# Clinical Trial Protocol Template

Facility, service and/or
clinical stream name

**Please read this explanatory information and then delete these blue notes when developing your research protocol.**

This document is a protocol for a research clinical trial.

**Statement of Compliance**

This study will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2023), and the NHMRC Australian Code for the Responsible Conduct of Research (2018). If the project is a clinical trial, it will comply with the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

A well written research protocol is essential for high-quality research. A research protocol generally follows a conventional layout. This clinical trial protocol template aims to offer a generic guide, suitable for a broad range of clinical research trials in Metro South Health.

The preparation of a research protocol is an important first step in the research process for the following reasons:

1. *It provides the background and justification for the project*
2. *It details the research question, research aims, hypothesis, methodology, risk management including data protection and statistical analysis.*
3. *It is the roadmap for the conduct of the research.*
4. *It provides the basis for Human Research Ethics Applications (HREAs).*

The template contains a broad outline of sections usually expected in a clinical trial protocol. It is a guide to the information conventionally required rather than aiming to be definitive. Therefore, not all of the sections will be relevant for every clinical trial protocol and may be modified or deleted as applicable.

**The following resources should be reviewed when preparing your research protocol**

National Statement on Ethical Conduct in Human Research (2023). The National Health and Medical Research Council, the Australian Research Council and Universities Australia. Commonwealth of Australia, Canberra

<https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2023>

Australian Code for the Responsible Conduct of Research (2018). National Health and Medical Research Council, Australian Research Council and Universities Australia. Commonwealth of Australia, Canberra

<https://www.nhmrc.gov.au/about-us/publications/australian-code-responsible-conduct-research-2018>

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191–2194. Doi:10.1001/jama.2013.281053

<https://jamanetwork.com/journals/jama/fullarticle/1760318>

### **Research project title (full)**

The clinical trial title should be descriptive, while clearly and concisely indicating the subject of inquiry. The title should be consistent across all related documents (including regulatory documents). Include the phase, the nature (open label/blinded, randomised), the sites (single or multi), the name of the drug and the disease setting, where applicable.

### **Research project title (short)**

You might also like to include a simplified or shorter title easily understood by non-medical or interdisciplinary persons and/or an acronym.

### **Protocol version number and date**

Insert protocol version number and date. See version history listed below.

### **Study investigators**

Please include investigator affiliations to ensure reviewers are aware of the organisations involved, as this may have implications for data transfer, privacy, and confidentiality, as well as requirements for S95 forms to be completed.

|  |  |
| --- | --- |
| Principal Investigator: *(for single site studies)**OR* | For example:Dr Sirius ResearcherStaff SpecialistPrincess Alexandra Hospital Surgical Unit Ph: 3176 xxxxEmail: Sirius.researcher@health.qld.gov.au |
| Coordinating Principal Investigator: *(for multi-centre studies)* | xxxxx1  |
| Associate Investigator:  | xxxxx1  |
| Medical Monitor *(if applicable)* |  |
| Project Manager *(if applicable)* | xxxxx1  |
| Study Coordinator/Contact person:*(if applicable)* | xxxxx1 |

**1**Name, Institution, Department, Contact details

### **Study sponsor**

Name and address of the sponsor. The sponsor is an individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of the research. A research sponsor accepts the risk of the project and responsibility for its conduct. Please see WI2023-303 Metro South Health sponsorship of Clinical Trial Notification (CTN) scheme trials for more information regarding Sponsors.

### **Funding**

### Sources and types of financial, material and other support – for example competitive research grants.

### **Version history**

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Change date | Section changed | Summary of changes |
| V1 | DD/MMM/YYYY | NA | First version |
|  |  |  |  |

### **List of abbreviations**

|  |  |
| --- | --- |
| MSH | Metro South Health |
| PICF | Participant Information and Consent Form |
| TGA | Therapeutic Goods Administration |

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### Introduction

The introduction is a very brief overview of the clinical trial (*~250 words*). The introduction should be concise but sufficient to orientate the reader to the main purpose of the trial, how it will be conducted and its expected benefits. It is a structured sketch of the research project that will provide an overview before examining the details. It should be written using lay language.

### Background

The background is an important aspect of a clinical trial protocol. In this section the research problem should be described in the context of a literature review. A literature review involves finding, reviewing and forming conclusions about the published literature to provide clarity of the research problem. This is an opportunity to outline why the research needs to be done.

The following key points may be used as a guide:

* Conduct a comprehensive literature search (PubMed, EMBASE, CINAHL, and Cochrane Library and other databases relevant to your area of research).
* Discuss the importance of the topic (public health, clinical importance, impact on individuals/community including incidence, prevalence, mortality and morbidity).
* Critically appraise the relevant literature and discuss the state of current knowledge on the topic (including deficiencies in knowledge or gaps that make the research worth doing).
* Indicate how the research question has emerged.
* Explain how your research will contribute to existing research and benefit individuals or the wider community.

The literature review should be concise and present only key references (limit to 20-25 references). The literature review should logically lead to the statement of the aims of the proposed research.

**Clinical drug trials (must be included for Clinical Drug Trials)**

Name and describe the investigational product, if applicable. A summary of non-clinical studies that potentially have clinical significance and clinical trials that are relevant to the trial should be included and a summary of the known and potential risks and benefits.

A description of and justification for the route of administration, dosage, dosage regimen and treatment periods needs to be included.

### Aim(s)

The aim(s) should be developed from the literature review and state what the research hopes to accomplish (both primary and secondary).

### Objective(s)

The aim needs to be further refined to one or more research objectives. The research objective(s) are usually quantifiable statement(s) that will provide answers to the research problem.

### Hypothesis (optional, depending on methodology)

Hypotheses are more specific than objectives and amenable to statistical evaluation. Your primary hypothesis is the statement of the hypothesised effect on the primary outcome measure. A hypothesis is worded very simply and written as a ‘testable’ statement. The experimental results will prove or disprove the hypothesis. Hypotheses are generally stated in the null form (Ho) as they have their basis in inferential statistics. Rejecting the null hypothesis increases confidence, with a given level of probability, that there is a relationship between the variables being studied. However, a classic scientific hypothesis includes both a null and alternative (Ha) hypothesis.

### Methods

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.

#### 6.1 Study type/design

Describe the design of the clinical trial (eg randomised, placebo controlled, double blind). Ensure that a clear description of the proposed design is provided. You need to justify the particular trial design that has been chosen.

Further information regarding clinical trial design can be found in the following article:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176693/>

#### 6.2 Setting/sites

Identify the location(s) where the research will be conducted (eg Orthopaedic Unit, Princess Alexandra Hospital) and state whether the research is going to be single-site or a multi-site research. If multi-site, describe each site where the research will be undertaken, and the research activities that will be undertaken at each site.

#### 6.3 Participants

This section should describe the target population, target number of participants as well as the inclusion and exclusion criteria to identify appropriate participants for the study.

##### **Inclusion criteria**

Inclusion criteria are the ‘characteristics’ that clearly describe the research population that are required for a participant to be included in the research. The criteria may be based on factors such as age, sex, gender, the type and stage of a disease, previous treatment history, and co-morbid medical conditions. If the study only includes adults, state that all participants will be 18 years or older.

##### **Exclusion criteria**

Provide details of participants who will be considered ineligible to participate and justification their exclusion. These criteria are not always clinical in nature, aiming principally to accommodate participants in a safe and ethical manner. Criteria may include circumstances that interfere with the participant’s ability to give informed consent (diminished understanding or comprehension, or a language other than English spoken and an interpreter unavailable), contraindications to the research treatment(s)/ procedure(s), taking certain concomitant medication(s), or conditions that interfere with a patient's ability to comply with all treatment(s)/ procedure(s).

#### 6.4 Research outcomes

##### **Primary outcome**

The primary outcome or qualitative outcome should be the most important and relevant measurable outcome (eg clinical, psychological, economic, or other) of the research. This isthe measure used to address the primary research aim. However, it is also the outcome used to calculate sample size and statistical power and test the primary research hypothesis. Generally, no more than 1-2 primary outcome measures are pre-specified. Primary outcome measures may be measured in various ways such as: binary (eg caesarean/no caesarean, blood loss ≥500mL/blood loss <500mL); continuous (eg weight - kg, blood loss - mL); ordinal (eg pain - mild, moderate, severe); time to event (eg survival), and counts (eg number of infections, number of events occurring).

##### **Secondary outcome(s)**

Secondary outcome(s) are measures of additional or less or equal important research interest. They may include additional clinical, psychological, economic, or safety outcomes (eg treatment related side effects/adverse events). However, as these endpoints are not used to calculate research power and sample size it is often not possible to draw robust conclusions from the results.

##### **Impact and dissemination** (delete if not required)

Explain the wider relevance of science to the community and/or MSH, how to build support for future research and innovation funding and ensure the uptake of results within the scientific community and open up potential opportunities.

### Procedures/assessments/interventions

This section should describe the intervention that will be conducted during the research. It is preferable to use the active voice and state in the future tense (eg “We will randomly allocate participants to…”). Include a table/schedule of assessments where there are numerous assessments/procedures and timepoints. Please indicate if the assessments are different for different sites and explain the differences in numbered footnotes (see example below).

A schematic diagram or flow chart may be useful for this section.

|  |
| --- |
| Schedule of Assessments |
|  | Screening | Timepoint 1 | Timepoint 2 | Timepoint 3 | End of Study |
| Informed consent | X |  |  |  |  |
| Inclusion/Exclusion | X |  |  |  |  |
| Assessment 1 |  | X1 |  |  | X |
| Assessment 2 |  |  | X |  |  |
| Assessment 3 |  |  |  | X | X |

1.This assessment will only be conducted at [insert site name].

#### 7.1 Recruitment of participants

This section should describe how potential participants will be identified and selected for recruitment (eg at the outpatient clinic), how they will be approached/invited to participate (eg by principal investigator at a clinic visit), and how informed consent will be obtained. Be specific in naming which members of the research team (and their affiliation) will be involved in each step of the recruitment process, (eg a researcher from PAH, a researcher from the University). If there are any members of staff from the institution who are not part of the research team, but will be involved in recruitment, please list them.

You need to outline the estimated time schedule and feasibility for recruitment of participants and any strategies for achieving the target sample size.

It is important to explicitly state how the research team intends to identify potential participants, including at what point the medical record might be accessed, by whom, and what details will be screened. All team members involved in any screening and recruitment need to be named and ideally at least one person from the department where the participants are located should be included. If there are no research team members from the target department, then Head of Department endorsement for the Metro South research study would be required with the submission to the HREC.

#### 7.2 Consent

Consent is a process by which a participant voluntarily confirms their willingness to participate in the clinical trial. Before enrolment into the trial, each potential participant will be given a full explanation of the clinical trial. Once the essential information has been provided to the potential participant, and the investigator is sure that the individual understands the implications of participating in the trial, the participant will be asked to sign the consent form.

Information on how informed consent is to be obtained should be included in the protocol, such as which members of the research team will perform this task and when this will occur.

1. **Participant Information and Consent Form (PICF)**

A PICF will need to be developed using Plain English. Further information regarding Plain English writing style can be found in the following documents:

* [Metro South Health Writing Style Guide](https://qheps.health.qld.gov.au/msh/per/mnc/writing-style-guide)
* [Health Literacy – Metro South Health](https://qheps.health.qld.gov.au/msh/cgrl/governance/partnering/how-to/health-literacy)
* [Queensland Health Editorial Style Guide](https://qheps.health.qld.gov.au/corro-templates)

The PICF needs to be concise while still providing all the necessary information. This will ensure that if participants can read and understand the information, they can make an informed decision about their voluntary participation. The PICF can be adapted to suit different population groups (eg Aboriginal and Torres Strait Islander people) where applicable.

* Substitute Decision Maker

If a participant is unable to provide informed consent, a substitute decision maker may be required. to provide informed consent.

* Participants aged < 18 years

A Parent/Guardian PICF may also be required if some participants are less than 18 years old.

Consider preparing an assent form that is age appropriate. Affording respect to the child participant through provision of information related to participation in the study is required.

Various PICF templates for research conducted in Australia are available on the following NHMRC website. <https://www.nhmrc.gov.au/research-policy/ethics/ethical-issues-and-resources>

#### 7.3 Randomisation (if applicable)

You need to outline the method (including any software) that will be used to generate the random allocation sequence. Describe the type of randomisation to be performed, ratio of assignment to groups*,* block size permutation and stratification if applicable. Explain the methods used to conceal group allocation until assignment. Also include information on who will generate the allocation sequence and who will assign participants into their groups.

This section should also discuss if participants, the investigators, and those assessing/analysing the outcome(s) will be blinded (or masked) to group assignment or if the research will be open-label research (investigators and participants know their assigned group). Describe the measures that will be taken to minimise bias and the unblinding rules when necessary.

#### 7.4 Research intervention (if applicable)

In this section comprehensively describe exactly what will happen to participants once they are enrolled in the clinical trial. Depending on the trial it might include the frequency and duration of visits or whether they are expected to self-complete a daily diary at home, the duration of the trial or follow-up, and any measurements taken at each visit (eg questionnaires, physical measurements, biological samples).Describe at what point the research data collection will occur.

You need to include precise details of the treatment(s) intended for each group including:

* the treatment to be administered, the name of the product, the dose, dosing schedule, route of administration and the treatment period,
* the follow-up schedule (i.e. the time between visits) for each arm of the trial, and
* medications/treatments permitted and not permitted before and /or during the trial.

Outline maintenance of trial treatment, randomisation codes and procedures for breaking codes if applicable.

For drugs and devices that are commercially available, the research protocol must state their proprietary names, manufacturer, chemical composition, dose, duration and frequency of administration. For investigational products include a description of the dosage form, packaging and labelling of the investigational drug (if applicable or include in pharmacy manual). Please include details on how the device/drug is being supplied and funded.

For drugs and devices that are still in the experimental stage (or commercially available and used for a different indication or mode of administration), an Investigators Brochure (IB) is a required accompanying document to the research protocol. The IB is a compilation of clinical and non-clinical data, available pre-clinical experiments in animals and/or results of Phase I/II clinical studies. Refer to the TGA website, for further information on submission requirements – Clinical Trials Therapeutic Goods Administration (TGA).

#### 7.5 Withdrawal of participants

Consider how the participant’s adherence with the treatment schedule will be monitored. Describe under which circumstances participants may be withdrawn, how this will occur and articulate follow-up requirement of withdrawn participants and what may happen to their data.

#### 7.6 Outcome measures

It is essential to state how the data will be collected to assess the primary and secondary outcome(s) of the research (eg participant questionnaire, medical charts, routinely collected hospital/research database, biological specimens). If there are biological specimens collected for the study, prepare a laboratory manual that explains how the collected biological specimens will be handled/shipped, processed, stored and used. Also, outline if one or more researchers will be collecting data, their level of training/experience (or how they will be trained), and if assessment of inter-rater reliability will be undertaken, if applicable.

#### 7.7 Surveys

Provide details of all the surveys that will be administered in the trial. Justify the validity of any research instruments being administered. Describe how the surveys will be administered for example in hard copy or online.

#### 7.8 Assessment of safety

Outline the safety parameters, and the methods and timing for assessing, recording and analysing safety parameters. Procedures and timelines for monitoring, recording and reporting adverse events (AEs) and Serious Adverse Events (SAEs) should be described as well as the follow-up of participants after these events.

### 8. Data analysis

#### 8.1 Sample size and statistical power

A sample size or power calculation should be performed. This calculation is used to estimate the number of participants required to achieve the study aim or research hypothesis with an accepted power. Conversely, it also allows an estimation of the power that can be achieved with a limited number of participants, eg a convenience sample. This number is calculated by specifying the magnitude of the effect that is expected (informed and clinically significant), variability of the measurements and the acceptable degree of type I and II errors. Specify the assumptions made for the calculation. It is recommended to consult with a statistician for this section. Also keep in mind the estimated recruitment rate and whether the sample size will need to be adjusted for anticipated non-responders and losses to follow up.

Metro South Researchers are eligible for a free consultation plan with QCIF. Please refer to [QCIF Forms](https://support.qcif.edu.au/msh-biostatistics-support) to request an appointment to ensure that this section is appropriately described and addressed.

#### 8.2 Statistical methods

The statistical methods used to analyse the data in accordance with the research objectives/hypotheses (eg t-test, chi-squared, multivariate modelling) must be sufficiently detailed. Include the timing of any planned interim analysis and the level of significance to be used. If conducting a randomised controlled study, state whether methods will include an “intention to treat” (ITT) analysis, per protocol analysis, or both. An ITT analysis is preferred as it compares all participants in the groups to which they were originally randomly assigned (despite withdrawal, treatment failure or cross-over). Consultation with a statistician is strongly recommended. Outline which researchers are involved with data analysis and state if external collaborators will be involved.

### 9. Data management

#### 9.1 Data storage, retention and disposal

This section addresses the storage, retention, disposal, sharing and re-use of data or information. It should address the following questions:

* How and by whom will the data or information be generated, collected and/or accessed?
* Will the data or information be disclosed or shared and, if so, with whom, and how?
	+ - Clarify whether data will only be accessible to named investigators.
* Where will all data (e.g., electronic, hard copy, audio recordings) be stored?
* In what format will the data be analysed and stored (e.g. identifiable, re-identifiable or non-identifiable)?
	+ Identifiable: data that can uniquely identify an individual. Examples of direct identifiers include name, address, driver’s licence number, patient UR number and Medicare number.
	+ Re-identifiable: data, from which identifiers have been removed and replaced by a code, but it remains possible to re-identify a specific individual by, for example, using the code or linking different data sets.
		- * How will the data be made re-identifiable (e.g. using a unique participant code)?
			* Confirm that a separate password-protected file will contain the participant code and corresponding participant’s potentially re-identifiable identifying information.
	+ Non-identifiable: data which have never been labelled with individual identifiers for the purposes of research.
		- * Who will obtain the identifiable data and make it re- or non-identifiable?

*Reference: Health Informatics Services (2021) “De-Identification and Anonymisation of Data Guideline” v1.*

<https://metrosouth.health.qld.gov.au/sites/default/files/content/de-identification-and-anonymisation-of-data-guideline.pdf>

The [Queensland Government data retention guidelines](https://www.forgov.qld.gov.au/information-and-communication-technology/recordkeeping-and-information-management/recordkeeping/disposal-of-records/search-for-a-retention-and-disposal-schedule/general-retention-and-disposal-schedule-grds) state research data should be retained for 25 years from publication for clinical interventional trials, for paediatric studies it must be kept until the youngest participant has turned 25 years old, permanently for Phase 1 or genetic focused research, and 7 years for all other types of research. Confirm that the data will be securely disposed of at the end of the retention period.

*Reference: Health Sector (Corporate records) Retention and Disposal Schedule (2023)*

#### 9.2 Data monitoring

Indicate whether there is an independent Data Safety Monitoring Board (DSMB) to monitor the progress of a study and to make recommendations on whether to continue, modify or stop the study for safety or ethical reasons. Include information on the personnel and processes of the DSMB, any stopping and discontinuation rules which have been pre-specified.

Please note that safety reporting to the MSH HREC is in accordance with the safety monitoring and reporting in clinical trials involving therapeutic goods (nhmrc.gov.au).

#### 9.3 Monitoring, auditing and inspecting

Provide information regarding the trial-related monitoring, quality audits, and inspections by government regulatory authorities, the Sponsor or its representative(s) of all trial-related documents (eg source documents, regulatory documents, data collection instruments, case report forms. State that the PI will ensure that the trial monitor or any other compliance or QA officer is given access to all trial-related documents and trial-related facilities.

### 10. Ethical considerations

#### 10.1 Research conduct

The safety of research participants is foremost. State that the research project will be conducted in full conformance with principles of the World Medical Association Declaration of Helsinki, Good Clinical Practice (ICH-GCP) and within the laws and regulations of the country in which the research is conducted. State that the study will be conducted in compliance with the protocol. Consider and articulate how the quality of the technical aspects have been assured, the potential risks and proposed benefits of the research procedures, the priority of the participants’ interests over those of science or of society and how those interests will be safeguarded, responsibility for liability of injury during the research, how the participants are informed of the research, and how they give voluntary consent to participate.

Declaration of interests for researchers should be included in this section.

#### 10.2 Participant confidentiality

This section addresses the confidentiality and privacy of patient’s personal data and how it will be protected in accordance with the relevant national data protection and confidentiality laws/acts, as applicable.

Please identify:

* What protected health information will be collected from patients
* Who will have access to that information and why
* Who will use or disclose that information
* What measures are in place to protect participant confidentiality (eg only a unique study number and initials will identify participants together with the date of birth, will be used in the database for participant identification, participant names or addresses will not be entered in the database, no material bearing a participant’s name will be shared with external stakeholders.

#### 10.3 Dissemination of research results

Outline plans to communicate research results/outcomes to participants, health care professionals and the public, including any publication restrictions. Confirm that no individually identifiable data will be included in the final research deliverables.

### 11. Risk assessment

The researcher will assess the level of risk for participants involved in this study to determine if this study meets the criteria to be submitted for review as a lower risk or higher risk study.

A risk is a potential for harm or discomfort. It involves:

* the likelihood that a harm or discomfort will occur, and
* the severity or magnitude of the harm or discomfort, including their consequences.

While discussion of the risk of harm or discomfort applies to risk to an individual research participant, it can also apply to groups or communities as well as to non-participants such as family members. Risk can be associated with the conduct of research or the proposed outcomes of the research.

Risk in research exists on a continuum with the risk profile of an individual research project falling somewhere along this continuum.

Low risk research describes research, including some types of clinical trials, in which the only foreseeable risk is no greater than discomfort. Accordingly, research in which the risk for participants or others is greater than discomfort is not low risk research. Research in this category is considered higher risk research and carries risk of harm.

*Reference: National Statement on Ethical Conduct in Human Research (2023). The National Health and Medical Research Council, the Australian Research Council and Universities Australia. Commonwealth of Australia, Canberra*

Refer to [Apply for ethics approval | Metro South Health](https://www.metrosouth.health.qld.gov.au/research/research-ethics-and-governance/apply-for-ethics-approval) for information and training which will help you understand, assess and plan for risks in your research project.

### 12. Outcomes and significance

Reiterate the potential benefits of answering the research question and conducting the research. This section restates the justification for the research in terms of the anticipated results. It may be important to specify the implications of the potential results and how the results of this research may inform future research or policy makers.

### 13. Study documentation and storage

In this section outline that the PI will maintain a list of appropriately qualified persons to whom he/she has delegated trial duties on the delegation log. All persons authorised to make entries and/or corrections on the study material are to be included on this document. All entries in the databases are to be supported by source documentation where appropriate. Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient’s data are obtained. These can include medical records, clinical and office charts, laboratory, pharmacy records, diaries, and correspondence.

Include information to indicate that a comprehensive filing system of all trial-related (essential) documentation, will be maintained and will be suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities.

The documents listed above must be retained by the PI for as long as needed to comply with national and international regulations (see Health-Sector-Clinical-Records-Retention-and-Disposal-Schedule.pdf.

### 14. Appendices

List additional study tools such as screening/enrolment logs, case report forms (CRFs), drug accountability logs, biological specimen logs, concomitant medications logs etc. Please do not include the PICF, study surveys/interview questions or other study documentation as an appendix in this protocol document. Instead, these documents should be uploaded separately, with separate version control.

### 15. References

Include references to support your protocol (limit to 20-25 references).