UNIVERSITY OF LINCOLN

CLINICAL GOVERNANCE - STANDARD OPERATING PROCEDURE

RANDOMISATION

CG-QMS SOP CGD6

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Version History	**Reason for change**

NOTE: All SOPs are subject to regular review. Please ensure that the version of this SOP is the most up-to-date.

OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED/

1 PURPOSE

To describe the procedure for randomisation of participants to control or intervention group. This may be part of the Statistical Analysis Plan (SAP).

2 SCOPE

This SOP is applicable to all clinical research that involves randomisation of participants where UoL is the sponsor, or where LinCTU are providing randomisation support.

3 BACKGROUND

3.1 Randomisation is the process of assigning patients by chance to groups that receive different treatments. In the simplest trial design, the investigational group receives the new treatment, and the control group receives standard therapy. Randomisation helps prevent bias.

3.2 All participants in a randomised trial must be assigned intervention or control group to reduce the impact of bias. A statistician or randomisation service must be involved in the method of randomisation.

3.3 The overall responsibility for preparing the randomisation protocol is delegated to the CI, a suitably qualified statistician or Clinical Trials Unit (CTU).

3.4 The randomisation must be drafted, finalised and agreed before commencing the randomisation in the study.

3.5 The sequence of the allocations must be as truly random as possible. 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. It must not be possible to know in advance what the next allocation in the sequence will be.

3.6 The Chief Investigator (CI) and Trial Statistician (where involved) agree the randomisation and include in the study/trial protocol.

4 CROSS REFERENCES

4.1 CG-QMS SOP CGD2 Data management

4.2 CG-QMS SOP CGS1 Statistical Principals

4.3 CG-QMS SOP CGS2 Statistical Analysis Plan (SAP)

4.4 CG-QMS SOP CGS3 Sample size

5 PROCEDURE

5.1 The CI (or delegate) must ensure that a trial statistician (or suitably qualified individual) is consulted for advice on the appropriate randomisation procedure. The following factors should be included, as appropriate:

- Definition of any strata (e.g. 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 (e.g. simple randomisation, blocked randomisation, minimisation).

- Method of implementation of randomisation (e.g. web-based system, telephone-based system).

5.2 All relevant information in a randomisation protocol shall pay 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 ('unblinding').

5.3 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.

5.4 A simulation run will be performed, and simulation verification result will be signed on the randomisation system before going live. 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.

5.5 Any deviations from or failures of the randomisation procedures during the recruitment phase shall be documented in the trial master file by the research team using a file note. Where appropriate, the data manager or trial manager may need to contact the statistician or person responsible for managing the randomisation system or process to correct errors on the system - for example this is essential in situations where the same patient may have been randomised accidentally twice (sometimes this has been known to occur if there is an interruption in internet/ telephone services or where new investigators are unfamiliar with the technology of the systems).

BLINDING

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

5.7 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.

5.8 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. The code break mechanism shall be stored with appropriate security measures and access control.

UNBLINDING

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

5.10 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.

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

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

5.13 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.

5.14 In double blind trials, 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.

5.15 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.

5.16 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. Interim analysis or reports to the Data Monitoring Committee (DMC) may require to be unblinded. 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

6 FLOW CHART

None Required