



Annotated Template: Protocol for a Randomised Controlled Trial of an Investigational Product

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Protocol Template:

Randomised Controlled Trial of an Investigational Product

NOTE TO USERS:

This template is appropriate for developing a protocol for use in a **Randomised Controlled Trial (RCT)** involving the use of an investigation product.

An **investigational product** is defined as:

- **a product not entered on the Australian Register of Therapeutic Goods, including any new formulation of an existing product or any new route of administration; or**
- **use of a registered or listed product outside the conditions of its marketing approval.**

The investigational product being tested in the trial may be a drug, placebo, vaccine or device, or substance such as an adapted blood product that is being administered to subjects. The term 'drug' is used commonly in this template to refer to the investigational product, and should be replaced with an alternative term, such as 'device' or 'vaccine', if this is more applicable to your study.

This template is **not** appropriate for developing protocols for observational studies, such as cohort, case-control and cross-sectional studies.

If you are not certain if this template is appropriate for your study, or you require guidance on developing a protocol for a different study type, please contact the:

Clinical Research Development Office - 03 9345 4112.

The Clinical Research Development Office recommends the structure described in this template, based on our experience with clinical research studies. However, **this is only a guideline and is designed to be generic**. Some subsections and suggestions will not be appropriate for your specific study.

You must tailor the protocol contents to meet the needs of your study. Only include sections pertinent to the study, omit irrelevant sections, reorder and add sections as needed.

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The most recent version of this document can be accessed via www.rch.org.au/CRDO

<STUDY IDENTIFIER>

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

<FULL STUDY TITLE>

The full study title should be kept brief but mention the study design, the population and the compound to be studied.

Example text:

“A randomised controlled trial of adjunctive corticosteroid treatment of clinical Pneumocystis jiroveci pneumonia in infants less than 18 months of age.”

<LAY STUDY TITLE>

A lay title for each study is required by the ethics committee. Include the lay title on this cover page, if desired.

<VERSION #, DATE>

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 the ethics submission.

CONFIDENTIAL

The following text is standard. Please edit as appropriate for your protocol:

This document is confidential and the property of <insert Institution name>. No part of it may be transmitted, reproduced, published, or used without prior written authorization from the institution.

STATEMENT OF COMPLIANCE

The following text is standard. Please edit as appropriate for your protocol:

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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*Insert a table of contents with page numbers for the subsections of the final protocol.
This table of contents provides page numbers for the subsections of this annotated template.*

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PROTOCOL SYNOPSIS

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

<i>Title</i>	
<i>Objectives</i>	
<i>Design</i>	
<i>Outcomes</i>	
<i>Study Duration</i>	
<i>Interventions</i>	
<i>Number of Subjects</i>	
<i>Population</i>	

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. Project specific abbreviations should be standardised within the protocol.

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 need not be defined in the text nor 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
ALT	alanine aminotransferase
BID	twice daily
BMI	body mass index
CRF	case report form
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HREC	human research ethics committee
ITT	intention-to-treat
LLN	lower limit of normal
MCRI	murdoch children's research institute
NHMRC	national health and medical research council
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PE	physical examination
PIC	patient informed consent
RCH	royal children's hospital
SDMC	safety and data monitoring committee

1. INVESTIGATORS AND FACILITIES

1.1 Study Location/s

Provide the name of the department and the address of all the sites where the research will be conducted.

If elements of the research are conducted at separate sites, add subheadings for the details of those locations. These may include facilities for randomisation, medical imaging, laboratory testing, biological sample storage, drug preparation or dispensing and study data management.

1.2 Study Management

Describe the roles and responsibilities of the study personnel involved in undertaking the study, with sufficient detail to allow a reader to understand how the study will be conducted. This may be supplemented by a separate document, if the breakdown of delegated responsibilities is complex.

Example text:

“The trial will be coordinated by a research team consisting of the Principal Investigator and a study coordinator. Informed consent discussions and clinical assessments will be conducted by the principal investigator. The study coordinator will be delegated responsibility for subject’s follow-up visits, data collection and maintenance of study documentation. Handling of investigational products will be the responsibility of an onsite pharmacist.”

Describe who will be involved in managing the study, explaining any arrangements such as central coordination for multisite trials or external management and monitoring, and provide contact details as applicable.

1.2.1 Principal Investigator

Provide the name, address, phone and fax details of the principal Investigator.

If the study is conducted across multiple sites, provide the details of the principal investigator at each site.

1.2.2 Statistician

Provide the name, address, phone and fax details of the person who will be responsible for statistical issues.

1.2.3 Internal Trial Committees

Describe the role and composition of any committees set up for the trial. (Define membership, function and frequency of review). Create subheadings for separate committees, which may include a Trial Steering Committee (TSC), a Safety Review Committee (SRC) or an Endpoint Review Committee (ERC). It is advisable to establish terms of reference for such committees and to include them as appendices to the protocol.

If none of these committees will be established, either delete this section or include a justification for not having the committees in this section.

1.2.4 Independent Safety and Data Monitoring Committee

Describe the role and composition of the Independent Safety and Data Monitoring Committee (SDMC) (Define membership, function, frequency of review, stopping rules). It is advisable to establish terms of reference for an SDMC and to include them as appendices to the protocol. If no SDMC will be established, either delete this section or include a justification for not having a SDMC in this section.

Example text:

“An independent data monitoring committee will be established to oversee the safety and progress the trial. The terms of reference of the Data Monitoring Committee, the draft template for reporting and the names and contact details are detailed in Appendix <#>”

1.3 Sponsor

Provide the details of the person, collaboration or institution accepting the responsibilities of the Sponsor for the study. A sponsor of a clinical research project takes responsibility for the initiation, management, and/or financing of research.

1.4 Funding and resources

This section should describe how the study will be financed, but should not contain specific dollar amounts .

Also state the source of other resources significant to the study, such as study drug, if these were provided separately.

Example text:

“This study is financed through a grant from the National Health and Medical Research Council”

2. INTRODUCTION AND BACKGROUND

The following sections (2.1-2.3) should be approximately 2 pages in total length and should not contain an exhaustive literature review. The reader should be given a clear idea of all of the following:

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

2.1 Background Information

Include the following:

- *Introduction to the topic or medical indication (but not in great detail), including any pathophysiology relevant to the action of the study drug;*
- *Current treatment options (if any) and the associated issues, risks and benefits;*
- *A brief and focused review of findings of previous related studies, highlighting inadequacies in the body of evidence.*

List references in section 14.

2.2 Research Question

Clearly state the question the study intends to answer in this section. Including the overarching research question of the study here in the introduction is optional, as the specific objectives of the study/hypotheses will be defined in section 3, however it is recommended.

2.3 Rationale for Current Study

Succinctly describe the reasons for conducting the study. If summaries of the following are available in the form of an investigator's/clinical brochure, reference should be made to those documents in this section.

- *Provide an outline of the background information on the properties of the investigational drug (biochemical, pharmacological, toxicological and clinical);*
- *Provide details of previous studies in children or adolescents, if available;*
- *Outline the drug's potential role in the clinical condition being studied with reference to available data;*
- *Summarize the known and potential risks of the intervention, giving a clear description of any expected adverse reactions (both serious and not serious);*
- *Outline the rationale for the route of administration, dosage, dosage regimen and dosage period selected for the proposed study. This should be based on available non-clinical and clinical data;*
- *Explain how the study will substantially add to science, change practice, save money, save lives and/or improve quality of life;*
- *Explain why the research needs to be conducted in the selected population.*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and or knowledge that might reasonably be expected from the results.*

3. STUDY OBJECTIVES

The following sections should be only a few sentences long. The objectives must be very precise statements about the goal that is to be achieved.

It is common for a study to have between 2 and 4 specific objectives that are components of an overarching research question. There should only be one primary objective.

Ensure that the text supports the statistical endpoints and that it is specific (not nebulous, open-ended or otherwise not assessable) and objective. Avoid biased statements that might suggest the author has prejudged the outcome.

3.1 Primary Objective

The primary objective reflects the main clinically relevant goal of the study. Every study must have a primary objective. Define the primary objective in terms of the population, intervention, comparator and outcome that will be measured in a single clear and concise statement.

Example text:

“The primary objective of this study is:

- *To evaluate the impact of <study treatment> on time to resolution of <condition> in <type of subjects> compared with placebo”*

3.2 Secondary Objectives

A study may or may not have secondary objectives. Delete this heading if there are no 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 because there is no ‘fit-all’ trial design and too many objectives may make the study logistically difficult to perform.

Also consider that the sample size calculation is based on the primary objective and it may not be possible to satisfy other objectives with this number.

The objectives should be stated in clear concise and specific statements.

Example text:

“The secondary objectives of this study are:

- *To determine the safety and tolerability of <study treatment> in <type of subjects> with <condition>.*
- *To determine the impact of <study treatment> on healthcare utilization in <type of subjects> with <condition>.”*

4. STUDY DESIGN

4.1 Type of Study

The proposed design of the trial is described in this section. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. The proposed design must be appropriate to the nature of the disease/problem and its indications, the definition and measurement of the endpoints, and practical constraints such as the availability of patients, the formulation of the trial medication and the availability of other resources.

- *Specify the basic design elements of the study, including:*
 - *The phase (e.g. Phase I, II, III or post-marketing);*
Please note that a drug or device may be marketed but classified as phase I, II or III trial if the dosage formulation, indication or population in the study differs from the marketed use of the product;
 - *The method of treatment allocation (e.g. randomised, parallel, crossover, sequential, dose-escalation);*
 - *Nature of the control (e.g. placebo controlled, active controlled, uncontrolled);*
 - *Nature of blinding: (e.g. open-label, double-blind, single-blind).*

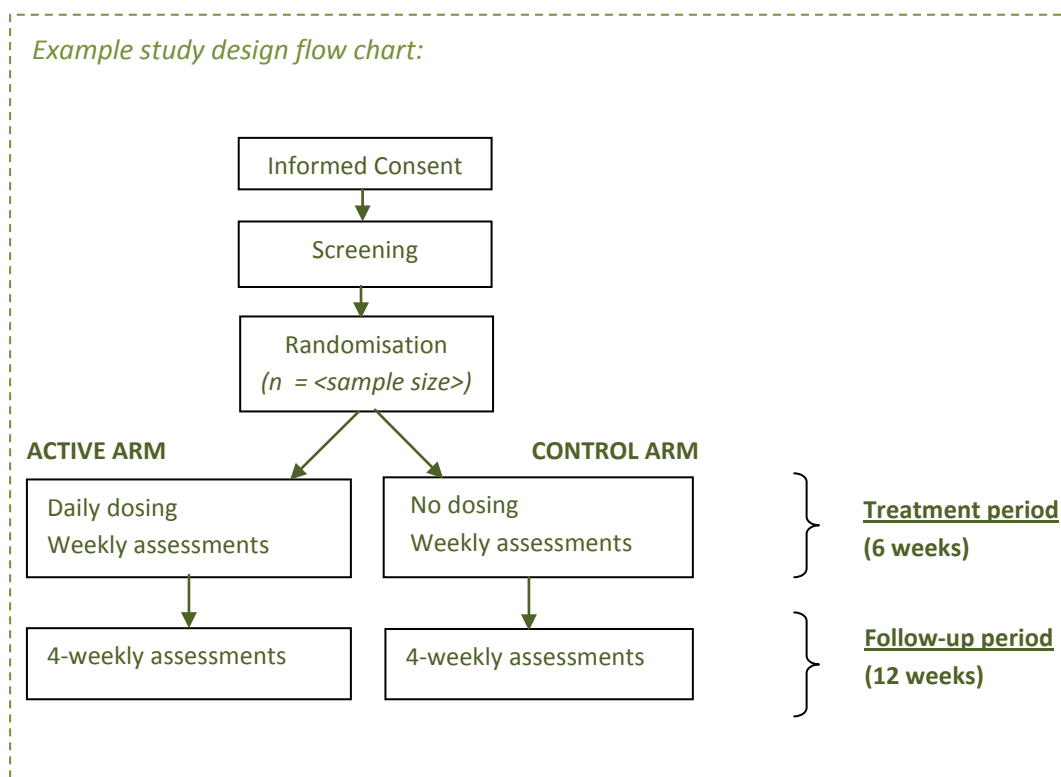
Example text:

“This is a phase II, observer-blind, randomised placebo-controlled, multicentre, dose escalation evaluation of the safety tolerability and immunogenicity of HPV immunotherapeutic.”

- *Specify the number of treatment groups;*
- *Specify the setting (e.g. hospital-based, in-patient, out-patient, multi-centre, single-centre, community);*
- *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’);*
- *State whether the study is designed to determine equivalence or superiority.*

4.2 Study Design Diagram

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



4.3 Number of Subjects

Specify the number, source and type of participants. If the study is a multicentre study, state the total number of participants.

4.4 Expected Duration of Study

State how long the study is expected to run, from start of subject screening to last subject finishing the study.

Specify the duration of the recruitment period. Specify the length of the treatment period and the follow-up period for an individual in the study.

4.5 Primary and Secondary Outcome Measures

This section of the protocol must clearly state what the variables to be measured are. How the assessments will be performed and when the assessments will occur should be described in sections 7 and 8. Specify the primary and secondary outcomes that will be measured in the study, which must correspond to the objectives in section 3.

The primary outcome measure should reflect the clinically relevant effects of the intervention and be based on the primary objective of the trial.

There should only be one primary outcome.

The secondary outcome measures are other effects to be measured in the study, these may or may not be related to the primary objective and are based on the secondary objectives.

Since the outcome variables will be used to evaluate the success or otherwise of the intervention, they need to be carefully selected and clearly defined in the protocol. Ensure endpoints are obtainable.

Efficacy variables are usually a quantitative measure of a clinical effect. Often the clinical effect to measure is obvious, but the method of measurement may be controversial. A surrogate endpoint does not measure the clinical effect, but is something that can be measured that is thought to relate to the clinical effect (e.g. bone density is related to a reduced fracture rate). Provide justification for any surrogate endpoints.

If a composite endpoint will be used explain its composite parts.

Primary and secondary outcome measures may be:

- *Objective assessments (e.g. mortality rates);*
- *Subjective clinical assessments (e.g. validated rating scales);*
- *Measurements of various physiological functions (e.g. blood pressure);*
- *Anatomical or histological assessments (e.g. tumour measurements)*
- *Biomarkers or biochemical markers (e.g. tumour markers, liver function tests); or*
- *Pharmacokinetic tests.*

5. STUDY TREATMENTS

5.1 Treatment Arms

Provide details in this section for every investigational product (including placebo). If there are multiple treatments, duplicate the sub-headings for each product.

5.1.1 Description

Specify the following, if available:

- *Dosage Form (e.g. tablet, capsule, powder)*
- *Ingredients*
- *Packaging (e.g. bottle, blister-pack, pre-filled syringe)*
- *Storage (e.g. room temperature, refrigerated, protected from light)*
- *Preparation (e.g. reconstituted)*

Note mechanisms (if any) for masking (i.e. blinding) study interventions. For example, if a placebo is being used, note whether it has similar color, taste, etc., to the active drug.

Summarise the label copy which should include the following, as appropriate:

- *Randomisation number*
- *Week number*
- *Batch number*
- *Expiry date*
- *The statement “For clinical trial use only”*
- *The statement “Keep out of reach of children”*
- *And any local or national requirements*

5.1.2 Dosage and Route of Administration

- *Specify the route of administration (e.g. oral, inhaled, intravenous, subcutaneous, self-administered)*
- *Specify the dose, or mg/kg, and strength of the dose unit. Consider dosage for all subjects throughout the trial period, taking into account the likely growth of babies and children*
- *Specify the dosage regimen (e.g. single-dosing, multiple-dosing, daily dosing, weekly dosing)*
- *Specify how long the drug will be administered for*
- *Specify any restrictions (e.g. with or without food, water, milk, posture, ambulation)*

5.1.3 Dose modification

Provide details for any allowable dose modifications and the circumstances for their use (e.g. toxicity).

5.2 Preparation and administration of study drug

Describe in detail all the steps necessary to properly prepare study treatment. Include whether the drug storage, preparation and dispensing will be done in a pharmacy or by a study team member. Fully describe how the study treatment is to be administered, where and by whom.

5.3 Dispensing and Product Accountability

Outline the procedures for pharmacy, particularly how and when the product will be dispensed and how accountability will be documented.

Specify what should happen to any unused medication. If applicable, this should include instructions to be given to the patient to return all leftover product, as well as empty containers.

Example text:

“The pharmacist (or the investigator’s designee) will maintain accurate records of the receipt of all study medication, including dates of receipt. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen will be recorded.

At the end of the study, there will be final reconciliation of study drug received, dispensed, consumed and returned. Any discrepancies will be investigated, resolved and documented by the study team .

Unused study drug will be destroyed in compliance with applicable regulations.”

5.4 Measurement of subject compliance

This section is most relevant for studies that require the subjects to administer medication at home. Delete this section if it does not apply.

Indicate whether compliance of subjects with the allocated intervention is to be assessed. If so, provide details as to how this will be carried out (e.g., pill counts, observation in the clinic, electronic monitoring devices, adherence questionnaires).

When appropriate, describe procedures that must be followed for any subject who is significantly non-compliant with the study treatment regime. Define ‘significantly non-compliant’.

Indicate if compliance will be recorded on the CRF.

5.5 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 study 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 patient from the study treatment*
- *Include drugs, devices, procedures, etc. from the exclusion criteria if they are also prohibited while the subject is on study.*

Give details of any applicable washout periods.

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

6. SUBJECT ENROLLMENT AND RANDOMISATION

6.1 Recruitment

Describe the sources and methods that will be employed in the identification and recruitment of potential subject. e.g. from investigator clinics, referring physicians, advertisements. Note in this section any information to be disseminated to subjects (e.g. handouts, advertisements or letters) and that this information will be approved by the HREC before use. Attach such information in the appendices of the protocol. Note that the identification and recruitment of subjects must protect privacy and be free of undue influence. Any steps taken to minimize undue influence should be outlined in the protocol.

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

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

State who will obtain consent and outline the roles and responsibilities of those involved in the consent process. State whether consent will be obtained from parents as well as the research subjects themselves.

Example text:

“Prior to performing any study specific procedure (including screening procedures to determine eligibility), a signed consent form will be obtained for each subject. For subjects below the legal age, a parent, legal guardian, or person with power of attorney, must also sign a consent form.

The consent form will describe the purpose of the study, 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 subject and their legally acceptable representative comprehend the information provided and answer any questions about the study. Consent will be voluntary and free from coercion.

The investigator that conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the subject or their legally acceptable representative and the fact that the subject has been consented to the study will be documented in the subject’s record.

When the all the inclusion exclusion criteria have been addressed and the eligibility of the subject confirmed, the subject may be assigned to a randomisation treatment in the study.”

Describe procedures for documentation of reasons for ineligibility for patients, and for reasons for nonparticipation of eligible subjects (i.e. maintaining a record of all subjects screened but not enrolled). Specify what data will be recorded on these subjects.

6.2 Eligibility Criteria

Eligibility criteria—stated as either exclusion or inclusion criteria—define and limit the kinds of patients that can participate in a clinical trial. They also define the population to which the trial results can be extrapolated.

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

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

Eligibility criteria should be clearly defined, straightforward and unambiguous.

The criteria should not be too restrictive, as overly restrictive criteria may:

- *Present a barrier to accrual of the required subject numbers*
- *Limit a study’s generalisability*
- *Fail to mimic clinical practice*
- *Increase the study complexity and/or costs*

Example text:

“Patients will be assigned to a randomised study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.”

6.2.1 Inclusion Criteria

The eligibility criteria will be highly specific for each study and the following is general guidance only and not an exhaustive list.

Provide details of each criterion that must be met to participate in the study.

Consider criteria related to:

- *Demographic characteristics (e.g. gender, age range).*
- *The disease or disorder under study: the specific definition of the disease state which will be used to assess patients for recruitment into the study and how it must be documented (e.g. diagnostic methods, criteria for classification, etc.).*
- *Clinical indicators of current status, as measured within <specify number of days> of randomization.*
- *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” subjects).*

Example text:

“Each patient must meet all of the following criteria to be enrolled in this study:

- 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 study purpose>*
- 4. Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the subject’s behalf.”*

6.2.2 Exclusion Criteria

Provide details of each criterion that, if met, would result in exclusion from participation in the study. Take into account known or suspected contraindications or side effects of the drug or factors likely to confound interpretation of the results.

Consider criteria related to:

- *Specific clinical contraindications (specify grades of signs and symptoms, obtained within XX days prior to randomization)*
- *Serious illness (requiring systemic treatment and/or hospitalization) until subject either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least XX days prior to study 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 study entry.*
- *Allergy/sensitivity to study drugs or their formulations.*
- *Inability or unwillingness of subject or legally acceptable representative to give written informed consent.*

Example text:

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

- 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 <study 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 study follow-up.”*

6.3 Randomisation Procedures

Describe the procedures for assigning participants to intervention groups/ the arms of the study.

- *Describe the potential results of the randomisation:*

Example text:

“Patients will be randomly assigned to receive <treatment> or <alternative allocation>”

- *State the type of randomisation (simple, block, stratified, minimisation) and define stratification variables where appropriate. Do not include details of the block sizes.*
- *State whether numbers assigned to each group will be equal or not, and provide supporting justification.*
- *State how the randomisation schedule, patient numbering and sequence of patient number assignment will be prepared and stored.*

Example text:

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

- *Describe the procedures that will occur for each participant randomisation. Specify who will be responsible for each step.*

6.4 Blinding Arrangements

If there will be no concealment of treatment allocation, delete this and the following section.

If some members of the research team and/or the subjects will be blinded to treatment allocation, specify in this section exactly who will be blinded and who will not be blinded.

Give reasons for the degree of blinding adopted.

6.5 Breaking of the Study Blind

6.5.1 On Study

Provide details about the circumstances that justify unblinding of a subject's treatment allocation during the study, and the procedures that will be followed. This should not be done unless absolutely necessary.

Example text:

“The randomisation code for an individual participant may only be unblinded in emergency situations, where the Investigator decides a participant cannot be adequately treated without knowing the identity of their treatment allocation.

To break the randomisation code the Investigator must open the emergency unblinding envelopes provided, or contact the randomisation facility/personnel.

If any unblinding envelope is opened, the time, date, subject number and reason for opening must be documented.

6.5.2 Following Completion of the Study

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

Example text:

“Trial drug codes will only be available once all data collected have been entered into the study 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.

6.6 Subject Withdrawal

6.6.1 Reasons for withdrawal

Describe criteria for a subject to cease participation in the trial prematurely.

If applicable, differentiate between criteria for ending study treatment (but continuing follow-up procedures and assessments) and criteria for complete withdrawal from the study.

Example text:

“The investigator may withdraw a patient from the study treatment and follow-up procedures if the patient:

- Is in violation of the protocol;*
- Experiences a serious or intolerable adverse event*
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria*
- Requires a medication that is prohibited by the protocol*
- Requires early discontinuation for any reason*

The investigator will also withdraw all participants from the study treatment if the study is terminated. Patients are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative.”

6.6.2 Handling of withdrawals and losses to follow-up

Describe the procedures to be followed when a subject ceases participation in the trial prematurely, including data to be collected and subsequent provision of care.

If abrupt termination of study treatment could affect subject safety, describe the procedure to transition subject off the study drug or to alternate therapy.

Clarify any applicable distinction between ending study treatment (but continuing follow-up procedures and assessments) and complete withdrawal from the study.

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect as much data for the protocol defined follow-up period as the subject will permit. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug.

If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period.

Note what attempts will be made to obtain this follow-up data and the point at which a subject will be declared lost to follow-up (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, medical record review, phone calls to other hospitals.).

Example text:

“When a patient withdraws from the study, the reasons for withdrawal shall be recorded by the investigator on the relevant page of the CRF. Whenever possible, all patients who withdraw from the study prematurely will continue to undergo scheduled visits for study assessments (follow-up). Patients who fail to return for study assessments will be contacted by the research team in an attempt to have them comply with the protocol. <give details regarding methods used to follow-up. Usually two documented phone calls and one registered letter>”

6.6.3 Replacements

Provide information on whether or not patients who discontinue the study will be replaced by further recruitment to maintain the required sample size.

6.7 Trial Closure

Describe the circumstances under which the study can be terminated prematurely or extended.

Describe the procedures that will be followed when the entire study is terminated, whether at the end of the expected study period or prematurely.

6.8 Continuation of therapy

Include a statement such as ‘No study medication will be issued to a patient after the day <#> visit, when <#> is the final treatment day.’

Otherwise, indicate arrangements and circumstances, procedures for the provision of study medication following the completion of the study.

Describe the procedures to transition subject off the study drug or to alternate therapy.

7. STUDY VISITS AND PROCEDURES SCHEDULE

This section is intended to explain the chronology of the study. Information about what procedures will be conducted at each time point should be provided, but the precise details of the assessments should be provided in the following section 8.

The conventional format for this section is a table, using an 'X' in a cell to indicate that a procedure occurs at a particular visit, as in the example below

The evaluations will be specific for the particular protocol and should be arranged for clearest presentation. Include any clinical tests, psychological/ psychiatric investigations, invasive procedures and questionnaires.

Specify visit windows if applicable: e.g. "screening procedures must be conducted between one and two weeks prior to randomization. Visit two must occur 2 weeks following randomization (+ or – one day) or it will be considered a missed visit."

The table on the following page is provided as an example only.

Additional columns may be needed to specify evaluations conducted in special circumstances or time points that require a different set of evaluations, such as intervention failure or premature discontinuation of study interventions.

For example, if there are particular assessments to be conducted in an end-of-study visit, detail these and state whether or not these are the same assessments if a patient terminates prematurely or the trial is completed.

Example table <#>. Schedule of Assessments:

STUDY PERIOD	Screening	Randomisation	Study Treatment	Follow-up	
VISIT NUMBER	Visit 0	Visit 1	Visits 2 , 3 and 4	Visits 5 and 6	
WEEK [#]	Week -2	Week 0	Weeks 2, 4 and 6	Weeks 12 and 24	
PROCEDURES	Informed Consent	X			
	Demographic Information	X			
	Medical History	X	X		
	Height measurement	X			
	Weight measurement	X	X	X	X
	Physical Examination	X	X	X	X
	Vital Sign Measurements	X	X	X	X
	Chest X-ray	X			
	Peak flow measurements	X	X	X	X
	Blood Collection*	X	X	X	X
	Urine Collection**	X	X	X	X
	Confirm eligibility		X		
	Randomisation		X		
	Study drug dispensing		X	X	
	Compliance check			X	X
	Participant Survey			X	X
	Adverse Event Check	X	X	X	X
Concomitant medication Check	X	X	X	X	

<#>: Insert footnotes to specify the allowable visit windows.

E.g. "Visit 2 will occur 2 weeks from the date of randomization, + or – 2 days".>

<* and **>: Insert footnotes to explain what will be done with the collected blood and urine. >

8. CLINICAL AND LABORATORY ASSESSMENTS

This section is for a discussion of the details of all the study assessments, including the procedures listed in section 7, specifying how the test will be conducted, how measurements will be obtained and what information will be collected and documented.

*The recommended arrangement of this section is to create subsections with headings for each assessment, according to their chronology in the study (i.e. define all of the rows in the **schedule of assessments table in Section 7**).*

For each assessment:

- *Include notation as to whether the test is included to measure eligibility, baseline values, PK, efficacy or safety, or alternatively group the subsections under headings to indicate this.*
- *Describe how the assessment will be done, what measurements will be obtained, where and by whom*
- *Reference to a separate manual may be necessary if tests are complicated.*
- *Specify units.*
- *It may be important to specify the timing of tests in relation to other as restrictions, such as ‘blood samples should be drawn after vital signs have been measured, but before administration of study drug’.*
- *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).*
- *Point out any procedures, situations or materials that may be hazardous and the precautions to be exercised to minimise the risks.*
- *Specify if any particular member of the research team must conduct certain assessments*

Example text:

“8.1 Vital Sign Measurements

Vital signs to be measures at every visit are: orthostatic blood pressure, respiratory rate, oral temperature and heart rate. Blood pressure and heart rate measurements will be obtained after the patient has been seated for at least 5 minutes. The measurements will be taken from each patient’s right arm, where possible. Oral temperature will be obtained in degrees Celsius. Heart rate will be counted for a full minute and documented in beats per minute (bpm). Respirations will be counted for a full minute and documented in breaths per minute. Vital signs measurements will be assessed to ensure they lie within normal limits, to determine patient eligibility and monitor patient safety throughout the study. The investigator will review results outside the normal range and document an assessment of their clinical significance.”

9. ADVERSE EVENT REPORTING

Each protocol requires a description of how adverse events will be defined for the purposes of the study, how adverse events occurring in the study participants are to be elicited and how they are to be reported. Details should include the definition of a Serious Adverse Event (SAE) and the reporting timeframes.

9.1 Definitions

This example text represents standard definitions. Adapt the text as appropriate.

Example text:

Adverse Event (AE) :

Any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment.

Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious.

An SAE is defined as any AE that:

- results in death; or*
- is immediately life threatening; or*
- requires inpatient hospitalisation; or*
- requires prolongation of existing hospitalisation; or*
- results in persistent or significant disability/incapacity; or*
- is a congenital anomaly/birth defect.*

Important medical events will be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected Unexpected Serious Adverse Reaction (SUSAR):

A SUSAR is any SAE that is both suspected to be related to the study treatment and is unexpected (i.e. not consistent with applicable product information).

9.2 Assessment and Documentation of Adverse Events

In this section, specify which adverse events will be reported on the CRF, and which details will be recorded, stating any exceptions and additions to the definition of an AE and SAE (defined in section 9.1) appropriate to the study.

The decision on the nature of adverse events to be recorded for each study will depend on the risk associated with the study (including the extent of knowledge of the risk profile of the drug and the population to be studied) and the objectives of the trial.

Example text:

“For the purposes of this study the investigator is responsible for recording all Adverse Events, regardless of their relationship to study drug, with the following exceptions:

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

The description of each AE on the CRF will include:

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

*The severity and relationship of an AE will be assessed as per appendix A [*attached to this template*].*

The seriousness of an AE will be assessed by an investigator according to the definition in section 9.1, with the following exception:

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

Changes in the severity of an AE will be reported. AEs characterized as intermittent will be documented for each episode.

All AEs will be followed to adequate resolution, where possible.

9.3 Eliciting Adverse Event Information

Outline how adverse event information will be collected.

Make sure the schedule and method matches the intent of the study.

Example text:

“Adverse events will be recorded from the time the patient signs the informed consent form until 30 days after the last dose of study medication. At every study visit patients will be asked “How have you felt since your last visit?” in order to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medication or changed concomitant medication regimens. In addition, AEs will be documented from physical examination findings, clinically significant lab results or other documents (including patient diaries and correspondence from their primary care physician) that are relevant to patient safety.”

9.4 Serious Adverse Event Reporting

Outline the reporting requirements and timelines for reporting SAEs and SUSARs to the Ethics Committee and/or Regulatory Agencies. Consider a flowchart to clarify the reporting requirements. State who will be responsible for submitting SAE reports to HRECs and regulatory authorities.

9.4.1 SAEs

*The following is standard text. Edit as appropriate for your study.
If the study is multi-centre, change ‘RCH HREC’ to ‘local HREC’.*

*“Any SAE occurring in a study participant will be reported to the RCH HREC within 24-72 hours of occurrence, in accordance with the safety reporting policy of the HREC.
The HREC safety reporting form will be completed, signed and submitted by an investigator.”*

9.4.2 SUSARs

The following is standard text. Edit as appropriate for your study:

*“All SUSARs occurring in a study participant will be reported to the Experimental Drugs Section, Drug Safety and Evaluation Branch of the TGA in an expedited fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe.
An investigator will complete, sign and submit the SUSAR report.”*

10. STATISTICAL METHODS

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

10.1 Sample Size Estimation

Specify the sample size and justify the number in terms of the trial objectives.

The methods or computer program used for the determination of sample size should be documented or referenced, as should the estimates of any quantities used in the calculation.

The justification normally states the following:

- *The relevant primary outcome*
- *The main treatment comparison of interest*
- *The assumed control mean or rate*
- *The minimum treatment effect for which statistical power is required*
- *The estimated underlying variability (only relevant for continuous outcomes)*
- *The values of Type I and Type II error rates.*

If it is likely that a proportion of patients 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 subject), detail methods for accomplishing this (e.g. Will it be conducted in a blinded and non-comparative way?).

10.2 Population to be analysed

Provide details of the rules that will be used to determine the evaluability of subjects, especially in cases of protocol violations, withdrawals or dropouts.

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

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

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

10.3 Statistical Analysis Plan

This section should provide details on how the primary and secondary outcomes will be analysed. Be clear on primary as well as any secondary analyses and ensure that the text is consistent with the stated objectives.

Major features of the analysis should be outlined, such as time-points at which comparisons will be made, use of covariates or change from baseline.

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

- *A description of the how the data will be presented (eg. mean, median, IQR)*
- *A description of the statistical method used for analysis*
- *Details of adjustment for covariates*
- *Details of the test of difference*

If there is a separate document detailing the statistical analysis plan (SAP), this section of the protocol should contain the key elements of the analysis plan, describing the general methodology for dealing with each category of data and addressing each of the objectives. However, it does not need to be detailed by variables. The full details for each variable will be included in the Statistical Analysis Plan (which can undergo edits and versioning outside of the protocol and therefore not trigger an IRB 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.

10.4 Interim Analyses

Describe all plans for formal or informal analyses or inspections of the data. Note that in a blinded study all unblindings of the data prior to finalisation of the trial represent an interim analysis. Include stopping rules.

If no interim analyses will be done for this study state so.

Add subsections for other analyses, if they will be done. Include their timing and what effect they will have on the trial.

11. DATA MANAGEMENT

11.1 Data Collection

The data collected must be relevant, measured in a consistent manner and appropriate in quantity.

Outline the methods for collecting data and recording the collected data. Outline the process by which recorded data will be reported and entered into the database. Give details about the timing of data recording and reporting.

The original record of the data is called 'source data', and generally includes documents such as patient records, laboratory reports and surveys.

Usually, case report forms (CRFs) are created with fields designed to collect all the data relevant to the study. The fields of the CRFs are completed from the recorded source data, so that the study data is verifiable. Subsequently, the data on the CRFs is entered into the database.

Specifically state any data that will be recorded directly on the CRF (i.e. without a prior written record of the data).

If there are no CRFs, all data to be collected during the trial should be identified here and procedures described for its collection and recording.

Describe all quality control processes in place to prevent inaccuracies in the data and to check for errors.

Example text:

"Completed case report forms will be checked for completeness and accuracy by <specify title>, against the source data. Original case report forms will be used when entering information into the computer database. The database will be checked against the case report forms for accuracy. No investigation of the data will begin until an accurate database has been assured."

11.2 Data Storage

Outline where and how the data and database will be stored. Describe all procedures for handling data, how data are coded, who has access to the source data, CRFs and database, by whom the key to the code is safeguarded, which steps will be taken to ensure data security and how the subjects' privacy is protected, such as de-identification.

11.3 Study Record Retention

Note that data must be kept for 15 years after the completion of a clinical trial, or until the 25th birthday of the youngest participant, whichever is later, in accordance with the requirements of the Therapeutic Goods Administration and Health Privacy Principals.

Describe how long and where all research data and study related documents will be kept, following the end of the study. Outline how they will be secured and how confidentiality of stored data will be ensured. State who will have access to the stored data and what procedures will be followed to dispose of the data at the end of the archival period.

12. ADMINISTRATIVE ASPECTS

The example text in the following sections represents standard text. Adapt as appropriate for each study and add further subsections, if required.

12.1 Confidentiality

Include procedures for maintaining subject confidentiality, including any special data security requirements.

Example text:

“Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Subject Identification Number (SID) to maintain subject confidentiality. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by HREC or regulatory agencies.”

12.2 Independent HREC Approval

Example text:

“This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the human research ethics committee (HREC). A letter of protocol approval by HREC will be obtained prior to the commencement of the study, as well as approval for other study documents subject to HREC review.”

12.3 Modifications of the protocol

Set out the procedure to be followed when a significant change is required to the protocol. Describe how the amendments will be written up and incorporated into the protocol.

Example text:

“This study 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, study design, patient safety, or may affect a participants willingness to continue participation in the study 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 becoming effective.”

12.4 Protocol Deviations

Outline the process that will be followed to detect, document, report and follow-up on any deviation from the procedures prescribed by the protocol.

Example text:

“All protocol deviations must be recorded in the patient record (source document) and on the CRF and must be reported to the PI. Protocol deviations will be assessed for significance by the Principal Investigator. Those deviations deemed to have a potential impact on the integrity of the study results, patient safety or the ethical acceptability of the trial will be reported to the HREC <insert timelines >.

Where deviations to the protocol identify issues for protocol review, the protocol will be amended as per section 12.3”

12.5 Participant Reimbursement

Describe any subject stipend or payment here. If there is no subject stipend or payment, delete this section.

12.6 Financial Disclosure and Conflicts of Interest

Describe researchers’ obligations for declaring any conflicts of interest or financial interest related to the study. This section should be written with reference to the relevant policies and procedures of the applicable institutions.

13. USE OF DATA AND PUBLICATIONS POLICY

The protocol must document clearly, prior to the trial start, the publication policy for this study. This should detail the publication approval process, timeframes and any restrictions on publication, e.g. if data from single centres in a multicentre trial will not be published or that publications will only be considered when all patients have completed the trial.

Identify who holds the primary responsibility for publication of the results of the study. Also define the need to first obtain approval from the primary responsible party before any information can be used or passed on to a third party. This section should be written with reference to the relevant policies and procedures of the applicable institutions.

14. REFERENCES

This is the bibliography section for any information cited in the protocol. Double-check all citations.

Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication

15. APPENDICES

This section should contain all pertinent documents that supplement the protocol. The following are examples of potential attachments:

- *Full details of the methodology for tests required by the protocol.*
- *Classification of the disease studied.*
- *Definitions of toxicity classifications or lab abnormalities.*
- *Committee terms of reference.*

Example text:

APPENDIX A

Causality and assessment of severity – Adverse Events

The severity of an Adverse Event will be assessed as follows:

- **Mild:** Events that require minimal or no treatment and do not interfere with the patient'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.

The relationship of the event to the study drug will be assessed as follows:

- **Unrelated:** There is no association between the study drug and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure to the test product, or can be explained by a commonly occurring alternative aetiology.
- **Possible:** The event could have caused or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and/or follow a known response pattern to the test article, but could also have been produced by other factors.
- **Probable:** The association of the event with the study medication seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure to the test product and are consistent with the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigators' clinical experience.
- **Definite:** The AE is a consequence of administration of the test product. 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.