University Hospitals Bristol NHS
NHS Foundation Trust

Research Guidance sheet No.1d
Guide to writing a Protocol for a non-IMP randomised trial

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The aim of this guide is to help researchers with the content and structure of protocols for randomised trials not involving the use of an Investigational Medicinal Product (IMP). It indicates the information that should generally be included in a protocol and has been constructed to cover important methodological considerations and requirements specified under Good Clinical Practice (GCP).

Advice of the methodological aspects of designing a research study and writing a protocol can be obtained from the Research Design Service, 0117 342 0233.

Where University Hospitals Bristol (UH Bristol) is the sponsor of the research study suggested standard wording is available for the sections of the protocol marked with a *, please refer to Research Guidance Sheet No. 3b available from the Research website.

General Information

Title

- It is useful to specify both a full title and short title.
- The full title should include summary study design, nature of the treatment, comparators, indication, patient population and setting.
- The short title is a summary of this.
- The titles specified must be consistent across all documents relevant to the trial.

Names (titles), roles and contact details of:

- Name and address of sponsor(s).*
- Name, title, address and telephone number of the Chief Investigator.
- Name, address, title and telephone number of all other Investigator(s).
- Address and telephone number of study site(s), including extension numbers, where relevant.
- Name, title, address and telephone number of the qualified physician who is responsible for all study related medical decisions (if different to the investigator).
- Names and addresses of the clinical laboratories and other medical and/or technical departments and/or institutions involved in the study.

Protocol details

- Version number and date, e.g. v2 12.09.2004.
- Final/draft.

List of abbreviations and definitions

Background

The detail given in this section should be backed up by a full literature review and should make reference to relevant papers, previous clinical experience and pilot work.
This section should include:

- A clear explanation of the main research question i.e. the hypothesis to be tested.
- Detailed justification for the trial including:
  - Explanation of why the study is appropriate, potential benefits to patients/health.
  - Service, relevance to current policies and priorities.
  - Description of the indication, its diagnosis, incidence, current treatments and their limitations.
  - Description of the treatment under investigation including reference to any previous evidence of its usefulness.
  - A statement of what would be a worthwhile improvement in study outcomes.
  - What evidence there is that the treatment under investigation may achieve this?

Aims and Objectives

- State the purpose of performing the study (e.g. student project, commercial/non commercial trial, licensing).
- State the primary and secondary objectives.

Study Design

The scientific integrity of a study and the credibility of results obtained are largely dependent upon the study design. A description of the study design should include the following:

- A description of the type/design of the study, e.g. double-blind, placebo controlled, parallel design etc.
- Summary of treatments being compared with reasons for choice of comparison group.
- The expected length of time for which each subject will participate in the study for and the sequence and duration of all study periods.
- Description of all procedures (sequentially) to be performed, identifying what is standard and non-standard care where possible.
- The criteria for discontinuation of parts of the study or the entire study.
- A schematic diagram of the trial design, procedures and stages (can be in a form of a table).

Primary and Secondary Endpoints

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

General information

- Summary of known and potential risks and benefits to human subjects.

Use within the trial

- Detail of who will be performing the treatments.
- Is the treatment invasive/does it involve radioactive substances?
- Arrangements for continuation of treatment for study patients after the end of the trial.

Subject selection

- Source of subjects (where they come from and why this group is appropriate).
- Number of centres involved.
- Expected number of eligible participants available per year and proportion of these expected to agree to the trial.

Inclusion Criteria

- List the inclusion criteria defining who is eligible for the study.

Exclusion Criteria

- List the exclusion criteria. Consider contra-indications to trial treatments, incompatible concurrent treatments, recent involvement in other research.

Subject recruitment

- Details of recruitment process including
  - Method of recruitment (e.g. via adverts, clinics).
  - Payment of participants.
  - Details of procedures, tests, and screenings carried out to assess trial suitability.
  - Provision of patient information sheet (include as appendix).
  - Gaining patient consent; how consent will be obtained, who will gain consent, whether a witness will be present, how long the subject will have to decide, the arrangements for non-English speakers and special groups (e.g. mentally ill, children, those suffering from dementia).
  - Detail of enrolment procedure.

Randomisation

- Including detail and justification for each of the following:
  - Patient/cluster randomised design (randomising individuals or groups (e.g. general practices, wards).
  - Type of randomisation to be used - simple, block, stratified, minimisation.

- If stratified include definition of stratification variables.
- If blocked define block sizes and whether these will vary.
- Use of equal or unequal allocation between treatment arms.
- Information regarding how randomisation will be implemented (including who, where, how).
- Approach to be used to conceal allocation (e.g. sealed envelopes, telephone central allocation office, computerised randomisation etc).

Blinding and other measures taken to avoid bias

- Detail and justification for:
  - Measurements to be blinded.
  - Level of blinding to be used – e.g. blinding of participants/investigators/assessors (i.e. double blind, single blind, open).
  - How blinding will be implemented.
- Other measures taken to minimise/avoid bias.

Subject compliance

- Recording of patient compliance information (what will be recorded, when and where).
- Detail of follow-up of non-compliant subjects.

Withdrawal of Subjects

- Subject withdrawal criteria and procedures identifying:
  - When and how to withdraw subjects.
  - The type and timing of any data to be collected for withdrawn subjects.
  - Whether subject should be replaced and if so the methods for doing this.
  - The follow up procedures for withdrawn subjects.

Data collection

- Provide a detailed list of all data (outcome variables, explanatory variables etc) to be collected, with each description including:
  - Source of the data (e.g. patient questionnaires, patient notes, electronic data, procedure).
  - Time point for collection (baseline, during treatment, at follow-up point).
  - Who will collect the data?
  - Why the data are being collected (e.g. baseline comparison data, main outcome, important prognostic/explanatory variable).
  - Whether the data are gathered using a standardised tool (e.g. McGill pain score), by means of a procedure (in which case full details should be supplied). If a non standard tool is to be used, detail on reliability and validity should be given.
  - What form the data will take (e.g. binary, continuous (numeric), time to event).
- Describe methods used to maximise completeness of data (e.g. telephoning patients who have not returned postal questionnaires).
- Include data collection forms as appendices.
- Plans for archiving at the end of the study and details of where documentation will be archived.

Data handling and record keeping

- State who is responsible for data collection, recording and quality.
- Describe procedures for data collection and recording (software to be used, location of the data etc).
- Detail methods implemented to ensure validity and quality of data (e.g. double entry, cross validation etc).
- Describe procedures for security / storage of data.
- Describe procedures for retention of source data including the duration and location*.
- Include statement on adherence to Data Protection Act 1998*.

Access to Source Data

- Include statement specifying that the Investigator(s)/Institution will permit monitoring, audits, REC and review and provide direct access to source data and documents.

Statistical analysis

- Detail of the variables to be used to assess baseline comparability of the randomised groups and how these will be reported (e.g. means, standard deviations, medians, proportions).
- Detailed plans for statistical analyses of primary and secondary outcomes including:
  - Summary measures to be reported.
  - Method of analysis (justified with consideration of assumptions of the method, structure of the data (e.g. unpaired, paired, hierarchical) etc).
  - Plans for handling missing data, non-compliers and withdrawals in analysis.
  - Plans for predefined subgroup analyses.
- Statement regarding use of intention to treat (ITT) analysis.
- Detail of approach for interim analyses and criteria for early termination of the trial.
- Detail of any non-statistical methods that might be used (e.g. qualitative methods).
- Statement of who will carry out analyses and at what point.

Sample size calculation

- Study sample size, for multi-centre studies the projected sample size for each site.
  - Estimates used (e.g. size of the clinically important effect to be detected, drop out / non compliance rates).
  - Assumptions made (e.g. assumptions of Normality).
  - Relevant justification (i.e. appropriate references or clinical arguments).
  - Allowance for planned subgroup analyses.
- The power of the study.
- The level of significance to be used.
- Statistical criteria for terminating the study.
- Procedures for accounting for missing, unused or counterfeit data.
- Procedures for reporting any deviations from the statistical plan.
- The selection of subjects to be used in the statistical analyses, e.g. all eligible subjects, all dosed subjects, all randomised subjects etc.
- An estimate of the recruitment period for the trial (calculated based on the expected number of eligible and recruited participants available per year) with justification that the required sample size will be attainable in practice.

Safety Assessments

- Specification of safety parameters and the methods for timing, assessing, recording and analysing safety parameters.
- Definition of serious adverse events for the trial that are expected e.g. hospitalisation in terminally ill patients.
- State which serious adverse events will not be reported.
- Detail the procedures that will be followed in the event of adverse events in the trial*
  - Who has what responsibility
- Describe the type and duration of follow up of subjects required after an adverse event/adverse reaction.

Stopping/discontinuation rules and breaking of randomisation code

- Define completion and premature discontinuation of the trial.
- Describe procedure regarding decisions on discontinuation of the trial (e.g. interim analyses, role of data monitoring committee).
- State documentation to be completed if part/all of the trial is discontinued.
- Describe circumstances under which the randomisation codes may need to be broken and the procedure for this.

Monitoring

- Arrangements for monitoring/auditing conduct of the research.*
- Detail of any other steps taken to ensure quality of research.
- Use and role of data monitoring groups and steering groups etc.

Ethical considerations

- Description of ethical issues for the trial.

Ethics and R&D approval

- A statement that the study will be conducted in accordance with approvals from relevant groups (e.g. MREC, Trust(s) and other specialist approvals e.g. ARSAC).*

Research Governance

- A statement that the study will be conducted in compliance with the Research Governance Framework for Health and Social Care, the Medicine for Human Use (Clinical Trials) Regulation 2004 and ICH GCP.*

Finance

- Provide any details of the financial arrangements for the study if not assessed in a different document.
- Provide details of any payments to be made to participants.

Indemnity

- Describe arrangements for providing cover for non-negligent and negligent harm.*

Reporting and dissemination

- Detail of plans for publicising the results of the study.

Tables, figures and references

Appendices

For example:

- Patient information sheet.
- Patient consent form.
- GP letter.
- Data collection forms/Case Report Forms
- Adverse Event/Serious Adverse Event reporting forms