Research Governance Office Sponsorship Standard Operating Procedures

Randomisation and Blinding

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1.0 Introduction and Scope

This Standard Operating Procedure (SOP) applies to all research studies (referred to as 'trials' hereafter) sponsored by the University of Leicester (UoL) where there is a requirement to blind or randomise interventions, and outlines the process required. In accordance with GCP each task must be conducted by appropriately qualified and trained individuals and it is expected that a statistician or other suitably qualified individual will undertake, or be involved in, the randomisation and blinding of a study.

2.0 Useful Definitions

Randomisation is the process by which participants in a trial are assigned to intervention groups in an unbiased and balanced manner, such that neither the participant or investigator can influence which intervention group the participant is assigned to.

Blinding is the process that keeps one or more parties involved in a trial (for example, the Sponsor, pharmacy, the investigator team and/or the participant) unaware of what intervention(s) participants have been randomised to. It is vital that the blind is maintained throughout the trial (with the exception of the circumstances described in Section 8) to ensure that no bias is introduced.

3.0 Randomisation Process

The protocol must describe the method of randomisation and any stratification factors. It is recommended that a "randomisation specification" is developed that contains the key features of the randomisation although this may not be necessary if the protocol contains sufficient information and the trial has a straightforward design.

4.0 Randomisation Methodology

The methods of preparing the randomisation schedule (or randomisation list) can be quite varied; including the use of random number tables, online randomisation programs and bespoke programs/macros. For the latter situation and for complex algorithms, where computer systems are used, there should be some method of Quality Control or validation of the program and documentation to demonstrate this must be retained. The method of generating the randomisation schedule should be clearly documented and should include who was responsible for its generation and who had access to the schedule before database lock. The randomisation schedule should be version controlled so it is clear which is the final version.

Methods of randomisation that cannot be verified and reconstructed at a later date must be avoided.

Where an interactive response technology (IRT) system is used, a statistician should be involved in any specification and programming of the system to undertake complex randomisation.

5.0 Distribution and Storage of the Randomisation Schedule

The randomisation schedule may consist of a paper record only or as an electronic version. There should be adequate control of all versions of the randomisation schedule. For electronic versions, records of both as it appears on the computer system and on the document, if printed, should be retained. It should be apparent which version is the final one.

The randomisation schedule can be used for numerous purposes and it is recommended that the distribution requirements are documented on the specification.

6.0 Blinding

In blinded trials there should be no indication whether a given participant is receiving the active, comparator or placebo intervention; if this is not possible then an unblinded operator may be responsible for preparation and/or administration of the intervention. This must not compromise the integrity of the blind for participants or blinded trial staff.

Consideration must be given to any identifiers associated with the intervention and packaging to ensure that they do not compromise the integrity of the blind. For example, in a blinded CTIMP trial investigators should consider if IMP and placebo/comparator drug production batch numbers or labelling conventions could lead to unblinding.

7.0 Maintenance of the Blinding

Maintaining the integrity of the blind is a key consideration for all those involved in the trial, as compromising the blinding will have a significant impact on the reliability and interpretation of the results.

The Sponsor, in collaboration with the Chief Investigator (CI, or delegate) should implement procedures to control the randomisation schedule to prevent accidental or deliberate unblinding. These procedures should include consideration of documented access restrictions for electronic schedules, so it is clear who had access and when, to the code throughout the conduct of the trial. The processes for handling code breaks, randomisation envelopes, master randomisation list and drug administration records are all important in maintaining the blinding and should all be taken into consideration. However, unnecessarily complex randomisation, packaging and dispensing procedures should be avoided as involving numerous individuals and process increases the risk of mistakes occurring.

In cases where data monitoring committees require interim unblinded analysis reports there should be robust procedures in place to protect the trial team from gaining access to unblinded data or the randomisation schedule. If possible, it is recommended that interim unblinded reports are produced by a separate statistician to the one who will undertake the final analysis.

Blinding processes should be defined in a formalised procedure and records must be available to reconstruct who had access to the randomisation schedule, who

assigned the intervention to the participants, who performed the blinding process and who released and administered the intervention.

7.1 Intervention Accountability

In those circumstances where it is necessary for an unblinded operator to perform the preparation, dispensing and administration of intervention it is important to demonstrate that the blinding has been maintained.

7.2 Efficacy and Safety Assessments

Where there are unblinded personnel there should be clear documentation (for example on the Delegation of Activity (DoA) Log) of who is authorised to perform the unblinded activities, to provide assurance that those performing efficacy and safety assessments remain blinded and, therefore, unbiased. This could take the form of a blinded and unblinded personnel DoA, or a separate document listing the various personnel and the status of their blind. In order to maintain the blinding, unblinded documentation should be retained separately from the rest of the trial documentation until the end of the trial or until the randomisation code has been broken for analysis. Should the case occur where a member of the blinded study team changes to the unblinded team, this should be clearly and formerly documented.

Where the design of the trial, or administration of the intervention, does not facilitate blinding of the participants or investigators, the assessors of the endpoint data must be blinded. For example, in a trial that compares an overnight dressing against a twice-daily application of steroid cream) the assessor for the skin condition would need to be blinded in order to perform the assessments objectively. In addition, the participants would need to be educated not to reveal the treatment to the assessor.

7.3 Monitoring

For blinded studies consideration should be given to allocating an unblinded monitor and how any visits and communication will be documented, reviewed and approved without compromising the blinding. This will be discussed during the Sponsor Risk Assessment Process (SOP S-1003).

7.4 Laboratory Data

For trials using laboratory data, review of this data may lead to unblinding. It is therefore important that any such laboratory data are only communicated and available to the appropriate people involved in the conduct of a trial. Laboratories that generate trial data should be aware of whether the trial is blinded or not and exercise due diligence when communicating data to ensure the blind is not compromised.

8.0 Unblinding

8.1 Unblinding in a Medical Emergency

There must be the ability to unblind a participant immediately and at all times in the case of a medical emergency. Unblinding should only occur if knowledge of

the intervention assignment is considered necessary to determine the optimal medical management of the participant. The process must be tested prior to initiation of the trial at that research location, and be available throughout the duration of the trial.

8.2 Unblinding for SUSAR Reporting

SUSARs need to be unblinded prior to reporting to the licensing authority, however, this unblinding must not be undertaken by the investigator or the research team. The Serious Adverse Event (SAE) process as per SOP S-1009 should be followed. Upon identification of a potential SUSAR, the Sponsor (or their delegate) who has appropriate authority to unblind the participant will complete the necessary task. Following a SUSAR, procedures need to be in place to cover how the unblinding necessary for expedited reporting purposes can be managed and documented without compromising the blinded members of the trial team. The protocol and risk assessment must address this aspect of the trial.

8.3 Unblinding of the Study for Analysis Purposes

There should be a formal process to control the unblinding of a trial for analysis purposes and this should be recorded. There should be documentation which confirms when the randomisation code was requested or provided and when the randomisation data were applied to the analysis datasets or database at final analysis. This information should contain times as well as dates.

9.0 Reconciliation of Code Breaks at the End of the Trial

Reconciliation of physical code breaks should be undertaken at the end of the trial and a check made that they have not been tampered with. When using an IRT system it should be possible to demonstrate that the blinding has not been compromised.

10.0 Randomisation Errors

Randomisation errors must be treated in the same way as Protocol Deviations.

11.0 Development Record

The table below summarises the revisions introduced in this version. Full historical change records are available within archived SOP versions.

Date	Issue Number	Description Of Changes (If Any)
April 2026	4.0	• Administrative changes • Minor updates to wording • Removal of responsibilities table as responsibilities are laid out within the body of the SOP. • Removal of full historical SOP review record; only the latest approved revision is now displayed, with prior versions retained in the document archive. • Update review schedule to every 3 years • Removal of distribution record