

GUIDE TO RANDOMISED CONTROLLED TRIAL PROTOCOL CONTENT AND FORMAT (FOR NON 'CTIMP'S)

The aim of this guide is to help researchers with the content and structure of protocols for randomised controlled trials of interventions not falling under the Medicines for Human Use (Clinical Trials) Regulations 2004 (MHRA) (i.e. non CTIMPs). Examples include licensed medicinal products, therapies, surgical procedures and devices. It indicates the information that should ideally be included in a protocol and has been constructed to cover important methodological considerations and requirements specified under [Good Clinical Practice](#). Researchers writing a protocol for a product coming under the MHRA regulations should refer to the Standard Operating Procedure for writing a Protocol for CTIMPs (JRBU/INV/S01/00). There are links in this document to obtain more information about some topics, and a list of recommended references at the end.

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 UCL/UCLH/RFH health researchers through the [Biostatistics Group](#) at the Joint UCLH/UCL /RFH Free Biomedical Research 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, product/treatment(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)
- 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, equivalence)
 - if crossover design, include information about possible carry over effects, detail of orderings, washout (/in) periods etc
- Type of trial (Pilot study/main trial)
- 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 number 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 (e.g. 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 intervention under investigation and any non placebo control. Detail in this section may be referenced to other documents, such as the Investigators Brochure. For each intervention/control please specify:

11.1 General information

Provide general information about the intervention/control treatment including detail of any previous use and current evidence of risks/benefits. For medicinal products in particular include full name, generic name/trade name and licence information and summary of Product Characteristics.

11.2 Use within the trial

- Detailed description of the interventions/treatments that will be provided in the trial, including how they will be administered/provided in the trial and by whom (e.g. patient, nurse, doctor, therapist, surgeon).
- Arrangements for continuation of intervention/treatment for study patients after the end of the trial
- Other treatment/therapies permitted during the trial – for example rescue medication, complimentary therapies. Important also to consider possible interactions or effects that could confound results/conclusions

For medicinal interventions include (if appropriate):

- Description and justification for the proposed route of administration, dosage, and treatment period

- Description of dosage form, dispensing records, accountability and disposal procedures during the trial
- Details of who will supply the products, shelf life, arrangements for storage etc

12. Randomisation

Including detail and justification for each of the following:

- Patient / [cluster](#) randomised design (i.e. whether 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 consider using varying sizes.
- Use of equal or unequal allocation between treatment arms
- Information regarding how the randomisation schedule will be generated (including who will generate the schedule and the software used)
- Information regarding how randomisation will be implemented (including who, where, how, and procedure for out of hours)
- Approach to be used to conceal allocation (e.g. sealed envelopes, telephone central allocation office, computerised randomisation etc)
- Define the circumstances under which randomisation codes may be broken and the procedure for doing it

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*

Describe any other methods, if any, for minimising/avoiding 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 follow up 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)
- It is useful to include a 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 (database software to be used, location of the data etc)
- Detail methods implemented to ensure validity and quality of data (e.g. double entry, range checks, cross validation etc)
- Describe methods for ensuring secure 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

Name of the statistician involved in the trial design and who carried out the sample size calculations.

15.1 Sample size calculation (some pilot/feasibility studies may not require a formal sample size calculation)

Sufficient information should be given for an independent statistician to reproduce the sample size calculation.

- Details of the precision or power calculation used to estimate the required sample size for analysis of the primary outcome(s), including :
 - [estimates used](#) (including the size of the [clinically important effect](#) to be detected, drop out and non compliance rates)
 - assumptions made (e.g. assumptions of Normality)
 - relevant justification (i.e. appropriate references or clinical arguments)
 - allowance for planned subgroup analyses or more than one primary outcome, when appropriate
 - chosen levels of [significance](#) and [power](#)
 - one or two sided test
 - 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.

15.2 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

16. Compliance and withdrawal

16.1 *Subject compliance*

- procedures for monitoring (e.g. watching subject swallow pills and checking their mouths afterwards, compliance diaries)
- 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 subjects who drop out of the trial or who are withdrawn from the trial (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 e.g. 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*

- 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 to the sponsor and how they will be recorded.
- Statements about how serious expected adverse events will be reported to the sponsor and how they will be recorded
- A statement about how non serious adverse events will be recorded.
- Details of the [procedures](#) that will be followed in the event of serious unexpected adverse events in the trial – who has what responsibility
- Methods and timing for any 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](#), 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? Specify planned publications/conference presentations)

Tables, Figures, References

Appendices

Including (where relevant):

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

Useful reading

Websites

- Martin Bland et al, Statistical guide for research grant applications
<http://www-users.york.ac.uk/~mb55/guide/guide.htm>
Includes detailed information and definitions of many aspects required for a research protocol as well as information about randomisation software and services
- Martin Bland, Directory of randomisation software and services
<http://www-users.york.ac.uk/~mb55/guide/randseriy.htm>
- Interactive textbook on clinical symptom research. 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 <http://www.consort-statement.org/>
A set of recommendations for improving the quality of reports of parallel group randomised trials
- Declaration of Helsinki
<http://www.wma.net/en/30publications/10policies/b3/index.html>
Provides ethical principles for medical research involving human subjects
- Integrated Research Application System
<https://www.myresearchproject.org.uk/signin.aspx>
- ICH Harmonised Tripartite Guidelines for Good Clinical Practice (1996)
<http://www.cgmh.org.tw/intr/intr1/c0040/web/C/ICH%20GCP%20E6.pdf>

Books

- Altman, DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991, Chapter 15.
- Machin D, Campbell MJ, Say BT, Sze HT. *Sample Size Tables for Clinical Studies*. Third Edition. BMJ Books, 2008.
- Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. 3rd 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*. 2nd edition. Chichester: Wiley, 2002.

BMJ statistics notes

[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.
- Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow-up measurements. *BMJ* 2001; **323**: 1123-1124.
- Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005; **330**: 843

Papers

- Pocock S. Current issues in the design and interpretation of clinical trials. *BMJ* 1985; **290**: 39-42.
- 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.
- Campbell MK, Grimshaw JM. Cluster randomised trials: time for improvement. *BMJ* 1998; **317**: 1171-1172.
- Lachin JM. Statistical considerations in the intent-to-treat principle. *Controlled Clinical Trials* 2000; **21**:167-189.
- 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.
- 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.
- Gibbons, A. Performing and publishing a randomised controlled trial. *BMJ* 2002 **324**, S131
- 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.
- Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002c; **359**: 781-785.
- Schulz KF, Grimes DA. Unequal group sizes in randomised trials: guarding against guessing. *Lancet* 2002d; **359**: 966-970.
- Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. *Lancet* 2005a; **365**: 1348-1353
- Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005b; **365**: 1591-1595
- Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. *Lancet* 2005c; **365**: 1657-1661

- Grimes DA, Hubacher D, Nanda K, Schulz KF, Moher D, Altman DG. The Good Clinical practice guideline: a bronze standard for clinical research. *Lancet*2005d; **366**: 172-174
- Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008; **371**: 281-283