Research Ethics and Governance – Protocol and Investigational Brochure Content, Design, Amendments and Compliance Procedure

TARGET AUDIENCE and SETTING

Principal Investigator and all staff conducting research.

PURPOSE

Research plays a critical and beneficial role in our society. Those conducting research enter into a social contract requiring them to be responsible and accountable for their activities. The right to conduct research is a privilege which is conditional on the rights and wellbeing of human participants, other living creatures and the good of the community being put foremost, in conformity with long established broad principles guiding research practice.

1 In Australia, any individual or organisation conducting research involving humans is required to consider the ethical aspects of their research.
2 The broad principles that guide research have long been established. Central to these are the maintenance of high ethical standards, and validity and accuracy in the collection and reporting of data. The responsibility of the research community to the public and to itself is acknowledged. This responsibility is particularly important where professional practice or public policy may be defined or modified in the light of research findings.

This procedure has been developed in accordance with the National Statement on Ethical Conduct in Human Research (2018), the Australian code for the Responsible Conduct of Research (2018) and the International Council on Harmonisation Guidance for Good Clinical Practice E6(R2) (2016)

PRECAUTIONS/CONTRAINDICATIONS

All researchers at Monash Health must conduct research in the manner indicated in the Human Research Policy and the Research Governance Procedure.

STANDARD REQUIREMENTS

All investigators must abide by relevant legislation, the Australian code for the responsible conduct of research (NHMRC, 2018), the National Statement on Ethical Conduct in Human Research (NHMRC 2018), the Safety monitoring and reporting in clinical trials involving therapeutic goods (NHMRC 2016) and the International Council on Harmonisation Guidance for Good Clinical Practice E6(R2) (2016)

PROCEDURE

Protocol content and design

Where the investigator is responsible for the protocol design and / or is the sponsor, they must (where applicable) provide the following information in the protocol:

General Information

- 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).
- 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 subjects.
- 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, Good Clinical Practice 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

Trial Objectives and Purpose

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

Trial 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) Randomisation.
  b) Blinding.
- A description of the trial treatment(s) and the dosage and dosage regime 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 subjects, 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 Case Report Forms (i.e. no prior written or electronic record of data), and to be considered to be source data.

Selection and Withdrawal of subjects

- Subject inclusion criteria.
- Subject exclusion criteria
- Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
  a) When and how to withdraw subjects from the trial/investigational product treatment.
  b) The type and timing of the data to be collected for withdrawn subjects.
  c) Whether and how subjects are to be replaced.
  d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

Treatment of subjects

- 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) for subjects 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 subject 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 subjects after adverse events.

Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
- The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects 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 subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

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, Human Research Ethics Committee review, and regulatory inspection(s), providing direct access to source data/documents.

Quality Control and Quality Assurance

Ethics

- Description of ethical considerations relating to the trial.

Data Handling and Record Keeping

Financing and Insurance

- Financing and Insurance if not addressed in a separate agreement.

Publication Policy

- Publication policy, if not addressed in a separate agreement.

Amendments to the Protocol.

The investigator(s) should:

- Inform the Human Research Ethics Committee, and seek its approval, of amendments to the protocol including amendments that:
  a) Are proposed or undertaken without prior Human Research Ethics Committee approval in order to eliminate immediate risks to participants;
  b) May increase the risks to participants; or
  c) Significantly affect the conduct of the trial.
- Inform the Human Research Ethics Committee 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 protocol. Notification to the Human Research Ethics Committee is site specific and the investigator should be familiar with the processes of their ethics committee.

Protocol Compliance.

The investigator(s) should:

- Conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval / favourable opinion by the Human Research Ethics Committee and Site Authorisation/Governance approval.
- Along with the sponsor, sign the protocol, or an alternative contract, to confirm agreement.
- Not implement any deviation from, or changes to the protocol, without agreement by the sponsor and prior review and documented approval / favourable opinion from the Human Research Ethics Committee of an amendment and Site Authorisation/Governance approval,

except where necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).

- Document and explain any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to the protocol to eliminate an immediate hazard(s) to trial participants without prior Human Research Ethics Committee and Site Authorisation/Governance approval. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
- To the Human Research Ethics Committee for review and approval and subsequent Site Authorisation/Governance approval,
- To the sponsor for agreement, and, if required,
- To the Regulatory authority(ies).

Investigational brochure content and design.

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 Investigator Brochure as a confidential document for the sole information and use of the investigator's team and the Human Research Ethics Committee.

Contents of the Investigator's Brochure

- The Investigator's Brochure 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

- 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)
  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:
    - Nature and frequency of pharmacological or toxic effects
    - Severity or intensity of pharmacological or toxic effects
    - Time to onset of effects
    - Reversibility of effects
    - Duration of effects
    - 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 milligram/kilogram 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.

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 Investigator Brochure 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 Investigator Brochure 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 Investigator Brochure 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.

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

- A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information of 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).

KEY STANDARDS, GUIDELINES OR LEGISLATION (optional)

Australian code for the responsible conduct of research (NHMRC, 2018),

National Statement on Ethical Conduct in Human Research (NHMRC 2018)

Safety monitoring and reporting in clinical trials involving therapeutic goods (NHMRC 2016)

International Council on Harmonisation Guidance for Good Clinical Practice E6(R2) (2016)

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KEYWORDS

Protocol, Investigator Brochure.

Document Governance	
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