

Standard Operating Procedure (SOP) for Randomisation and Blinding for Randomised Controlled Trials

For Completion by SOP Author	
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If you are reading this SOP in printed form then you are reading an uncontrolled document. You must therefore verify that the version number and date given below are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

Portsmouth Hospitals NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

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1.

2. INTRODUCTION

The randomised controlled trial (RCT) is the standard by which all trials are judged since other study types are open to numerous potential biases. In the simplest case, randomisation is a process by which each participant has the same chance of being assigned to either intervention or control. Randomisation tends to produce study groups comparable with respect to known, as well as unknown risk factors, removes investigator bias in the allocation of participants, and establishes the basis for testing the statistical significance of differences between these groups in the measured outcome.

However, randomisation can only produce groups that are comparable at the start of the study, and introduction of bias is one of the main concerns. Bias can be caused by conscious factors, unconscious factors, or both. Bias can occur at a number of places in a clinical trial, from the initial design through to data analysis and interpretation. One general solution to the problem of bias is to keep the participant and the investigator blinded to the identity of the assigned intervention. One can also blind several other aspects of a trial including the assessment, classification, and evaluation of the response variables.

3. PURPOSE

The purpose of this document is to describe the Standard Operating Procedures for randomisation and blinding and must be used at the protocol development stage for randomised controlled trials.

4. SCOPE

This SOP applies to all randomised controlled trials (RCT) Sponsored by Portsmouth Hospitals NHS Trust.

Who should use this SOP

- All individuals involved in PHT Sponsored randomised controlled trials.

The Trust recognises that some external networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from the Director of Research.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety

5. ABBREVIATIONS & DEFINITIONS

CI: Chief Investigator
CTU: Clinical Trials Unit
RCT: Randomised controlled trial
RDS: Research Design Service
SOP: Standard Operating Procedure

6. DUTIES AND RESPONSIBILITIES

Chief Investigator: The individual who is ultimately responsible for delivering the project and overall responsible for the success of the study.

Methodologist: The individual in charge of designing the study.

Data manager: The individual responsible for the design, development and validation of the tools used for data collection. Also responsible for assuring the quality of the data.

Statistician: The individual responsible for analysing the data collected during the study and delivering a data analysis report.

7. PROCESS

6.1 Randomisation design

- Contact the RDS and book an appointment with the RDS Methodologist at PHT. The RDS Methodologist will advise with regards to study design and the best randomisation strategy. For information on how to book please visit:

<http://www.rds.nihr.ac.uk/>

- Once a suitable randomisation strategy has been agreed by the research team with the help of the Methodologist, a statistician must be contacted in order to calculate sample size and help create a randomisation list or schedule. The methods of preparing the randomisation list can be quite varied and should be detailed in the protocol. Methods of randomisation that cannot be verified at a later date and reconstructed must be avoided.
- For further information on common randomisation strategies please see Appendix 1.

6.2 Randomisation list

- A randomisation list should be obtained in a way that is reproducible. A record should be made of the method used for computer generated lists and the randomisation list/scheme should provide an associated unique study identification number.
- The randomisation list should be saved as a document in a format which assigns appropriate identifiers to the study subjects and which clearly shows the treatment allocation in words

rather than symbols. This document should be carefully and securely kept by the statistician along with a log of the code used to generate the list.

- For investigator blinded studies the randomisation list should be sent to a carefully chosen person in order to preserve any blinding and concealed allocation. The blinded investigators/research team should not see the randomisation list during the running of the trial.
- When the need to unblind arises, procedures need to be in place so that the randomisation list can be accessed whether it is a paper version (e.g. in a locked cabinet) or electronic version (e.g. a password protected file).

6.3 Documentation of randomisation

The following information should be discussed, agreed and documented between the methodologist, the CI and the statistician for all randomisation schemes:

- Method of generation of randomised code list, including software package.
- Name and job title of person responsible for preparing and checking the randomised code list.
- Precise details of blocking method and stratification variables (if applicable), including exact specification of any cut-offs or algorithms used. Research team needs to identify stratification variables, statistician needs to implement.
- Randomisation system (envelope, telephone, internet) and related procedures (including telephone numbers, websites etc.).
- Who will have access to the randomisation codes throughout the study, and where the data on treatment codes will be stored.
- For studies in which the treating team is blinded to the treatment, the method by which the emergency access to the code for individual subjects is to be organised during the study.
- How the treatment allocated will be compared with the treatment received at the end of the study (verification). There should be a record of the treatment subjects received, as well as what they were allocated (using pack numbers if placebo controlled/blinded) and reasons collected for any differences.
- Any changes to the randomisation schedule through the course of the study, along with the date when the new scheme became active.

6.4 Blinding

Blinding is the process that keeps one or more parties involved in a trial unaware of what treatment arm subjects have been randomised to. It is vital that blinding is maintained throughout the trial to ensure that no bias is introduced when making safety and efficacy assessments. According to trial design blinding can be:

Open-label trial – Both team and subjects know the treatment being administered.

Single-blind trial – One party, either the investigator or the subject, is unaware of treatment.

Double-blind trial – Neither the subjects nor the study team know which subject is receiving the treatment or the control.

Double blind trials are thought to produce the most unbiased results, since the expectations by the doctor and or the participant regarding the experimental treatment do not affect the outcome. However, double blinded conditions cannot always be achieved in practice since often the operator must know the treatment being used (for example surgery trials).

In general, the following conditions should be considered when designing a blind trial:

- The study protocol should define all individuals involved in the study who will be blinded to treatment and those who will not.
- Where possible, make sure that the outcome is assessed blind to treatment allocation. When carrying out interim analyses of blinded results, the integrity of the blinding of the study should not be compromised.
- Only personnel not directly involved in the running or conduct of the study should have access to the randomisation list/code.
- In ideal conditions, the analysis should be performed blinded, therefore it is recommended that the randomisation list and analysis of data are performed by different individuals. If a single statistician is responsible for all statistical aspects of the trial, decisions on how the data will be analysed and presented should be made before the first unblinded analysis of the data.
- Take adequate steps to ensure that the treatments are indistinguishable in placebo-controlled trials (for example, the smell, colour and texture of the placebo should be identical to the Investigational Product).

6.5 Unblinding

It is a fundamental part of blinded trials to take measures to avoid accidental unblinding (see the “maintaining the blind” document). However, unblinding will be necessary in certain circumstances such as:

- After the end of the trial: make sure a formal process to control the unblinding of the trial is agreed and documented.
- Emergency and safety: ensure procedures are in place to instruct how unblinding can be dealt with for expedited reporting purposes without compromising the blinded members of the trial team.
- Interim analyses: all unblinded interim review of the data should be pre-planned, specified in the trial protocol and conducted by personnel who have no further involvement in the conduct of the trial or the final analysis (normally the Data Monitoring Committee)

Therefore, prior to initiating a blinded trial the PI should ensure that:

- 1) a robust unblinding process has been implemented and documented;
- 2) the code breaks are on site in a designated place;
- 3) all staff involved in the trial and process are aware of the arrangements.

Examples of code breaks include:

- A master randomisation list held by the pharmacy
- Code break envelopes
- Scratch off panels on medication containers
- A sealed tear off portion on medication labels that would be filed in the pharmacy or with the participant's records

- An “on call” 24 hour-a-day process

The PI should ensure the reasons and circumstances of any code break are documented appropriately.

8. TRAINING REQUIREMENTS

- All researchers planning to conduct randomised, and blinded protocols should be trained in this SOP. Evidence of training shall be required for all chief investigators and individual’s delegated specific roles and responsibilities in Trust Sponsored studies.
- The Research Dept will endeavour to notify individuals of SOP developments that may be relevant to them. Updates on SOPs will feature in research newsletters and communications. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them. A study specific SOP training plan will be developed for investigators on high risk PHT Sponsored studies.
- When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process.
- Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.
- All staff are responsible for maintaining their own SOP training records and copies must be made available to line managers, the SOP Controller or study monitors and sponsors on request.

9. REFERENCES AND ASSOCIATED DOCUMENTATION

- The Good Clinical Practice Guide, MHRA ISBN 978 0 11 708107 9
- Randomisation in Clinical Trials. University of the West of England, Bristol. Version 1.0 May 2011
- University College London: SOP for producing randomisation lists
- Hulley et al. 2007. Designing Clinical Research. Wolters Kluwer. 367 pages.
- Randomised Controlled Trials 2015 course notes. Pembroke College, Oxford.

10. VERSION HISTORY LOG

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
V1.0	23 May 2016	New document

11. APPENDICES

11.1. Common Randomisation Strategies:

Randomisation procedures will be determined for individual research studies by discussion between the methodologist, the Chief Investigator and the statistician during the protocol development stage. Some common randomization strategies are described below:

- Simple randomisation:** For large sample sizes (greater than around 200) simple randomisation can be appropriate. A commonly encountered situation is when comparing two treatments. A randomisation list is then produced using a computer algorithm which allocates treatment A or B to each individual in the total sample. A common method to allocate treatment is by creating opaque envelopes containing the allocated treatment. The process is relatively simple to organise, the original allocation to each individual (i.e randomisation list) is documented and verifiable, and the process can be readily extended to situations where multiple treatments are to be compared. Envelopes can be kept in the pharmacy for example where the pharmacist dispensing the treatment/placebo will open the envelope to reveal the allocation
- Block randomisation:** For smaller sample sizes blocking is often used to ensure similar numbers in the randomised groups. Random permuted blocks (e.g. randomly varying blocks in sizes of multiples of 2) help maintain blinding and concealed allocation. Block randomisation is commonly used in the two treatment situation where sample sizes for the two treatments are to be equal or approximately equal. The process involves recruiting participants in short blocks and ensuring that half of the participants within each block are allocated to treatment A and the other half to treatment B. Within each block however the order of patient is random.
- Stratification:** this technique should be used to ensure balance between randomised groups for important prognostic factors (particularly in smaller studies). The number of strata must be limited to ensure reasonable sample sizes in each. For example, in the two treatment comparison situation, some eligible participants may already be taking medicaments for their condition while other eligible participants may not. In order to avoid the introduction of imbalance in a potential confounding factor, the researchers may want to stratify the randomisation list into two separate groups: one including participants on medicament and one including those who are not.
- Minimisation:** In this procedure, the first patient is truly randomly allocated; for each subsequent patient, the treatment allocation is identified, which minimises the imbalance between groups at that time. This is achieved by keeping a current list of the total patients on each treatment for each stratification factor level. Minimisation is suitable for complex trials with several strata making it difficult to allocate equal numbers of participant to each treatment.
- Multicentre trials should always be stratified by centre. Furthermore, the use of opaque envelopes to conceal allocation is suitable for small, single centre trials. Researchers planning larger, multicentre trials are advised to consider the use of online randomisation services such as www.sealedenvelope.com. This however comes with a cost (approximately £2000.00)

- In blinded studies the clinical staff involved should not be informed of the details of stratification/minimisation variables or block sizes unless absolute necessary.

11.1. Training Record

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
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Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
<p>I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities</p> <p>Signature of Trainee Date</p>
<p>I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities</p>

Signature of Trainer Date

Additional Notes & Signatures

Signature of Trainer (where appropriate)

I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities

Signature of Trainer Date

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