit (CEBU) for the Melbourne Children's Trials Centre (MCTC).
Why do you need a protocol?	The protocol is essential for the conduct, review, reporting, and interpretation of any research study.
Why use this template?	This template is appropriate for **clinical trials*** of drug, biologic or device interventions. These may be **investigational products** or marketed products** being used within the conditions of their TGA approval. * The World Health Organization (WHO) definition of 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". ** An **investigational product** is defined as "any investigational medicine/device, reference product/device or placebo being tested or used as reference in a clinical study" (*Access to unapproved therapeutic goods - clinical trials in Australia, 2004 Therapeutic Goods Administration [TGA]*). Note that investigational products used in clinical trials are often products that are not currently approved by Australia's regulatory body (the TGA) *OR* they may be approved but in the trial will be used outside their approved indication. Through TGA's CTN and CTX schemes, the TGA regulates access to unapproved products being used in a clinical trial. The schemes allow access to a product that is: • not listed on the Australian Register of Therapeutic Goods (ARTG), including any new formulation of an existing product or any new route of administration; *or* • listed on the ARTG but is planned to be used outside the conditions of its approval. The investigational product being tested in the trial may be: • An **Investigational Medicinal Product (IMP)** defined as 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, a new patient group or when used to gain further information about an approved use. This definition includes biologicals used as investigational medicinal products."

	• Or an **Investigational Medicinal Device (IMD) defined as a "**Medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes. If your research involves an investigational medicinal device, note the following: • The term used throughout this template is "investigational medicinal product". For clarity, replace with investigational device. • Note that the good clinical practice guidelines adopted by the TGA ["Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016" do not cover IMDs. A separate good clinical practice guideline specific to investigations of devices (ISO 14155 version 2011) is available for purchase (single-user licenses) at https://www.iso.org/standard/45557.html All researchers please also note: • For trials conducted under the CTN/CTX schemes, please contact CRDO/MCTC for assistance with the additional documentation required. • Safety-related reporting guidance is also provided in "NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (dated November 2016)" at https://www.nhmrc.gov.au/guidelines-publications/eh59 • Internal staff should contact CRDO for advice on how to comply with this guidance. • If the trial results are to be submitted to the U.S. Food & Drug Administration (FDA), you should use the protocol template provided by the FDA. Contact CRDO for further information (including how to also include wording to cover Australian safety reporting requirements). • If you are not certain if this template is appropriate for your research, or you require guidance on developing a protocol, please contact CRDO Note that on the CRDO website you will also find protocol templates for use in the following research: ○ Clinical trial using a non-drug, non-device intervention ○ Research not involving an intervention • The guidance in this template has been derived from a number of sources (see the 'Resources' section of this table for details).
How to use this template?	There is a brief explanation in ***purple italics*** under each heading stating the information that should be contained in that section. A paragraph of suggested or example wording is included after this for

	standard sections in *green italics*. You will need to input your clinical trial specific information under each heading and remove explanatory information. It is not necessary to include text under a major numbered heading (e.g., 1, 2) that is immediately followed by numbered subheadings, (e.g., 2.1, 2.2). That is because certain numbered headings are used only for organisational purposes. Text should be entered under all numbered subheadings. As this is a template, users are reminded that not all sections or examples may be applicable to their clinical trial. Please delete any sections that are not relevant to your clinical trial.
Having completed the Human Research Ethics Application (HREA) do I still need a protocol?	Yes, in fact you should finalise your protocol prior to completing the HREA. The HREA form is used by ethics committees to conduct standard review of all projects. While you need to refer to your protocol to answer most questions in the HREA, it does not replace the need for a detailed protocol.
Resources	The guidance in this template has been derived from a number of sources including:
	• NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template at https://osp.od.nih.gov/clinical-research/clinical-trials/ • NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (dated November 2016) https://www.nhmrc.gov.au/guidelines-publications/eh59 • Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 Annotated with TGA comments http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf • CONSORT statement at http://www.consort-statement.org/ • ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies available from https://prsinfo.clinicaltrials.gov/definitions.html • CRDO – various standard operating procedures and templates (refer to the CRDO internet site at https://www.mcri.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative

PROTOCOL

<CLINICAL TRIAL IDENTIFIER>

A short reference for the clinical trial, such as a protocol number or acronym, is optional. However it can be more practical than the full clinical trial title. The specified identifiers and titles must be consistent across all documents related to the clinical trial.

[Insert full clinical trial title]

The full clinical trial title should be kept brief but mention the trial design, the population and the intervention to be studied.

Protocol Number (if applicable): *[insert protocol number]*

Protocol Version # and date: *[insert version # and date here & in footer]*

Document history:

Table each change made to the protocol, with the most recent at the top of the table. The protocol may be updated due to queries raised by an ethics committee, or changes may be required during the life of the project.

A version date must always be present on every page (header or footer) of the draft and final protocols. The version date of an approved protocol should reflect the date of the last changes prior to an ethics submission.

Version Number and Date	Summary of changes
	Include here a simple reason for why the change was made, for example "updated post HREC review"

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

Or for research to be conducted internationally (delete if not appropriate): <This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.>

Delete if not appropriate <This clinical trial is not sponsored by any pharmaceutical company or other commercial entity.>

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PROTOCOL SYNOPSIS

The protocol synopsis provides a brief outline of the key elements of the trial. It allows a quick reference to the project details (as an abstract allows for a manuscript). The protocol synopsis should generally not exceed two pages in length) and is ideally presented as a table such as the following.

TITLE	*Insert full title*
TRIAL DESCRIPTION	*A brief overview of the trial design, including trial groups (if applicable).* *This should be only a few sentences in length. A detailed schematic describing all visits and assessments should be included in the main protocol.*
OBJECTIVES	*Insert objectives copied from the body of the protocol. Include the primary objective and all secondary objectives.* • *<Insert primary objective>* • *<Insert secondary objectives>*
OUTCOMES AND OUTCOME MEASURES	*Specify specific outcomes and outcome measures (i.e. how the outcomes will be measured) for the objectives listed above* *N.B. Outcomes are also known by the term "Endpoint"* • *<Insert Outcome and outcome measure* *e.g. > IQ at 4 years of age as assessed by FSIQ*
TRIAL POPULATION	*Population information, including any restrictions on gender, age, demographic group, general health status, geographic location. This should also include the planned sample size.(total number of participants for the project , and the approximate number per group if more than one group.*
DESCRIPTION OF SITES ENROLLING PARTICIPANTS	*Provide a brief description of participating sites (e.g. planned countries, planned number of sites)*
DESCRIPTION OF INTERVENTIONS	*Describe EACH trial intervention (including the intervention in the control group if applicable).* • *For a drug or biologic, include dose and route of administration.* • *For devices, provide a description of each important component, ingredient, property and the principle of operation of the device.*
TRIAL DURATION	*Estimated time (in months) from when the trial opens to enrolment until completion of data analyses.*
PARTICIPANT DURATION	*Time (e.g., in months) it will take for each individual participant to complete all participant visits.*

GLOSSARY OF ABBREVIATIONS

All abbreviations used in the protocol, including appendices, should be listed with an explanation of each abbreviation. Accepted international medical abbreviations should be used. All abbreviations should be spelled out when first used in the text, followed by the abbreviation in parentheses. Common units of measure like mg or mL don't need to be defined in the text or this list.

*The following list is an **example only**. Add and delete abbreviations as appropriate for your protocol.*

ABBREVIATION	*TERM*
AE	*Adverse Event*
ANOVA	*Analysis of Variance*
AR	*Adverse Reaction*
BRF	*Biobank Registration Form (MCRI)*
CRF / eCRF	*Case Report Form / electronic Case Report Form*
DMC SMC	*Data Monitoring Committee / Safety Monitoring Committee*
DSMB	*Data Safety Monitoring Board*
FDA	*Food and Drug Administration*
GCP	*Good Clinical Practice*
GLP	*Good Laboratory Practices*
GMP	*Good Manufacturing Practices*
HREC	*Human Research Ethics Committee*
IB	*Investigator's Brochure*
ICH	*International Conference on Harmonisation*
IMP	*Investigational Medicinal Product*
ISO	*International Organization for Standardization*
ITT	*Intention To Treat*
MCRI	*Murdoch Children's Research Institute*
MCRI	*Murdoch Children's Research Institute*
MedDRA	*Medical Dictionary for Regulatory Activities*
MSDS	*Material Safety Data Sheet*
NHMRC	*National Health and Medical Research Council*
PI / CPI	*Principal Investigator / Coordinating or Chief Principal Investigator*
PI	*Product Information (available for an approved drug or device)*
QA	*Quality Assurance*
QC	*Quality Control*
RGO	*Research Governance Office*
RCH	*Royal Children's Hospital (Melbourne)*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SAR	*Serious Adverse Reaction*
SMC	*Safety Monitoring Committee*
SoA	*Schedule of Assessments*
SOP	*Standard Operating Procedure*
SSI	*Significant Safety Issue*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
TGA	*Therapeutic Goods Administration*

UAR	*Unexpected Adverse Reaction*
USM	*Urgent Safety Measure*

Abbreviations specific to Investigational Medical Device trials:

ADE	*Adverse Device Effect*
IMD	*Investigational Medical Device*
SADE	*Serious Adverse Device Effect*
USADE	*Unanticipated Serious Adverse Device Effect*

This template uses the following terminology with regards to the term 'investigators':

- ***Sponsor-Investigator** – is used to describe the **overall trial level** Investigator for both multi-site (i.e. replaces the term Coordinating Principal Investigator) and single-site (i.e. replaces the term Principal Investigator) trials. This person has the role of both Sponsor and Investigator as defined in ICH GCP.*
- ***Participating Site Principal Investigator** – is used to describe **the site-level** Investigator (i.e. the site Principal Investigator) at a participating site (i.e. not the lead site) in a multi-site trial.*

INVESTIGATOR AGREEMENT

The investigator / institution should conduct the trial in compliance with the protocol…which was given approval by the HREC/IRB/IEC. The investigator / institution should sign the protocol or an alternative contract to confirm agreement.

I have read the protocol entitled "<***Enter trial title***>".

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki and the good clinical practice guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].

Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee or Institutional Review Board (as appropriate), with the exception of medical emergencies.

I will ensure that trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log.

Name	Role	Signature and date

1. ADMINISTRATIVE INFORMATION

1.1. Trial registration

1.1.1. Trial registry

Trial identifier and registry name. If not yet registered, name of intended registry e.g. ClinicalTrials.gov or http://www.anzctr.org.au/

The Melbourne Children's Trials Centre's (MCTC's) registry of choice is ClinicalTrials.gov for several reasons, which include oversight of the registration process by MCTC and superior quality assurance review by ClinicalTrials.gov
Review CRDO's guidance on the requirements for and process of clinical trial registration – available on the CRDO website.

1.2. Sponsor

Provide name and contact information for the trial sponsor. The sponsor is the company or institution that takes responsibility for the initiation, management and financing (or arranging the financing) of the trial. The factors which determine sponsorship include: the nature of the funding, the employer of the principal investigator and the duty of care to participants. Include, if applicable, the role of trial sponsor in trial design; collection, management, analysis, and interpretation of data; writing of the report and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

For MCRI investigator-initiated clinical trials without an external sponsor, the sponsor should be listed as MCRI. Taking on the role of Sponsor means taking on the liability for harm caused by the trial design, the liability for not working to Australian regulation. In addition there is also the reputational risk associated with the potential discover of poor quality or unsafe research audit or regulatory inspection. To mitigate these risks, the Sponsor must ensure that the trial is conducted in accordance with the National Statement, the Australian Code, GCP and relevant regulatory requirements. Where MCRI is the Sponsor, MCRI delegates some Sponsor responsibilities to the Coordinating Principal Investigator leading the trial. The term "Sponsor-Investigator" has been adopted by MCRI for this role.

A listing of the responsibilities delegated to the Sponsor-Investigator should be documented either as an appendix to the protocol or in a separate document which is referred to in the protocol.

Trial Sponsor	
Contact name	*If MCRI is the sponsor, insert Sponsor-Investigator (Coordinating Principal Investigator) name*
Address	
Sponsor-Investigator *(where applicable)*	

Example text where MCRI is the Sponsor:
"On behalf of the Sponsor, MCRI, the Sponsor-Investigator leading the trial will undertake and/or oversee those Sponsor responsibilities delegated by the Sponsor. The delegated Sponsor responsibilities are documented in <Appendix # of the protocol / in the document <insert name>)."

1.3. Expected duration of study

Specify the expected duration of the recruitment period.

Specify the length of the treatment period and the follow-up period for an individual in the trial.

*When entering information into **CLINICALTRIALS.GOV** note that **THE ANTICIPATED PRIMARY COMPLETION DATE WILL BE THE PERIOD** from the start of participant screening to collection of the primary outcome data for the last participant.*

1.4. Contributorship

Names, affiliations, and roles of protocol contributors

Name	Summary of contribution

1.5. Stakeholder involvement

A stakeholder can be understood as a person, group or organisation who has an interest (something to gain or lose) in the outcome of a planning process, program or project. Stakeholders can be internal or external and can include, for example, supporting departments on campus, other health organisations (primary, secondary, tertiary), government (local, state, federal), professional bodies, educational organisations, community organisations and, of course, children and adolescents, parents and families. Some may be consumers, in particular children and adolescents, parents and families.

The NHMRC states that "Engagement with stakeholders is integral to the development and implementation of NHMRC clinical trial reform initiatives." (https://www.nhmrc.gov.au/research/clinical-trials/overview-nhmrc-engagement-stakeholders).

The NHMRC increasingly expects that researchers will have involved stakeholders and consumers in the development of clinical trial protocols. Explain here how the protocol authors have consulted with stakeholders and how they have engaged consumers.

2. INTRODUCTION AND BACKGROUND

The following subsections should include the rationale for the clinical trial, relevant background information and a risk/benefit assessment. This should be a brief overview (e.g., approximately 3-7 pages). It is appropriate to refer readers to the Investigator's Brochure (IB) or Product Information for more detail on the investigational medicinal product if relevant.

The reader should be given a clear idea of the following:

- *What the research question is;*
- *An understanding that it is original and relevant;*
- *How the proposed trial will help fill the gap in the literature.*

The background should therefore include:

- *A summary of findings from nonclinical studies that have potential clinical significance*
- *A summary of relevant clinical research and any history of human use or exposure to the trial intervention, including use in other countries, and clinical pharmacology studies*
- *Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference, citations)*

- *Note that the NHMRC increasingly expects to see reference to a systematic review in grant applications so it is recommended that, where such reviews exist, researchers refer to these.*

- *Applicable clinical, epidemiological, or public health background or context of the clinical trial*
- *Importance of the clinical trial and any relevant treatment issues or controversies*

2.1. Trial rationale and aim

Briefly state the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy) and the reason for conducting the clinical trial.

Specify the overall aim of the trial - for example, you aim to verify, to investigate, to measure, to determine, to compare or to calculate…

- *Use the verb form starting with 'to' (e.g. 'to investigate').*
- *Avoid the noun form which often ends in '-ion' (e.g. 'investigation').*

***Example text:** The aim of this trial is to assess the efficacy and safety of <product A> in children after tonsillectomy compared to <product B>…*

2.2. Background

Provide background information on the condition/disease being studied. Suggested flow:

- *Current prevalence and outcomes of the condition/disease state.*
- *What we know about the disease state.*

Provide background information on the current treatment options (if any), investigational medicinal product and comparators. Suggested flow:

- *Current treatment options (if any) and the associated issues, risks and benefits;*
- *Outline the investigational drug's potential role in the clinical condition being studied, with reference to available data. Provide a focused review of findings from previous related studies (if available) from (i) studies in children and/or adolescents and (ii) non- human studies with potential clinical significance;*
- *Explain why (if applicable) you have chosen the comparator(s) you have OR Justify why (if applicable) you plan not to consider any comparison group in your investigation; Explain why the research needs to be conducted in the selected population;*
- *Demonstrate that the outcome measures (i.e. the measures used to assess the objectives) are valid across the age groups studied and, if applicable, gender;*
- *Explain how the trial will substantially add to science, change practice, save money, save lives and/or improve quality of life.*

2.3. Risk/Benefit assessment

2.3.1. Known potential risks

Include a discussion of known potential risks from either clinical or nonclinical studies of the intervention under investigation. If a package insert or device labelling from a licensed or approved product (Product Information) is available, it should be used as the primary source of risk information. If the product is investigational, the IB should be the primary source of the risk information. In addition, relevant published literature can also provide relevant risk information. If the risk profile cannot be described from the package insert, device labelling, or the IB, the risk information discussion will result from published literature and should be included and referenced appropriately.

Describe any physical, psychological, social, legal, economic, or any other risks to participants by participating in the trial that the Site Principal Investigator (PI) foresees by taking part in the trial, addressing each of the following:

- *Immediate risks*
- *Long-range risks*

If risk is related to proposed procedures included in the protocol, describe alternative procedures that have been considered and explain why alternative procedures are not included

2.3.2. Known potential benefits

Include a discussion of known potential benefits from either clinical or nonclinical studies of the intervention under investigation. If Product Information is available for a licensed or approved product is available, it should be used as the primary source of potential benefit information. If the product is investigational, the IB should be the primary source of the potential benefit information. In addition, relevant published literature can also provide potential relevant benefit information. If the potential benefit cannot be described from the package insert, device labelling, or the IB, the potential benefit information discussion will result from published literature and should be included and referenced appropriately.

Describe any physical, psychological, social, legal, or any other potential benefits to individual participants or society in general, as a result of participating in the trial, addressing each of the following:

- *Immediate potential benefits*
- *Long-range potential benefits*

Note that payment to participants, whether as an inducement to participate or as compensation for time and inconvenience, is not considered a "benefit." Provision of incidental care is also not to be considered a benefit.

2.3.3. Assessment of potential risks and benefits

Include an assessment of known potential risks and benefits of the intervention under investigation and discuss why the risks to participants are reasonable in relation to the anticipated benefits and or knowledge that might reasonably be expected from the results ensuring that the following are addressed:

- *Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the trial design;*
- *Justification as to why the risks of participation in the trial outweigh the value of the information to be gained.*

3 TRIAL OBJECTIVES AND OUTCOMES

*An **objective** is the purpose for performing the trial (i.e. the scientific questions to be answered). Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., efficacy, effectiveness, safety) and/or specific purpose (e.g., dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behaviour).*

*An **outcome** is a specific measurement or observation to assess the effect of the trial intervention. Trial outcomes should be prioritized and should correspond to the trial objectives and hypotheses being*

tested. Give succinct, but precise definitions of the trial outcomes used to address the trial's primary objective and secondary objectives (e.g., specific laboratory tests that define safety or efficacy, clinical assessments of disease status, assessments of psychological characteristics, participant-reported outcomes, behaviours or health outcomes). Include the trial visits or time points at which data will be recorded or samples will be obtained. Describe how outcomes(s) will be adjudicated, if applicable.

Notes:

- *A table can be used to present the objectives along with their associated outcome and outcome measurement (see end of section for suggested format).*
- *When registering and reporting trials to the trial registry ClinicalTrials.gov, the terms Objectives and Outcomes (also known as Endpoints) as used in this template align with the terms Primary Purpose and Outcome Measures in ClinicalTrials.gov, respectively.*

3.1 Objectives

The objectives must be very precise statements about the overall aim that is to be achieved. It is common for a trial to have between 2 and 4 specific objectives that are components of the overarching aim. ***There should only be one primary objective*** *- ensure that this supports the statistical outcomes, and that it is specific and objective.*

3.1.1 Primary objective

The primary objective is the main question to be addressed within the trial. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).
Define the primary objective in terms of the population, intervention, comparator and outcome that will be measured in a single clear and concise statement.

Example text: *"The primary objective of this trial is to evaluate the impact of <trial treatment> on time to resolution of <condition> in <type of participants> compared with placebo"*

3.1.2 Secondary objectives

A trial may or may not have secondary objectives. Secondary objectives consider outcomes of interest that may or may not be related to the primary objective. Secondary objectives may or may not be hypothesis-driven and may include more general non-experimental objectives (e.g. to develop a registry, to collect natural history data). The number of objectives should be kept low as too many objectives may make the trial logistically difficult to perform. Also consider that the sample size calculation is based on the primary objective and it may not be possible to satisfy other objectives with this sample size.

Example text*: "The secondary objectives of this trial are:*

1. *To determine the safety and tolerability of <trial treatment> in <type of participants> with <condition>.*
2. *To determine the impact of <trial treatment> on healthcare utilisation in < type of participants> with <condition>."*

3.1.3 Exploratory objectives

A trial may or may not have additional exploratory objectives. Their purpose is to further explain or support findings of primary and secondary analyses and to suggest further hypotheses for later research.

3.2 Outcomes

*The **outcomes** (also known as endpoints) are the variables which are used to assess the effect of the trial intervention and therefore the trial objectives. Primary, secondary, and exploratory outcomes should be clearly specified and include:*

- *Their respective outcome measures (i.e. the method for measuring an outcome e.g., systolic blood pressure or a specified validated questionnaire)*
- *description of the metric used to characterise the measure (e.g., change from baseline, final value, time to event, maximum)*
- *The timeframe (i.e., total duration of the time period, specific time points) over which the measurement will be assessed.*
- *All of **this information is required for registration of the trial on ClinicalTrials.gov***

This section should also include any definitions used to characterize outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterization of a stroke as thrombotic or haemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully.

A brief explanation (i.e. a justification) should be provided to explain why these outcomes were chosen.

Primary outcome *The primary outcome is the basis for concluding whether or not the trial has met its primary objective. There should be just one primary outcome that will provide a clinically relevant, valid, and reliable measure of the primary objective. In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit.*

The primary outcome should incorporate the selected outcome measure, which is the method for measuring an outcome (e.g., systolic blood pressure or a specified validated questionnaire or clinical assessment scale.

Secondary outcomes *The secondary outcomes are measurements of treatment effect that are related to the secondary objectives. If there are multiple outcomes associated with each secondary objective, consider listing the secondary outcomes under relevant subheadings (e.g., efficacy, immunogenicity, and safety). Follow the same guidelines provided under primary outcomes to describe each of the secondary outcomes. It is recommended that the list of secondary outcomes be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly large as the number of outcomes increases. Ensure outcomes are obtainable.*

The information provided for primary and secondary outcomes will be used for registration of the trial on ClinicalTrials.gov.

Exploratory outcomes *Where exploratory objectives are included in the protocol, exploratory outcomes should be specified. Exploratory outcomes may include clinically important events that are expected to occur too infrequently to show a treatment effect or outcomes that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses. If there are multiple exploratory outcomes associated with each objective, consider listing the outcomes under relevant subheadings (e.g., efficacy, pharmacokinetics, pharmacodynamics, and safety). If there are no exploratory objectives / outcomes, delete this section.*

The objectives and outcomes can be entered in either of the formats shown below (text versus tabulated):

Primary objective and outcome

<insert>

Second objectives and outcomes

<insert>

Exploratory objectives and outcomes

<insert>

Table listing objectives and outcomes

OBJECTIVE	OUTCOME & OUTCOME MEASURE
Primary	
"The primary objective of this trial is to evaluate the impact of <trial treatment> on time to resolution of <condition> in <type of participants> compared with placebo"	*"Complete recovery at 1 month post randomisation, where recovery is defined as a HB score of 1.*
Secondary	
"To determine the impact of <trial treatment> compared with placebo on emotional and functional outcomes at 1, 3 and 6 months"	*"Improved emotional and functional wellbeing of the participant assessed by the parent/guardian and participant using the Pediatric Quality of Life Inventory (PedsQL) at1, 3 and 6 months"*
Exploratory	

4 TRIAL DESIGN

4.1 Overall design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. The description of the trial design should be consistent with the Protocol Synopsis.

Specify the basic design elements of the trial, including:

- *The type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)*
    - *Discuss the rationale for the type of trial design (e.g., non-inferiority as opposed to superiority).*
- *The phase of the trial (e.g. Phase I, II, III or post-marketing if appropriate);*
    - *Note that a drug or device may be already marketed but would be classified as phase I, II or III trial if the dosage formulation, indication or population in the trial differs from the marketed use of the product;*
- *Name of trial intervention(s)*

- *Nature of the control (e.g. placebo controlled, active controlled, historical, uncontrolled) discuss known or potential problems associated with the control group chosen in light of the specific disease and intervention(s) being studied*
- *The number of trial groups/arms and trial intervention duration*
    - *Mention any distinction between the treatment period and follow-up period, if applicable (e.g. 'a 6 week treatment period with a two year follow-up');*
- *A description of methods to be used to minimize bias including blinding: (e.g. open-label, who is blinded to trial interventions);*
- *The setting (Indicate if single site or multi-site, and, if to be conducted in countries other than Australia list the participating countries);*
- *List any sub-studies included in this protocol;*
- *Additional notes*
    - *Dose escalation or dose-ranging details should be contained in the protocol section Intervention*
    - *Note if interim analysis is planned and refer to details in the protocol section Statistical Methods*
    - *Note whether the trial includes any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose) and refer to details in the protocol section Statistical Methods*

Note regarding adaptive trial design:

If there is any adaptive element planned within the trial (e.g. the number of treatment arms, the sample size, the allocation ratio), the planned adaptations should be pre-defined and outlined here. The specific details of the rules governing the adaptations should be included in the relevant section of the protocol.

4.2 Justification for dose

Provide a justification for the route of administration, planned maximum dosage, and dosing regimen, including starting dose, of the trial intervention(s) and control product(s).

4.3 Trial population

The following subsections should include a description of the trial population and participant recruitment. The trial population should be appropriate for clinical trial phase and the development stage of the trial intervention. Given the continuing challenges in achieving clinically relevant demographic inclusion in clinical trials, it is important to focus on clinically relevant potential participants at the earliest stages of protocol development. Therefore, it is essential that the population's characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the trial intervention under evaluation (e.g., elderly and paediatric populations, women, and minorities).

Use the following guidelines when developing participant eligibility criteria (Inclusion Criteria and Exclusion Criteria):

- *The eligibility criteria should provide a definition of participant characteristics required for trial entry/enrolment.*
- *The risks of the trial intervention should be considered in the development of the inclusion/exclusion criteria so that risks are minimised.*
- *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion).*

- *Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrolment or exclusion.*
- *If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g., licensed hormonal or barrier methods).*
- *If you have more than one trial population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation.*

4.4 Eligibility criteria

Eligibility criteria define and limit the participants that can be enrolled in a trial (e.g., those criteria that every potential participant must satisfy, to qualify for trial entry). They also define the population to which the trial results can be extrapolated.

Reasons for imposing eligibility criteria can include scientific rationales, safety concerns, regulatory issues and practical considerations.

Under the subheadings in this section, list all the criteria that will be applied to determine a person's eligibility or ineligibility for the trial.

The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion).

Eligibility criteria should be clearly defined, straightforward and unambiguous.

***Example text**: "Participants will be assigned to a randomised trial treatment only if they meet all of the inclusion criteria and none of the exclusion criteria."*

4.4.1 Inclusion criteria

The inclusion criteria will be highly specific for each trial and the following is general guidance only and not an exhaustive list. Consider criteria related to:

- *Demographic characteristics (e.g., gender, age range).*
- *The disease or disorder under study: the specific definition of the disease state which will be used to assess patients for recruitment into the trial and how it must be documented (e.g. diagnostic methods, criteria for classification, etc.).*
- *Clinical indicators of current status, as measured within <specify number of days> of randomisation.*
- *Prior therapy, if any. Consider listing specific prior treatments. Consider listing the allowable duration of prior therapy for the specific population to be studied (e.g. treatment-naïve, treatment-experienced or prior-treatment-failed "salvage" participants).*

Example text:

"Each patient must meet all of the following criteria to be enrolled in this trial:

- *Is between the ages of <# and #> years at the time of randomisation*
- *Weighs between <# and #> kg at the time of randomisation*
- *Has <condition> as determined by <insert detail of test necessary for definitive diagnosis for the trial purpose>*
- *Provide a signed and dated informed consent form / (and/or for paediatrics) has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf."*

4.4.2 Exclusion criteria

Exclusion criteria are characteristics that make an individual ineligible for trial participation. Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from

trial participation and then list each criterion. Take into account known or suspected contraindications or side effects of the drug or factors likely to confound interpretation of the results.
Consider criteria related to:

- *Specific clinical contraindications (specify grades of signs and symptoms, obtained within xx days prior to randomisation)*
- *Serious illness (requiring systemic treatment and/or hospitalization) until participant either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least <insert> days prior to trial entry. List specific illnesses and acceptable time.*
- *Specify any clinical (e.g. life expectancy, co-existing disease), demographic (e.g. age) or other characteristic that precludes appropriate diagnosis, treatment or follow-up in the trial.*
- *Abnormal laboratory values (either define a limit, e.g. 2 times the upper limit of normal, or state that clinically significant abnormal values will result in exclusion).*
- *Specify any exclusion related to pregnancy, lactation, or plans to become pregnant, if applicable. Specify methods for assessing current status and willingness to use contraception, if applicable.*
- *Use of <excluded drugs, devices, etc.> within xx days prior to trial entry.*
- *Allergy/sensitivity to trial drugs or their formulations.*
- *Inability or unwillingness of participant or legally acceptable representative to give written informed consent.*

Example text: *"Patients meeting any of the following criteria will be excluded from the trial:*

- *Has a recent (within <months > of randomisation) history of < Fracture, surgery, etc.>;*
- *Has clinically significant <list any abnormalities that are not allowed>*
- *Has a prior diagnosis of <condition>*
- *Has a known hypersensitivity to <trial drug/ other compound>*
- *Has had treatment with any other investigational drug within <weeks> prior to randomisation*
- *Is known to require <procedure or drug treatment prohibited by the protocol> prior to the completion of the trial follow-up."*

Justification for exclusion of a specific population: *If specific populations are excluded (e.g., elderly or pediatric populations, women or minorities), provide a clear and compelling rationale and justification, to establish that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Limited English proficiency should not be an exclusion criterion.*

4.5 Lifestyle considerations

Include content in this section if applicable, otherwise note as not-applicable.
Describe any restrictions during any parts of the trial pertaining to lifestyle and/or diet (e.g., food or drink restrictions, timing of meals relative to dosing, limits on activity),

4.6 Screen failures

For the purposes of investigator-initiated trials at the Melbourne Children's campus, screening is defined as the period involving determination of the eligibility of a potential participant for trial inclusion. Once the potential participant has been deemed eligible and can be assigned to the trial intervention/randomised, the participant is considered enrolled.

Determining eligibility can only commence once the trial has received ethical approval and site-specific authorisation (governance). Eligibility information can be obtained directly from the person themselves (where they contact the trial researcher) or indirectly (e.g. from the medical record). The process for

accessing the person's Royal Children's Hospital (RCH) medical record prior to obtaining their consent for the trial is that:

- *the treating clinician will record in the electronic medical record (EMR) that the patient is willing to be contacted by the researcher (coded in EMR as "Interested").*
- *or that the Human Research Ethics Committee (HREC) approval has granted approval to the researcher to access the medical record prior to consent (note that justification for pre-consent access must have been included in the initial application for ethical approval - and also note that approval for this is granted in particular circumstances only).*

Once the participant/legal guardian has provided consent, the code in EMR is changed to "Consented: enrolled" if eligibility has been finalised. In some cases, further assessments are needed to determine eligibility and the code is changed to "Consented: in screening". Those who are found, during the screening procedures, to be ineligible for trial inclusion are termed "Screen failures and they are not assigned to the intervention / are not randomised.

In a small number of investigator-initiated trials, a minimal set of screen failure information is retained to aid in describing screen failures (including demography, the reason for ineligibility and documentation of any trial assessment-related adverse event and/or any serious adverse event ([AE]). High risk trials and those looking at commercialisation of the investigational product may fall into this category.

Example text:

"Screen failures are defined as participants who consent to participate in the trial but who are found, during the screening procedures, to be ineligible to continue in the trial. They therefore do not receive the intervention / are not randomised.

4.7 Recruitment and identification of potential participants

Describe the sources and methods that will be employed in the identification and recruitment of potential participants (e.g. from clinics, referring physicians, advertisements). Note that the identification and recruitment of participants must protect privacy and be free of undue influence. Include details of who will be performing the recruitment activities and strategies for retention once the participants are on the trial.

Full details may be given in this section of the protocol or alternatively this section may refer to a detailed recruitment and retention plan in a separate document (e.g. a Trial Manual). Include the information below either in this section or in the Trial Manual.

- *The target trial population – describe the population (gender, race and ethnicity, age) and identify anticipated estimated number to be enrolled in order to reach the target of <insert>' participants treated/randomised/participants (keeping in mind that some participants who provide consent may be found to be ineligible during the screening procedures).*
- *Anticipated accrual (recruitment) rate and timeline*
- *Anticipated number of sites, countries (if applicable) and participants to be enrolled and/or randomised/treated.*
- *Recruitment settings (e.g. inpatient hospital setting, outpatient clinics, community services, or general public)*
- *How potential participants will be identified and approached*
- *Types of recruitment strategies planned (e.g. patient advocacy groups, national newspaper, local flyers; social media)*
- *If the trial requires long-term participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).*

If participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for trial participation, describe this here or alternatively in Section 14.

4.8 Consent

The National Statement on Ethical Conduct in Human Research states that if you want people to take part in your research project, you need to get their informed consent. This means that they and/or their parent/legal guardian:

- *Voluntarily agree to take part in the study and*
- *Understand what the study involves.*

Describe the consent procedures. State that the following fundamental conditions for a valid informed consent will be met for each participant:

- *Disclosure of relevant information to prospective research participants and/or their legally acceptable representatives*
- *Comprehension of the information provided*
- *Voluntary agreement of the participant, free from coercion*

Research involving children and young people raises specific ethical concerns in that the capability of minors to provide fully informed consent will vary with their maturity and intelligence as well as the complexity of the research. Researchers should bear in mind that, even without full competence, minors may have some understanding of the research as well as the benefits and burdens of participation. They should therefore be involved in the discussion and decision making even where not asked to provide consent themselves. Researchers should refer to the RCH procedure "Informed Consent in Research", available on the RCH Research Ethics Governance website.

In the protocol, state whether consent from minors will be sought as well as the parent/legal guardian. State who will obtain consent and outline the roles and responsibilities of those involved in the consent process, including the responsibility for determining the capability of the minor to provide consent. Also identify different consent forms that are needed for the trial (e.g., screening, trial participation, future use of specimens, and information statements for minors) and whether consent will be written, verbal, implied or opt-out.

***Example text**:*

"Prior to performing any trial-specific procedure (including screening procedures to determine eligibility), a signed consent form will be obtained for each participant.

The process will be that the investigator or delegated member of the trial team will discuss the trial with relevant family members: parent/legal guardian and where appropriate the child/adolescent participant. Age appropriate (clarify <written, oral or other>) information should be provided to the child/adolescent in accordance with their level of maturity where required.

The investigator will provide the Participant Information and Consent Form to the parent/legal guardian and, where appropriate, to the child/adolescent. This document will describe the purpose of the trial, the procedures to be followed, and the risks and benefits of participation.

The investigator will conduct the informed consent discussion and will check that the parent/guardian and, where appropriate, the participant comprehend the information provided. The investigator will answer any questions about the trial.

The parent/legal guardian4 will be invited to provide written consent. Where deemed competent and mature to provide consent, the child/adolescent will also be invited to provide written consent. The level of maturity will be determined by the Investigator in accordance with local process. Consent will be voluntary and free from coercion.

The investigator who conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the parent/legal guardian and the participant where the participant has signed.

It will be documented in the participant's record that consent has been provided. When the all the inclusion/exclusion criteria have been addressed and the eligibility of the participant confirmed, the participant may be assigned to a trial arm/intervention".

Describe the procedures for the documentation of ineligibility for participants, and for reasons for the non-participation of eligible participants (i.e. maintaining a record of all participants screened but not entered into the trial). Specify what data will be recorded on these participants.

5 INTERVENTION

*The following subsections should describe **the trial intervention** that is being tested for safety and/or efficacy in the trial, **and any control product** (e.g. a comparator or placebo) being used in the trial.*

The trial intervention may be a drug (including a biological product) or device that has not yet been approved by Australia's Therapeutic Goods Administration (TGA) for marketing. Alternatively, It may be a drug or device that has been approved by the TGA for marketing but the product is being used or assembled (formulated or packaged) in a way different from the approved form or is being used for an unapproved indication or a different population or is being used to gain further information about an approved use.

Ensure that each intervention and control is clearly described in the following subsections and where multiple interventions are to be used, clearly differentiate between each product in all sections.

5.1 Treatment arms

Provide details of each treatment arm including controls (i.e. comparator or placebo).

5.2 Trial Intervention(s)

In the following sub-sections, detail the interventions for each group with sufficient detail to allow replication including: formulation (main active ingredients only), dosage form, route of administration, dosage and frequency, storage and preparation. Include details of comparator or placebo where applicable.

Indicate if the trial intervention is commercially available and will be used in accordance with the approved labelling.

***For investigational drugs and biologics:** The information should be detailed in the Investigator's Brochure (IB) for unapproved products and in the product information (package insert) for approved, marketed products.*

***For device studies:** Note if any modifications have been performed for the trial. Include the following information: device size(s); device model(s); description of each component; device settings and programming (if applicable); duration of implant or exposure (if applicable); frequency of exposure (if applicable); if a device has not been approved or cleared for the indications the protocol is designed to investigate, then a summary/report of test validation studies should accompany this protocol.*

Additional notes *Detail mechanisms (if any) for masking (i.e. blinding) trial interventions. For example, if a placebo is being used, note whether it has similar colour, taste, etc., to the active drug. Summarise the label copy which should include the following, as appropriate: Randomisation number, Week number, Batch number, Expiry date and the statements "For clinical trial use only" and "Keep out of reach of children" along with any local or national requirements*

5.2.1 Description of trial investigational products

5.2.1.1 <Trial Product insert>

Repeat for each trial product (investigational product, comparator, placebo).

Complete relevant table for medicine or device as applicable to the trial.

Complete table below if trial intervention is an investigational medicinal product.

Active substance	*<List main active ingredients, quantity and unit>*
Trade or Generic name	*<Insert Trade Name> or <Insert Generic Name followed by the word GENERIC>*
Dosage form	*<Insert dosage form>* *e.g. tablet, capsule, injection, IV infusion*
Route of administration	*<Insert route of administration>* *e.g. oral, inhaled, intravenous, subcutaneous, self-administered*

Complete table below if trial intervention is an investigational medical device.

Product name	*<Insert Product Name>*
Device Type	*<Insert Device Type>* *e.g. single device, system, procedure pack, software.*

5.2.2 Dosage

For each trial product, specify:

- *The dose, or mg/kg, and strength of the dose unit. Consider dosage for all subjects throughout the trial period, taking into account the likely growth of babies and children*
- *The dosing regimen including*
  - *Dosing intervals (single-dosing, multiple-dosing, daily dosing, weekly dosing)*
  - *Dose escalation (e.g. a starting dose which is then increased - state any minimum period required before a participant's dose might be raised to the next higher dose or dose range)*
  - *Dosing period (the period over which the dosing occurs)*

- *Any restrictions (e.g. with or without food/water/milk, posture, ambulation)*

5.2.3 Dose modification

Provide details for any allowable dose modifications and the circumstances for their use (e.g. toxicity). The protocol should state the conditions under which a dose change (where applicable) will be made, particularly in regard to failure to respond or to toxic or untoward changes (e.g., white blood cell count in cancer chemotherapy). Address dose modifications for specific abnormal laboratory values of concern or other adverse events (AEs) that are known to be associated with the planned trial intervention. The protocol must state explicitly the dose-limiting effects that are anticipated.

5.2.4 Storage, preparation, dispensing and administration of trial drug

Include the following information in this section of the protocol or within a Pharmacy Manual or Standard Operating Procedure (SOP).

Describe in detail all the steps necessary to properly prepare trial treatment and include:

- *Instructions for thawing, diluting, mixing, and reconstitution/preparation instructions (where applicable) and maximum hold time once thawed/mixed before administration (where applicable)*
- *Responsibility for drug storage, preparation and dispensing (e.g. will this be done by pharmacy or by a trial team member).*
- *How the trial treatment is to be administered, where and by whom.*
- *Any specific instructions or safety precautions for administration of the trial intervention.*
- *How delayed or missed doses should be handled.*

For devices, include any relevant assembly or use instructions. In addition, similar considerations to those outlined above for drug interventions apply to certain devices. For example, some devices have adjustable settings including those related to energy delivery to participants. Other devices must be sized correctly for individual participants. Similar to the discussion above for dosage of drugs, such considerations should be described for devices, as applicable.

5.2.5 Product accountability

State how the trial intervention(s) and control product(s) will be provided to the investigator.

Describe how and by whom the trial intervention will be distributed (e.g. to Pharmacy. Outline).

Outline plans for disposal of expired product or return of unused product; this should include (where applicable) instructions to be given to the participant to return all leftover product, as well as empty containers.

Detailed information may be provided in a Trial or Pharmacy Manual or a separate SOP.

***Example text:** "The pharmacist (or the investigator's designee) will maintain accurate records of the receipt of all trial medication, including dates of receipt. In addition, accurate records will be kept regarding when and how much trial medication is dispensed and used by each participant in the trial. Reasons for departure from the expected dispensing regimen will be recorded. At the end of the trial, there will be final reconciliation of trial drug received, dispensed, consumed and returned. Any discrepancies will be investigated, resolved and documented by the trial team. Unused trial drug will be destroyed in compliance with applicable regulations.*

5.2.6 Measurement of participant compliance

This section is most relevant for studies that require the participants to administer investigational treatment (drug/device) at home - delete this section if it does not apply.

Indicate whether compliance of participants with the allocated intervention is to be assessed. If so, provide details as to how this will be carried out (e.g., pill counts, observation in the clinic, electronic monitoring devices, adherence (compliance) questionnaires). Discuss which documents will be mandatory to complete and what source documents/records will be used to calculate trial intervention compliance. Indicate if compliance will be recorded on the CRF.

When appropriate, describe procedures that must be followed for any participant who is significantly non-compliant with the trial treatment regime. Define 'significantly non-compliant'.

5.2.7 Excluded medications and treatments

Specify which concomitant medications, medical procedures or foods are restricted and when, clarifying any exceptions to the restrictions.

- *Describe known interactions of the trial treatments with other drugs*
- *Give specific exceptions to prohibited medications and procedures, such as allowable low doses or occasional use (define these if applicable)*
- *Describe those restrictions that will result in withdrawal of the participant from the trial treatment*
- *Include drugs, devices, procedures, etc. from the exclusion criteria if they are also prohibited while the subject is on trial.*

Give details of any applicable washout periods.

Add a sub-heading if applicable, to provide details of any required medications and treatments during the trial, such as continuing standard treatments, contraception or mineral supplements.

5.2.8 Concomitant therapy

Include content in this section if applicable, otherwise note as not-applicable.

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe the data that will be recorded related to permitted concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures. Include details about when the information will be collected (e.g., screening, all trial visits). Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the trial endpoints) and how the independent effects of concomitant and trial interventions could be ascertained.

5.2.9 Discontinuation from trial intervention

See Section 7.5.

6 RANDOMISATION AND BLINDING

This section should contain a description of randomization and blinding procedures (if applicable to the trial design) including how trial participants will be assigned to trial groups. This should include the method of generating the allocation sequence (e.g., computer-generated random numbers, block randomisation, minimisation), a list of any factors for stratification and the randomisation ratio (e.g. the ratio between intervention and placebo groups).

State how the randomisation schedule, participant numbering and sequence of participant number assignment will be prepared and stored.

***Example text:** "A statistician not directly involved in the analysis of the trial results will prepare the randomisation schedule using block randomisation to maintain balance between treatment arms. The schedule will be provided to the pharmacist and sealed envelopes containing the treatment allocation of each randomisation code will be provided to the investigator in case of emergency."*

Note regarding adaptive trial design:
If an un-equal treatment allocation will be used, then provide a justification. If the allocation ratio may adaptively evolve over the course of the trial, then provide a short overview statement to that effect and refer to the full description in the "Interim Analysis" section".

6.1 Concealment mechanism

This section should describe the mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Information: *Differences between allocation concealment and blinding (masking) for trials with individual randomisation.*

	Allocation concealment	Blinding (masking)
Definition	Unawareness of the next trial group assignment in the allocation sequence	Unawareness of the trial group to which trial participants have already been assigned
Purpose	Prevent selection bias by facilitating enrolment of comparable participants in each trial group	Prevent ascertainment, performance, and attrition biases by facilitating comparable concomitant care (aside from trial interventions) and evaluation of participants in each trial group
Timing of implementation	Before trial group assignment	Upon trial group assignment and beyond
Who is kept unaware	Trial participants and individuals enrolling them	One or more of the following: Trial participants, investigators, care providers, outcome assessors. Other groups: Endpoint adjudication committee, data handlers, data analysts
Always possible to implement?	Yes	No

6.2 Breaking of the trial blind

6.2.1 On trial

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial should be described, including who will conduct the unblinding and whom the unblinding should be reported to.

Sometimes blinding is attempted but is known to be imperfect because of obvious effects related to trial intervention or control product in some participants (e.g., dry mouth, bradycardia, fever, injection site reactions, and changes in laboratory data). Such problems or potential problems should be identified and, if there are plans to assess the magnitude of the problem or manage it, these should be described (e.g., having endpoint measurements carried out by trial staff shielded from information that might reveal trial group assignment).

If the trial allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Describe efforts to ensure that the trial intervention and control/placebo are as indistinguishable as possible. Measures to prevent unblinding by laboratory measurements, if used, should be described.

Include a description of your plans to manage and report inadvertent unblinding. If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained. If blinding is considered desirable but not feasible, the reasons and implications should be discussed.

***Example text**: "The randomisation code for an individual participant may only be unblinded in emergency situations, where the Investigator decides a participant cannot be adequately treated without knowing the identity of their treatment allocation. To break the randomisation code the Investigator must open the emergency unblinding envelopes provided, or contact the randomisation facility/personnel. If any unblinding envelope is opened, the time, date, participant number and reason for opening must be documented.*

6.2.2 On completion of the trial

Provide details about when the treatment allocations for all participants will be unblinded. This should not be done until after the end of the trial.

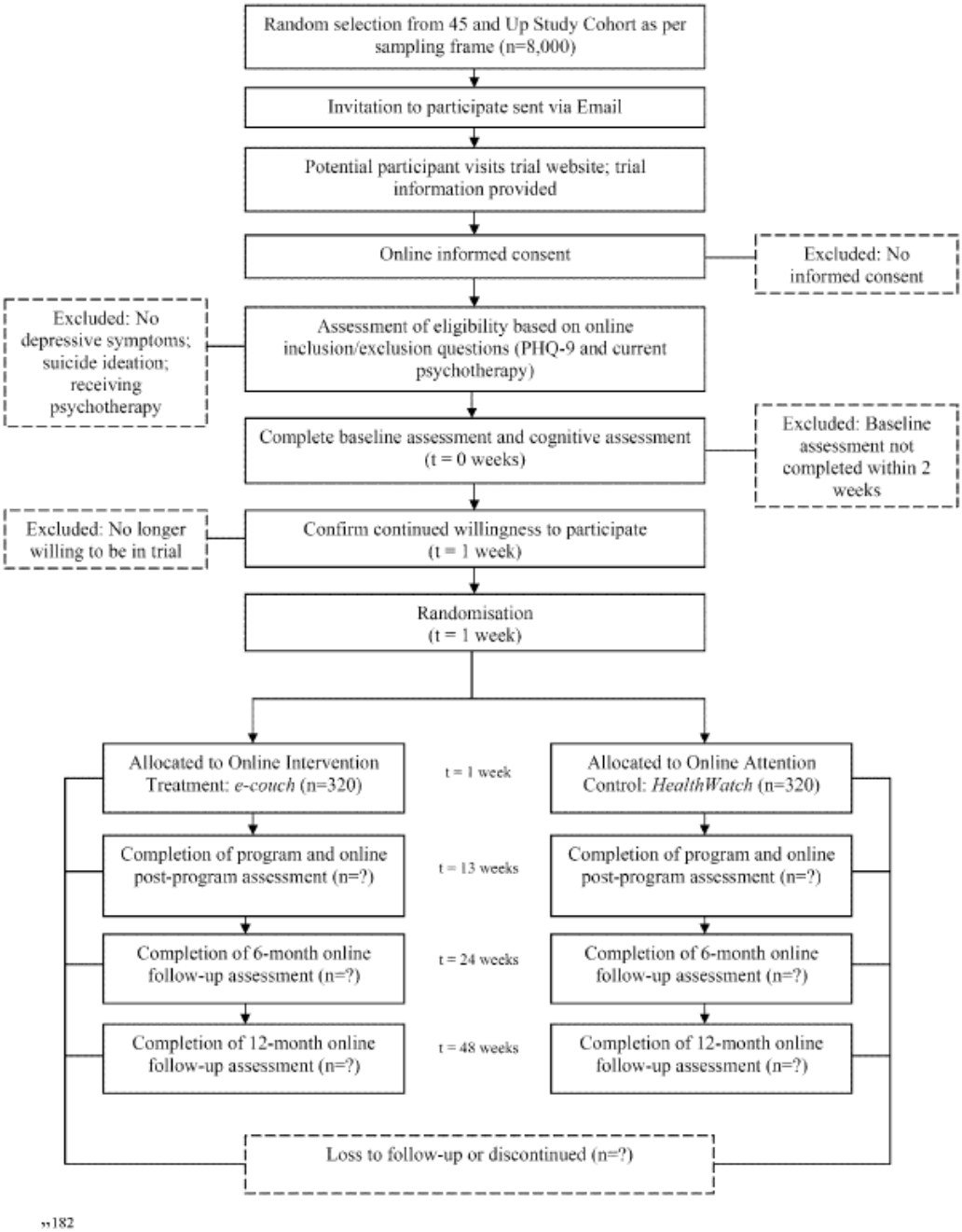
***Example text:** "Trial drug codes will only be available once all data collected have been entered into the trial database for every participant and the database has been finalised, except in the case of an emergency, as detailed above".*

Explain the process by which the treatment allocation information will be made available.

7 TRIAL VISITS AND PROCEDURES

7.1 Trial timeline

To help the reader understand complex protocols it is very useful to include a flow chart of the trial design, as in the following example.



[182]

7.2 Schedule of assessments

The Schedule of Assessments (SoA) details the specific timing of procedures/evaluations.

Include the procedures involved in administering the trial intervention and the follow-up procedures after administration (e.g., assessment of vital signs), as well as any specifics about subsequent follow-up visits, and unscheduled visits.

Note whether a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments.

The timing of trial visits should be defined by day or week (to avoid ambiguity, do not use month). The day on which the investigational product is first administered should be defined as Day 1. There should be no Day 0 or Week 0. The day before Day 1 is defined as Day -1. Day 1 is the first day of Week 1, and the week before the investigational product is first administered is Week -1.

Where applicable, permissible time windows for evaluations should be presented (i.e. ± x minutes/days/weeks).

Example 1 of recommended content for the schedule of assessments*

	TRIAL PERIOD							
	Enrolment	Allocation to intervention	Post-allocation					Close-out
TIME POINT**	$-t_1$	0	t_1	t_2	t_3	t_4	*etc.*	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
[List other procedures]	X							
Allocation to intervention		X						
INTERVENTIONS:								
[Intervention A]			←	—	→			
[Intervention B]			X		X			
[List other trial groups]			←	—	—	→		
ASSESSMENTS:								
[List baseline variables]	X	X						
[List outcome variables]				X		X	etc.	X
[List other data variables]			X	X	X	X	etc.	X

*Recommended content can be displayed using various schematic formats.
**List specific time points in this row.

7.3 Description of procedures

List and describe all trial procedures and evaluations to be done as part of the trial to:

- *determine participant eligibility and enrol participants*
- *support the determination of efficacy and/or safety, as per the primary secondary and exploratory objectives outlined in this protocol*

Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrolment within which screening procedures/ evaluations must be performed (e.g., within 28 days prior to enrolment). If a separate screening protocol is developed, describe how the screening protocol will be used to identify participants for this trial.

Discuss any special conditions that must be achieved during the enrolment and/or initial administration of trial intervention. Include the procedures for administering the trial intervention and follow-up procedures after administration (e.g., assessment of vital signs), as well as any specifics about subsequent follow-up visits, and unscheduled visits.

The protocol should provide a high-level discussion of all procedures. More detailed information can be provided in a Trial Manual or SOP.

Note that the specific timing of procedures/evaluations to be done at each trial visit is captured in the Schedule of Assessments (SoA) - the time points of these procedures do not need to be included here.

For each assessment:

- *Specify how the test (e.g. diagnostics, physical or mental performance assessments) will be conducted, who will conduct it, how measurements will be obtained (specify units where applicable) and what information will be collected and documented. Reference to a separate manual/SOP may be necessary if tests are complicated.*
- *Specify if any particular member of the research team must conduct certain assessments and whether they will be required to undertake trial-specific training or certification*
- *Specify whether the tests need to be timed in relation to other activities, such as 'blood samples should be drawn after vital signs have been measured, but before administration of trial intervention'*
- *Detail efforts to standardise procedures and assessments (where applicable) such as the required equipment specifications for a radiology assessment, a consistent laboratory method throughout the trial; use of single, central laboratory for multi-site studies).*
- *Specify whether there are any samples being collected and stored for future research (Refer to Section 9.2.4 - details relating to the storage of the samples must be included)*
- *Other*
    - *Provide justification for any sensitive procedures (e.g., provocative testing, deception).*
    - *Point out any procedures, situations or materials that may be hazardous and the precautions to be exercised to minimise the risks*
    - *Procedures, tests and interventions that are considered experimental and/or procedures performed exclusively for research purposes must be identified and differentiated from those that would occur regardless of the research (i.e. standard of care)*

The procedures could include:

- ***Physical examination*** *(e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
- ***Vital signs*** *(e.g., temperature, pulse, respirations, blood pressure). Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs.*
- ***Electrocardiograms (ECGs)****: specify if the ECG is for screening purposes only. Include any specific instructions for the collection and interpretation of the ECG (e.g., time points relative to dosing with trial intervention or other evaluations). If ECGs will be analysed at a central laboratory, instructions for the collection (e.g., equipment), transmission and archiving of the ECG data should be summarized in this protocol, and further outlined in the Trial Manual. If the ECG will be read locally, indicate how these will be handled and in what format (e.g., digital or paper), as well as instructions with respect to local review.*
- ***Administration of questionnaires or other instruments by researchers*** *(such as gait assessment tools)*
- ***Completion of participant-reported outcomes by parents/participants*** *(such as a daily diary, periodic quality of life questionnaires).*
- ***Radiographic or other imaging assessments****. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the Trial Manual or a separate SOP.*
- ***Biological specimen collection and laboratory evaluations****. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout trial, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the Trial Manual.*
- ***Special assays or procedures required*** *(e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the Trial Manual.*
- ***Assessment of trial intervention adherence***
- ***Assessment of adverse events.*** *Describe provisions for follow-up of ongoing AEs/SAEs.*
- ***Counselling procedures, including any dietary or activity considerations*** *that need to be adhered to during trial participation.*

Include in this section a discussion of the results of any trial specific procedures that will be provided to participant (e.g., radiographic or other imaging or laboratory evaluations).

Address when outcomes will be assessed with respect to dosing of rescue medication, if applicable.

7.4 Notes on specific trial visits

7.4.1 Screening

Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the maximum time following consent for finalising eligibility (i.e. screening tests and evaluations to be completed within, for example 28 days of consent).

7.4.2 Final trial visit

Define when the final trial visit should occur and any special procedures/evaluations or instructions to the participant. If trial results will be shared with participants, discuss when and how they will receive this information. Think about whether you will want to contact the participants in the future, and whether consent needs to be obtained now to do so.

Note that all safety events (adverse events, serious adverse events etc) will be followed until resolution or alternatively to stabilisation – and ensure referrals are in place where applicable

7.4.3 Unscheduled visit

Specify how unscheduled visits (e.g. for safety review) will be handled and documented.

7.5 Treatment discontinuation, participant withdrawals and losses to follow up

It is important to differentiate between:

(i) discontinuation from trial treatment - where a participant stops trial treatment but should continue follow-up procedures and assessments

(ii) withdrawal of consent for all trial participation by the participant or legal guardian (the participant may withdraw consent prior to or during the trial treatment phase or during follow-up).

7.5.1 Discontinuation of treatment - participant remains in trial for follow up

Discontinuation from the trial intervention may follow the participant wishing to cease the trial intervention or the PI discontinuing a participant from the trial intervention (e.g. following toxicity or non-compliance). Discontinuing a trial intervention does not mean discontinuation from the trial.

This section should state which adverse events would result in temporary and/or permanent discontinuation of trial intervention. Describe the criteria for discontinuation (e.g., stopping rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the trial intervention (e.g., type and quantity of AEs), clearly stating the length of time and approaches for restarting administration of or re-challenging with trial intervention (if applicable). Describe the data to be collected at the time of discontinuation of treatment and recommencement).

This section should also describe the procedures to be followed when a participant ceases treatment prematurely, including the data to be collected and subsequent provision of care. For the participant's safety, protocol-specified safety evaluations to capture new safety events and to review existing, unresolved safety events should be undertaken. Describe also the procedure to transition participant off the trial drug or to alternate therapy.

Example text *"Participants who discontinue trial treatment will remain in the trial. The remaining trial procedures should be completed as indicated by the trial protocol.*

Participants may discontinue trial treatment for the following reasons:

- *Participant / legal guardian request to discontinue trial intervention*
- *Investigator decision to discontinue a participant from the trial intervention if the participant:*
  - *Is pregnant*
  - *Experiences a serious or intolerable adverse event such that continued trial intervention would not be in the best interest of the participant*

- *Develops, during the course of the trial, symptoms or conditions listed in the exclusion criteria*
- *Requires a medication that is prohibited by the protocol*
- *Requires early discontinuation for any other reason*

The investigator may also withdraw all trial participants from the trial treatment if the trial is terminated.

The procedure for transitioning a participant off the trial drug and/or onto alternate therapy is as follows <insert>.

For the safety of all participants ceasing trial treatment, the protocol-specified safety evaluations should be undertaken to capture new safety events and to assess existing, unresolved safety events. All scheduled follow-ups of trial participants should also occur following treatment discontinuation, where possible.

In addition to the safety evaluations, the data to be collected at the time of trial intervention discontinuation will include the following:

- *<Describe the procedures and data to be collected>*

A dedicated Case Report Form (CRF) page will capture the date and the specific underlying reason for discontinuation of the trial intervention.

The participant should remain in the trial for scheduled visits for trial assessments (follow-up) per protocol.

7.5.2 Withdrawal of consent - participant withdraws from all trial participation

Participant withdrawal from the trial should only occur if the participant or their legal guardian withdraws their consent to continue any trial involvement. This can occur at any stage of the trial following consent (prior to receiving the intervention, while receiving the intervention or during the follow up phase).

For the safety of participants, reasonable efforts should be made to undertake protocol-specified safety evaluations to capture new safety events and to assess existing, unresolved safety events following withdrawal. This is particularly the case for those participants receiving the trial intervention at the time of withdrawal. For these participants, describe also the procedure to transition participant off the trial drug (if applicable) and/or referral for alternate therapy (if applicable).

***Example text** "Participants are free to withdraw from the trial at any time upon their request or the request of their legally acceptable representative. Withdrawing from the trial will not affect their access to standard treatment or their relationship with the hospital and affiliated health care professionals.*

"For the safety of all participants ceasing trial treatment, reasonable efforts should be made to undertake protocol-specified safety evaluations to capture new safety events and to assess existing, unresolved safety events following withdrawal.

(Insert where applicable arrangements for transition of participant off the trial drug and/or appropriate referral for ongoing care.>).

A dedicated Case Report Form (CRF) page will be used to capture the date of participant withdrawal of consent.

7.5.3 Losses to follow-up

Describe the nature and duration of trial follow-up. Validity of the trial is a potential issue when participants are lost to follow-up, as information that is important to the outcome evaluation is then lost. Participants are considered lost to follow-up when they stop reporting to scheduled trial visits and cannot be reached to complete all protocol-required trial procedures. Describe the plans to minimise loss to follow-up and missing data.

Example text: *[A participant will be considered lost to follow-up if he or she fails to return for <specify number of visits> scheduled visits and is unable to be contacted by the trial site staff. The following actions must be taken if a participant fails to return to the clinic for a required trial visit:*

- *The site will attempt to contact the participant and reschedule the missed visit <specify time frame> and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the trial.*
- *Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or trial file.*
- *Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.]*

7.5.4 Replacements

Provide information on whether or not participants who withdraw from the trial will be replaced by further recruitment to maintain the required sample size.

Example text*:*
"Participants who sign the informed consent form and are not randomised / assigned trial intervention may be replaced.
Participants who have been randomised / assigned trial intervention may NOT be replaced.

7.5.5 Trial Closure

The end of the trial for a given participant is defined as completion of all phases of the trial including the last visit or the last scheduled procedure shown in the Schedule of Assessments.

The end of the trial is considered completed when participants are no longer being examined or the last participant's last trial visit has occurred. At the end of the trial, the Sponsor-Investigator should ensure that Human Research Ethics Committees (HRECs) and Research Governance Offices (RGOs) are informed along with regulatory bodies (in Australia this will be the TGA where the trial has been conducted under a CTN/CTX scheme) and funding bodies (where applicable).

Example text:

A participant is considered to have completed the trial if he or she has completed all phases of the trial including the last visit or the last scheduled procedure shown in the Schedule of Assessments,

The end of the trial is defined as completion of the last visit or procedure shown in the Schedule of Assessments in the trial at all sites. At this stage, the Sponsor-Investigator will ensure that all HRECs and RGOs as well as all regulatory and funding bodies have been notified.

Describe also the circumstances under which the trial can be suspended, terminated prematurely or extended (i.e. who can make decisions regarding trial suspension, termination or extension, who must be notified of this, and the procedures to be followed including handling and follow-up of enrolled participants.

Example text for temporary halt or early termination of a trial: *This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the trial is prematurely terminated or suspended, the Sponsor-Investigator will promptly inform trial participants, HREC and RGO, the funding (where applicable) and regulatory bodies, providing the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:*

- *Determination of an unexpected, significant, or unacceptable risk to participants that meets the definition of a Significant Safety Issue (SSI) (for the definition refer to Section 8.1).*
- *Insufficient compliance to protocol requirements*
- *Data that are not sufficiently complete and/or evaluable*
- *Demonstration of efficacy that would warrant stopping*
- *Determination that the primary endpoint has been met*
- *Determination of futility*

In the case of concerns about safety, protocol compliance or data quality, the trial may resume once the concerns have been addressed to the satisfaction of the sponsor, HREC, RGO,, funding and/or regulatory bodies.

7.5.6 Continuation of therapy

Include a statement such as 'No trial medication will be issued to a participant after the day <#> visit, when <#> is the final treatment day.' Otherwise, indicate arrangements and circumstances, procedures for the provision of trial medication following the completion of the trial. Describe the procedures to transition participant off the trial drug or to alternate therapy.

For trials involving an investigational medical device, include a statement (similar to above) or, where appropriate, insert "Not applicable".

8 SAFETY MONITORING AND REPORTING

You must consult the following documents when completing the safety section of the protocol:

- *CRDO's SOP Safety Monitoring and Reporting Procedure for MCRI-sponsored Investigator-Initiated Trials of Medicines/Medical Devices see the CRDO website*
- *NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (dated November 2016)* https://www.nhmrc.gov.au/guidelines-publications/eh59
- *NHMRC Guidance: Risk-based management and monitoring of clinical trials involving therapeutic goods (dated 2018)* https://www.nhmrc.gov.au/guidelines-publications/eh59

Major risks in undertaking a clinical trial can be broadly categorised into:

- *PART 1 - Risks to the safety and rights of the study participants (the risks and other unintended effects of trial interventions or trial conduct)*
- *PART 2 - Risks to the successful conduct of the study (e.g. inadequate funding, poor recruitment, poor quality data/samples, inadequate accountability of the investigational product).*

Researchers should conduct a trial-specific risk assessment and develop a plan to manage the identified risks to the safety and rights of the study participants as well as the risks to the successful conduct of the study - refer to the CRDO ***Risk Assessment and Risk Management Plan*** *available on the CRDO website. In this section of the protocol, details should be provided on the* ***risks to the participant (Part 1) only****. You should* ***liaise with your sponsoring institution regarding the management of Part 2*** *risks.*

Part 1 risks (risks to the safety and rights of the study participants)

- *When determining the risks to participants, include an assessment of the risk of the investigational product in Australia (i.e. whether or not the product has been entered into the Australian Register of Therapeutic Goods [ARTG] by the TGA enabling marketing in Australia) and, where ARTG-registered, whether the product will be used within its current approved indication or outside this (e.g. different population, indication, or dosing changes). Ensure that you review and reference the applicable sources of safety information, such as the Investigator's Brochure (for unapproved products) or the product information (i.e. package insert or device labelling) for approved, marketed products). Review also the literature and other sources that describe the trial intervention.*
- *Include also an assessment of the risks to study participants of trial conduct (e.g. trial procedures).*

Detail the identified risks and planned management strategies on the trial-specific Risk Assessment and Risk Management Plan. The assessment results may assist in deciding on the risk-based approach to safety monitoring and reporting. For example, the risk assessment may suggest that targeted collection of non-serious adverse events is appropriate (i.e. limited to adverse events of key interest) rather than the collection of all non-serious adverse events (which may or may not be related to the investigational product or trial conduct) which is usual in the early stages of investigational product development. ***If a targeted approach is used, the study team still need to ensure they collect any "possibly related" events to account for events which may seem unrelated until a trend appears.***

8.1 Definitions

The text below uses the definitions listed in NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (dated November 2016)
https://www.nhmrc.gov.au/guidelines-publications/eh59

Note that adverse events and adverse reactions to investigational medical products are classified as non-serious (AE and AR) or serious (SAE or SAR).Adverse investigational device events are classified as non-serious (AE & ADE) or serious (USADE). See full terms and definitions below. ***Please delete Section 8.1.1 if the trial will not involve investigational medicinal products. Please delete Section 8.1.2 if the trial will not involve investigational medical devices.***

8.1.1 Definitions for use in trials involving investigational medicinal products

Participant-specific adverse events

Adverse events must be assessed to determine each of the following:

1. *Seriousness*
2. *Relatedness (i.e. causal relationship)*
3. *Expectedness*

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this

treatment. If the collection of non-serious AEs will be targeted (i.e. events of key interest), provide details here.

Adverse Reaction (AR): Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

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.

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. ***Important medical events*** *that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.*

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.
Consider a SUSAR as any SAE that is both suspected to be related to the trial treatment and is unexpected (i.e. not consistent with the available safety information in the Investigator's Brochure (for unapproved products) /approved Product Information or device labelling (for approved products).
Note that SUSARs require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA.

Safety issues (requiring expedited reporting) *(see Appendix 2 for examples of SSIs).*

The following definitions describe additional safety events that require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA.

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Comment: A SSI is a new safety issue or validated signal considered by the Sponsor in relation to the investigational medicinal product that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the investigational medicinal product, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the investigational medicinal product.

Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This is a type of SSI that can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

8.1.2 Definitions for use in trials involving investigational medical devices

Participant-specific adverse events

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device

Note: This definition includes adverse events resulting from insufficient or inadequate instruction for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device.

Note: This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Where collection of non-serious AEs will be targeted (i.e. events of key interest), provide details here.

Device Deficiencies: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences of a Serious Adverse Event (SAE).

Serious Adverse Event (SAE): An adverse event that:

a. *Led to death*
b. *Led to serious deterioration in the health of the participant, that either resulted in*
   - *a life-threatening illness or injury, or*
   - *a permanent impairment of a body structure or a body function, or*
   - *in-patient or prolonged hospitalisation, or*
   - *medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function*
c. *Led to fetal distress, fetal death or a congenital anomaly or birth defect.*

Note: Planned hospitalisation for a pre-existing condition, or a procedure require by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report. USADEs require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA.

Safety issues (require expedited reporting)

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Comment: An SSI is a new safety issue or validated signal considered by the Sponsor in relation to the IMD that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the IMD which could prompt regulatory action and/or

changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the IMD.

Urgent Safety Measure (USM)
A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

Note: This is a type of SSI that can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

8.2 Capturing and eliciting adverse event/reaction information

Outline when adverse events will be captured (e.g. collected) – when you will start collecting new adverse events and when you will stop capturing new events (keeping in mind that all ongoing adverse events must be followed until resolution or stabilisation)? In commercial trials, adverse events are captured either from the time of consent or from the time of first administration of the investigational product and capture continues until (usually) 30 days after the last administration of the investigational product. For some investigator-initiated trials, it will be appropriate to collect from the time of consent those adverse events related to the screening procedures (undertaken to determine eligibility) – particularly where these procedures are invasive and/or high risk. Researchers could opt to collect all adverse events occurring during the screening period or alternatively collect events of interest (i.e. per a pre-specified list).

Also outline how adverse event information will be collected (e.g. participant questioning or participant records* [e.g. diary], physical examination findings, clinically significant lab results or other documents such as health carer correspondence).*

** For participant questioning/ records, consider whether participants will be asked about events of specific interest (i.e. 'active' eliciting which may result in higher reporting of events by participants), whether questioning will be more open (e.g. "How have you felt since your last visit?" which is termed 'passive' eliciting) or whether a combination will be used.*

Example text:
"Adverse events and adverse reactions (non-serious and serious) will be captured from the time of administration of the investigational medicinal product/device until <insert timeframe (e.g. 30 days after the final dose) and will be followed until resolution or stabilisation.

At every trial visit participants will be asked "How have you felt since your last visit?" in order to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medication or changed concomitant medication regimens. In addition, AEs will be documented from physical examination findings, clinically significant lab results or other documents (including participant diaries and correspondence from their primary care physician) that are relevant to participant safety."

For clinical trials involving an investigational medical device, consider adding questions and/or assessments to elicit information on events such as procedural/post-procedural pain, device deficiencies (i.e. durability, reliability, safety or performance) and user error.
The International Standard ISO 14155 (Version 2011) "Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice" provides the following guidance on the duration of safety event data: "The follow-up period during a clinical investigation shall permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the investigational device and allow any risks associated with adverse device effects over that period to be identified and assessed."

8.3 Documentation of AEs

In this section, specify which adverse events will be reported on the CRF, and which details will be recorded, stating any exceptions and additions to the definitions of AE, ADE, SAE and SADE (defined in Section 9.1) appropriate to the trial. The decision on the nature of adverse events to be recorded for each trial will depend on the risk associated with the trial (including the extent of knowledge of the risk profile of the drug/device and the population to be studied) and the objectives of the trial.

Example text: *"For the purposes of this trial the investigator is responsible for recording all Adverse Events, regardless of their relationship to trial drug, with the following exceptions:*

- *Conditions that are present at screening and do not deteriorate will not be considered adverse events.*
- *Abnormal laboratory values will not be considered adverse events unless deemed clinically significant by the investigator and documented as such.*

The AE will be described in the source documents (e.g. medical record or trial shadow file) and captured on the CRF and will include:

- *A description of the AE*
- *The onset date, duration, date of resolution*
- *Severity (mild, moderate or severe – what is the impact on the participant's daily life?)*
- *Seriousness (i.e. is it an SAE?)*
- *Any action taken, (e.g. treatment, follow-up tests)*
- *The outcome (recovery, death, continuing, worsening)*
- *The likelihood of the relationship of the AE to the trial treatment (Unrelated, Possible, Probable, Definite)*

Changes in the severity of an AE will be reported. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

8.4 Assessing the seriousness of a participant's AE

An AE must be assessed for 'seriousness'. The terms "serious" and "severe" are not synonymous.

The term "serious," is based on participant event outcome or action taken and is usually associated with events that pose a threat to a participant's life or functioning – see the definition in the preceding section covering definitions of safety events.

Severity is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations (NHMRC).

Example text *The seriousness of an AE will be assessed by an investigator according to the definition in in the preceding section on definitions with the following exception(s):*

- *Hospitalisation due to progression of disease will not be considered an SAE for the purposes of this trial.*

** The severity and relationship of an AE will be assessed as per the following section.*

*** The seriousness of an AE will be assessed by an investigator according to the definition in Section 8.1, with the following exceptions:*

- *Hospitalisation due to progression of disease will not be considered an SAE for the purposes of this trial.*
- *Elective surgery planned at the time of enrolment.*

8.5 Assessing the relatedness (causality) of a participant's AE

An AE must be assessed to determine if it is related to the investigational medical product or trial procedures; in another words whether there is a causal relationship between the investigational medical product and the adverse event. ***Describe the method of determining the relationship of an AE to a trial intervention. Some protocols may use a binary assessment (related/not related); others may have a scale of relatedness. Evaluation of relatedness must consider aetiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, trial-related procedures, accidents, and other external factors. In a clinical trial, the trial intervention should always be suspected.***

***Example text** provided as a guide, customize as needed:*
All adverse events must have their relationship to trial intervention assessed by the investigator who evaluates the adverse event based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the trial product should always be suspected.

Example text:
The relationship of the event to the trial intervention will be assessed as follows:

- ***Unrelated:** There is no association between the trial intervention and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure to the test product, or can be explained by a commonly occurring alternative aetiology.*
- ***Possible:** The event could have cause or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the intervention and/or follow a known response pattern to the test article, but could also have been produced by other factors.*
- ***Probable:** The association of the event with the trial intervention seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and are consistent with the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigators clinical experience.*
- ***Definite:** The AE is a consequence of administration of the trial intervention. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the test product or that they occur after rechallenge.*

8.6 Assessing the expectedness of a participant's AE

An AE must be assessed to determine whether the event is or expected or unexpected in terms of the current known safety profile of the investigational medicinal product. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the trial intervention.

Expected adverse reactions are AEs that are known to occur for the trial intervention being studied and are referenced in the Investigator's Brochure (for products not yet approved for marketing) or the Product Information or approved labelling/package insert (for products approved for marketing. Expectedness is assessed ***based on the awareness of AEs previously observed, not on the basis of what might be anticipated*** *from the properties of the trial intervention.*

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure or package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure or package insert listed only cerebral vascular accidents.

The Common Terminology Criteria for Adverse Events (CTCAE) produced by the National Cancer Institute (U.S) provides guidance on how to categorise severity (with grading 1-5) for most body systems https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Alternatively, the protocol can define how severity will be interpreted (see example text below).

***Example text** provided as a guide, customize as needed:*

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the trial intervention.

The severity of an Adverse Event will be assessed:

- *With reference to the Common Terminology Criteria for Adverse Events (CTCAE) produced by the National Cancer Institute (U.S).*
  https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

OR

- *The severity of an Adverse Event will be assessed as follows:*
  - ***Mild**: Events that require minimal or no treatment and do not interfere with the participant's daily activities.*
  - ***Moderate**: Events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication.*
  - ***Severe:** Events that prevent usual daily activity or require complex treatment.*

8.7 Reporting of safety events

Outline the reporting requirements and timelines for reporting safety events to the Human Research Ethics Committee(s), Research Governance Office(s) and/or Regulatory Agencies. Consider a flowchart to clarify the reporting requirements. State who will be responsible for submitting SAE reports to HRECs and regulatory authorities.

***Example text**:*

Site Principal Investigator Reporting Procedures
The Site Principal Investigator/delegate is responsible for recording all safety events in the source document.

The Investigator is responsible for expedited reporting (within 24 hours of becoming aware of the event) to the Sponsor-Investigator the following local safety events:

1. *USMs*
2. *SUSARs*
3. *All SAEs /SARs, except those that are identified below as expected in the trial population:*
   - *<e.g. insert here disease-related events common in the trial population and describe how these will be recorded and monitored>*

The Site Principal Investigator is responsible for reporting SAEs (including SUSARs) to the Sponsor-Investigator as soon as possible but within 24 hours of the first knowledge of the event. These reports should be submitted using the trial Expedited Safety Report Form (see Appendix 3).

The Site Principal Investigator is also responsible for reporting SSIs, local USMs and local SUSARs to their research governance office within 72 hours of becoming aware of the event and in accordance with their local governance authorisation.

Sponsor-Investigator Reporting Procedures

MCRI's Clinical Research Development Office will be updating the safety monitoring and reporting SOP to provide detailed instructions for how to monitor and report safety events in accordance with the new NHMRC guideline. This SOP will be available in the second half of 2018. Please refer to the CRDO website to check for updates on the availability of this SOP.

The Sponsor-Investigator must assess and categorise the Expedited Safety Reports received from Investigators and report these to all Site Principal Investigators, the approving HREC and TGA in accordance with the NHMRC's 'Safety monitoring and reporting in clinical trials involving therapeutic goods' (November 2016) and any additional requirements of the approving HREC. All safety reports must clarify the impact of the safety event on participant safety, trial conduct and trial documentation.

The Sponsor-Investigator is responsible for the following reporting to PIs, the HREC(s) and TGA:

1. *All SSIs that meet the definition of a USM within 72 hours of becoming aware of the issue.*
2. *All other SSIs within 15 calendar days of instigating or becoming aware of the issue*
3. *For SSIs leading to an amendment of trial documentation:*
    a. *Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.*
    b. *Submit amendment to the HREC without undue delay.*
4. *For SSIs leading to temporary halt or early termination of a trial for safety reasons:*
    a. *Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.*
    b. *For a temporary halt, notify the PIs, HREC and TGA when the trial restarts, including evidence that it is safe to do so.*

The Sponsor will also report SUSARs to the TGA as follows:

1. *Fatal or life-threatening SUSARs immediately, but no later than 7 calendar days after being made aware of the issue (follow up info within a further 8 calendar days)*
2. *All other SUSARs no later than 15 calendar days of being made aware of the issue*

The Sponsor is responsible for providing the additional safety information to the approving HREC:

1. *Provide an annual safety report, including a summary of the evolving safety profile of the trial*
2. *Provide any updated Product Information/Investigator's Brochure for the investigational products (if applicable)*

The Sponsor is also responsible for providing any updated Product Information/Investigator's Brochure to Investigators.

9 DATA AND INFORMATION MANAGEMENT

*As noted in the National Statement (NS 2007, updated 2018 chapter 3.1 Element 4), the **term 'data'** is intended to refer to bits of information in their raw form, whereas the **term 'information'** is intended to refer to data that have been interpreted, analysed or contextualised.*

All research results in data to be analysed which supports or refutes the trial hypothesis. Poor data and information results in a waste of effort and resources and puts participants at risk of harm. It is for this reason that institutions, sponsors, and regulators should invest effort into ensuring that research data and information is of high quality and validity as well as protecting the confidentiality of research participants.

*The following sub-sections should include a brief description of the data handling (generation, collection, access, use, analysis, disclosure, storage, retention, disposal, sharing and re-use) and record keeping for the conduct of the trial. As outlined in the National Statement [NS 3.1.45], each trial should develop a separate **Data Management Plan** to provide full detail. **Standard Operating Procedures** should also be developed to detail trial operations, including participant recruitment, data collection and data management (including change management).*

*Note that a description of the analysis activities should be provided in section 10 of the protocol and a separate **Statistical Data Management Plan** should also be developed.*

9.1 Overview

National guidelines (National Statement on Ethical Conduct in Human Research [NHMRC, 2007 updated 2018; The Australian Code for the Responsible Conduct of Research 2007, updated 2018) require that the Principal Investigator maintains (during the trial and archives retains for the minimum, mandatory archive period) appropriate research records along with a record of their location. For data and information management, this includes:

- *Essential Documents for the trial related to data management **(e.g. Data Management Plan, Data Dictionary)** (refer to the CRDO website for the relevant SOP). Essential documents are those documents which, when taken together, support the validity, quality and integrity of the data produced and demonstrate compliance by the investigators with regulatory and good clinical practice requirements as applicable.*
- *The Principal Investigator should also maintain a site-specific record of the location(s) of source documents, bearing in mind all locations for these (e.g. pathology, radiology, Investigator's office). Source documents contain all original data and information, records of clinical findings, observations, and other activities necessary for the reconstruction and evaluation of the trial. They can be hard copy or electronic. A **template Source Document Plan** is available on the CRDO website.*

Example text

The Principal Investigator is responsible for storing essential trial documents relevant to data management and maintaining a site-specific record of the location(s) of the site's data management-related Essential Documents.

*The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring and available. Changes to source data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary. A site-specific **Source Document Plan** will be maintained to indicate the location(s) of source documents.*

The Principal Investigator will also maintain accurate case report forms (CRFs) (i.e. the data collection forms) and be responsible for ensuring that the collected and reported data is accurate, legible, complete, entered in a timely manner and enduring. To maintain the integrity of the data, any changes to data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

Any person delegated to collect data, perform data entry or sign for data completeness will be recorded on the delegation log and will be trained to perform these trial-related duties and functions.

*Full details of all processes are provided in a separate trial-level **Data Management Plan**.*

9.2 Data management

*Describe the plan to ensure that the data collected are attributable, legible, contemporaneous, original, accurate, enduring, available, and complete. Full details covering the following should be provided in a separate **Data Management Plan** but a summary (at minimum) must be provided in the protocol. The data management plan should be supplemented by **Standard Operating Procedures** to address operations such as data collection, data management, data analysis, safety reporting and management of changes to data.*

Generation and collection – how and data be generated and collected	### 9.2.1 Data generation (source data) *What is the source of the data you will capture? Will you collect existing data, will you generate new data or will you use both?* *Source data are all information, original records of clinical findings, observations, or other activities in a trial necessary for the reconstruction and evaluation of the trial. Electronic source data are data initially recorded in electronic form.* *Source data are contained in source documents (paper or electronic). Examples of paper or electronic source documents are: medical records [at RCH the Electronic Medical Record (EMR) is Epic]; participant diaries; researcher diaries; memos; recorded data from automated instruments (e.g. blood pressure measurement); participant- or researcher-completed questionnaires or rating scales; videos; photographs; laboratory results; ECGs and reports; and imaging scans and reports.* ***Source document plan*** *For each discrete item of source data (e.g. blood pressure, standard lab test results, demographics), the location of the source should be clearly defined prior to participant recruitment; this can be defined in:* • *a trial-specific Source Document Plan (refer to template on the CRDO website)* • *and/or the Data Management Plan.* *Note The following regarding the collection of source data directly onto the data collection form* • *When data is entered directly into your electronic data collection forms, the data collection form /database becomes your source document for that information. For source data being captured directly into an instrument (the data collection form, a diary or other site-designed worksheet), whether it be paper or electronic, and the following factors should be considered when designing the instrument:* o *The data to be collected directly should be specified in the protocol.* o *The investigator or participant response should not be biased by pre-set values present within the instrument. An optional comment field may be appropriate to record additional information, in an event where the pre-set values available do not match the type of data collected.*

	○ *Note that the data collection form should not be the only record of a participant's inclusion in the trial. Trial eligibility and participation should, ideally, be captured in a participant's medical record to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial. Alternatively, trial eligibility and inclusion should be documented in a Participant Shadow File – this is an individual participant folder labelled with the name of the trial. It contains identified documents such as the signed informed consent form (photocopy or original), test results to confirm eligibility (if applicable).* ***Example text*** *In this trial, the following types of data will be collected (examples only given below):* • *personal identifying information (names, dates of birth, contact details, Epic ID)* • *sensitive information including health data (genetic information, disease/diagnosis, medical history)* ***Source Document Plan*** *The source documents for this trial include the RCH electronic medical record, questionnaires completed by the participant and/or researcher (paper); recorded data from automated instruments, laboratory reports and the signed parent/guardian (and, where applicable participant) information and consent forms. Each site participating in the trial will maintain a site-specific* ***Source Document Plan*** *that will document the source, i.e. original recording, for each data discrete item/ category of items collected for the trial. This Source Document Plan, signed and dated by the Site Principal Investigator, will be prepared prior to recruitment of the first participant and will be filed in the site's Investigator Site File.*
Generation and collection – how and by whom will data be generated and collected *Use – how and by whom* *Storage and access during the trial.* *Access – how and by whom, conditions under which access may be granted to others* *Disclosure – the purpose for which it will be disclosed, to whom?*	9.2.2 Data capture methods and data use, storage, access and disclosure during the trial *Your* ***Data Management Plan*** *will cover in detail the management of the captured data but your protocol should cover the points listed below.* ***Data collection*** *In this section of the protocol, provide a brief outline of the following:* • *Whether data capture and entry will be paper and/or electronic.* • *Whether any relevant data standards (e.g. ICD10 for disease coding, CTCAE for coding adverse events, CDASH for standardising data collection formats and structures across studies and sponsors) that are being utilised as a part of the trial.* • *Data capture processes - who will process the collected data, how, when and where* *Note: You should develop a Data Dictionary to provide a detailed description for each data variable (i.e. the source of the variable, coding information if used [for example, MedDRA, SNOMED CT], and expected ranges [if relevant]) or can be exported from the project's database(s) – for example, REDCap).*

Data storage and access

State how and where hardcopy data will be stored and how access will be restricted. State how and where electronic data will be stored, how it will be backed up and how access will be restricted (e.g. setting user permissions).

Use of the data

Specify how the data will be used (e.g. for the analyses specified in the protocol and Statistical Analysis Plan).

Complete also the section overleaf on data sharing.

Access to data

Describe in this section who will have access to the data and trial documents, noting that for the purposes of quality assurance reviews, audits, and evaluation of trial safety, progress, and data validity, each site must permit authorised representatives of the sponsor, HREC, Research Governance Office and regulatory agencies to examine source records for participants.

Disclosure of data

Describe whether there are any situations in which personally identifiable information or data will be released to third parties.

Example text – customise for your trial

Data collection methods

Data for this trial will be collected and entered using hardcopy and electronic data collection forms which will be completed by the parent/guardian (and/or participant where applicable) and researchers.

The following publicly available research data collection tools will be used:
<insert>

- *<insert>*

The following licensed research data collection tools will be used:

- *<insert>*
- *<insert>*

The following data standards will be used for coding the data:

- *<insert e.g. ICD10 for disease coding>*

Full information on the data variables is located in the Trial Data Management Plan.

Use of the data

The data will be used for the analyses specified in the protocol and Statistical Analysis Plan.

Following the completion and analysis of the trial, the data will be retained long-term following the mandatory archive period for use in future research projects.

Storage and access

Hard copy data will be stored by the Site in a locked cabinet in a secure location,

	accessible to the research team only. *Electronic data will be securely stored in MCRI's REDCap database system and in files stored in MCRI's network file servers, which are backed up nightly.* ***Files containing private or confidential data will be stored only in locations accessible only by appropriate designated members of the research team.*** *REDCap is hosted on MCRI infrastructure and is subject to the same security and backup regimen as other systems (e.g. the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data create/update/delete events that is accessible to project users who are granted permission to view it. Access to REDCap will be provided via an MCRI user account or (for external collaborators) via a REDCap user account created by the MCRI system administrator. The permissions granted to each user within each REDCap project will be controlled by, and will be the responsibility of, the trial team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed prior to personnel commencing data entry on REDCap.* *Authorised representatives of the sponsoring institution as well as representatives from the HREC, Research Governance Office and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this trial. The trialsite will permit access to such records.* *Disclosure* *The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the HREC, Research Governance Office or regulatory agencies.*
Methods to reduce identification of participants	9.2.3 Data confidentiality *Detail how personal information and data about potential and enrolled participants will be collected and maintained in order to protect confidentiality before, during, and after the trial. Include procedures for maintaining participant confidentiality, privacy protections, and any special data security requirements. (Refer to section 3.1.40 of the National Statement for discussion about research where removal or separation of identifiers may not be required).* ***Note that the 2018 update of the National Statement no longer uses the terms 'identifiable', 'potentially identifiable', 're-identifiable', 'non-identifiable' or 'de-identified' as descriptive categories for data or information due to ambiguities in their meanings. Rather, the identifiability of information is a characteristic that exists on a continuum.*** ***The risks related to identifiability of data and information in research are greatest where the identity of a specific individual can reasonably be ascertained by reference to an identifier or a combination of identifiers (examples of identifiers include the individual's name, image, date of birth or address, attribute or group affiliation). Risk may also arise where identifiers have been removed from the data***

or information and replaced by a code, but where it remains possible to re-identify a specific individual (by, for example, unlocking the code or linking to other data sets that contain identifiers). Due to technological advances, risks may arise in relation to data and/or information that has never been labelled with individual identifiers or from which identifiers have been permanently removed.

As outlined in the updated National Statement (2018):

- *Researchers and reviewers must consider the identifiability of data and information in order to assess the risk of harm or discomfort to research participants or others who may be at risk.*
- *Researchers should adopt methods to reduce the risk of identification during collection, analysis and storage of data and information. Methods to reduce identifiability and the consequent risks may include:*
  (a) minimising the number of variables collected for each individual;
  (b) separation and separate storage of identifiers and content information; and
  (c) separating the roles of those responsible for management of identifiers and those responsible for analysing content." (NS 3.1.41)
- *Where research involves linkage of data sets with the consent of participants, researchers should advise participants that use of data or information that could be used to identify them may be required to ensure that the linkage is accurate. They should also be given information about the security measures that will be adopted, for example the removal of identifiers once linkage is completed.*

Additional comments:

- *If data are to be generated in one location and transferred to another group, describe the responsibilities of each party, including the expectations regarding time to transfer.*
- *Discuss any additional features to protect confidentiality and privacy.*

The security arrangements should be proportional to the risks of the research project and the sensitivity of the information (NS 3.1.46).

Example text

Data confidentiality

"Participant confidentiality is strictly held in trust by the Site Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken:

(1) The number of private/confidential variables collected for each individual has been

	minimised. The data collected will be limited to that required to address the primary and secondary objectives (include exploratory where applicable). *(2) Participant identifiers will be stored separately to the data collected; documents with identifiers will be stored separately to participant data. (This is the ideal situation – if any data and identifiers are not stored separately, ensure there is restricted access e.g. use REDCap's permission control functionality. Amend wording in this section to reflect your planned practice). Participant data and samples will be identified through use of a unique participant trial number/code assigned to the trial participant ("re-identifiable"). The Site Principal Investigator is responsible for the storage of a master-file of names and other identifiable data with the participant ID; access to this document will be restricted to the site trial team and authorised persons as listed previously. The master file should be stored securely, and separately, from trial data in locked/ password-protected databases with passwords kept separately. If additional information such as age, ethnicity, sex or diagnosis especially where rare) is included in the data, discuss whether this might make specific individuals or families identifiable and outline strategies to address.* ***Consult with the CEBU team to discuss strategies*** *(e.g. "top and bottom coding" of data to limit identification of outliers).* *(3) Separation of the roles responsible for management of identifiers and those responsible for analysing content. The data will be analysed by the statistician, who will be provided with anonymised data identified only by the unique participant trial ID. As above, if any included data items might make specific individuals or families identifiable discuss and outline strategies to address -* ***consult with CEBU to discuss strategies.***
Quality assurance	9.2.4 Quality assurance *Provide a brief description of:* • *Plans for data cleaning (e.g. checks for invalid characters, out-of-range values, invalid dates, data that is not consistent with data in other data fields, repeated participant IDs etc).* • *Plans for source data verification (where applicable) to assess the accuracy, completeness, or representativeness of data by comparing the data in the database to the original source of the data (not applicable for data items where data is entered directly into the database and therefore the database is also the source).* • *Plans for site monitoring and auditing (where applicable)*
Analysis – how and by whom	*Ensure that this is covered in the STATISTICS section*
Storage post-trial ARCHIVE (after trial finished and during archive period) • *how will the data be stored post-trial* • *what is the retention period* *Disposal –process for*	9.2.5 Archiving - Data and document retention ***Archiving*** *How will the data be stored post-trial? What is the minimum, mandatory retention period for the data?* *The time period for which trial data, information and documents must be retained (the archive period) is determined by the type of research and relevant legislation, code and guidelines. Where more than one legislation/code/guideline is relevant, the one with the longest retention period applies.* ***However, also keep in mind the importance***

safe and secure disposal	***placed in the updated (2018) National Statement on collecting and retaining data and information for use by future research projects so that the benefits of research can be shared [NS 3.1.50).*** *Below is some guidance on current minimum retention requirements for research in Australia - contact the RCH Research Ethics Governance group to further discuss the requirements for your particular trial. You must also comply with MCRI data management policies.* • *All research – in general at least 5 years from publication (The Australian Code for the Responsible Conduct of Research 2007)** • *All research – retention of any new health data for at least 7 years for adults or until age 25 for children [VIC HRA]* • *Clinical trials - must archive for at least 15 year post-trial completion (TGA) or until child aged 25 years (whichever is the later) (VIC HRA)* • *Gene therapy research data - must retain permanently (The Australian Code for the Responsible Conduct of Research 2007)** • *Research that has community or heritage value - must retain permanently, preferably within a national collection (The Australian Code for the Responsible Conduct of Research 2007)** ** The revamped Code (2018) does not include guidance on required data retention periods - we are awaiting the release of the supporting guide "Management of Data and Information in Research".* *Describe how long and where all research data, information and documents will be kept following the end of the trial. During the archive period, data should be stored in a way that allows re-identification in case this is needed (e.g. for regulatory audits). Outline how the data will be secured and how confidentiality of stored data will be ensured.* *State who (i.e. person's position) will be the custodian during the archive period, who will have access to the stored data and outline any procedures that may be followed to dispose of the data at the end of the archival period.* *Specify that records should not be destroyed without the written consent of the Sponsor Investigator / Site Principal Investigator. In multi-site studies, the Sponsor-Investigator should inform Site Principal Investigators when these documents no longer need to be retained.* ***Destruction*** *If the plan is to destroy data and documents after the required archive period, state this here and describe the planned method of destruction. Secure destruction of research data involves using irreversible methods to ensure that the data is no longer usable. It is particularly critical that confidential or sensitive data is made unreadable.* *Hardcopies should be disposed of via a confidential shredding process.* *For electronic data, note that deleting files does not destroy the information completely; it may be necessary to utilise software which permanently erases data* (Seek guidance from MCRI IT). Consider also other data devices.* ** It may not actually be possible to completely expunge data from institutional*

	backups [i.e. those back-up tapes held off-site].
Data sharing – plans for permitting re-use of data both internal and external?	9.2.6 Data sharing *Except where there are justifiable ethical reasons, the National Statement requires research data be made available for future research projects (see extract below). Indicate the plan for whether data will be shared following completion, analysis and publication of this trial; justify if the plan is not to share the data.* • *"In the absence of justifiable ethical reasons (such as respect for cultural ownership or unmanageable risks to the privacy of research participants) and to promote access to the benefits of research, researchers should collect and store data or information generated by research projects in such a way that they can be used in future research projects. Where a researcher believes there are valid reasons for not making data or information accessible, this must be justified." (NS 3.1.50).* • *Data sharing statements should indicate the following: whether individual de-identified participant data (including data dictionaries) will be shared; what data in particular will be shared; whether additional, related documents will be available (e.g. trial protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analysis).* ○ *MCRI is currently (as of May 2019) developing a policy/procedure for the process involved in sharing data for future ethically-approved research.* *Ensure you seek appropriate consent (i.e. extended or unspecified consent) for this.* *Data sharing (review and customise for your trial)* *Beginning 'x' months following analysis and article publication, the following will be made available long-term for use by future researchers from a recognised research institution whose proposed use of the data has been ethically reviewed and approved by an independent committee and who accept MCRI's conditions for access:* • *Individual participant data that underlie the results reported in this article after de-identification (text, tables, figures and appendices)* • *Trial protocol, Statistical Analysis Plan, PICF*
Long-term custodianship (after archive period finished)	***Long-term custodianship (after archive period finished)*** *As noted previously, the National Statement specifies that research data should be retained and made available for future research projects, except where there are justifiable ethical reasons. Indicate the plan for long-term data retention for this research project.* *After the archive period, the data may be anonymised for preservation to reduce the risk of re-identification. As outlined previously, technological advances mean that identification can occur even where data and/or information has never been labelled with individual identifiers or from which identifiers have been permanently removed (e.g. linking to other data sets that contain identifiers). The risk of re-identification is related to the data context as well as what it will be used with and for.* *State who (i.e. person's position) will be the long-term custodian following the archive period.*

Sample management	***Sample management: Specimen & Biobanking*** *A biobank is defined as "…collections of human biological materials (biospecimens) linked to relevant personal and health information (which may include health records, family history, lifestyle and genetic information) and held specifically for use in health and medical research" (NHMRC Biobanks Information Paper, 2010).* ***In this section of the protocol, outline whether a biobank will be established.*** ***Registration of a Biobank*** *If your research includes the collection of samples and associated data to be stored for use in future research with extended* or unspecified consent**, you will need to register your biobank.* *For biobanking with the Melbourne Children's Bioresource Centre (MCBC) [note that the **MCRI Biobanking** Facility forms part of the MCBC] - complete a Biobank Registration Form (BRF). The BRF is available on request (biobanking@mcri.edu.au) or via the RCH Research Ethics Governance website (click on the link on the Application Coversheet).* ** Extended consent is defined as that given for the use of data or samples in future research projects that are (i) an extension of, or closely related to, the original project; or (ii) in the same general area or research (e.g. genealogical, ethnographical, epidemiological, or chronic illness research).* **Unspecified consent is defined as that given for the use of data or samples in any future research.* ***Sample storage and management*** *MCBC encourages standardised processing of biospecimens through the use of common processing protocols. These protocols are located on the MCBC website (MCRI intranet) at https://intranet.mcri.edu.au/rso/scientific-services/biobanking* *This link provides details of general laboratory protocols for sample types commonly processed by the Facility. In devising these protocols, the MCRI Biospecimen Advisory Committee and MCBC have drawn upon local, national, and international expertise, and published evidence that compares and contrasts various methodological approaches.* *Some trials will have specific downstream requirements that may not be fully met by these general protocols, so that flexibility will be required. MCBC staff are available to discuss such trial-specific processing requirements.* ***If an investigator seeks an alternative facility to store and manage samples, provide full detail on the items listed below and describe all sample processes relevant to your trial, including how samples are tracked (using the approved institutional database), stored and retrieved for use. In this section of the protocol, outline the following (N.B. if not using MCBC to manage and store the biobank provide full detail here):*** • *Biobank name, location and custodian (position with overall responsibility for the biobank)* • *Purpose of the biobank (purpose and timeframe i.e. fixed date or indefinite)* • *Types of samples and type of associated data*

	• *Consent type and process* ○ *Sample/record identification and confidentiality (e.g. how will samples/records be identified, who will have access to the identification codes?)* • *Access to samples/data – who may access and what are the requirements for access (e.g. prior independent ethical approval).* • *Security and back up – what systems will be in place to ensure integrity of the tissue samples (e.g. temperature alarms on storage units)* • *Destruction – in what circumstances will this be done (e.g. participant request, consent expiry, biobank expiry or other discontinuation of data bank).*

10 TRIAL OVERSIGHT

10.1 Governance structure

Appropriate oversight of trial conduct, protocol compliance and safety should be established for each trial.

10.1.1Trial Management Group (TMG)

All trials should establish a small group at each site to oversee the day-to-day conduct of the trial. This group should include the key individuals responsible for the day-to-day management of the trial, such as the Site Principal Investigator, trial coordinator, research nurse, data manager, statistician etc. The group should closely review all aspects of the conduct and progress of the trial and should meet regularly (informally or formally) to ensure that there is a forum for identifying and addressing issues. Particular attention should be paid to: progress towards trial milestones (recruitment accrual, timelines etc); adherence to the protocol; and adherence to good research practices. Evidence of this oversight should be documented in meeting minutes, emails and documented phone calls.

Example text: *The Site Principal Investigator is responsible for supervising any individual or party to whom they have delegated tasks at the trial site. They must provide continuous supervision and documentation of their oversight. To meet this GCP requirement, a small group will be responsible for the day-to-day management of the trial and will include at a minimum the Site PI and project manager/research nurse/trial coordinator. The group will closely review all aspects of the conduct and progress of the trial, ensuring that there is a forum for identifying and addressing issues. Meetings must be minuted with attendees listed, pertinent emails retained and phone calls documented.*

10.1.2Trial Steering Committee (TSC)

A TSC may be established for studies that are large, complex or potentially controversial or where there is a need to include key stakeholders in oversight of the trial. A Trial Steering Committee should include member(s), independent of the PI and Institution, who can provide expert advice. The TSC provides overall supervision and ensures that the trial is conducted to the required standards but it should be noted that the day-to-day management of the trial remains the responsibility of the Site Principal Investigator and the Trial Management Group. The TSC, through the Committee Chairperson, provides advice to the PI.

Example text: *"A TSC will be established to provide expert advice and overall supervision, and ensure that the trial is conducted to the required standards. The SSC will meet at least annually, with more frequent meetings as needed, and will work to a Terms of Reference.*

10.1.3Safety Monitoring

According to ICH GCP, the responsibility for the ongoing safety evaluation of the investigational product lies with the sponsor - in investigator-initiated studies this will be the Sponsor-Investigator. Safety monitoring processes should be based on the risk, size and complexity of the research. In studies with small numbers of participants, risks may be more readily become apparent through close monitoring of adverse events whereas in larger studies risks are often better assessed through statistical comparisons of treatments. The "Safety monitoring and reporting on clinical trials involving therapeutic goods" (NHMRC, 2016) states that "To ensure there is appropriate independent oversight of safety within a clinical trial, sponsors should generally utilise an independent committee or independent individuals (e.g. a medical monitor) to review accruing safety data. Below are some examples for independent safety monitoring.

Independent Safety Monitor

An Independent Safety Monitor is an individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The Independent Safety Monitor evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the trial.

***Example text:** "Safety oversight will be under the direction of an Independent Safety Monitor, whose primary responsibility is to provide independent safety monitoring in a timely fashion. The Independent Safety Monitor will operate within agreed terms of reference / approved charter and will provide input to the Sponsor-Investigator."*

Independent Data Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the trial investigators. The members of the DSMB provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated trial data for participant safety, trial conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers trial-specific data as well as relevant background knowledge about the disease, intervention, or target population under trial. Refer to CRDO's "Data and Safety Monitoring Board - Standard Operating Procedure" and template charter available on the CRDO website and also the NHMRC's supplementary guidance "Data Safety Monitoring Boards (DSMBs)" at https://www.nhmrc.gov.au/guidelines-publications/eh59

Example text: "Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). It will be composed of individuals with the appropriate expertise, including at least three independent clinicians and/or biostatisticians who, collectively, have experience in the management of paediatrics, biostatistics and the conduct and monitoring of randomised controlled trials. Members of the DSMB will be independent of trial conduct. The DSMB will meet at least <insert e.g. annually> to assess <insert (e.g. safety and efficacy data) on each arm of the trial. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organisational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Sponsor-Investigator."

10.2 Site Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of

the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Monitoring should be risk-based (i.e. tailored to the specific human protection and data integrity risks for the trial); the plan for monitoring should focus on preventing or mitigating important and likely risks to critical data and processes. A ***Risk Assessment and Risk Management Plan*** *(available on the* ***CRDO website****) should be used to help identify and document the risks and their management. The assessment results may assist in deciding on the risk-based approach to site monitoring: low versus moderate versus higher intensity monitoring (See* ***NHMRC Guidance: Risk-based management and monitoring of clinical trials involving therapeutic goods (dated 2018) https://www.nhmrc.gov.au/guidelines-publications/eh59)***

The risk assessment should take into account a range of factors including the complexity of the trial design, types of trial outcomes,, clinical complexity of the trial population, geography, relative experience of the Sponsor-Investigator and Site Principal Investigator(s), the relative safety of the trial intervention, the stage of the trial, how the data is captured (e.g. electronic) and the quantity of data.

In this section, you should provide a general description of how the monitoring of the conduct and progress of the trial will be conducted. Full details should, ideally, be provided in a separate, detailed Clinical Monitoring Plan (CMP) which can be referred to in this section (refer to the SOP on monitoring and a template CMP on the CRDO website).

*The CMP should describe the monitoring strategy, who will conduct the monitoring, the monitoring methods (e.g., on-site, centralised) and rationale for their use, the frequency (e.g., early, for initial assessment and training versus throughout the trial) and extent (****e.g., review 100% of original signed consent forms, trial eligibility data and data related to primary outcome, safety and other key data variables; review of all withdrawals from trial treatment and/or trial follow up; targeted review of other data including investigational medicinal product administration and accountability****); and the distribution of monitoring reports*

Regular monitoring and an independent audit (if conducted) should be performed according to good clinical practice guidelines.

Example text (customize as needed):
"Trial site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and amendment(s), good clinical practice and applicable regulatory requirements.

Full details of trial site monitoring are documented in the Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Monitoring for this trial will be performed by <insert text>. <Insert brief description of type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the trial), and extent (e.g., review of 100% of original signed consent forms, trial eligibility data and data related to primary outcome, safety and other key data variables; review of all withdrawals from trial treatment and/or trial follow up; targeted review of other data including investigational medicinal product administration and accountability).>

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.3 Quality Control and Quality Assurance

Quality Management is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities. Both the Sponsor-Investigator and Site Investigator have responsibilities in relation to quality management.

The Sponsor-Investigator will develop SOPs that identify, evaluate and control risk for all aspects of the trial, e.g. trial design, source data management, training, eligibility, informed consent and adverse event reporting.

In addition to trial-specific SOPs and/or a Trial Manual provided by the Sponsor-Investigator, each site (both clinical and laboratory) should implement a quality management plan using SOPs that describe:

- *Who will be responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting errors in, for example, data entry).*
- *Staff training methods and how such training will be tracked.*
    - *If applicable, calibration exercises conducted prior to and during the trial to train examiners and maintain acceptable intra- and inter-examiner agreement.*
- *How data and biological specimens (when applicable) will be evaluated for compliance with the protocol and for accuracy in relation to source documents, which documents are to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.*

Example text (customise as needed):

"Both the Sponsor-Investigator and Site Investigator have responsibilities in relation to quality management.

The Sponsor-Investigator will develop SOPs that identify, evaluate and control risk for all aspects of the trial, e.g. trial design, source data management, training, eligibility, informed consent and adverse event reporting. The Sponsor-Investigator will also implement quality control (QC) procedures, which will include the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

As outlined in the previous section (Site Monitoring), the trial monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, good clinical practice and applicable regulatory requirements.

In the event of non-compliance that significantly affects human participant protection or reliability of results, the Sponsor-Investigator will perform a root cause analysis and corrective and preventative action plan (CAPA).

In addition, each clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation and completion. An individualised quality management plan will be developed to describe a site's quality management."

11 STATISTICAL METHODS

This section should be prepared in close collaboration with the trial statistician.

11.1 Sample Size Estimation

Specify the sample size and justify the number in terms of the trial objectives. The methods or computer program used for the determination of sample size should be documented or referenced, as should the estimates of any quantities used in the calculation. The justification normally states the following:

- *The relevant primary outcome*
- *The main treatment comparison of interest*
- *The assumed control mean or rate*
- *The minimum treatment effect for which statistical power is required*
- *The estimated underlying variability (only relevant for continuous outcomes)*
- *The estimated underlying proportion (only relevant for categorical outcomes)*
- *For time-to-event outcomes, the number of expected events within the planned follow-up period*
- *The values of Type I and Type II error rates and (if applicable) related considerations how to address multiplicity (e.g. planned interim analyses, multiple group comparisons).*

If it is likely that a proportion of participants will not complete the trial, you may want to allow for this in the sample size estimation. This should be stated. If there are plans for a sample size review (with a view to altering the planned number of participants), detail methods for accomplishing this (e.g. will it be conducted in a blinded and non-comparative way?).

This section should also discuss whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses.

11.2 Population to be analysed

This section should be very specific in defining the participant populations whose data will be subjected to the trial analyses. Examples of such populations include:

- *Intention to treat population (ITT): Includes any participant randomised into the trial, regardless of whether they received trial drug.*
- *All-treated population: Includes any participant randomised into the trial that received at least one dose of trial drug*
- *Per-protocol population (PP): Includes any participant who was randomised and received the protocol-required doses of trial drug and fulfilled all protocol required assessments*

Generally the intention to treat population is used in the analyses, unless there is a specific reason to do otherwise. In an intention to treat analysis participants are compared according to the group to which they were randomly allocated, regardless of participants' compliance, crossover to other treatments or withdrawal from the trial. This approach preserves the prognostic balance in the trial arms achieved by randomisation.

11.2.1 Handling of missing data

Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation).

11.3 Methods of analysis

Describe how the baseline characteristics will be presented.

Detail the statistical methods for analysing primary, secondary and exploratory outcomes. This may be in one section, or for large studies could be separated into primary outcome, secondary outcomes, exploratory outcomes and safety data.

List each outcome variable, beginning with the primary outcome, and provide for each

- *The population for which the analysis will be conducted*
- *A definition of the measurement or observation and describe how it is calculated, if not readily apparent*
- *A description of the how the data will be presented (e.g. mean, median, IQR)*
- *A description of the statistical method used for analysis and how results of statistical procedure(s) will be presented (e.g., adjusted means with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
- *A description of any checks of the assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)*

It is important to ensure that the text is consistent with the stated objectives and the analysis strategy used to determine the sample size. Major features of the analysis should be outlined such as time-points at which comparisons will be made as well as covariates that will be adjusted for in the analysis. State the type I error level that is considered in the primary efficacy analysis and if one or two-sided tests are going to be used. In non-inferiority or equivalence trials, clearly state the non-inferiority or equivalence margin, the level of confidence and if one or two-sided confidence intervals are going to be used.

Include methods for any additional analyses (e.g. subgroup and adjusted analyses). If results of these additional analyses will be considered to be supportive/exploratory in nature or if they are an integral part of the confirmatory primary efficacy analysis they need to be included here. Outline sensitivity analyses that will be performed to assess robustness of the results with respect to potential violations of assumptions for valid statistical inference.

For the safety data, describe how AEs will be coded (e.g., Medical Dictionary for Regulatory Activities (MedDRA)), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g., severity, frequency, and relationship of AEs to trial intervention will be presented by System Organ Class (SOC) and preferred term groupings) and what information will be reported about each AE (e.g., start date, stop date, severity, relationship, expectedness, outcome, and duration). Adverse events leading to premature discontinuation from the trial intervention and serious treatment-emergent AEs should be presented either in a table or a listing.

If there is a separate document detailing the statistical analysis plan (SAP), this section of the protocol should contain the key elements of the analysis plan, describing the general methodology for dealing with each category of data and addressing each of the objectives. However, it does not need to be detailed by variables. The full details for each variable will be included in the SAP (which can undergo edits and versioning outside of the protocol and therefore not trigger an HREC re-review with every version or edit, as long as the key elements of the plan do not change). If there is a separate SAP, refer to the SAP in this section of the protocol.

11.4 Interim Analyses

Include content in this section if applicable, otherwise note as not-applicable.

This section should describe the types of statistical interim analyses and halting guidelines (if any) that are proposed, including their timing and who reviews the interim analyses. In addition, if the interim analyses could result in an adjusted sample size, discuss the statistical algorithm to be used when evaluating results. Pre-specify, to the extent possible, the criteria that would prompt an interim review of safety and efficacy data and trial futility. Describe who performs the statistical analysis and who reviews the analysis. In addition, discuss whether they are unblinded and how the blinding will be preserved.

If statistical rules will be used to halt enrolment into all or a portion of the trial (e.g., for safety or futility), describe the statistical techniques and their operating characteristics. If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

Describe safety findings that would prompt temporary suspension of enrolment and/or trial intervention use until a safety review is convened (either routine or ad hoc). Provide details of the proposed rules for halting trial enrolment or trial intervention/administration of trial product for safety, including whether they pertain to the entire trial, specific trial arms or participant subgroups, or other components of the trial.

State how endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed halting guidelines. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

Note regarding adaptive trial design:
If any interim analyses of the trial data are required to guide the adaptive component of the trial these should be detailed here along with the rules governing the adaptations.

12 ETHICS AND DISSEMINATION

All research must be approved by a Human Research Ethics Committee (HREC) and receive institutional governance authorisation via the local Research Governance Office (RGO) before it can commence. In this section, you should detail how you will seek HREC approval and RGO authorisation and how any changes to the trial will be communicated to the HREC, RGO and others.

12.1 Research Ethics Approval & Local Governance Authorisation

Example text: *"This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by the human research ethics committee (HREC) prior to commencing the research. A letter of protocol approval by HREC will be obtained prior to the commencement of the trial, as well as approval for other trial documents requiring HREC review.*

Each participating institution will also obtain institutional governance authorisation for the research and associated HREC-approved documents. A letter of authorisation will be obtained from the RGO prior to the commencement of the research at that institution. Institutional governance authorisation for any subsequent HREC-approved amendments will be obtained prior to implementation at each site.

12.2 Amendments to the protocol

Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes analyses) to relevant parties (e.g., investigators, HRECs, trial participants, trial registries, journals, regulators).

Example text: *"This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participants willingness to continue participation in the trial is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to being implemented."*

12.3 Protocol Deviations and Serious Breaches

A protocol deviation is "Any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol" (Reporting of serious breaches of good clinical practice or the protocol for trials involving therapeutic goods, NHMRC, 2018). All protocol deviations must be documented and reported to the Sponsor (which will be MCRI in the case of campus-led investigator-initiated trials).

Those deviations that are deemed "likely to affect to a significant degree the rights of a trial participant or the reliability and robustness of the data generated in the clinical trial" are classed as ***Serious Breaches****. See below for the reporting requirements for serious breaches*.*

In this section, outline the process that will be followed to detect, document, report and follow-up on protocol deviations and serious breaches.

** The site Principal Investigator must report serious breaches within 72 hours to the Sponsor (which in the case of campus-led investigator-initiated trials will be the Coordinating Principal Investigator at MCRI) and within 7 days to the site's Research Governance Office. The Sponsor must review and report serious breaches to the approving HREC within 7 days.*

Example text: *"All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the Site Principal Investigator, who will assess for seriousness.*

Those deviations deemed to affect to a significant degree rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done in a timely manner (Site Principal Investigator to report to the Sponsor-Investigator within 72 hours and to the Site RGO within 7 day; Sponsor-Investigator to review and submit to the approving HREC within 7 days).

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

13 CONFIDENTIALITY

Detail how personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

Include procedures for maintaining participant confidentiality, privacy protections, any special data security requirements, and record retention per national requirements. Describe who would have access to records, including the investigator and other trial staff, the clinical monitor, funding institutions, representatives from the HREC, Research Governance Office, regulatory agencies, and sponsor representatives. In addition, consider inclusion of the following information:

- *Describe whether identifiers will be attached to data/samples (termed 'identifiable'), or whether data will be identified by a unique code (termed 're-identifiable') or not identified (termed 'non-identifiable').*
    - *If re-identifiable or non-identifiable but additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.*
    - *If research data/samples will be re-identifiable, describe how access to the "key" for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.*
- *Include a discussion of the circumstances in which data or samples will be shared with other researchers.*
- *Include a discussion of plans to publish participant's family pedigrees (where applicable), with a description of measures to minimize the chance of identifying specific families.*
- *State who has access to records, data, and samples. Consider if monitors or auditors outside of trial investigators will need access.*
- *Describe any situations in which personally identifiable information will be released to third parties.*
- *Discuss any additional features to protect confidentiality and privacy.*

Example text:

"Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Participant Identification Number (SID) to maintain participant confidentiality.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies."

14 PARTICIPANT REIMBURSEMENT

If participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for trial participation, describe amount, form and timing of such compensation in relation to trial activities (include financial and non-financial incentives). Describe who will receive incentives (if not the participant). For example, if minors, state whether the minor or the parent/guardian will receive the

incentive. If incapacitated adults, state if payment will be provided to the participant or to a legally authorized representative or guardian.

15 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

Detail any financial or other competing interests for investigators for the overall trial and each trial site.

16 DISSEMINATION AND TRANSLATION PLAN

Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions.
Identify who holds the primary responsibility for publication of the results of the trial.

17 ADDITIONAL CONSIDERATIONS

This section should include a description of any additional considerations not currently covered in this protocol template.

18 REFERENCES

List references here

19 APPENDICES

19.1 Appendix 1: Division of sponsor responsibilities between sponsor and sponsor-investigator

For non-commercial trials, the overall responsibility for initiating and managing the trial, lies with the sponsor. However, as the person responsible for leading the team of researchers undertaking the design, conduct and reporting of the trial, the Sponsor-Investigator should have oversight of all activities, even when they are delegated to third parties such as clinical trial units or coordinating centres.

Before taking on the role of Sponsor-Investigator, it is important to understand:

- *What you need to have in place before you start a trial*
- *What aspects of the trial you need to review as the trial progresses*

This document sets out the typical allocation of clinical trial functions between the Sponsor-Investigator and the sponsor for investigator-led or collaborative group clinical trials; note that this is an example and may be amended on a case by case basis).

Sponsor-Investigator:	*Insert name*	
Responsibility	**Sponsor**	**Sponsor-Investigator**
Ensure a peer review/independent expert review has demonstrated that the trial proposal is worthwhile and is of high scientific quality.	X	
Ensure the Sponsor-Investigator has adequate procedures in place for all key trial management activities	X	
Assign an overall risk category based on type of intervention	X	
Ensure that the Sponsor-Investigator has the necessary expertise and experience to conduct the trial	X	
Ensure that the Sponsor-Investigator has the resources needed to complete the trial successfully or that plans are in place to raise additional funds.	X	
Confirm provision of insurance and indemnity for the trial and trial related staff as well as measures for participant compensation for trial related injury	X	
Ensure all the roles and responsibilities for the clinical trial are delegated, agreed and documented appropriately	X	
Oversee/sign-off all contract negotiations with external providers (e.g. external lab facilities; pharmaceutical companies for supply of investigational product,)	X	
Ensure the protocol (or other document) details appropriate monitoring and management plans commensurate to the risk and complexity of the trial	X	
Maintain oversight to include audit, where applicable	X	
Ensure that the trial is based on a thorough review of scientific literature including whether any relevant systematic review exists.		X
Secure funding and/or confirm sufficient resources are available to conduct the trial (e.g. trial subjects, time, staff, facilities, finances) or put in place plans to raise additional funds.		X
Ensure that trials are registered on clinical.trials.gov, ANZCTR or other appropriate registry before first patient is enrolled and that appropriate plans for the dissemination of trial findings are in place		X
Unless delegated to a third party, undertake/oversee the design, conduct and		X

reporting of the trial with support from all relevant specialist staff (e.g. statistician, research methodologist) including the development of a protocol that is compliant with international standards including the SPIRIT Statement. Where appropriate, prepare the regulatory dossier for trials aiming to commercialise a new investigational medicinal product/investigational medical device.		
Ensure a trial risk assessment has been carried out and proportionate trial management and monitoring plans are in place		X
For investigational medicinal product trials, ensure (through the appointed pharmacist, medical engineering) that all requirements for IMP/IMD supplies are met (e.g. manufacture/ packaging/labelling).		X
Develop/endorse an appropriate strategy for independent trial oversight (e.g. Trial Management Group, Trial Steering Committee, Data Safety Monitoring Board) If a Data Safety Monitoring Board is not warranted, ensure alternative mechanisms for ongoing safety monitoring are in place		X
Document trial specific delegation of duty on a Staff Signature and Delegation Log		X
Confirm each member of the trial team are aware of their trial-related duties		X
Ensure the development of all relevant trial documentation (e.g. protocol, Participant Information and Consent Form and Case Report Form)		X
Develop/obtain the investigator's brochure or where appropriate, the Product Information to be used for the trial and ensure that the reference safety information for identifying expectedness of adverse events is clearly identified		X
Oversee the set-up of a clinical trial database		X
Ensure all trial approvals and notification are in place before the trial commences (e.g. HREC, SSA, TGA)		X
Ensure relevant agreements/signatories from service departments supporting the trial (e.g. pharmacy, laboratories, radiology) are obtained		X
Ensure arrangements are in place for the effective financial management of the trial		x
Prepare and submit amendments to the trial		X
Implement procedures to ensure the collection of high quality and accurate data		X
Oversee the set-up and maintenance of a Trial Master File		X
Ensure safety reporting and monitoring for the trial complies with the requirements of the NHMRC Guidance for Safety Monitoring and confirm and execute any sponsor reporting responsibilities that are delegated		X
Submit annual report(s) to the HREC and Research Office in accordance with Australian Guidance and local requirements		X
Report suspected serious breaches of GCP/protocol to the HREC and Research Office in accordance with the NHMRC Guidance		X
Notify HREC, Research Office, TGA and other relevant bodies of the completion of the trial		X
Produce all necessary reports to funders and others		X
Disseminate trial findings through publication/dissemination of trial results where applicable, following the CONSORT Statement		X
Fulfil commitments to trial participants, such as providing information about the outcome(s) of the trial, re-obtaining consent if required due to change in risk-benefit ratio (of investigational medicinal product) or change in protocol procedures		X
Ensure all trial data (including the Trial Master File) and materials, are archived appropriately and retrievable for audit purposes		X
Maintain trial registration record in accordance with the registry's requirements		X

19.2 APPENDIX 2: Significant Safety Issues (SSI) - some examples

Examples below have been extracted from the NHMRC's "Safety monitoring and reporting in clinical trials involving therapeutic goods" (November 2016)

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt/termination of a trial for safety reasons
- recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction
- single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure

Examples below have been extracted from the TGA's "Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements" Version 2.0, September 2017

- safety-related actions by comparable international regulatory agencies such as the:
  - withdrawal or suspension of the medicine's availability
  - addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information or label
  - modification or removal, for safety reasons, of an indication.
- changes in the nature, severity or frequency of known serious adverse reactions which are medically significant
- detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction that may impact on the safety or benefit-risk balance of the medicine
- series of reports of similar or linked adverse reactions reported at the same time (that is, a cluster) assessed to suggest a quality defect issue that may have implications for public health
- an unusual and significant lack of efficacy occurring in or outside Australia that may have implications for public health
- major safety findings from a newly completed non-clinical study, post-registration study or clinical trial that may impact the benefit-risk balance of the medicine on the ARTG
- a signal of a possible teratogenic effect or of significant hazard to public health
- safety issues related to any raw materials used in the medicine that may impact the safety of the medicine and/or have implications for public health
- safety issues due to misinformation in the product information or label that may impact the safety of the medicine
- safety issues related to use outside the approved indication or intended use that may impact the safety or benefit-risk balance of the medicine

19.3 APPENDIX 3: Expedited Safety Report Form

Below is a template form – adapt for your trial.

EXPEDITED SAFETY REPORT FORM	
Reporting requirement: All sites to report to Sponsor-Investigator all *SAEs, SUSARs and USMs within 24 hours of **trial** staff becoming aware of the event. **Except those identified in the protocol as not needing immediate reporting*	
HREC Reference #	
Project title	

Section A: To be completed by the Local Site	
Site:	
Local Site Principal Investigator:	
Participant Enrolment OR Randomisation No.:	
Date the safety event occurred:	
Date Local Site Principal Investigator became aware of the safety event:	
Participant's date of birth, age and weight:	
Event description and management:	
Event outcome (synopsis):	
Trial phase *(amend to reflect protocol)*	☐ Screening ☐ Treatment ☐ Follow Up
Relationship to the trial drug	☐ Unrelated ☐ Unlikely to be related ☐ Possibly related ☐ Probably related

Expectedness (only complete for SAEs that are probably/possibly related):	☐ Not applicable ☐ Expected ☐ *Unexpected *Report SUSAR to local RGO within 72 hours of becoming aware of event
Was an Urgent Safety Measure (USM) instigated? *A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.*	* ☐ Yes ☐ No *Report to local RGO within 72 hours of becoming aware of event
Name and Signature (of local PI or delegate)	Date

Section B: To be completed by the Sponsor-Investigator only	
Is this event a 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. Often SSIs do not fall within the definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR), thus are not reported as SUSARs but require other action such as the reporting of an urgent safety measure (USM), an amendment, a temporary halt or early termination of a trial.*	*☐ Yes ☐ No * Report to TGA, HREC and all site PIs within 15 days of becoming aware of event
Is this event an Urgent Safety Measure (USM)? *A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.*	* ☐ Yes ☐ No *Report to TGA, HREC and all site PIs within 72 hours of becoming aware of event
Is this event a SUSAR?	* ☐ Yes ☐ No *Report to TGA within 7 days of becoming aware of the event if fatal/life threatening, otherwise report within 15 calendar days
Does the <u>protocol</u> require amending as a result of this safety event? (If Yes, submit an amended protocol to approving HREC)	☐ Yes ☐ No
Do the <u>participant information statements</u> require amending as a result of this safety event? (If Yes, submit a**n amendment** request to approving HREC and RGOs with the amended forms)	☐ Yes ☐ No
Is a temporary halt or early termination of the trial required as a result of this safety event? (If Yes, ensure actions are taken within 15 days of decision to halt)	☐ Yes ☐ No
Name and Signature (of Sponsor-Investigator)	Date

Please email one signed copy to the Sponsor–Investigator <*insert name and email address***) and retain the signed original in the Site Investigator File**

19.4 APPENDIX 4: Specimens for biobanking - completed biobank registration form

If samples are being collected and stored for future research, include a scanned copy of the completed and signed BioBank Registration Form" in this section.*

** Available from the Biobanking page on the MCRI intranet*