LOUGHBOROUGH UNIVERSITY RESEARCH OFFICE
STANDARD OPERATING PROCEDURE

Loughborough University (LU) Research Office
SOP–1035 LU

Randomisation and Blinding for NHS Research Studies Sponsored by Loughborough University

Effective Date: January 2016

1.0 Introduction

Loughborough University (LU) sponsors a wide range of studies. It is not always necessary to randomise and/or blind treatments or assessments but these options may be appropriate when designing a study. 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 trial.

2.0 Scope

This SOP applies to all research studies sponsored by Loughborough University where there is a requirement to blind or randomise.

3.0 Definition

Randomisation is the process used for assigning subjects in a research study to different groups without taking any similarities or differences between them into account. It means that each individual has the same chance of receiving each intervention.

Blinding is the process that keeps one or more parties involved in a study (for example, the Sponsor, pharmacy, the investigator team and/or the subject) unaware of what treatment arm subjects have been randomised to. It is vital that the blind is maintained throughout the trial (with the exception of the circumstances described in Section 9) to ensure that no bias is introduced.

4.0 Randomisation Process

Randomisation can be a very simple process or more complex algorithms may be used. The protocol should 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.

5.0 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 at a later date and reconstructed must be avoided.

Where an interactive response technologies (IRT) system is used, a statistician should be involved in any specification and programming of the system to undertake complex randomisation. This is not needed if the statistician is just providing a randomisation schedule (that the system uses as a ‘look up’ table).

6.0 Distribution and Storage of the Randomisation Schedule

The randomisation schedule may consist of a paper record only or also as an electronic version. There should be adequate control of all electronic versions of the randomisation schedule, both as it appears on the computer system and on the document, if printed. 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.

7.0 Blinding

The only difference between various treatments provided as part of a trial should be the subject number on the label.

8.0 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 may have a significant impact on the interpretation of the results.

The Chief Investigator (CI) (delegated by the Sponsor) 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.

8.1 Drug Accountability

In those circumstances where it is necessary for an unblinded operator to perform the reconstitution, dispensing and dosing of treatment it is important to demonstrate that the blinding has been maintained.
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 treatment to the subjects, who performed the blinding process and who released the medicinal product to the person who administered it.

8.2 Efficacy and Safety Assessments

Where there are unblinded personnel there should be clear documentation (for example on the Delegation 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. 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.

In cases where the method of administration between the arms of a trial are so different that it is not possible to blind the subjects and the investigator (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 subjects would need to be educated not to reveal the treatment to the assessor.

8.3 Monitoring

For blinded trials consideration should be given to allocating an unblinded monitor for medicinal aspects and how any visits and communication will be documented, reviewed and approved without compromising the blinding. This will be discussed during the Sponsor Review Process.

8.4 Laboratory Data

For studies 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 clinical 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.

9.0 Unblinding

9.1 Unblinding in a Medical Emergency

There must be the ability to unblind a subject immediately in the case of a medical emergency. This may be undertaken by the use of physical code breaks or via an interactive response technologies (IRT) system. There should be a backup system in place to enable breaking of the blind in the event that an IRT system is not functioning.

9.2 Unblinding for SUSAR Reporting

SUSARs need to be unblinded prior to reporting to the competent authority and REC, however, this unblinding must not be undertaken by the investigator or the research team. The SUSAR should be reported to the Sponsor who will have an appropriate individual identified for each trial to unblind the event and report it. To reduce the potential for bias to occur, 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.

9.3 Unblinding of the Trial 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.

10.0 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.

11. Responsibilities

	Responsibility Undertaken by		Activity
1	LU Research Governance Officer/CI	Research Governance Officer or delegate & CI	Appoint an individual (not the investigator or a member of the research team) during the Sponsor review process to be responsible for SUSAR reporting.
2	CI	Statistician or suitably qualified individual	Produce the randomisation schedule.

	Responsibility Undertaken by		Activity
3	CI (delegated by the Sponsor)	CI or delegate	Implement procedures to control the randomisation schedule and other documents to prevent unblinding throughout the lifetime of the trial.

This table is used to track the development and approval of the document and any changes made on revised / reviewed versions:

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Jackie Green	**Job Title:** Research Governance Officer
Approved by:	**Ethics Committee**	**Date Approved: 5/2/16**

REVIEW RECORD			
Date	**Issue No.**	**Reviewed By**	**Description Of Changes (If Any)**

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**