

The Leeds Teaching Hospitals NHS Trust
Research & Development Department

WRITING A RESEARCH PROTOCOL
GUIDANCE NOTES FOR RESEARCHERS

Introduction

A protocol is an essential starting point for high quality research and all research studies must be protocol based.

R&D and Research Ethics Committee approval will only be granted to studies with a protocol.

A protocol gives written evidence for the necessity and feasibility of a research study and also provides a detailed plan of investigation.

It allows the peer reviewer, Research Ethics Committee or statistical advisor to make a judgement about the scientific aspects of the study. It can be used as a reference to answer any questions, which are not immediately apparent from the R&D and REC application forms.

The protocol is also used by the researchers as a reference tool throughout the duration of the study.

Contents of a Protocol

A protocol should include:

- a **front page** with full title, a protocol number (ISRCTN, EudraCT number or R&D number) and a version number & date. The protocol that is submitted to ethics should ideally be numbered version 1.0 and dated with the date of finalisation of the protocol. If any protocol amendments are made, then the protocol version number and date must be updated accordingly.
- A **content page** detailing all relevant section / sub-sections and page numbers.
- a **signature page** which senior members of the research team sign / date to confirm that the version has been approved and is final. This should also apply to protocol amendments.
- study **team contact** details of the chief / principle investigators, research nurse / fellow, trial co-ordinators and statisticians.
- a **summary** of the main study issues, which can act as reference point and should include the: title, objectives, design, treatment schedule, treatment groups, study endpoints and a flowchart of the schedule.
- the **introduction** to the study, justifying why it is necessary (hypothesis) and evidence of a literature search. May include a general background, structure & mechanism of the main study drug / investigation being assessed, any relevant pre-clinical issues, previous studies with the main study drug / investigation, rationale for the study.
- a simply stated **trial aim / objective** that clearly defines the research question, with primary / secondary endpoints.
- the **population** to be studied along with a clear listing of the **inclusion and exclusion criteria** and how subjects will be identified.
- the **sample size** - number of subjects to be studied and evidence that this number is available. How subjects will be recruited and randomised.

- a detailed section of the **randomisation process** – the type of randomisation procedure to be used, allocation ratio, any stratification factors (with levels) and any other factors considered in the process. Other things to consider are where allocation codes are kept, will it be a manual or automated randomisation process, who will assign the randomisation, how will it be documented, who will have access to break the code in case of emergency. If the study is **double-blind**, detail the procedure and allowable reasons for breaking the blind (eg. Clinical management purposes, treatment of overdose).
- the process for obtaining **informed written consent** from the subjects. What systems have been put into place to copy with subjects who require the use of a legal representative or minors?
- the **study procedure / treatment of subjects** - a detailed description of how the study will be conducted and what is performed at each study visit, including examinations, blood tests, other investigations, questionnaires, assessments for efficacy, end-points and safety. If different arms of the study have different treatments / interventions, then this needs to be stated.
- **study drug** supply – how this will be supplied (of the shelf, from a pharma company), packaged and labelled. When it will be dispensed to subjects and how accountability should be documented.
- Issues clarifying **concurrent medication / treatment** – what medication the subject may / may not take during the study.
- a statement defining **the end of the study** – A study involving long term follow-up (mainly oncology studies) may be split into 2 parts: (1) Randomised to treatment – this would include the study period from the first patient being randomised into the study up to the last patient completing study treatment. (2) Follow-up of all patients – the date the last randomised patient started long term follow-up up to the last patient completing follow-up as stated in the protocol.
- **assessment of efficacy** – What investigations will be used to look at efficacy?
- **assessment of safety** – All studies using drugs / devices must have a defined pharmacovigilance procedure in place. This section should included information on the collection of toxicity data, definitions of adverse events (AEs) / serious adverse events (SAEs) / suspected unexpected serious adverse drug reactions (SUSARs). How these are to be recorded during the study and then reported to the study team / ethics / sponsor / regulatory authority and within what timeframes. Who within the study team takes responsibility for ensuring this process is adhered to. The researcher should consider a process for recording adverse events / effects of minors / vulnerable subjects for other types of studies (questionnaire / interviews), as a change in the process of the study may be required to minimise this effect.
- How to handles issues around **subject withdrawal** from the study (and how this is defined – withdrawal from study medication / intervention, withdrawal from study follow-up, withdrawal of subject consent and therefore possible further subject data use. Studies using drugs should have a case report form page that lists reasons for withdrawals) and protocol **deviations / violations**.
- **data recording** – when and how data will be recorded on a case report form and who will be responsible for this.
- **statistical considerations** – (1) how has the sample size been determined. The significance level and power used in the calculation should be stated. Realistic estimates of expected accrual rates and duration of patient entry into the study on estimated sample size should be provided as well as expected drop-out rates. All parameters used in the sample size calculation should be fully justified. (2) include an outline of the analysis plan for the primary and secondary end-points. (3) will there be an interim analysis? (4)
- **source data / documents / confidentiality** – How and where source data is to be documented and who will have access to this. Storage and handling of confidential study data and documents, according to the Data Protection Act 1998. How will subject anonymity be maintained. How long study data and documents will be archived for.

- **quality control / quality assurance** – how aspects of this will be implemented for the study (e.g. data monitoring committee, data monitoring and ethics committee, review of adverse events).
- a statement of the **ethical considerations** involved and indicating that there is compliance with the principles of the World Medical Association Declaration of Helsinki (October 2000) and MRC/ICH good clinical practice..
- a statement defining the **publication policy** – when and where results will be published. Who will be able to publish results?
- **references**
- a copy of the **patient information sheet and consent form** – this should be included as an appendix. These should also be marked with the appropriate version numbers and dates.

The length and complexity of a scientific protocol will reflect the nature and scope of the project. A summary, synopsis or diagram of the protocol in non-technical language would also be helpful.

Research within the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004

If your study falls within the scope of the UK Clinical Trials Regulations there are specific guidelines on the contents of a study protocol. The DH & MRC have produced guidance on writing protocols specifically for non-commercial trials that fall under these regulations and following these guidelines will help minimise unnecessary work

Specifically there is guidance on the following:

- Contents of the protocol
- Document control
- Serious adverse events - how to define SAE's, SUSARs etc
- Definition of end of trial – and separation of the intervention and non-interventional arms of a trial and therefore limit MHRA charges
- Protocol amendments – how to minimise the need for protocol amendments and who to report amends to. A well designed initial protocol should minimise the need for amendments to be written.