Purpose

This document explains what must be included in the 'protocol', or project plan, that must accompany any submission and enables the Committee to complete its review. There are several templates available for the protocol, which must describe the objective(s), background, rationale, study design, methodology, statistical considerations, and overall support for the study.

Guidance

Protocol Title

The title should be brief and self-explanatory and must appear on all information sheets and consent forms related to the study. The protocol also requires a reference number (the principal investigator's reference number for the study).

Study registration

If the study is to be registered, the protocol should include the trial identifier and registry name.

Investigators and qualifications

The protocol must include the address and contact telephone number of the Principal Investigator and any Co-Investigators. Applications for multi-centre trials must include the name of the Principal Investigator of each participating institution.

Sponsor information

A sponsored study must include the name and address of the sponsor.

Site location

The location where the study is to be conducted should be listed, including site name, address and contact phone number. Applications for multi-centre trials should list all sites requiring Bellberry HREC review.

Purpose of study

The protocol must explain in no more than 10 lines why the study is being undertaken, e.g. "to test the hypothesis that Drug A is superior to Drug B in the treatment of X Disease".

Background information

- A succinct review of literature should allow the Committee to appreciate the importance of the proposed project (no more than one page).
- Name and description of the investigational product(s).
- A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- Summary of the known and potential risks and benefits, if any, to human participants.
- Description of and justification for the route of administration, dosage, dosage regimen and treatment period(s).
- A statement that the trial will be documented in compliance with the protocol, GCP and the applicable regulatory requirements.
- Description of the population to be studied.
- References to literature and data that are relevant to the trial and that provide background for the trial.

Hypothesis/aims and objectives

The protocol should briefly and clearly outline the hypothesis and predictions. The hypothesis must be testable and specific enough to be investigated. If using Objectives, these must be detailed and precise.

In the early phases of empirical studies where there may not be sufficient information to justify a rigorous hypothesis and where the intent is to assess the interplay of several variables, the possible interplay must be defined, and the problem statement formulated as precisely as possible.

Methodology

The protocol must include:

- A detailed description of the study's participants, expected duration of participation, and a description of the sequence and duration of all trial periods, including any follow-up
- a description of any procedures being performed for diagnostic or treatment purposes
- A description of the stopping rules or discontinuation criteria for individual participants, parts of the trial and entire trial. *A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. (ICH GCP 4.3.1) During and following participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware (ICH GCP 4.3.2)
- accountability procedures for the investigational product(s), including any placebo(s) and comparator(s)
- Maintenance of trial treatment randomisation codes and procedures for breaking codes. *The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s). (ICH GCP 4.7)
- a detailed trial description of the trial's instrumentation and design (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and states
- a specific statement of primary and/or secondary endpoints
- what will be measured and how data will be collected
- statistical justification of participant numbers using a power calculation. If an active-controlled trial seeking to define non-inferiority, the margin of non-inferiority specified must be justified.
- A description of any pilot study
- definitions of possibly unfamiliar concepts and terminology
- how principles of 'informed consent' and confidentiality are addressed.

Study procedures

Describe what is going to happen during the study. This should include how participants will be recruited, what tools will be used to collect and analyse the study information or data, what the participants will be expected to do, and what will happen to them.

- Ensuring that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, suitable equipment, and space.
- Ensure that research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study.

The protocol should provide adequate detail to allow the HREC to assess these responsibilities.

Participant considerations

It should be noted that during and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial. (ICH GCP 4.3.2)

The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding.

A qualified physician (or dentist, when appropriate), who is a researcher or a co- researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions.

Researchers inform participants when medical care is needed for other illnesses of which the researchers become aware.

Selection of volunteers/participants

Researchers should note that volunteers involved in research projects must remain true 'volunteers,' i.e. the participation in the research is the result of choice made by the participant. A participant cannot be induced to stay in a study for financial or another reward.

Participants who are employees or students within a researcher's department should be excluded from any research protocols conducted by the Principal Investigator.

It should be ascertained whether the participant is insured or uninsured. While this factor should not influence their selection, care should be taken if it is foreseeable that the participant may require hospitalisation. In that event, it should be clearly stated who will pay for any necessary treatment and any support services needed. Refer to the National Statement on Ethical Conduct in Human Research (2023).

Advertising

The protocol is required to include information on the advertising relating to the research project and its mode of communication to participants. If utilised, a Social Media Plan is also to be submitted.

Data handling and record-keeping

This should be set out in some detail, including the methods to be used to ensure that information is not accessible to unauthorised persons. Information is also required regarding:

- How data will be collected.
- Who will have access to the data.
- How Privacy and Confidentiality will be managed and maintained.

If participants will be exposed to radiation above the standard of care at any research site, the protocol must include a Radiation Safety Report. The attached PICFs must also include a statement informing participants of the radiation risks.

Inclusion criteria

The protocol must explain how the following will be documented (as applicable):

- sex and/or age range

- disease status and severity
- the patient's ability to give informed consent
- the patient's ability to co-operate sufficiently to allow the proposed study to progress
- allowable concomitant medications.

Exclusion criteria

The protocol must include any criteria relating to:

- the age range
- whether women of childbearing age are to be excluded and/or acceptable contraceptive measures
- the development of serious, adverse events/reactions (to be defined) and any associated decisions
- medications that are not allowed
- previous sensitivity to medications which might exclude patients.

Withdrawal criteria

The protocol must indicate how the following will be addressed:

- when and how participants will be withdrawn
- the type and timing of the data to be collected for withdrawn participants
- whether and how participants will be replaced
- the follow-up for withdrawn participants
- patient request
- how any exclusion criteria were developed
- a patient's noncompliance with the study protocol
- the development of any serious adverse drug reaction.

Other participants

For Research involving people in dependent or unequal relationships, children and young people, people with intellectual or mental impairment, people highly dependent on medical care or research involving Aboriginal and Torres Strait Islander people please refer to Chapter 4 of the National Statement on Ethical Conduct in Human Research (2023).

Efficacy

The protocol must explain the efficacy of the drug or the research procedure. This information will assist Committee Members in their deliberations of the benefits to be gained versus any risks or potential harm.

Investigational or unlicensed test articles

The protocol must:

- specify how investigational or unlicensed test articles will be manufactured, handled and stored according to applicable good manufacturing practice (GMP). Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.

- state how the Investigator, pharmacist, or other designated individual will record:
    - dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants

- the product's delivery to the trial site
- the inventory at the site
- the use by each participant
- the return of the product to the sponsor or otherwise dispose of unused products.

Additionally, investigators should maintain records that document adequately that the participants are provided with the doses specified by the protocol and reconcile all investigational products received from the Sponsor.

Amendments

The Investigator (s) should inform the HREC, and seek its approval, of amendments to the protocol including changes that:

- Are proposed or are undertaken without prior HREC approval in order to eliminate immediate risks to participants;
- May increase the risks to participants; or
- Significantly affect the conduct of the trial.

Investigators must also inform the HREC as soon as possible of any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol.

Provisions for data monitoring/safety

Describe the arrangements for monitoring data to ensure participant safety.

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial (ICH GCP 1.25).

The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding.

A qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions.

Researchers inform participants when medical care is needed for other illnesses, of which the researchers become aware.

Data analysis and reporting of results

This should be set out in some detail, including the methods to be used to ensure that information is not accessible to unauthorised persons and that wherever possible an indication is given of how results will be disseminated to the scientific community.

Time frames

Date of commencement, as well as the study time frames, should be stated.

Ethics

Describe the ethical considerations relating to the trial with reference to the National Statement on Ethical Conduct in Human Research (2023), and any other relevant guidance. Include a statement naming the HREC that is providing the review and whether the study has been submitted to other Ethics Committees. Written evidence of any decisions made by other Committees must be attached to the application.

Direct access to source data/documents

Specify that the investigator(s)/institution(s) will permit study-related monitoring, audits, HREC review, and regulatory inspection(s), providing direct access to source data/documents.

Financing and insurance

The protocol must describe how the study will be funded and what insurance is in place.

Publication policy

The protocol must outline the publication policy and plan and outline any information that will be provided to participants about publication.

Formatting

It is recommended that the protocol include the study title, date, version number and page number in a footer. This will enable the reviewers to identify items for discussion and assists in document control.

Other relevant information

The protocol may include other information such as letters of support from heads of university departments or other institutions.

Student research

The protocol for any research by a student must include a letter of support from the student's supervisor, stating that they have reviewed the design and approve the study. A letter from the relevant university is also required, stating that approval is granted for the relevant Bellberry HREC to undertake a review.

References

National Statement on Ethical Conduct in Human Research (2023)
Guideline for Good Clinical Practice
TGA - GMP Good Manufacturing Practice
BA G4 Protocol Development - Non-Clinical
BA G5 PICF Development Guide