Northern Health

Northern Health Research
How to write:

- **Protocol**
- **Investigator's Brochure**
- **Patient Information Consent Form**

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Acknowledgements

This document is based on sections within the VMIA Standard Operating Procedures to achieve Good Clinical Practice in Australian Research (2007) that refer to writing protocols, Investigator's Brochure, and patient information consent forms. It has been adapted to meet current ICH-GCP guidelines and Northern Health requirements.

Disclaimer: The following detail is no way exhaustive and is provided as a guide only. For further guidance contact the Northern Health Office of Research - ethics@nh.org.au

Protocol content and Design

The detail below includes information for therapeutic interventions, the terms should be adapted appropriately and followed where applicable. All elements may not be applicable for non-interventional research.

For interventional Research that require a CTN/CTX or if the project is considered to be of high risk, use the Northern Health high risk protocol template.

For research that does not require a CTN/CTX or is low risk, use the Northern Health low risk protocol template

General Information to be included in the protocol:

- Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).

Note: If the project is only being conducted at Northern Health and there is no collaboration with external parties (e.g. universities, networks, other organisations) then Northern Health is the sponsor. If the project is collaborative then it needs to be ascertained which party is the sponsor.

- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

- 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 conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- 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.
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Research Objectives and Purpose

- A detailed description of the objectives and the purpose of the trial.

Research Design

- The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

  a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

  b. A description of the type/design of trial to be conducted (e.g. double-blind, placebo controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

- ·A description of the measures taken to minimize/avoid bias, including:

  a. Randomization.

  b. Blinding.

- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

- Maintenance of trial treatment randomization codes and procedures for breaking codes.

- The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

Risk Assessment

- Complete a Risk Assessment, including risk identification, evaluation, control, communication, review and reporting of risks of the investigational medicinal product and the risks associated with trial conduct, design and methods. Refer to NHMRC guidelines.
- The risk assessment must address all risks of the protocol and the nominated mitigation strategies.

Monitoring Plan

- Prepare a monitoring plan based on the risk assessment and protocol. Refer to Section 9 of the NH Research Operating Procedure (link)

Selection and Withdrawal of participants

- Participant inclusion criteria.

- Participant exclusion criteria.

- Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

  a. When and how to withdraw participants from the trial/ investigational product treatment.

  b. The type and timing of the data to be collected for withdrawn participants.

  c. Whether and how participants are to be replaced.

d. The follow-up for participants withdrawn from investigational product treatment/trial treatment.

Treatment of Participants

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- Procedures for monitoring participant compliance.

Assessment of Efficacy

- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

Assessment of Safety

- Specification of safety parameters.
- The methods and timing for assessing, recording, and analysing safety parameters.
- Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- The type and duration of the follow-up of participants after adverse events.

Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
- The number of participants planned to be enrolled. In multicentre trials, the numbers of enrolled participants projected for each trial site should be specified.
- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- The level of significance to be used.
- Criteria for the termination of the trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate.
- The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

Direct Access to Source Data/Documents

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, HREC review, and regulatory inspection(s), providing direct access to source data/documents.

Ethics

- Description of ethical considerations relating to the trial. Ethical submission plan as be entered here if not included elsewhere e.g. time line of study.

Data Handling and Record Keeping

- Data storage and protection, data collection and data destruction plan. Destruction plan should be as per the National Statement on Ethical Conduct in Human Research 2007 (updated 2018) and the Public Record Office Victoria guidelines (see NH Research Digitization activity plan on PROMPT)

Financing and Insurance

- Financing and insurance if not addressed in a separate agreement or elsewhere.

Publication Plan

- Publication plan, if not addressed in a separate agreement. Include timeline if not included elsewhere.

Supplements

- Any appendices or additional information

Investigator brochure content and design

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants.

Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study participants during the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

As part of their written application to the HREC, provide the HREC with a current copy of the Investigator's Brochure and if updated during the trial, the Investigator/institution should supply a copy to the HREC in accordance with that HRECs procedures.

In the case of a marketed product being studied, it may be acceptable to use the Product Information as a substitute for the Investigational Brochure. The ICH-GCP E6 R2 (9NOV2016) guidelines (section 7.1, page 38) state:

"If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e, a new indication), an IB specific to that new use should be prepared."

The Investigator Brochure should provide the following information:

Title Page

- This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

Confidentiality Statement

- The sponsor may wish to include a statement instructing the investigator/ recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the HREC.

Contents of the Investigator's Brochure

- The IB should contain the following sections, each with literature references where appropriate:

Table of Contents

Summary

- A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product or device.

Introduction

- A brief introductory statement should be provided that contains:
- The chemical name (and generic and trade name(s) when approved) of the investigational product(s).
- All active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages).
- The rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s).
- The introductory statement should provide the general approach to be followed in evaluating the investigational product or device.

Physical, Chemical, and Pharmaceutical Properties and Formulation

- A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.
- To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.
- Any structural similarities to other known compounds should be mentioned.

Non-Clinical Studies

Introduction

The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form.

- This summary should address:

a. The methodology used;

b. The results, and a discussion of the relevance of the findings to the investigated therapeutic; and

c. The possible unfavourable and unintended effects in humans.

- The information provided may include the following, as appropriate, if known/available:

a. species tested

b. number and sex of animals in each group

c. unit dose (e.g., milligram/kilogram (mg/kg))

d. dose interval

e. route of administration

f. duration of dosing

g. information on systemic distribution

h. duration of post-exposure follow-up

i. results, including the following aspects:

j. nature and frequency of pharmacological or toxic effects

k. severity or intensity of pharmacological or toxic effects

l. time to onset of effects

m. reversibility of effects

n. duration of effects

o. dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans.

If applicable, the effective and non-toxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed).

The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

Non-clinical Pharmacology

- A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included.

- Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

Pharmacokinetics and Product Metabolism in Animals

- A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given.

- The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

Toxicology

- A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

a. Single dose

b. Repeated dose

c. Carcinogenicity

d. special studies (e.g. irritancy and sensitisation)

e. Reproductive toxicity

f. Genotoxicity (mutagenicity)

Effects in Humans

Introduction

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities:

- Where possible, a summary of each completed clinical trial should be provided.

- Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

a. Pharmacokinetics (including metabolism, as appropriate, and absorption;

b. Plasma protein binding, distribution, and elimination);

c. Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form;

d. Population subgroups (e.g., gender, age, and impaired organ function);

e. Interactions (e.g., product-product interactions and effects of food); and

f. Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

Safety and Efficacy

- A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients).

- The implications of this information should be discussed.
- In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data.
- Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful.
- Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.
- The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

Marketing Experience

- The IB should identify countries where the investigational product has been marketed or approved.
- Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions).
- The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

Summary of Data and Guidance for the Investigator

This section should provide a brief summary of the fundamental requirements or information available for a particular investigational product in order to allow a quick reference for the investigator. Summaries included in this section should not replace the information to be contained in the main body of the document.

Special emphasis should be placed on provision of quick reference safety aspects in order to find information as efficiently as possible.

Patient information consent form

For single site research the master version is usually the only version however for multisite research there should be a master version which is devoid of any logo's and adapted to include site specific space for any barcodes, spaces for labels etc. by the individual sites. The master version needs ethics approval and then local governance approval for the site specific versions. Northern Health Governance will require copies of any master and local version. All amended versions submitted to either the ethics committee or research governance should be tracked so changes can clearly be seen.

Health.vic PICF templates (section 5)

Northern Health template (includes branding and bar code)

Further information regarding PICF templates can be found on the DHHS website or the NHMRC website.

The Investigator(s) should:

- Ensure the written informed consent form and any other written information provided to participants include explanations of the following:

  a) That the research/trial involves research.

  b) The purpose of the research/trial.

  c) The research/trial treatment(s) and the probability for random assignment to each treatment.

  d) The research/trial procedures to be followed, including all invasive procedures.

  e) The participant's responsibilities.

  f) Those aspects of the research/trial that are experimental.

  g) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.

  h) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.

  i) The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.

  j) The compensation and/or treatment available to the participant in the event of research/trial related injury.

  k) The anticipated prorated payment, if any, to the participant for participating in the research/trial.

  l) The anticipated expenses, if any, to the participant for participating in the research/trial.

  m) That the participant's participation in the research/trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.

  n) That the monitor(s), the auditor(s), the HREC, and the regulatory authority(ies) will be granted direct access to the participant's original Health Records for verification of research/clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's medical treatment decision maker is authorising such access.

  o) That records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the participant’s identity will remain confidential.

  p) That the participant or the participant's medical treatment decision maker will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the research/trial.

  q) The person(s) to contact for further information regarding the research/trial and the rights of trial participants, and whom to contact in the event of trial-related injury.

  r) The foreseeable circumstances and/or reasons under which the participant's participation in the research/trial may be terminated.

  s) The expected duration of the participant's participation in the research/trial.

t) The approximate number of participants involved in the research/trial.

u) If interpreter services are considered or required, an additional signature box should be added to allow for interpreter signatures. At Northern Health the interpreters cannot be a witness.