

## **GUIDE TO CLINICAL TRIAL PROTOCOL CONTENT AND FORMAT**

The aim of this guide is to help researchers with the content and structure of protocols for clinical trials. 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](#). This guide refers primarily to trials of medicinal products, however many aspects will also be relevant to other types of intervention. There are links in this document to obtain more information about some topics, and a list of recommended references at the end.

Please note that if you are submitting your trial to the MHRA for a Clinical Trials Authorisation then other information will also be required. The UCL Clinical Research Network have written a guidance document which can be obtained from [jessica.crellin@royalfree.nhs.uk](mailto:jessica.crellin@royalfree.nhs.uk). Detailed information can also be obtained from the [MHRA website](#).

Many of the methodological aspects of designing a research study and writing a protocol can benefit from the advice of a statistician. Such advice should be sought at an early stage and is available for UCLH researchers through the [R&D Medical Statistics Unit](#).

### **1. TITLE PAGE**

#### **1.1 Title**

It is useful to specify both a full title and short title

- The full title should include summary study design, medicinal product(s), nature of the treatment, comparators and/or any [placebo](#), 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

#### **1.2 Names (titles), roles and contact details of:**

- Authors, investigators, experts and advisors involved in the trial
- Sponsor & monitor – as agreed with Chief / principal investigator's employer and the host Trust
- Trial site(s), clinical laboratory(s), technical departments and institutions involved in the study

#### **1.3 Protocol details**

- Version number
- final / draft
- Date

### **2. SIGNATURE PAGE**

Signatures of all healthcare professionals involved in the trial

### **3. CONTENTS PAGE**

### **4. LIST OF ABBREVIATIONS AND DEFINITIONS**

## **5. SUMMARY**

1 or 2 page summary including:

- Aim and rationale for the trial
- Summary of trial disorder / interventions / measures
- Primary & secondary objectives
- Brief description of methods

## **6. 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 and what evidence there is that the treatment under investigation may achieve this.

## **7. TRIAL OBJECTIVES AND PURPOSE**

- Purpose of research (e.g student project, commercial / non commercial trial, licensing)
- clearly define and distinguish primary and secondary objectives (including examination of effects for defined subgroups of patients)

## **8. STUDY DESIGN**

- statement of the primary and secondary endpoints / [outcomes](#) (including at what point in the trial these will be measured)
- clear description and justification of the [type of design](#) (e.g parallel group / [crossover](#), sequential, cluster randomised and equivalence)
  - if crossover design, include information about possible carry over effects, detail of orderings, washout (/in) periods etc
- Phase of the trial (e.g. phase I / II / III / pilot study)
- summary of treatments being compared with reasons for [choice of comparison group](#) (e.g active control / [placebo](#))
- schematic diagram(s) of the trial design, procedures, stages and data collection
- description and justification of the duration of treatment, subject participation and trial follow-up

## **9. SUBJECT SELECTION**

Include detail of:

- Source of subjects (where they come from and why this group is appropriate)
- Number of centres involved
- Subject inclusion and exclusion criteria (with justification if necessary – for example consider contra-indications to trial treatments, incompatible concurrent treatments, recent involvement in other research)
- Expected no of eligible participants available per year and proportion of these expected to agree to the trial

## **10. SUBJECT RECRUITMENT**

Details of recruitment process including

- method of recruitment (eg via adverts, clinics)
- payment of participants
- details of procedures, tests, 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

## **11. TRIAL INTERVENTIONS**

This refers to the treatment under investigation and any active control treatment. Detail in this section may be referenced to other documents, such as the Investigators Brochure.

### **11.1 General information**

- full name, generic name (if appropriate) and if licensed in UK trade name.
- licence information - UK or EU (as appropriate)
- The Summary of Product Characteristics or the Data Sheet for Licensed Medicinal Products.
- summary of known and potential risks and benefits to human subjects

### **11.2 Use within the trial**

- description and justification for the proposed route of administration, dosage, and treatment period
- detail of who will be administering the product ( eg patient, nurse, doctor, carer)
- is the treatment invasive / does it involve radioactive substances?
- description of dosage form, packaging and labelling of products
- description of dispensing records, accountability and disposal procedures during the trial
- details of who will supply the products
- other detail including shelf life, arrangements for storage etc
- arrangements for continuation of treatment for study patients after the end of the trial
- Other medications permitted during the trial - include rescue medication (could be standardised for the purposes of the trial). Important also to consider possible interactions or effects that could confound results / conclusions

## **12. 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)

## **13. BLINDING & OTHER MEASURES TAKEN TO AVOID BIAS**

### **13.1 Blinding**

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 (e.g. through use of identical placebo)

### **13.2 Other measures taken to minimise / avoid bias**

## **14. DATA**

### **14.1 Data to be collected**

- 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 followup point)
  - who will collect the data
  - why the data is being collected (e.g. baseline comparison data, main outcome, important prognostic / explanatory variable)
  - whether the data is from a standardised tool (e.g. McGill pain score) / involves 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)
- useful to include table / diagram describing schedule for data collection.
- describe methods used to maximise completeness of data (e.g. telephoning patients who have not returned postal questionnaires)
- include data collection forms as appendices

### **14.2 Data handling and record keeping**

- 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)
- Security / storage of data
- Records retention – duration and location
- Adherence to Data Protection Act 1998
- statement of who is responsible for data collection, recording and quality

## **15. STATISTICAL CONSIDERATIONS**

### **15.1 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

### **15.2 Sample size calculation**

- Details of the precision or power calculation used to estimate the required sample size (for analysis of the primary outcome), including :
  - [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
  - chosen levels of [significance](#) and [power](#)
  - methods / formula / software used
- 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.

## **16. COMPLIANCE AND WITHDRAWAL**

### **16.1 Subject compliance**

- procedures for monitoring (e.g. watching subject swallow pills and checking their mouths afterwards)
- recording of patient compliance information (what will be recorded, when and where)
- detail of follow-up of non compliant subjects

### **16.2 Withdrawal / dropout of subjects**

- describe under what circumstances and how subjects will be withdrawn from the trial
- give details of documentation to be completed on subject withdrawal (including recording reasons for withdrawal and any follow-up information collected)
- whether and how subjects would be replaced

## **17. INTERIM ANALYSIS AND DATA MONITORING**

### **17.1 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.

### **17.2 Monitoring, quality control and assurance**

- use and role of monitors eg data monitoring groups and steering groups and arrangements for monitoring / auditing conduct of the research
- Assurance on good clinical practice and adherence to research governance guidelines
- Detail of any other steps taken to ensure quality of research

### **17.3 Assessment of safety or pharmacovigilance**

**NB With the implementation of the Clinical Trial Regulations 2004 there are new requirements around the reporting of adverse events. The final guidance has not yet been issued and further links to relevant policies will be made when these become available.**

- Definition of [serious adverse events](#) for the trial which are expected e.g. hospitalisation in terminally ill patients.
- Statements about which serious expected adverse events will not be reported.
- A statement about how non serious adverse events will be recorded and reported.
- Details of the [procedures](#) that will be followed in the event of adverse events in the trial – who has what responsibility
- methods and timing for assessing, recording and analysing safety parameters (e.g interim analyses)
- The type and duration of follow up for subjects after adverse events

### **18 ETHICAL CONSIDERATIONS**

Description of ethical issues for the trial. For example consider:

- Approvals from relevant groups (e.g. [MREC](#), [LREC](#), [MHRA](#), Trust(s))
- Informed consent (append information sheet and informed consent form)
- Allowances for special groups (e.g non English speakers, children, mentally ill)
- Patient withdrawal / discontinuation
- Trial monitoring

### **19 FINANCING AND INSURANCE**

- Finance and insurance details (if not addressed in separate agreement)
- Cover for non negligent and negligent harm

### **20 REPORTING AND DISSEMINATION**

Detail of publication policy (e.g. Following the study, will there be access to raw data and right to publication freely by all investigators in the study?, what publications / conference presentations will be planned)

### **TABLES, FIGURES, REFERENCES**

#### **APPENDICES**

Including (where relevant):

- Patient information sheet
- Patient consent form
- Data collection forms and validation information
- Summary of product characteristics
- ethics form
- investigators brochure

## Useful reading

### Websites

- Martin Bland et al, Statistics guide for research grant applications (<http://www.sghms.ac.uk/depts/phs/guide/guide.htm#brief>) includes detailed information and definitions of many aspects required for a research protocol as well as information about randomisation software and services
- Symptoms research : Methods and opportunities. Edited by M. Mitchell & J. Lynn (<http://symptomresearch.nih.gov/preface/index.htm>) This online textbook includes some useful chapters for clinical trials, in particular a chapter on cross over trials by Stephen Senn.
- CONSORT statement ([www.consort-statement.org](http://www.consort-statement.org)) A set of recommendations for improving the quality of reports of parallel group randomised trials
- Declaration of Helsinki ([www.wma.net/e/policy/b3.htm](http://www.wma.net/e/policy/b3.htm)) Provides ethical principles for medical research involving human subjects
- COREC guidelines ([www.corec.org.uk](http://www.corec.org.uk)) Includes patient information sheet and consent form guidelines
- ICH Harmonised Tripartite Guidelines for Good Clinical Practice (1996) ([www.emea.eu.int/pdfs/human/ich/01359sen.pdf](http://www.emea.eu.int/pdfs/human/ich/01359sen.pdf))

### Books

Altman, DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991, Chapter 15.

Machin D, Campbell MJ, Fayers PM and Pinol APY *Sample Size Tables for Clinical Studies*. Second Edition. Oxford: Blackwell Science, 1997.

Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. 3<sup>rd</sup> edition. New York: Springer; 1998.

Jadad A. *Randomised Controlled Trials*. London: BMJ Books, 1998.

Pocock S. *Clinical trials: a practical approach*. Chichester: Wiley, 1983.

Senn S. *Cross-over trials in clinical research*. Chichester: Wiley, 1993.

### Papers

[BMJ statistics notes](#) provide some brief but useful information on various topics including :

Bland JM, Kerry SM. Trials randomised in clusters. *BMJ* 1997; **315**:600

Kerry SM, Bland JM. Analysis of a trial randomised in clusters. *BMJ* 1998; **316**:54

Altman DG, Bland JM. Treatment allocation in controlled trials: why randomise. *BMJ* 1999; **318**:1209

Altman DG, Bland JM. How to randomise. *BMJ* 1999; **319**:703-704

Day JD, Altman DG. Blinding in clinical trials and other studies. *BMJ* 2000; **321**: 504

Altman DG, Schulz KF. Concealing treatment allocation in randomised trials. *BMJ* 2001; **323**:446-447.

*Other relevant papers are:*

Altman DG. The comparability of randomised groups. *Statistician* 1985; **34**: 125-136.

Altman DG, Doré CJ. Randomisation and baseline comparisons in clinical trials. *Lancet* 1990; **335**: 149-153.

Moher D, Schulz KF, Altman DG for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**:1191-1194.

Altman DG, Schulz KF, Moher D, Egger M, Davidoff, Elbourne D, Gøtzsche PC, Lang T for the CONSORT Group. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Annals of Internal Medicine* 2001; **134**: 663-694.

Campbell MK, Grimshaw JM. Cluster randomised trials: time for improvement. *BMJ* 1998; **317**: 1171-1172.

Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimisation for allocation to clinical trials: a review. *Controlled Clinical Trials* 2002; **23**: 662-674

Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *British Medical Journal* 2001; **323**: 42-46.

Lachin JM. Statistical considerations in the intent-to-treat principle. *Controlled Clinical Trials* 2000; **21**:167-189.

Pocock S. Current issues in the design and interpretation of clinical trials. *BMJ* 1985; **290**: 39-42.

Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002a; **359**: 614-618.

Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002b; **359**: 696-700.

Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow-up measurements. *BMJ* 2001; **323**: 1123-1124.

Gibbons, A. Performing and publishing a randomised controlled trial. *BMJ* 2002 **324**, S131.

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**January 2006**