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 19 December 2024** |   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 therapeutic good (including placebos) being tested or used as reference in a clinical trial” (*Australian clinical trial handbook: Guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods, 2018 Therapeutic Goods Administration [TGA]* <https://www.tga.gov.au/publication/australian-clinical-trial-handbook>). 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 guideline adopted by the TGA [“Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016” does not cover IMDs. A separate good clinical practice guideline specific to investigations of devices (ISO 14155 version 2020) is available for purchase (single-user licenses) at <https://www.iso.org/standard/71690.html> Note also that the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (dated November 2016) <https://www.nhmrc.gov.au/guidelines-publications/eh59> covers the main aspects of the ISO guideline.   All researchers please also note:   * For trials conducted under the CTN/CTA schemes, please contact [CRDO](mailto:crdo.info@mcri.edu.au)/[MCTC](mailto:mctc@mcri.edu.au) for assistance with the additional documentation required. * 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](mailto:crdo.info@mcri.edu.au) for further information (including how to 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](mailto:crdo.info@mcri.edu.au) Note that on the [CRDO website](https://www.mcri.edu.au/research/researcher-training-resources/research-process-resources/development) 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** | This template uses typefaces described below to distinguish between their intended use and applicability.  There are instructions in **purple** stating the information that should be contained in that section.  Boilerplate text is included in black and should be retained as the information conveyed is applicable to all clinical trials. Modifications will require a justification to be included as this would be a deviation from local SOPs and/or relevant local/national/international regulations.  Example wording is included in ***green****. Usually, you will need to modify this text to tailor to your trial.*  Wording (explanation and example wording) that is specifically related to conducting the trial internationally is in ***blue***.  Purple text shaded light blue is included to assist with writing each section in accordance with applicable regulations, legislation, and/or Melbourne Children’s clinical trial Standard Operating Procedures (SOPs).  You will need to input your clinical trial specific information under each heading and remove all instructional and example text. There should be no purple, green or blue text in the final document.  The order of instructional text, boilerplate text and example text within any given section is intention. Retain this order when adding your trial specific information to ensure the content flow is logical and not interrupted.  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.  **Do not delete sections that you have decided are not applicable to your trial. Instead add text under these sections to indicate why they are not applicable.**  **Delete all the Notes to Users pages before you finalise the document.**  **Remove Creative Commons License from footnote before you finalise the document.** |

|  |  |
| --- | --- |
| **Resources** | The guidance in this template has been derived from a number of sources including: |
|  | Australian Clinical Trial Handbook: Guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods, 2021 Therapeutic Goods Administration<https://www.tga.gov.au/publication/australian-clinical-trial-handbook>  ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies available from <https://prsinfo.clinicaltrials.gov/definitions.html>  SPIRIT & CONSORT statements at <http://www.consort-statement.org/>  [Clinical Electronic Structured Harmonised Protocol (CESHARP) M11 Template, Step 2b Draft for consultation, 2022 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m11-template-step-2b_en.pdf)  [Clinical e-Protocol Writing Tool](https://e-protocol.od.nih.gov/#/home), National Institutes of Health (NIH) Office of Science Policy  [Common Protocol Template, TransCelerate](https://www.transceleratebiopharmainc.com/wp-content/uploads/2024/01/CPT_CoreBWE_v010.docx)  [MCTC005 SOP | Safety Monitoring and Reporting Procedure for MCRI-Sponsored IITs of Medicines/Medical Devices](https://metis.melbournechildrens.com/MCTC005)  CRDO – other standard operating procedures and templates – available from [METIS](https://metis.melbournechildrens.com)  Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 Annotated with TGA comments <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>  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: Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods <https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1>  NHMRC Guidance: Risk-based management and monitoring of clinical trials involving therapeutic goods (dated 2018) <https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1>  **Regulations specific to EU sites**  Clinical Trials - Regulation EU No 536/2014 (applicable to European trials/sites) at <https://ec.europa.eu/health/human-use/clinical-trials/regulation_en>  Clinical Trial – REGULATION (EU) 2016/679 General Data Protection Regulation (GDPR) (applicable to European trials/sites) at <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679>  *For country-specific regulations; refer to: https://red.ecrin.org/en*  **Regulations specific to UK sites**  The Medicines for Human Use (Clinical Trials) Regulations 2004, UK Parliament (Current through to May 2024), at <https://www.legislation.gov.uk/uksi/2004/1031/contents>  UK Policy Framework for Health and Social Care Research, 6 Sep 2023, at [https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/%20%20%20)  Data Protection Act 2018([UK-DPAct](https://www.legislation.gov.uk/ukpga/2018/12/contents)) (Current through May 13, 2024)  UK Parliament, at <https://www.legislation.gov.uk/ukpga/2018/12/contents>  UK General Data Protection Regulation [Regulation 2016/679 of the European Parliament] (UK-GDPR) (Effective January 1, 2021) UK Parliament, at <https://www.legislation.gov.uk/eur/2016/679/contents>  For up-to-date regulations refer to: [https://clinregs.niaid.nih.gov/country/united-kingdom#requirements](https://clinregs.niaid.nih.gov/country/united-kingdom%23requirements)  **Regulations specific to US sites**  FDA – Selected GCP and Clinical Trial Application Guidance Documents at <https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/selected-fda-gcpclinical-trial-guidance-documents>  Health Insurance Portability and Accountability Act of 1996 (HIPAA) (August 21, 1996) US Congress, at <https://www.govinfo.gov/content/pkg/PLAW-104publ191/pdf/PLAW-104publ191.pdf> |

|  |  |
| --- | --- |
| protocol  [**Insert full clinical trial title**]  The full clinical trial title is required to enable retrieval from literature or internet searches and should include the following information: Information on participant population; intervention; comparison groups; outcomes; phase; and trial design.  **SHORT PROTOCOL TITLE**  **[Insert short title of the trial]**  The short title should be written in language intended for the lay public and suitable for use as the “Brief Title” in global clinical trial registries. It can also be used with informed consent documents and ethics submissions. The title should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.  Do not include technical study design terms (e.g., Phase 2, Single Group, Double Blind, Randomised, Pharmacokinetics) – instead include these in the full title] Character Limit: 300  **<CLINICAL TRIAL ACRONYM>**  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. | |
| Protocol Number:  Complete if applicable, otherwise delete |  |
| Protocol Version # and Date: |  |
| Clinical Trial Registry Identifier: |  |
| CTN/CTA ID Number:  Complete if applicable, otherwise delete  For CTNs, use format CT-YYYY-CTN-XXXXX-X |  |
| EudraCT Number:  Complete if applicable, otherwise delete |  |
| IND Number:  Complete if applicable, otherwise delete |  |
| IND Sponsor:  Complete if applicable, otherwise delete |  |
| Sponsor Name: |  |
| Sponsor Address: |  |
| Sponsor-Investigator Name: |  |

**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 [DD-MMM-YY]** | **Summary of Changes** |
| --- | --- |
|  | Include here a brief description of the change(s) made and reason for the change(s), for example "updated post HREC review" |
|  |  |
|  |  |

**AUTHORSHIP**

Include only main author/s – remember the Australian Code for the Responsible Conduct of Research (the Code) requires a substantive contribution. Also see the MCRI Authorship Guideline, available on the [MCRI intranet](https://intranet.mcri.edu.au/research-and-science/research-integrity/policies-information-and-tools) for further information on how to approach authorship.

| **Author Name** | **Signature** | **Date of Signature** |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |

**SPONSOR-INVESTIGATOR AGREEMENT & SIGNATURE PAGE**

The Sponsor-Investigator should conduct the trial in compliance with the protocol, which was given approval by the HREC/IRB/IEC. The Sponsor-Investigator should sign the protocol to confirm agreement.

By signing this protocol, the undersigned 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]. In addition, the Sponsor-Investigatorwill ensure that the trial is conducted in compliance with all applicable laws and regulatory requirements relevant to each participating country.

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
* Any additional required authorisations (e.g. institutional authorisation).

I, as Sponsor-Investigator, agree that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation.

I, as Sponsor-Investigator, agree to undertake and/or oversee those Sponsor responsibilities delegated by the Sponsor, as listed in the MCRI Certificate of Sponsorship.

**For and on behalf of the Study Sponsor:**

|  |  |
| --- | --- |
| **Name** (please print) | **Signature and Date** |
|  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SITE PRINCIPAL INVESTIGATOR AGREEMENT & SIGNATURE PAGE The Site Principal Investigator should conduct the trial in compliance with the protocol, which was given approval by the HREC/IRB/IEC. The Site Principal Investigator should sign the protocol to confirm agreement.  The Site Principal Investigator (PI) is the term 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.  By signing this protocol, the undersigned 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]. In addition, the trial will be conducted in compliance with all applicable laws and regulatory requirements relevant to each participating country.  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; and * Any additional required authorisation (e.g. institutional authorisation).   I, as Site Principal Investigator, agree that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor, and will ensure that trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log.   |  |  |  | | --- | --- | --- | | **Name** (please print) | **Role/Position** | **Signature and Date** | |  | Site Principal Investigator |  | |

Contents

[SITE PRINCIPAL INVESTIGATOR AGREEMENT & SIGNATURE PAGE 10](#_Toc185495175)

[PROTOCOL SYNOPSIS 15](#_Toc185495176)

[GLOSSARY OF ABBREVIATIONS 17](#_Toc185495177)

[1. ADMINISTRATIVE INFORMATION 19](#_Toc185495178)

[1.1. Trial Registration 19](#_Toc185495179)

[1.1.1. Trial registry 19](#_Toc185495180)

[1.2. Expected duration of study 19](#_Toc185495181)

[The end of the study is defined as the date of the last visit of the last participant in the study. 19](#_Toc185495182)

[1.3. Consumer involvement 19](#_Toc185495183)

[2. INTRODUCTION AND BACKGROUND 20](#_Toc185495184)

[2.1. Trial rationale and aim 21](#_Toc185495185)

[2.2. Background 21](#_Toc185495186)

[2.3. Risk/Benefit assessment 21](#_Toc185495187)

[2.3.1. Known potential risks 21](#_Toc185495188)

[2.3.2. Known potential benefits 22](#_Toc185495189)

[2.3.3. Assessment of potential risks and benefits 23](#_Toc185495190)

[3 TRIAL OBJECTIVES AND OUTCOMES 23](#_Toc185495191)

[3.1 Objectives 23](#_Toc185495192)

[3.1.1 Primary objective 24](#_Toc185495193)

[3.1.2 Secondary objectives 24](#_Toc185495194)

[3.1.3 Exploratory objectives 24](#_Toc185495195)

[3.2 Outcomes (Endpoints) 24](#_Toc185495196)

[3.2.1 Primary Outcome Measure 25](#_Toc185495197)

[3.2.2 Secondary Outcome Measures 25](#_Toc185495198)

[3.2.3 Exploratory Outcome Measures 26](#_Toc185495199)

[3.3 Table of Objectives & Outcomes 26](#_Toc185495200)

[4 TRIAL DESIGN 26](#_Toc185495201)

[4.1 Trial Schema 26](#_Toc185495202)

[4.2 Overall design 26](#_Toc185495203)

[4.3 Justification for dose 27](#_Toc185495204)

[4.4 Study setting 27](#_Toc185495205)

[5 TRIAL POPULATION 28](#_Toc185495206)

[5.1 Inclusion criteria 28](#_Toc185495207)

[5.2 Exclusion criteria 29](#_Toc185495208)

[5.3 Lifestyle considerations 30](#_Toc185495209)

[5.3.1 Use of contraception 30](#_Toc185495210)

[5.4 Screen failures 30](#_Toc185495211)

[5.5 Recruitment and identification of potential participants 31](#_Toc185495212)

[5.6 Consent 32](#_Toc185495213)

[6 INTERVENTION 33](#_Toc185495214)

[6.1 Treatment arms 34](#_Toc185495215)

[6.2 Trial Intervention(s) 34](#_Toc185495216)

[6.2.1 Description of trial investigational products 34](#_Toc185495217)

[6.2.1.1 <Trial Product insert> 34](#_Toc185495218)

[6.2.2 Dosage 35](#_Toc185495219)

[6.2.3 Dose modifications and delays 35](#_Toc185495220)

[6.2.4 Storage, preparation, dispensing and administration of trial drug 35](#_Toc185495221)

[6.2.5 Product accountability 36](#_Toc185495222)

[6.2.6 Measurement of participant compliance 36](#_Toc185495223)

[6.2.7 Excluded medications and treatments 36](#_Toc185495224)

[6.2.8 Concomitant therapy 37](#_Toc185495225)

[6.2.9 Discontinuation from trial intervention 37](#_Toc185495226)

[7 PARTICIPANT ASSIGNMENT, RANDOMISATION AND BLINDING 37](#_Toc185495227)

[7.1 Participant Assignment 37](#_Toc185495228)

[7.2 Randomisation 37](#_Toc185495229)

[7.3 Allocation concealment mechanism 38](#_Toc185495230)

[7.4 Blinding (masking) 38](#_Toc185495231)

[7.5 Breaking of the trial blind 39](#_Toc185495232)

[7.5.1 On trial 39](#_Toc185495233)

[7.5.2 On completion of the trial 39](#_Toc185495234)

[8 TRIAL VISITS AND PROCEDURES 39](#_Toc185495235)

[8.1 Trial Flowchart 39](#_Toc185495236)

[8.2 Schedule of assessments 41](#_Toc185495237)

[8.3 Description of procedures 42](#_Toc185495238)

[8.4 Notes on specific trial visits 43](#_Toc185495239)

[8.4.1 Screening 43](#_Toc185495240)

[8.4.2 Final trial visit 44](#_Toc185495241)

[8.4.3 Unscheduled visit 44](#_Toc185495242)

[8.5 Treatment discontinuation, participant withdrawals and losses to follow up 44](#_Toc185495243)

[8.5.1 Discontinuation of treatment - participant remains in trial for follow up 44](#_Toc185495244)

[8.5.2 Withdrawal of consent - participant withdraws from all trial participation 45](#_Toc185495245)

[8.5.3 Losses to follow-up 45](#_Toc185495246)

[8.5.4 Replacements 46](#_Toc185495247)

[8.5.5 Trial Closure 46](#_Toc185495248)

[8.5.6 Continuation of therapy 47](#_Toc185495249)

[9 SAFETY MONITORING AND REPORTING 47](#_Toc185495250)

[9.1 Definitions 48](#_Toc185495251)

[9.2 Capturing, documenting, and eliciting adverse event/reaction information 52](#_Toc185495252)

[9.3 Assessment of laboratory and other test results as AEs and SAEs 54](#_Toc185495253)

[9.4 Assessment of safety events 54](#_Toc185495254)

[9.4.1 Assessing the seriousness of a participant’s AE 54](#_Toc185495255)

[9.4.2 Assessing the causality of a participant’s AE 54](#_Toc185495256)

[9.4.3 Assessing the severity of a participant’s AE 55](#_Toc185495257)

[9.4.4 Assessment of expectedness of AEs 56](#_Toc185495258)

[9.5 Known Adverse Events, Harms, Risks or Discomforts 56](#_Toc185495259)

[9.6 Recording and Reporting of safety events 57](#_Toc185495260)

[9.6.1 Recording of adverse events and serious adverse events 57](#_Toc185495261)

[9.6.2 Expedited reporting of safety events 57](#_Toc185495262)

[9.6.3 Events exempt from reporting as adverse events (inclusive of SAEs, ARs, SARs) 60](#_Toc185495263)

[9.6.4 Pregnancy reporting 60](#_Toc185495264)

[10 DATA AND ESSENTIAL DOCUMENT MANAGEMENT 60](#_Toc185495265)

[10.1 Management of Essential Records 61](#_Toc185495266)

[10.2 Data management 62](#_Toc185495267)

[10.2.1 Data generation (source data) 62](#_Toc185495268)

[10.2.2 Data collection methods 64](#_Toc185495269)

[10.2.3 Data storage and access 65](#_Toc185495270)

[10.2.4 Data use 65](#_Toc185495271)

[10.2.5 Disclosure of data 66](#_Toc185495272)

[10.2.6 Data Confidentiality 66](#_Toc185495273)

[10.2.7 Data Quality Control 68](#_Toc185495274)

[10.2.8 Archiving – Data and document retention 68](#_Toc185495275)

[10.2.9 Destruction of data and documents 69](#_Toc185495276)

[10.2.10 Data Sharing Plan and Data Sharing Statement 70](#_Toc185495277)

[10.2.11 Long-term custodianship (after archive period finished) 71](#_Toc185495278)

[10.2.12 Sample management: Specimen & Biobanking 71](#_Toc185495279)

[11 TRIAL OVERSIGHT 73](#_Toc185495280)

[11.1 Governance structure 73](#_Toc185495281)

[11.1.1 Trial Management Group (TMG) 73](#_Toc185495282)

[11.1.2 Trial Steering Committee (TSC) 73](#_Toc185495283)

[11.1.3 Safety Monitoring 73](#_Toc185495284)

[11.2 Site Monitoring 75](#_Toc185495285)

[11.3 Quality Control and Quality Assurance 76](#_Toc185495286)

[12 STATISTICAL METHODS 77](#_Toc185495287)

[12.1 Sample Size Estimation 77](#_Toc185495288)

[12.2 Population to be analysed 77](#_Toc185495289)

[12.3 Methods of analysis 77](#_Toc185495290)

[12.3.1 Handling of missing data 78](#_Toc185495291)

[12.4 Interim Analyses 78](#_Toc185495292)

[13 ETHICS AND DISSEMINATION 79](#_Toc185495293)

[13.1 Research Ethics Approval & Local Governance Authorisation 79](#_Toc185495294)

[13.2 Amendments to the protocol 80](#_Toc185495295)

[13.3 Non-compliance with the protocol and/or Good Clinical Practice (including Serious Breaches) 80](#_Toc185495296)

[13.4 Confidentiality 81](#_Toc185495297)

[13.5 Participant Reimbursement 81](#_Toc185495298)

[13.6 Financial Disclosure and Conflicts of Interest 81](#_Toc185495299)

[13.7 Dissemination and Translation Plan 82](#_Toc185495300)

[14 ADDITIONAL CONSIDERATIONS 82](#_Toc185495301)

[15 REFERENCES 82](#_Toc185495302)

# 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. The protocol synopsis should generally not exceed two pages in length) and presented as a table such as the following.

Please ensure that there are no discrepancies between the protocol synopsis and the text in the body of the protocol.

|  |  |
| --- | --- |
| **Protocol Title** | Insert full title – keep same as title on first page of protocol |
| **short Protocol Title** | Insert short protocol title – keep same as title on first page of protocol |
| **Trial acronym** | Insert trial acronym if there is one. Delete row if not applicable. |
| **Trial Description** | A brief overview of the trial design, including trial groups (if applicable).  This should only be a few sentences in length. A detailed schematic describing all visits and assessments should be included in the main protocol. |
| **clinical phase** | Insert clinical trial phase. For medicine/biological intervention insert Phase 0, I, II, III or IV as appropriate.  For medical device intervention, select pre-market pilot, pre-market pivotal or post-market. Refer to [TGA definitions for trial phases](https://www.tga.gov.au/resources/guidance/conducting-clinical-trials-australia-using-unapproved-therapeutic-goods#clinical-trial-phases-and-stages) for guidance. |
| **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 primary and secondary 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 – Inclusion & Exclusion criteria** | Outline key inclusion and exclusion criteria |
| **Trial Population – Other** | Include any other population information, for example the planned sample size (total number of participants for the project, and the approximate number per group if more than one group). |
| **Participant Duration** | Time (in months/years) it will take for each individual participant to complete all participant visits, including any follow-up visits. |
| **Planned Recruitment and follow up Periods** | Indicate duration/period of recruitment. e.g., Approximately XX months/years recruitment period.  Indicate duration/period of follow up. e.g., Follow-up period is 24 months. |
| **Trial Duration** | Estimated time (in months/years) from when the trial opens to enrolment until completion of data analyses. |
| **Description of Sites Enrolling Participants/Study Setting** | Provide a brief description of the study setting and approximate number of participating trial sites (e.g. planned countries, planned number of sites, primary recruiting sites vs sites identified as continuing care sites if applicable) |
| **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. |

# 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) |
| CPI | Coordinating Principal Investigator |
| 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 |
| GDPR | General Data Protection Regulation |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| HREC | Human Research Ethics Committee |
| IB | Investigator’s Brochure |
| ICH | International Conference on Harmonisation |
| IMD | Investigational Medical Device |
| IMP | Investigational Medicinal Product |
| ISO | International Organization for Standardization |
| ITT | Intention to Treat |
| MCC | Melbourne Children’s Campus |
| 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 | Product Information (available for an approved drug or device) |
| PI | (Site) Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| RCH | Royal Children’s Hospital (Melbourne) |
| RGO | Research Governance Office |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse Reaction |
| SI | Sponsor-Investigator |
| 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 |

# ADMINISTRATIVE INFORMATION

# Trial Registration

# Trial registry

Specify trial registry name and registration identifier. If not yet registered, specify name of intended registry.

|  |
| --- |
| All RCH/MCRI IITs should be registered before the first participant is consented to be compliant with the International Committee of Medical Journal Editors (ICMJE) and the Declaration of Helsinki. When MCRI is the trial Sponsor, trials must be registered with ClinicalTrials.gov due to the oversight that is provided:  • The ClinicalTrials.gov Protocol Registration System (PRS) undertakes direct oversight of ClinicalTrials.gov records and also mandates institutional (i.e. MCRI) oversight - this oversight allows the MCRI Sponsorship Committee to fulfil its sponsor responsibilities.  • ANZCTR does not provide this level of oversight.  See [MCTC026 SOP | Clinical Trial Registration of Investigator-Initiated Trials (IITs](https://metis.melbournechildrens.com/MCTC026)) for the procedure to register your trial. |

# 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.

Provide the end of study definition.

Example text

The study is expected to take approximately <insert months/years> to recruit the required number of participants from the date of when the first participant is enrolled into the trial. It is anticipated that recruitment will cease <enter date/year>, with the last participant ceasing the <insert months/years> -year follow up period by <enter date/year>.

The trial intervention phase is defined as <insert intervention period>.

The entire study duration for each participant commences from <insert start time> and is completed at the X-year follow-up timepoint.

The end of the study is defined as the date of the last visit of the last participant in the study.

# Consumer involvement

Describe details of, or plans for, consumer involvement in the design, conduct and reporting of the trial.

Include if children and young people (CYP) and/or their families are actively involved in the design and conduct of the research. State if CYP/families have contributed to refining the research question and designing the protocol, and plans for consumer involvement in collecting and/or analysing the trial data and dissemination of results.

Include considerations taken to protect privacy of CYP who are partners in the research, such as providing opinions regarding including their names in project materials, particularly around conditions that may be associated with stigma or may lead to assumptions about their health.

Include considerations taken to avoid missing school, other activities, and integrating alternative methods of receiving and giving information to CYP.

Include the level of involvement, e.g. consultation, collaboration, child/adolescent-led with support of adults.

Include any governance and training elements related to the involvement of CYP, and/or families.

Discuss outcome and impact of consumer involvement on the trial design. If no impact, this should be stated.

|  |
| --- |
| The NHMRC expects that research is aligned with consumer and community expectations; researchers should involve relevant consumers and community members in the early planning stages of research at a level that will have a direct effect on the development of the research project.   For further details, see the [NHMRC’s Statement on Consumer and Community Involvement in Health and Medical Research (2016).](https://www.nhmrc.gov.au/about-us/publications/statement-consumer-and-community-involvement-health-and-medical-research) |

# 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

# 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>

# 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.

# Risk/Benefit assessment

# Known potential risks

Include a discussion of known potential risks related to trial-specific treatments and interventions and trial procedures under the subheadings below. Note this information may also be contained in Section 9.5 Known adverse events, harms, risks or discomforts.

Risks related to trial-specific treatments and interventions

Discuss key risks related to treatments and interventions for this trial.

Provide a brief description of strategies to mitigate identified risks and cross-reference the trial-specific Risk Assessment & Management Plan for further details.

Risks related to trial design and procedures

Discuss unique risks associated with the trial design (for example placebo arm) and any less common or high-risk procedures specific to this trial. Discuss alternative procedures that have been considered and explain why not included.

Provide a brief description of strategies to mitigate identified risks and cross reference the trial-specific Risk Assessment & Management Plan for further details.

|  |
| --- |
| **Considerations for risk identification**  Consider physical, psychological, social, legal, economic, or any other risks to participants by participating in the trial that the Site Principal Investigator (PI), consumer representatives, study coordinators etc, foresee by taking part in the trial, addressing each of the following:   * Immediate risks * Long-range risks   **Risks related to IMP/IMD**  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. |

# Known potential benefits

This section should be written from the perspective of an individual participant.

Include a discussion of known potential benefits to participants because of participating in the trial. Benefits to society in general may also be included but should be discussed separately.

Clearly state if no benefits to an individual participant can be anticipated, or if potential benefits are unknown.

|  |
| --- |
| **Considerations for identifying potential benefits**  Describe any physical, psychological, social, legal, or any other potential benefits to individual participants, 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.  **Benefits related to IMP/IMD**  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 potentially 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. |

# Assessment of potential risks and benefits

Provide a succinct, concluding statement on the perceived balance between risks identified from the cumulative safety data and protocol procedures, and anticipated efficacy/benefits within the context of the trial.

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.

# TRIAL OBJECTIVES AND OUTCOMES

No text is to be entered in this section. Instead enter text under the relevant subheadings below.

# Objectives

No text is to be entered in this section. Instead enter text under the relevant subheadings below.

|  |
| --- |
| 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).   The objectives must be 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.** 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). Ensure it is specific and objective.  **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 i other objectives may not have adequate power with this sample size.  **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. |

# Primary objective

Define the primary objective in terms of the population, intervention, comparator, outcome and timepoint (PICOT) 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 <outcome> in <type of participants> compared with placebo at <time point>.”

# Secondary objectives

Define the secondary objectives.

Example text

“The secondary objectives of this trial are:

1. To determine the safety and tolerability of <trial treatment> at <insert time point> in <type of participants> with <condition>.
2. To determine the impact of <trial treatment> on healthcare utilisation at <insert time point> in < type of participants> with <condition>.”

# Exploratory objectives

Define any exploratory objectives (if applicable).

# Outcomes (Endpoints)

No text is to be entered in this section. Instead enter text under the relevant subheadings below

|  |
| --- |
| An **outcome** (also known as **endpoint**) is a specific measurement or observation to assess the effect of the trial intervention. Trial outcomes should correspond to the trial objectives and hypotheses being tested.  **Primary outcome:** 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 (e.g., systolic blood pressure or a specified validated questionnaire or clinical assessment scale) should incorporate the selected outcome measure, which is the method for measuring an outcome (e.g. Number of, proportion of, Change in outcome measure over time).  **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. Ensure outcomes are measurable.  **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.  **Note:**  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. |

# Primary Outcome Measure

Define the primary outcome measure to answer the primary objective. Include the following:

* The specific measurement that will be used, e.g. systolic blood pressure
* The metric used to characterise the measure (e.g., mean change from baseline, final value, time to event, maximum)
* Method of aggregation (e.g. median, proportion)
* The timeframe (i.e., total duration of the time period, specific time points) over which the measure will be assessed.
* Explanation of the validity, feasibility, and responsiveness of outcome measure instruments for the pre-specified age groups
* Include any definitions used to characterise outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterisation of a stroke as thrombotic or haemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully.

Provide a brief explanation (i.e. a justification) to explain why these outcomes were chosen.

# Secondary Outcome Measures

Define the secondary outcome measures that are related to the secondary objectives. For each one, include the following:

* The specific measurement that will be used, e.g. systolic blood pressure
* The metric used to characterise the measure (e.g., mean change from baseline, final value, time to event, maximum)
* Method of aggregation (e.g. median, proportion)
* The timeframe (i.e., total duration of the time period, specific time points) over which the measure will be assessed.
* Explanation of the validity, feasibility, and responsiveness of outcome measure instruments for the pre-specified age groups
* Include any definitions used to characterise outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterisation of a stroke as thrombotic or haemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully.

Provide a brief explanation (i.e. a justification) to explain why these outcomes were chosen.

# Exploratory Outcome Measures

Define the exploratory outcome measures that are related to the exploratory objectives. For each one, include the following:

* The specific measurement that will be used, e.g. systolic blood pressure
* The metric used to characterise the measure (e.g., mean change from baseline, final value, time to event, maximum)
* Method of aggregation (e.g. median, proportion)
* The timeframe (i.e., total duration of the time period, specific time points) over which the measure will be assessed.
* Explanation of the validity, feasibility, and responsiveness of outcome measure instruments for the pre-specified age groups
* Include any definitions used to characterise outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterisation of a stroke as thrombotic or haemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully.

# Table of Objectives & Outcomes

Provide a table linking each objective with its respective outcome and outcome measure.

| OBJECTIVE | OUTCOME &OUTCOME MEASURE |
| --- | --- |
| Primary |  |
| “The primary objective of this trial is to evaluate the impact of <trial treatment> on <outcome> 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” | “emotional and functional wellbeing of the participant assessed by the parent/guardian and participant using the Pediatric Quality of Life Inventory (PedsQL) at 1, 3 and 6 months” |
| Exploratory |  |
|  |  |

# TRIAL DESIGN

# Trial Schema

Provide a flow-chart/graphic outlining the participant flow through the trial from screening through to follow-up.

# 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 control, active control, historical control, 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 minimise bias including blinding. Specify who is blinded to trial interventions.
* List any sub-studies included in this protocol
* Additional notes
  + Dose escalation or dose-ranging details should be provided Section 6.2.3 Dose Modifications and Delays
  + Note if interim analysis is planned, refer to details in Section 12 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.

# 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). If the trial intervention is not a medicine but a device, delete this section.

# Study setting

Briefly summarise the trial setting (e.g., hospitals, GP surgeries, care homes, academic centres etc.) indicating number of trial sites, types of sites (e.g., recruiting, providing intervention, continuing care etc.,) and, where there are non-Australian sites naming the countries where trial data will be collected.

For multi-centre trials, it may be pertinent to include a broad statement here to confirm that, if participant recruitment is not adequate you wish to have the option to open more participating centres. For example: we plan to include approximately 10 centres within this trial, however we may increase the number of centres to recruit the required number of participants.

If appropriate also include whether there are different “types” of sites (e.g. identifying, recruiting, treating, continuing care, etc.). Are participants with the condition of interest found in primary or secondary care? If using secondary care sites, will primary care Participant Identification Centres (PICs) be needed to recruit participants, or are participants found in secondary care?

We do not advise listing the sites in the protocol as any additional site or change to the site listing will require a new version of the protocol to be produced and approved.

Example text

This trial is conducted within the Delivery Room and Neonatal Intensive Care Units (NICU) of tertiary perinatal centres in Australia, Europe, the UK, and North America who deliver infants born <29 weeks Post Menstrual Age (PMA) and have an established research culture and infrastructure. Continuing Care Sites in all relevant jurisdictions will also be identified and established to continue to follow participants to the end of the study.

# TRIAL POPULATION

No text is to be entered in this section. Instead include information under the relevant subheadings below.

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 utilise the trial intervention under evaluation (e.g., elderly and paediatric populations, women, and minorities).

Use the guidance listed under 5.1 and 5.2 and also consider the following:

* The eligibility criteria should provide a definition of participant characteristics required for trial entry/enrolment.
* Distinguish between screening participants vs enrolling participant, if applicable. Determine if screening procedures will be performed under a separate screening consent form
* 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 of specific concern, 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.*

# Inclusion criteria

Participants must meet all the inclusion criteria to be considered for the study. Provide a numbered list of 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/sex, age range). * The disease or disorder under study: the specific definition of the disease state which will be used to assess participants for recruitment into the trial and how it must be documented (e.g. diagnostic methods, criteria for classification, etc.). * Clinical indicators of current health 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). * If female participants of childbearing potential (FOCBP)\* are required to avoid pregnancy (i.e. use highly effective contraception), specify this and detail which methods of contraception are considered acceptable for trial inclusion (see sample wording below) and the timeframe that this must be used.   \* FOCBP is defined as “fertile, following menarche and until becoming post-menopausal unless permanently sterile.” |

Example text

“Each person must meet all of the following criteria to be enrolled in this trial:

1. Is between the ages of <# and #> years at the time of randomisation
2. Weighs between <# and #> kg at the time of randomisation
3. Has <condition> as determined by <insert detail of test necessary for definitive diagnosis for the trial purpose>
4. 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.”
5. Females of childbearing potential are willing to use a highly effective contraception method to avoid pregnancy from the time of providing consent to <insert >. Acceptable methods of contraception are:
   * Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal, or transdermal
   * Progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable
   * Intrauterine device (IUD)
   * Intrauterine hormone-releasing system (IUS)
   * Bilateral tubal occlusion\*\*
   * Vasectomised partner\*\*
   * Sexual abstinence with the proviso that the reliability of this method needs to be evaluated in relation to the preferred and usual lifestyle of the participant.

\*\* delete if not appropriate for population age group

# Exclusion criteria

Participants meeting any of the following criteria will be excluded from the study:

Provide a numbered list of criteria:

|  |
| --- |
| Take into account known or suspected contraindications or side effects of the drug or factors likely to confound interpretation of the results or cause a safety concern.  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 hospitalisation) 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.   **Justification for exclusion of a specific population:** If specific populations are excluded (e.g., elderly or ae 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. |

Example text

“Patients meeting any of the following criteria will be excluded from the trial:

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

# Lifestyle considerations

Include content in this section if applicable, otherwise delete this section.

Describe any restrictions during any parts of the trial pertaining to lifestyle and/or diet (e.g., contraceptive use, food or drink restrictions, the timing of meals relative to dosing, limits on activity). Describe what action will be taken if prohibited medications, treatments or procedures are indicated for care (e.g., early withdrawal).

# Use of contraception

If female participants of childbearing potential (FOCBP) are required to avoid pregnancy, outline the timeframe here. Also list the acceptable methods of contraception or refer to the Inclusion Criteria if this is listed there.

# 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 any required site-specific authorisation required prior to the site being allowed to commence recruitment. In Australia, site-specific authorisation is required and Research Governance Authorisation [governance] must be in place; internationally, sites will require approval from Regulatory Bodies/Competent Authorities in addition to approval from their IRB/REBs before being able to screen and consent participants.

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.

To ensure transparent reporting of screen failure participants (i.e. to meet the Consolidated Standards of Reporting Trials [CONSORT] reporting requirements), a minimal set of screen failure information should be retained to aid in describing screen failures (including demography, the reason for ineligibility and documentation of any trial assessment-related adverse event (AE) and/or any serious adverse event (SAE). See Section 9.1 Table 1 for terms and definitions related to safety events.

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.

# 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. Provide 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 estimated number to be enrolled in order to reach the target number of participants treated/randomised (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.

Explain how Participant Identification Numbers (Participant IDs) are allocated to participants and reference the trial-specific Participant Consent, Screening & Enrolment Log to capture the link between the participant’s personal identifiers and their assigned Participant ID.

# Consent

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

State whether consent from minors will be sought as well as the parent/legal guardian.

State who (what skills, experience, training must they have) can 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.

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.

Describe the consent process from provision of information about the trial through to signing of the consent form and documenting how consent was obtained in the source document/record. Specify which steps of the consent process are conducted in person and remotely and justify the approach chosen.

Discuss use of electronic consent (eConsent) if it will be used in your trial including how it will be used and justification for its use:

* use of any electronic systems/platforms to provide information to potential participants/families, whether it is the participant information or other supplementary materials, e.g. information videos or animations.
* How signatures will be obtained on the consent form and the type of signature.

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.

|  |
| --- |
| 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 [RCH 0499 Procedure, Informed Consent in Research](https://app.prompt.org.au/download/222552?code=4a5cfc95-d0aa-40fc-9a9e-c5e1b1c1fff1). Also refer to the National Statement, Chapter 3.1 Element 3 and Chapter 4.2. |

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.

r

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 guardian 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 medical record that consent has been provided. When all the inclusion/exclusion criteria have been assessed and the eligibility of the participant confirmed, the participant may be enrolled in the trial ”.

# 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.

# Treatment arms

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

# 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: Participant ID, 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

# Description of trial investigational products

# <Trial Product insert>

Repeat for each trial product (i.e. investigational product, comparator, and/or 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. |

# Dosage

For each investigational medicinal product, specify:

* Dose and formulation adjustments based on age, weight, or body surface area, as applicable. Include supporting data from paediatric studies or recommended practices where available.
* 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)

# Dose modifications and delays

This section should contain the following information:

* Provide details for any allowable dose modifications and/or dose delays and the circumstances for their use (e.g. toxicity).
* State the conditions under which a dose change (where applicable) will be made, particularly regarding to failure to respond or to toxic or untoward changes (e.g., white blood cell count in cancer chemotherapy), including criteria for temporary cessation of intervention and when to recommence.
* Criteria for permanent cessation of intervention.
* Provide details regarding dose re-escalation (if applicable).
* Address dose modifications and delays for specific abnormal laboratory values of concern or other adverse events (AEs) that are known to be associated with the planned trial intervention.
* State explicitly the dose-limiting effects that are anticipated.

# 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. Like the discussion above for dosage of drugs, such considerations should be described for devices, as applicable.

# 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.

# 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, and 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’.

# 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 participant 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.

# Concomitant therapy

Include content in this section if applicable, otherwise delete this section.

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.

# Discontinuation from trial intervention

See Section 8.5 Treatment discontinuation, participant withdrawals and losses to follow-up.

# PARTICIPANT ASSIGNMENT, RANDOMISATION AND BLINDING

No text is to be entered in this section. Instead include information under the relevant subheadings below.

# Participant Assignment

Describe the method of assigning participants to trial intervention without being so specific that blinding or randomisation might be compromised. If assignment to trial intervention is by randomisation, describe when randomisation occurs relative to screening. If participants will be assigned to intervention sequences as in a cross-over trial, then describe these sequences.

If adaptive randomisation or other methods of covariate balancing/minimisation are employed, include a cross-reference to the methods of analysis in Section 12, Statistical Methods. As applicable, details regarding the implementation of procedures to minimise bias should be described.

# Randomisation

Describe the following in this section with support from the trial biostatistician:

* Randomisation procedures (for example, central randomisation procedures)
* Method used to generate the randomisation schedule (for example, computer generated, block randomisation, minimisation)
* Source of the randomisation schedule (for example, sponsor, investigator, or other), and
* To maintain the integrity of the blinding, do not include the block size.
* the randomisation ratio (e.g. 1:1; the ratio between treatment groups).
* Any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose) and refer to details in Section 12 Statistical Methods.
* Use and validation of any computer systems or programmes in randomisation, stratification, and unblinding.

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.”

# Allocation concealment mechanism

Discuss how participants will be assigned to treatment groups (e.g. an Interactive Voice Response System or Interactive Web Response System, sequentially numbered, opaque, sealed envelopes).

Include steps to conceal the sequence until interventions are assigned.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Differences between allocation concealment and blinding (masking) for trials with individual randomisation are shown below.   |  | **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 ensuring that group assignment is not known when the decision is made to enrol a participant** | **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** | |

# Blinding (masking)

Specify who will be blinded after assignment to interventions (e.g. trial participants, care providers, Principal Investigator, Study Coordinator, Data Manager, Statistician) and how this will be managed.

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.

# Breaking of the trial blind

# 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.

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 study pharmacist, where the pharmacy is unblinded. If any unblinding envelope is opened, the time, date, Participant ID and reason for opening must be documented.

# 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.

# TRIAL VISITS AND PROCEDURES

No text is to be entered in this section. Instead include under relevant subheadings below.

# Trial Flowchart

Include a flow chart/schema of the trial design and include timeline of study visits, enrolment process, interventions and assessments, as in the following example. Timepoints indicated in the flowchart should correspond to timepoints in Section 8.2, Schedule of Assessments (SoA).

Example Flowchart

****

# 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 of recommended content for the schedule of assessments\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TRIAL PERIOD** | | | | | | | | |
|  | **Enrolment**  **<visit window>** | **Allocation to intervention** | **Study Visit Timepoints**  **<visit window>** | | | | | **Final Study Visit**  **<visit window>** |
| **TIME POINT\*\*** | ***-t1*** | **0** | ***t1*** | ***t2*** | ***t3*** | ***t4*** | ***etc.*** | ***tx*** |
| **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.

# 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 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.

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)

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.

|  |
| --- |
| 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 theSchedule of Assessments (SoA) - the time points of these procedures do not need to be included in this section.  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. |

# Notes on specific trial visits

# Screening

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.

# 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 (AEs, SAEs, etc) will be followed until resolution or alternatively to stabilisation – and ensure referrals are in place where applicable.

# Unscheduled visit

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

# 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).

# 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. All 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.

# 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.

# 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.]

# 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.

# 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 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.

# 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”.**

# SAFETY MONITORING AND REPORTING

No text is to be entered in this section, instead include text in the relevant subheadings below.

|  |
| --- |
| 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](https://www.mcri.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative) * 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](https://www.mcri.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative). 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.** |

# 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.

Include boilerplate text below for safety definitions as applicable to the type of intervention in the trial. Only keep both Table 1 and Table 2 if your trial is evaluating both IMP(s) and IMD(s). If you are only evaluating an IMP(s), delete Table 2. If you are only evaluating an IMD(s), delete Table 1.

For this trial, the following safety definitions will be observed:

**Table 1: Definitions used for investigational medicinal products** (Delete this table if the trial is not evaluating an IMP)

|  |  |
| --- | --- |
| 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. |
| 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, or * is life threatening, or * requires hospitalisation or prolongation of existing hospitalisation, or * 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. |
| 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. |

**Table 2:** **Definitions used for investigational medical devices** (Delete this table if the trial is not evaluating an IMD)

|  |  |
| --- | --- |
| 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. |
| 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:   1. Led to death 2. 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  1. Led to fetal distress, fetal death or a congenital anomaly or birth defect.   Note: Planned hospitalisation for a pre-existing condition, an Emergency Department visit that did not result in an admission to the hospital, 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. |
| 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. |

# Capturing, documenting, and eliciting adverse event/reaction information

Describe the following for Adverse Events and for (Serious) Adverse Reactions (S)ARs):

1. If the trial will have full or selective safety monitoring data collection and provide justification for the approach and exclusions based on the trial risk assessment and objectives.
2. If selective safety monitoring is applicable, outline the protocol-specific safety events which require recording and reporting (e.g. which AEs require reporting and which SAEs require expedited reporting to the Sponsor)
3. Identify that the Site Principal Investigator or qualified delegate is responsible for determining the following attributes for each AE: seriousness, relatedness (causality) and severity (intensity) and refer to relevant subsection below
4. Identify that the Sponsor-Investigator/medically qualified delegate is responsible for determining expectedness of the AE and refer to relevant subsection below
5. Identify what will be reported to the Sponsor and methods of reporting
6. Specify the period of time for which AEs will be captured (based on the risks associated with the trial), e.g. From screening or randomisation/administration of the IP, 30 days/five half-lives after administration of IP, after completion of all study-related procedures.
7. Confirm the limit of investigator follow up of AEs (e.g., follow up until event resolution or stabilisation, to participant completion of the trial, to trial end etc.). Confirm if the follow up requirement is the same for all AEs or differs for some events (e.g., follow up until event resolution required for related events only)

|  |
| --- |
| **Determining what AEs will be captured (i.e. collected)**  The decision on which AEs will be recorded will **depend on the risk associated with the trial** (including the extent of knowledge of the risk profile of the investigational medicine/device and the population to be studied) **and the objectives of the trial**.  **Full safety monitoring** (i.e. all AEs) is usually only required for higher risk trials such as trials of new investigational medicines/devices and phase I/first in human trials.  **Selective safety monitoring** (i.e. targeted to capturing AEs of key interest – usually according to a pre-specified list), is usually more appropriate for investigator-initiated trials. It may be implemented where:   * the investigational medicine/device is well characterised, and * the occurrence of common, non-serious adverse events in the population to be studied is expected to be similar to rates observed in previously conducted trials, and * the trial risk assessment does not suggest that the different population/indication/dose/ route of administration “will lead to new or more severe or frequent adverse reactions or new drug-drug interactions.” (see Australian NHMRC Guidance: Risk-based management and monitoring of clinical trials involving therapeutic goods 2018).   Note: Most Melbourne Children’s investigator-initiated trials will use a registered medicine/device but will usually use this differently from its marketing approval (e.g. a different population/indication/dose /route of administration approved) so your trial risk assessment must assess the likelihood of new or more severe/more frequent adverse reactions or new drug-drug interactions.  **Considerations for how AE data is captured**  For participant questioning/ records, specify whether participants will be asked about events of specific interest (i.e. ‘active’ eliciting which may result in higher reporting of events by participants), or 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.  **Considerations for time period for AE collection**   * e.g. From screening or randomisation/administration of the IP, 30 days/five half-lives after administration of IP, after completion of all study-related procedures. * For trials involving an investigational medical device, consider the time period that will 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 |

Example text

(Note this example has sample text for some of the elements required in this section. If using, you will need to modify to meet your study and also supplement with additional information).

[THE WHAT] For the purposes of this trial the Site Principal Investigator or qualified delegate is responsible for capturing Adverse Events of key interest as listed below. Targeted collection and documentation is appropriate because <insert>.

OR

For the purposes of this trial the Site Principal 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.

Adverse events must be assessed by the Site Principal Investigator/qualified delegate\* to determine the seriousness and relatedness (i.e. causal relationship). Expectedness will be assessed by the Sponsor-Investigator, who may delegate this to site Investigators once training has been given to ensure accurate identification and reporting.

\* The delegate must be be listed on the Delegation Log.

[THE WHEN] “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. Serious adverse events will be captured from the time that informed consent was given.

[THE HOW] Trial participants will be asked at each visit, “How have you felt since your last visit?”, 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.

# Assessment of laboratory and other test results as AEs and SAEs

Confirm which trial assessments are relevant (e.g., only laboratory results or also others such as ECGs, chest x-rays or other scans). Specify any predefined criteria for ‘abnormality’ that signify that an out-of-range result is to be reported as serious (e.g., Grade ≥3 elevation of ALT or AST lasting 8 days or more).

Consider providing tables of adverse event grading criteria for the relevant trial assessments (e.g., a Laboratory AE Grading Chart indicating the limits at which ‘out of range’ laboratory results are Grade 1, Grade 2, Grade 3, and the point they are reportable as SAEs etc.). Where relevant, confirm if the clinical significance of an abnormal result will be determined on a case-by-case basis by the medically qualified investigator.

# Assessment of safety events

# Assessing the seriousness of a participant’s AE

Seriousness is assessed against the criteria in Section 9.1 Definitions. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction.

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

# Assessing the causality of a participant’s AE

Recorded 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.

Describe the method of determining the relationship of an AE to the 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. |

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

* **Not assessable:** There is insufficient or incomplete evidence to make a clinical judgement of the causality
* **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.
* **Unlikely:** There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the IMP/IMD). There is another reasonable explanation for the event (e.g. the participant’s medical condition, other concomitant treatments)..
* **Possible:** There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the IMP/IMD). However, the influence of other factors may have contributed to the event (e.g. the participant’s medical condition, other concomitant treatments).
* **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 IMP/IMD 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 IMP/IMD. 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.

Unlikely and Unrelated causalities are considered NOT to be IMP/IMD related. Definitely, Probable and Possible causalities are considered to be IMP/IMD related as explained in table below.

|  |  |  |
| --- | --- | --- |
| **Causal Relationship** | | **Description** |
| Unrelated | Unrelated | The AE is clearly NOT related to the intervention |
| Unlikely | The AE is doubtfully related to the intervention |
| Possible | Related | The AE may be related to the intervention |
| Probable | The AE is likely related to the intervention |
| Definite | The AE is clearly related to the intervention |

# 

# Assessing the severity of a participant’s AE

The Site Principal Investigator/delegate is responsible for assessing the severity of an adverse event (AE). The determination of severity for all adverse events should be made by the investigator based upon medical judgment and using the following grading scale:

* + **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.
  + **Life Threatening:** Life-threatening consequences; urgent intervention indicated
  + **Fatal:** Death related to AE

**For Oncology Trials** – you may replace this with the NCI CTCAE criteria for reporting severity (Grade 1-5). The following wording may be used:

All events should be graded for severity according to the NCI-CTCAE Toxicity Criteria (Version#. ##). CTCAE v#. ## can be downloaded from the following URL: <Insert web link>.

# Assessment of expectedness of AEs

Expected adverse reactions are AEs that are known to occur for the trial intervention being studied. Expectedness is assessed based on the awareness of AEs/SAEs previously observed, not on the basis of what might be anticipated from the properties of the trial intervention.

SARs/SADEs (delete SAR or SADE as relevant to intervention type in your trial) must be assessed to determine whether the event is expected or unexpected in terms of the current known safety profile of the intervention. An SAR will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the Reference Safety Information (RSI) for the trial intervention.

Identify the source of the reference safety information used to determine expectedness of AEs that are deemed to be related to the trial intervention, e.g For IMPs this may be an Investigator Brochure, TGA-approved Product Information or protocol. For IMDs this may be Instructions for Use, the risk assessment and management plan, or protocol.

Expectedness is determined by the Sponsor-Investigator or their delegate who must be medically qualified and delegated this responsibility by the Sponsor-Investigator.

# Known Adverse Events, Harms, Risks or Discomforts

Provide the following information in this section and/or cross-reference Section 2.3.1 Known potential risks:

Expected adverse reactions are AEs that are known to occur for the study intervention being studied, not **what might be anticipated** from the properties of the trial intervention.

Provide a detailed list of all adverse effects associated with the trial IMP/IMD that participants may (or have the potential) to experience.

Provide a detailed list of all adverse effects associated with the trial IMP/IMD that participants may (or have the potential) to experience

Specify the source of the reference safety information used to determine the expectedness of the AE, e.g. in the Investigator Brochure, TGA approved Product Information.

# Recording and Reporting of safety events

# Recording of adverse events and serious adverse events

Adverse events (inclusive of ARs, SAEs, SARs, SUSARs) should be recorded in the medical record and the appropriate section of the CRF and/or AE/AR log.

Serious Adverse Events (inclusive of SARs and SUSARs) also require expedited reporting to the Sponsor as detailed in section 8.5.2.

# Expedited reporting of safety events

Site Principal Investigator Reporting Procedures

The Site Principal Investigator is responsible for reporting the following safety events to the Sponsor-Investigator as soon as possible but within 24 hours of the first knowledge of the event:

1. SSIs/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>

These reports should be submitted using an Expedited Safety Report Form customised for this trial and reported to the stakeholders listed in the table below.

|  |  |
| --- | --- |
| **Report To:** | **Email To:** |
| Sponsor c/o Sponsor-Investigator | [<insert](mailto:safetydesk.mctc@mcri.edu.au) email address> |
| Trial Coordinating Centre | [<insert](mailto:safetydesk.mctc@mcri.edu.au) email address> |
| Manufacturer of Investigational Product (\*if applicable) | [<insert](mailto:safetydesk.mctc@mcri.edu.au) email address> |
| Local Sponsor/Legal Representative (if applicable) | [<insert](mailto:safetydesk.mctc@mcri.edu.au) email address> |

\* Where the manufacturer (pharmaceutical/medical device company) is providing the investigational product for the clinical trial, they may require that SAEs be reported to them in real time. The Sponsor-Investigator (as Sponsor) should check the agreement with the manufacturer to determine the requirements and then enter the details in this table where required.

The Site Principal Investigator/delegate is ultimately responsible for reporting the safety event and must sign the final Expedited Safety Report form. Should the Investigator not be available to sign the form within the required 24-hour reporting time period, a comment to this effect must be written on the report and the report signed by the clinician attending to the patient at the time and emailed to the Sponsor-Investigator. The Investigator must sign the Expedited Safety Report form at the next earliest possible convenience and resend to the Sponsor-Investigator.

See Table below for clarification regarding reporting timelines for the initial report and any follow up reports.

|  |  |
| --- | --- |
| **Initial Report** | Within one working day/24 hours of discovery or notification of the event. If the reporting of the safety event is delayed by more than 24 hours, an explanation must be provided. |
| **Incomplete Reports** | If all details are not available at the time of the initial report a completed report must be sent within the next 10 days. |
| **Updated Report** | If the event is not resolved (or ‘on-going’) at the time of the initial report, the Expedited Safety Report Form must be submitted every 30 days until the event is resolved, death has occurred or the condition has stabilised. If a change occurs in a stable condition (i.e. either worsens or improves), then a new Expedited Safety Report Form should be emailed. |

The Investigator at the participating Site is responsible for determining the local expedited safety reporting requirements of the responsible Sponsor, HREC/IRB, local RGO and Competent Authorities/Regulatory Agencies and subsequently notifying them, as required.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient’s participation in the study, must be followed until any of the following occurs:

* The event resolves
* The event stabilizes
* The event returns to baseline, if a baseline value/status is available
* The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
* It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

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

Sponsor-Investigator Reporting Procedures

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:
   1. Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.
   2. Submit amendment to the HREC without undue delay.
4. For SSIs leading to temporary halt or early termination of a trial for safety reasons:
   1. Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.
   2. 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-Investigator (as 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-Investigator (as 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-Investigator (as Sponsor) is also responsible for providing the following to all Site Principal Investigators:

1. All SSIs and USMs occurring at any site
2. All SUSARs/USADEs (local site participants only – confirmation of site assessment)
3. Updated Reference Safety Information, e.g. Product Information/Investigator’s Brochure to Investigators.

|  |
| --- |
| This section outlines the Site PI and Sponsor-Investigator reporting requirements and timelines for reporting safety events to the HREC (s), institutional authorities (known as Research Governance Offices (RGOs) in Australia) and/or Regulatory Agencies. Consider a flowchart to clarify the reporting requirements. State who will be responsible for submitting reports to HRECs and regulatory authorities.  It must also identify if there are any SAEs that fit the standard SAE definition but for the purpose of this trial, do not require expedited reporting. If yes, cross-reference Section 9.6.3 Events exempt from immediate reporting as adverse events.  **International Sites:** For trials with international participating sites, highlight the requirement for those sites to comply with local regulatory safety reporting requirements.  Expedited reporting refers to rapid reporting of a safety event; the ESR form is therefore used to facilitate rapid reporting by site teams – for a template see [MCTC008 Template | Expedited Safety Report Form](https://metis.melbournechildrens.com/MCTC008)  Refer to the following resources available for METIS to further understand responsibilities and procedures related to safety monitoring and reporting:   * [MCTC005 SOP | Safety Monitoring and Reporting Procedure for MCRI-Sponsored IITs of Medicines/Medical Devices](https://metis.melbournechildrens.com/MCTC005) * [MCTC094 Process Map | Responsibilities of Site PIs in MCRI-sponsored IITs: Safety Assessment, Documentation and Reporting](https://metis.melbournechildrens.com/MCTC094) * [MCTC095 Process Map | Responsibilities of the Sponsor-Investigator in MCRI-sponsored IITs: Safety Assessment, Documentation and Reporting](https://metis.melbournechildrens.com/MCTC095) |

# Events exempt from reporting as adverse events (inclusive of SAEs, ARs, SARs)

Identify if there are any AEs that fit the standard definitions for all types of AEs in terms of seriousness and relatedness) but for the purpose of this trial, do not require reporting to the Sponsor-Investigator. List the exclusions and provide the justification for why this is the case.

If relevant: specify if types of hospitalisation are not classed as SAEs: e.g., Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event; e.g., Hospitalisation for procedures and treatments specified within the protocol, and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

If relevant: specify if deaths due to the disease under study are exempt from reporting as SAEs (with instruction as to where in the trial CRF the information about death is captured).

If relevant: specify if disease progression/relapse/recurrence are exempt from reporting as SAEs (with instruction as to where in the trial CRF this information about this is captured).

In all cases AEs and / or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor-Investigator. These may be volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation. AEs that do not require reporting to the Sponsor-Investigator must still be recorded in the participant’s medical records.

# Pregnancy reporting

If this section is not relevant to the trial, please state that clearly and retain the section header.

Information should be provided here to give details of how long after the trial has closed or last dose provided, pregnancies should be reported. For example, if you have a 10 year survival follow-up period on your trial, you would not necessarily want to receive pregnancy notifications 6 years after the participant completed the active phase of the trial. You may want to specify that pregnancy reporting would stop 6 months after the participant’s last dose of IMP for example.

All pregnancies within the trial (either the trial participant or the participant’s partner) should be reported to the Sponsor-Investigator using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/fetus. If the outcome meets the serious criteria, this would be considered an SAE.

Include whether pregnancies need to be reported to IMP Manufacturer if it is a requirement of the supply agreement.

# DATA AND ESSENTIAL DOCUMENT MANAGEMENT

No additional text is to be entered in this section.

This section addresses the management of both data and essential documents.

Refer to the subsections below for site responsibilities related to essential record management and a high-level summary of data management activities related to data handling (generation, collection, access, use, analysis, disclosure, storage, retention, disposal, sharing and re-use). Full details are provided in a separate **Data Management Plan.**

|  |
| --- |
| The following sub-sections should address:   1. The management of essential documents as described in the current version of ICH Good Clinical Practice (as applicable in the jurisdictions where the trial is conducted); and 2. The ethical issues related to data management (generation, collection, access, use, analysis, disclosure, storage, retention, disposal, sharing and re-use) and record keeping of data or information for the conduct of the trial as outlined in the National Statement (2023, Chapter 3.1, Element 4).   Keep the detail in the **protocol high-level** with the details provided in a separate Clinical Trial Data Management Plan. Refer to [MCTC195 Template | Data Management Plan (DMP)](https://metis.melbournechildrens.com/MCTC195) for guidance and template.  Note 1: Researchers must also complete the [MCRI DMP via DataConnect](https://murdochchildrens.sharepoint.com/sites/DataConnect/SitePages/Data%20Management%20Plan.aspx). This does mean you will have two separate DMPs for each clinical trial. They serve a different audience and have some overlap in content but not all. The MCRI DMP is used by the institute to support data governance oversight. It is a living document for a research project, that outlines data creation, data policies, access and ownership rules, management practices, management facilities and equipment, and responsibilities. The Clinical Trial DMP is version controlled signed document designed to meet requirements of ICH GCP and other national/international regulators. It covers the same aspects as the MCRI DMP but also covers data processing across the lifecycle of the trial.  Note 2: The Clinical Trial DMP should be supplemented by **Standard Operating Procedures** to address operations such as CRF design and CRF change version management, data collection, data cleaning and validation, data query resolution management, data analysis, safety reporting, and data deletion. |

# Management of Essential Records

The National Statement (2023) and The Australian Code for the Responsible Conduct of Research 2007, updated 2018) and ICH GCP require that the Site 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.

ICH GCP uses the term “essential records” to describe the records that should be maintained. These are documents and data in any format, associated with the trial that facilitate the ongoing management of the trial and allow the evaluation of the methods used, factors affecting the trial, and actions taken during the trial to determine reliability of trial results and verification that the trial was conducted in accordance with GCP and applicable regulatory requirements.

The Site Principal Investigator and site team must file the site essential records in an Investigator Site File (ISF). Insert instructions here regarding use of paper or electronic binder platform.

Example text

Trial related essential documents maintained for the study will be filed within the trial’s electronic Trial Master File (eTMF) platform, Florence eBinders™, a cloud-based SaaS software maintained by Florence Healthcare, hosted in [select: Germany or Australia], via Amazon Web-Services (AWS) and backed up daily.

Investigator Site Files (ISF) pertaining to each participating site will also be maintained electronically via the Florence eBinders™ platform by each participating site, to enable remote monitoring of essential trial and regulatory documentation.

The Site Principal Investigator should use a Site File Index to explain the location of documents stored outside the Investigator Site File during the trial.

Additional instructions related to management of essential records are in Sections 10.2.8 Archiving – Data and document retention and 10.2.11 Long-term custodianship.

|  |
| --- |
| Refer to guidance below to assist with ensuring sites can fulfill their responsibilities for essential record management:   * Contact [mctc@mcri.edu.au](mailto:mctc@mcri.edu.au) for guidance on setting up Investigator Site Files * Essential records for the trial related to data management that are specific to data include Data Management Plan, Data Dictionary, Data Sharing Plan) (refer to [METIS](https://metis.melbournechildrens.com) for SOPs, forms and templates. * [MCTC011 Guidance | Investigator Site File - Table of Contents Document Filing](https://metis.melbournechildrens.com/MCTC011) * [MCTC173 Form | eISF Filing Index for IITs](https://metis.melbournechildrens.com/MCTC173) |

# Data management

Do not enter text in this section.

# Data generation (source data)

The Site Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data must 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.

Each site participating in the trial will maintain a site-specific **Source Document Plan** that will document the source record/document and their location for each data variable to be collected in the CRF. 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. It must be updated if the source record changes during the study.

Describe the following in this section:

* Document if you plan to use any sections of the CRF or any other document which would not routinely be used for source data (and would routinely be considered as a data collection tool) – this must be clearly outlined here. NOTE: It is not acceptable to use sections of the CRF as source unless you have fully outlined this in the protocol – it WILL be an Audit/Inspection finding.
* Specify if you will use existing data and what that data is
* Specify all data variables that will be captured directly into a trial-specific instrument (e.g. data collection form, a diary or other site-designed worksheet), whether it be paper or electronic.
* Specify the record/document, separate to the Case Report Form, where to record the participant’s inclusion in the trial, e.g. participant’s medical record.

**Note:** It is important for clinical care that anyone accessing the 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):

* sensitive information including health data (genetic information, disease/diagnosis, medical history)

In this trial, source data will be the electronic or paper-based medical record (hospital records, observation charts) for each participant. Source data will be entered directly into the appropriate electronic CRF or onto the pre-printed paper CRF for collecting data. Paper CRFs are provided in the following instances only and are considered source data: <Insert list>

Any data recorded directly onto paper CRFs, for which no other written or electronic record exists, will be considered source data (e.g. participant questionnaires).

CRFs and source documents must always be available for inspection by authorised representatives of the Sponsor and competent authorities.

The Site Principal Investigator is required to maintain a participant identification code list to allow unambiguous identification of each participant included in the trial. This list should contain the participant’s full name, data of birth and their Participant Identification Number (PID). This list must be held in confidence at the Principal Investigator’s site.

|  |
| --- |
| 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.  Source data are contained in source records/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. The Case Report Form is also considered the source record/document if this is the first place the data is recorded.  Source documents can be hard copy or electronic. ASource Document Plan Guidance and Template is available on METIS at [MCTC015 Template | Source document plan](https://metis.melbournechildrens.com/MCTC015) |

# Data collection methods

The Site Principal Investigator must 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 site delegation log and will be trained to perform these trial-related duties and functions.

Provide a clear description of the data collection process – including the personnel, methods, instruments, and measures to promote data quality.

Discuss risks associated with the site team’s collection of data and how these will be minimised.

Discuss the following when applicable to the trial:

* duplicate measurements
* controlled use of automated data validation checks in the CRF, e.g. verification prompts that the data are in the proper format or within expected range of values
* training and testing of outcome assessors to promote consistency. Cross-reference Section 8.3 Description of procedures, for details of qualifications required to perform these assessments.
* training of site personnel on: CRF data entry; respond to data discrepancy queries and general information about obtaining quality research quality data.
* training of trial participants on how to record/capture data when using data acquisition instruments, e.g. patient diaries, ePROs, medical devices/apps. Cross-reference Section 7.3 Description of procedures, for details of training methods.

Reference the trial Manual of Operations/Manual of Procedures or SOP related to data collection and or CRF Completion Guidelines as well as the DMP.

Explain that data collection is the responsibility of the research staff at each site under the supervision of the Principal Investigator. Include details about expectations for timing of data entry and if it may be batched. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Example text

Data for this trial will be collected and entered using hardcopy and electronic case report forms (CRFs) 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 data:

* <insert e.g. MedDRA, ICD10 >

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

# Data storage and access

Document data security measures to prevent unauthorised access to or loss of participant data, as well as plans for data storage (including timeframe) during and after the trial. For electronic data, also describe how the data will be backed up. This information facilitates an assessment of adherence to applicable standards and regulations.

Data should not be stored in Excel. Specify the software/tools that will be used and the organisation providing the tool. MCRI’s installation of REDCap on MCRI infrastructure is the current approved data collection tool for MCRI-sponsored trials. Include details regarding validation of the database and where validation documentation is filed.

Describe in this section who will have access to the data and trial documents and how they will have access. Note 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, RGO and regulatory agencies to examine source records for participants.

Example Text

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 member delegated this task by the Principal Investigator.

Refer to the trial’s Data Management Plan (DMP) for detailed information on data storage.

Authorised representatives of the sponsoring institution as well as representatives from the HREC, RGO and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this trial. The trial site will permit access to such records.

# Data use

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

Complete also the section on data sharing [cross reference section on data sharing]

Example Text

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.

# Disclosure of data

Describe whether there are any situations in which personally identifiable information or data will be released to third parties. Identify the third parties and the purpose for which the data will be disclosed. Clarify whether the disclosure is subject to participant consent, other voluntary agreements or mandatory requirements. [National Statement Section 3.1.58].

Example Text

The trial 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, RGO or regulatory agencies.

# Data Confidentiality

Provide the following information in this section of the protocol:

* Detail how personal information and data about potential and enrolled participants will be collected and maintained to protect confidentiality and privacy before, during, and after the trial. (Refer to section 3.1.39 of the National Statement for discussion about research where removal or separation of identifiers may not be required).
* 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 National Statement (2023) provides the following guidance and instructions for researchers related to data confidentiality:  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.   * 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:  1. minimising the number of variables collected for each individual 2. separation and separate storage of identifiers and content information; and 3. separating the roles of those responsible for management of identifiers and those responsible for analysing content.” (NS 3.1.40)  * 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. * The security arrangements should be proportional to the risks of the research project and the sensitivity of the information (NS 3.1.45). |

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 (Participant ID) 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 will 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.**

(4) The study participant’s contact information will be securely stored at each site for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for the duration of the archiving retention period as dictated by the relevant legislation.

**Researchers planning to conduct trials at sites in the EU should note the following:**

Example text:

“The study will comply with Australian Privacy Laws and, the EU General Data Protection Regulation (GDPR) and all other relevant Data Protection Laws, which requires data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique Participant ID number only on all study documents and any electronic database(s), <with the exception of the XXX CRF, where participant initials may be added>. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants’ personal data.”

**Refer to** [**MCTC106 Guidance | Principles of the General Data Protection Regulation (GDPR) & Data Protection in a Research Context**](https://metis.melbournechildrens.com/MCTC106) **for further information. You may also** **contact** [MCTC](mailto:mctc@mcri.edu.au) **for assistance if required.**

# Data Quality Control

Provide a brief description of data quality control procedures that are described in the Clinical Trial DMP and Clinical Monitoring Plan such as:

* 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 entered directly into the database and therefore the database is also the source). If source data verification will be done remotely, insert wording to this effect (see example text below).

Example text

Source documents pertaining to the trial must be maintained by participating sites and de-identified/redacted copies provided to the Trial Monitor/s.

* Plans for expert review of source documentation (where applicable). This could include, for example: a Medical Review Committee (e.g. for review of protocol deviations, compliance with the intervention etc); or a Trial Outcomes (aka Endpoint Adjudication Committee) to review primary outcome data in a blinded fashion.

Plans for site monitoring and auditing are provided in Sections 11.2 Site Monitoring and 11.3 Quality Control and Quality Assurance, respectively.

# Archiving – Data and document retention

In this section, specify the following regarding storage of data and documents during the archival period:

* How long trial data, information and documents will be retained by the sites after the trial has finished.
* Indicate if the retention period is the minimum period required by relevant regulations and/or legislation or longer.
* The form in which participant data will be stored and how confidentiality will be maintained.

Note: 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).

* Where the data and documents will be stored. If using Florence eBinders™, consider long-term archival storage location/s of electronic files.
* Who will be the custodian during the archive period, who will have access to the data and documents, and conditions under which access may be granted to others. If using Florence eBinders™, the long-term custodian will be the “MCRI Florence Archivist”.

|  |
| --- |
| 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 2018) * 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 2018) * Research that has community or heritage value - must retain permanently, preferably within a national collection (The Australian Code for the Responsible Conduct of Research 2018) |

# Destruction of data and documents

Records should not be destroyed without the written consent of the Sponsor-Investigator.

The Sponsor-Investigator will inform Site Principal Investigators when the retention period has ended and they can destroy their records.

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 Plan and Data Sharing Statement

Include if there are any existing arrangements to share data with specific third parties, including open or mediated access repositories, e.g. Vivli Clinical Data Repository, FigShare

Include your Data Sharing Statement here.

Reference the trial-specific Data Sharing Plan for further details.

|  |
| --- |
| 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 Plan:  Refer to [MCTC079 SOP | Data sharing and access procedure for the release of data from the Murdoch Children's sponsored investigator-initiated clinical trials](https://metis.melbournechildrens.com/MCTC079) and [MCTC091 Form | Data Sharing Plan](https://metis.melbournechildrens.com/MCTC091) for the procedure to develop your Data Sharing Plan.  Data Sharing Statement:  Data sharing statements should indicate the following: whether individual de-identified participant data (including data dictionaries) will be shared; what data (variables) 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).  In determining if and what research data should be made available for access by others at the end of a research project, researchers must consider many factors including the value of the research data, ownership and data rights, the potential for the research data to identify participants, and any potential restriction on the research data and unintended consequences of releasing the research data. Ensure you seek appropriate consent (i.e. extended or unspecified consent) for data sharing.  Before completing this section,   * Read [MCTC079 SOP | Data sharing and access procedure for the release of data from the Murdoch Children's sponsored investigator-initiated clinical trials](https://metis.melbournechildrens.com/MCTC079) * Download the [MCTC091 Form | Data Sharing Plan](https://metis.melbournechildrens.com/MCTC091) for the template to develop your Data Sharing Plan and ensure this is completed and retained on file prior to enrolment of the first participant. * Summarise the statement and plan in this section of the protocol and refer to your completed MCRI Data Sharing Plan for this trial. |

Example text

Data sharing statement

The trial recognises the value of open data sharing and adherence to data sharing principles that align with applicable laws, regulations, and ethical guidelines, therefore, anonymised data from this clinical trial will be made available via a controlled access data sharing mechanism. Interested researchers may request access to the data by submitting a formal data sharing request to the Sponsor. The request will be reviewed by the Sponsor and the Sponsor-Investigator, and any relevant MCRI data sharing committee, considering factors such as scientific merit, data security, and adherence to the approved research objectives.

The anonymised data set collected for the analysis of this trial will be made available ‘x’ months following analysis and publication of the primary outcome. The following will be made available long-term for use by future researchers from a recognised research institution:

* Individual participant data that underlie the results reported after anonymisation (text, tables, figures and appendices)
* Trial protocol, PICF
* Statistical Analysis Plan (SAP), statistical code

The data may be obtained from the Murdoch Children's Research Institute by emailing [MCTC@mcri.edu.au](mailto:MCTC@mcri.edu.au).

# Long-term custodianship (after archive period finished)

State who (i.e. person’s position) will be the long-term custodian following the archive period and include contact details.

|  |
| --- |
| 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. |

# Sample management: Specimen & Biobanking

Provide the following information for all labs being used to process/analyse biospecimens and any biobanks used to store biospecimens for future research:

* Procedure for tracking biospecimens from their point of collection through processing, storage, transport, through to disposal

Note: For Melbourne Children’s trial teams sending samples to external labs/biobanks use [MCTC054 SOP | Handling, Processing, Storage and Transport of Biospecimens in Human Research](https://metis.melbournechildrens.com/MCTC054)

* Lab/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 - 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 of biospecimens and information derived from them - in what circumstances will this be done (e.g. participant request, consent expiry, biobank expiry or other discontinuation of biobank).

|  |
| --- |
| 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](https://www.nhmrc.gov.au/guidelines-publications/e110)).  **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](mailto:%20biobanking@mcri.edu.au)) or via the RCH Research Ethics Governance (REG) website (click on the link on the REG 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. |

# TRIAL OVERSIGHT

# Governance structure

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

# Trial 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.

# Trial 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 TSC will meet at least annually, with more frequent meetings as needed, and will work to a Terms of Reference. The TSC will include <list role categories, e.g. Representative from MCRI Sponsorship Committee, external independent clinical expert, participating site Investigator>.

# Safety Monitoring

In this section, specify the type of safety oversight along with known responsibilities for the oversight of safety and data integrity in the trial. Describe the composition of the Data Safety and Monitoring Board (DSMB) if using, frequency of safety data review, and method of reviews. Reference the trial specific DMSB Charter for further detail regarding DSMB membership, responsibilities and administration of the DSMB.

Example text 1

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.

Example text 2

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 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 annually. 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 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.

|  |
| --- |
| 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.  **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](https://www.mcri.edu.au/sites/default/files/media/guidance_dsmb_2feb2017.pdf)” and template charter available on the [CRDO](https://www.mcri.edu.au/research/training-and-resources/clinical-research-development-office-crdo/resources-quantitative) website and also the NHMRC’s supplementary guidance “Data Safety Monitoring Boards (DSMBs)” at <https://www.nhmrc.gov.au/guidelines-publications/eh59> |

# Site Monitoring

In this section, provide a general description of how the monitoring of the conduct and progress of the trial will be conducted. Include who will conduct the monitoring, the type, frequency and extent of monitoring, who will be provided reports of monitoring, and if independent audits of the monitoring 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 [MCTC046 SOP | Monitoring Visit Activities for Clinical Trials of Investigational Products](https://metis.melbournechildrens.com/MCTC046) and [MCTC047 Template | Clinical Monitoring Plan for IITs](https://metis.melbournechildrens.com/MCTC047) for further instructions and tools to assist with meeting Sponsor-Investigator monitoring responsibilities.

Example text

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 <insert x%> 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.

|  |
| --- |
| 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. Use [MCTC035 Template | Risk Assessment and Risk Management Tool for Clinical Trials](https://metis.melbournechildrens.com/MCTC035) to develop your trial Risk Assessment and Management Plan –this will help identify and document the risks and their management. The assessment results will 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/file/2901/download?token=3_uEcQmH) for additional guidance.  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 CPI 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.  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 |

# Quality Control and Quality Assurance

Text in black font should remain in all protocols.

The Sponsor-Investigator will develop a trial risk assessment and management plan to 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. Where required to control identified risks, trial-specific SOPs will be developed. These have been incorporated into a Trial Manual of Procedures for sites.

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 Section 11.2 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).

Each site (both clinical and laboratory) should implement a quality management plan using SOPs that describe the following site team roles, responsibilities and procedures:

* 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.

|  |
| --- |
| 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 CPI and Site Principal Investigator have responsibilities in relation to quality management. |

# STATISTICAL METHODS

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

# Sample Size Estimation

Specify the sample size and justify the number in terms of the trial objectives. The methods and 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, especially if two arms are being compared:

* The relevant primary outcome
* The main treatment comparison of interest
* Assumed values in the control group (e.g. mean, standard deviation or proportion)
* The minimum treatment effect for which statistical power is required
* The estimated underlying variability (continuous outcomes)
* 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 or non-blinded way?).

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

# Population to be analysed

Define 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   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 minimisation of selection bias achieved by randomisation. |

# 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
* 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)
* 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 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 and supplemental 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)), summarised (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. The full details for each objective 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.

# Handling of missing data

Describe the statistical methods that will be used to handle missing data (e.g., multiple imputation).

# Interim Analyses

Include content in this section if applicable, otherwise write “No interim analyses are planned”

This section should describe the types of statistical interim analyses and halting guidelines (if any) that are proposed, including their timing. If the interim analyses could result in an adjusted sample size, discuss the statistical algorithm to be used when recalculating the sample size. Pre-specify 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. This should also be reflected in the sample size section, and in Section 11.3 where the final analysis is described.

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.

# ETHICS AND DISSEMINATION

All research must be approved by a HREC and receive institutional governance authorisation via the local 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.

# 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 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.

# 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 participant’s 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.”

# Non-compliance with the protocol and/or Good Clinical Practice (including Serious Breaches)

Non-compliance (also known as a deviation) is defined as “Any breach, divergence or departure from the requirements of **Good Clinical Practice** (GCP) or **the clinical trial protocol**” (“[Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods](https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1), NHMRC, 2018).

ICH-GCP requires that all non-compliances be documented and reported to the Sponsor- Investigator (as the sponsor delegate for MCRI-sponsored investigator-initiated trials).

In the majority of cases, non-compliances are deviations that do not result in harm to trial participants or significantly affect the scientific merit of the reported results of the trial. Some are unavoidable (e.g. a participant missing a visit), or permitted (e.g. a deviation from the protocol to protect a participant from an immediate hazard (USM). Certain instances of non-compliance are deemed a Serious Breach - this includes those that result in harm to trial participants or significantly affect the scientific merit of the reported trial results. Serious Breaches must be reported promptly to the Sponsor- Investigator, who should conduct a root cause analysis to determine the underlying factors leading to the breach and facilitating a corrective and preventive action plan (CAPA)) and report in accordance with local regulatory requirements. Further information regarding examples of serious breaches and reporting requirements can be found in the NHMRC Guidance “[Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods](https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1)” and the European Union’s (EU) Clinical Trials Regulation (536) at <https://ec.europa.eu/health/human-use/clinical-trials/regulation_en>

Refer to [MCTC123 SOP | MCRI Sponsor-Investigator Management of Non-Compliance: Protocol Deviations and Serious Breaches](https://metis.melbournechildrens.com/MCTC123) for further information about the Sponsor-Investigator responsibilities for managing non-compliance.

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

Example text

All non-compliance (protocol deviations, serious breaches) with the protocol and GCP must be reported to the Sponsor-Investigator.

A protocol deviation is defined as any breach, divergence, or departure from the requirements of Good Clinical Practice (GCP) or the clinical trial protocol that does not meet the definition of a serious breach. A serious breach is a subset of non-compliance that is likely to affect to a significant degree either the safety or rights of a trial participant or the reliability and robustness of the trial data and requires expedited reporting to the Sponsor-Investigator and HREC/IRB.

**Documenting and reporting non-compliance**

All non-compliance will be recorded in the participant record (source document) and on the CRF and will be assessed for seriousness by the Site Principal Investigator.

Any serious breach will be reported to the Sponsor-Investigator (as the Sponsor-Investigator’s delegate) within 24 hours of awareness. The Sponsor-Investigator will review the breach, conducting a root cause analysis and preparing a corrective and preventative action plan. Where non-compliance identifies protocol-related issues, the protocol will be reviewed and, amended if applicable.

The Sponsor-Investigator will notify the approving HREC/IRB within 7 days or as per the approving HREC/IRB’s reporting requirements. The Sponsor-Investigator and site Principal Investigator will ensure that reporting is compliant with all applicable laws and regulatory requirements relevant to each participating country.

# Confidentiality

If detailed in full in Section 9.2.3, leave this section header intact but refer the reader to that section.

If confidentiality was not covered in full in Section 10.2.6 Data Confidentiality complete this section. Refer to Section 10.2.6 for example text.

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

# 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 authorised representative or guardian.

# Financial Disclosure and Conflicts of Interest

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

|  |
| --- |
| From the National Statement, Section 5.3.11  A researcher must disclose to the review body any interests that may constitute an actual or potential conflict of interest, including any financial or other interest or affiliation that bears on the research (see Chapter 5.6 and the *Australian Code for the Responsible Conduct of Research* and its supporting guides). Where applicable, this disclosure should specify any business, financial or other relevant association between a researcher and the developer, manufacturer or supplier of a drug, device or other product of potential commercial value to be used in the research. A researcher must disclose to the review body any restrictions on publication or dissemination of research findings. |

# Dissemination and Translation Plan

Describe plans for investigators and the 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. Specify authorship eligibility guidelines.

Describe plans for granting public access to the full protocol and data sharing plans, cross-referencing Section 10.2.10, Data sharing plan & data sharing statement.

# ADDITIONAL CONSIDERATIONS

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

# REFERENCES

List references here