SOP-QA-18 V5

Title: Randomisation and blinding for controlled trials

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Document History

Version	Description of update	Date Effective
4	Change of author Updated verification process at 3.6 Reference to SOP-QA-35 at 3.11 and emergency unblinding at 3.15	1-8-20
5	Scheduled review at three years Word "approximately" added into section 3.6	9-9-23

1. Scope

1.1 This SOP applies to all randomised controlled trials sponsored or co-sponsored by the University of Aberdeen (UoA) and/or NHS Grampian (NHSG). It applies to any personnel involved in the development or implementation of the randomisation and/or blinding procedures.

1.2 A randomised controlled trial is any research study that prospectively assigns human participants or groups of humans to one or more interventions to evaluate the effects on health or other research outcomes. Randomisation is the process by which participants in a trial are allocated to intervention groups. Random allocation ensures that any differences between the groups at trial entry are due to chance alone. The aims of the randomisation and blinding procedures are to avoid the introduction of bias into the conduct of the trial.

1.3 The randomisation and blinding methods apply to lists prepared before the start of the trial and dynamic randomisation methods. A statistician or randomisation service provider should be involved in the development and review of the randomisation methods to ensure that the system achieves the above aims.

1.4 This procedure provides guidance which shall be followed, unless a different procedure is to be used; as detailed and justified in the study protocol and agreed by the Sponsor/Co-Sponsor.

2. Responsibilities

Chief Investigator (CI)	Production and implementation of the randomisation specification and protocol (delegated to an appropriately qualified and trained individual).
Randomisation Service Provider	Preparing a randomisation protocol, generating and testing the randomisation list/algorithm.

3. Procedure

Randomisation procedure

3.1 The sequence of allocations must be truly random. It must be based on random number generation or other random process. Non-random processes such as alternate allocation are not acceptable. Allocation must be concealed in advance of randomisation and it must not be possible to know in advance what the next allocation in the sequence will be. It must not be possible to change the randomised allocation after randomisation; although there may instances where it is not possible to deliver the randomised allocation.

3.2 The CI must ensure that a trial statistician (or suitably qualified individual) is consulted for advice on the appropriate randomisation procedure and that a randomisation specification is produced and documented. When developing the randomisation specification, the following factors should be included, as appropriate:

- Definition of any strata (eg to handle randomisation in a multi-centre trial and to ensure balance for baseline prognostic factors).
- Any factors that may be the subject of blocking. The clinical staff involved in the study shall not be informed of the block size(s) used.
- Number of groups (and strata where appropriate).
- Number of participants to be randomised to each group.
- Method of allocation (eg simple randomisation, blocked randomisation, minimisation, etc).
- Method of implementation (eg web based system, telephone based system, etc).
- How the allocation method is to be tested (eg by means of simulations).

3.3 The randomisation service provider shall document all relevant information in a randomisation protocol, with particular consideration of the following:

- Method of production of the allocation list/algorithm.
- Persons responsible for preparing and checking the allocation list/algorithm.
- Outputs from any testing and simulation.
- Person(s) responsible for the implementation and use of the allocation list/algorithm.
- Guidelines for users of the allocation list/algorithm.
- Storage and access control for any copies of the allocation list/algorithm.
- Method by which emergency access to the allocation for individual participants is to be organised during the trial (this is termed 'unblinding' (see 3.11)).
- The randomisation protocol must be produced and implemented prior to recruitment.

3.4 A description of the randomisation procedure must be included in the trial protocol, although it may not be appropriate to include all details from the randomisation protocol; in order to avoid intervention allocation bias.

3.5 In trials involving medicinal product(s), the individual responsible for the generation of the randomisation protocol shall be aware of the arrangements for drug packaging and distribution to ensure that the randomisation protocol shall be compatible with these (see SOP-QA-15 - Management of Medicinal Products used in Research).

3.6 A simulation run will be performed and simulation verification result will be signed on the randomisation system before going live. Further checks at approximately 20% and at 50% of the randomisation recruitment target and at the end of the trial shall also be performed. At these points, the randomisation allocation list/algorithm for each centre, or each unit of randomisation, shall be checked by the trial statistician (or other suitable qualified person, independent from the randomisation service provider) to determine that it has been followed.

⚠ Unusual patterns of randomisation may indicate fraud and the statistician may have to undertake a statistical examination of the data for results indicative of this.

3.7 Any deviations from or failures of the randomisation procedures during the recruitment phase shall be documented in the Trial Master File (TMF) by the research team using a file note.

Blinding

3.8 ❗ In blinded trials, adequate steps shall be taken to ensure that the interventions are indistinguishable, as specified by the trial protocol.

3.9 ❗ The trial protocol shall define any individuals involved in the trial who should not/cannot be blinded to treatment. For example, laboratory staff may have access to laboratory measurements which would unblind the trial. Such data shall be withheld from other research team members until the end of the trial.

3.10 The randomisation code break mechanism shall be held by individuals not directly involved in the day-to-day management of the trial, for example the pharmacy, trial data management team or the randomisation service provider (see SOP-QA-15 - Management of Medicinal Products used in research). ❗ The code break mechanism shall be stored with appropriate security measures and access control.

Unblinding (see also SOP-QA-35 – Unblinding)

3.11 Unblinding of participants during the conduct of a blinded trial is not permitted unless there are compelling medical or safety reasons to do so (eg knowledge of the treatment allocation is necessary for treatment of severe adverse advents (SAE)).

3.12 ❗ The circumstances for breaking of the randomisation code in a blinded trial, such that the intervention allocation can be ascertained for any individual(s), must be clearly described in the trial protocol and/or a specific unblinding procedure document for the trial.

3.13 ❗ If participant unblinding is permitted during the conduct of a trial, the protocol must state procedures for obtaining permission to unblind.

3.14 ❗ Where possible the CI's advice should be sought before requests for unblinding are made.

3.15 ⚠ In situations where future treatment decisions need to be made quickly there needs to be a mechanism for emergency unblinding 24 hours a day. If emergency unblinding is not required, this shall be documented in the protocol.

3.16 If a participant has been unblinded, the participant should be encouraged to remain in the trial and, if possible, on trial treatment, unless medically contraindicated. All unblindings of the randomisation code for specific participants shall be fully documented and justified.

3.17 In the event of individual unblinding, knowledge of the intervention allocation shall be restricted as far as is practical until the trial is fully unblinded.

3.18 For planned interim analyses, decisions on how the data will be analysed and presented should be made before the trial begins, and be fully described (see SOP-QA-23 - Statistical analysis plans for clinical trials). Interim analysis or reports to the Data Monitoring Committee (DMC) may require to be unblinded (see SOP-QA-17 – Project committees). When carrying out interim analyses or preparing DMC reports, the integrity of the blinding of the trial shall not be compromised. Only a person not directly involved in the running or conduct of the trial shall have access to the randomisation code breaks and any unblinded outputs from the analysis.

⚠ The CI shall **never** see unblinded output before the end of the trial.

4. Abbreviations and definitions

Randomisation Specification

4.1 A document generated by the researcher to request randomisation capability.

Randomisation Protocol

4.2 A document generated by the trial statistician or a randomisation service provider to capture the randomisation specification and provide an exact set of instructions for generation of the randomisation allocation list or dynamic algorithm.

Randomisation List/Algorithm

4.3 Actual allocation of intervention.

Randomisation Service Provider

4.4 An appropriately qualified and trained individual or external vendor delegated the responsibility for generation of the randomisation protocol and list/algorithm. The randomisation service provider must be independent from the research team, to avoid intervention allocation bias.

4.5

CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
TMF	Trial Master File

5. Related documentation and references

SOP-QA-3	Protocol guidance for high risk trials and CTIMPs
SOP-QA-12	Case Report Forms
SOP-QA-15	Management of Medicinal Products used in research
SOP-QA-17	Project committees
SOP-QA-19	Amendments
SOP-QA-23	Statistical analysis plans for clinical trials
SOP-QA-35	Unblinding