1. Introduction

The purpose of this Standard Operating Procedure (SOP) is to outline the process required when research includes either or both randomisation and blinding where the research is HOSTED by the University Hospitals of Leicester NHS Trust (UHL) or for where the UHL is a Research SITE.

1.1)
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 Good Clinical Practice 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. Scope

This SOP applies to all research studies Hosted by the UHL where there is a requirement to randomise or blind.

3. Definition

Randomisation is the process by which participants in a clinical trial are randomly assigned to treatment groups in an unbiased and balanced manner, such that neither the participant nor investigator can influence which treatment group the participant is assigned to.

3.1)
Suspected Unexpected Serious Adverse Reactions (**SUSAR**) An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the **definition** of a Serious Adverse Reaction.

3.2)
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 study (with the exception of the circumstances described in Section 9) to ensure that no bias is introduced.

4. 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 study has a straightforward design.

5. 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 must be clearly documented and must include who was responsible for its generation and who had access to the schedule before database lock. The randomisation schedule must be version controlled so it is clear which the final version is.

5.1)
Methods of randomisation that cannot be verified at a later date and reconstructed must be avoided.

5.2)
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. Distribution and Storage of the Randomisation Schedule

The randomisation schedule may consist of a paper record only or as an electronic version. There must 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 must be apparent which version is the final one.

6.1)
There should be a record of the randomisation process and relevant training records held within the Investigator Site File (ISF) to ensure all members of the research team are aware of the randomisation requirements.

6.2)
The randomisation schedule can be used for numerous purposes and it is recommended that the distribution requirements are documented on the specification.

7. Blinding

The only difference between various treatments provided as part of a study should be the subject number on the label. In the case of Investigational Medicinal Product (IMP) studies, there must be no indication whether a given subject is receiving active drug, comparator or placebo; if this is not possible then an unblinded operator may be responsible for reconstitution and/or administering the IMP.

8. Maintenance of the Blinding

8.1)
Maintaining the integrity of the blind is a key consideration for all those involved in the study, as compromising the blinding may have a significant impact on the interpretation of the results.

(8.1.1)
The Sponsor and CI/PI must implement procedures to control the randomisation schedule to prevent accidental or deliberate unblinding. These procedures must 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 study. The processes for handling code breaks, randomisation envelopes, master randomisation list and drug administration records are all important in maintaining the blinding and must 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.

(8.1.2)
Consideration must be given to the identifiers present on IMP packaging to ensure that they do not compromise the integrity of the blind. For example, investigators should consider if IMP and placebo/comparator drug production batch numbers could lead to unblinding.

(8.1.3)
In cases where data monitoring committees require interim unblinded analysis reports there must be robust procedures in place to protect the study 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.

8.2) 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.

(8.2.1)
Blinding processes must 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 IMP to the person who administered it.

8.3) Efficacy and Safety Assessments
Where there are unblinded personnel there must 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 must be retained separately from the rest of the study documentation until the end of the study or until the randomisation code has been broken for analysis.

(8.3.1)
Where the design of the study, 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 study 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.

8.4) Monitoring

For blinded studies, consideration must be given to accommodating an unblinded monitor for the IMP aspects and how any visits and communication will be documented, reviewed and approved without compromising the blinding.

8.5) 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 study. Laboratories that generate clinical study data should be aware of whether the study is blinded or not and exercise due diligence when communicating data to ensure the blind is not compromised.

9. 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 must be a backup system in place to enable breaking of the blind in the event that an IRT system is not functioning.
Unblinding should only occur if knowledge of the treatment assignment is considered necessary to determine the optimal medical management of the patient.

(9.1.1)
UHL requires that the IRT system is checked to ensure that access can be gained and that the correct permissions are in place for the PI/delegate to access the system prior to commencement of recruitment and during the study to ensure access is maintained.

(9.1.2)
The PI should ensure that there is cover for unblinding by a delegated medic, where either planned or unplanned leave is taken by the Principal Investigator. This role should be clearly documented on the delegation log and relevant access and training on the procedure undertaken. This must be in place before study commencement and updated as applicable during the timespan of the study.

9.2) Unblinding for SUSAR Reporting

SUSARs need to be unblinded prior to reporting to the competent authority and specific REC, however, this unblinding must not be undertaken by the investigator or the research team. The SUSAR must be reported to the Sponsor who will have an appropriate individual identified for each study 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 study team.

The PI should ensure that there is cover for unblinding and SUSAR reporting by a delegated medic, where either planned or unplanned leave is taken by the Principal Investigator. This role should be clearly documented on the delegation log and relevant access and training on the procedure undertaken. This must be in place before study commencement and updated as applicable during the timespan of the study.

9.3) Unblinding of the Study for Analysis Purposes

There must be a formal process to control the unblinding of a study for analysis purposes and this must be recorded. There must 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 must contain times as well as dates.

10. Reconciliation of Code Breaks at the End of the Study

Reconciliation of physical code breaks must be undertaken at the end of the study 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. Randomisation Errors

Randomisation errors must be treated in the same way as Protocol Deviations and reported to the Sponsor as per the relevant Sponsors SOP process.

12. Responsibilities

	Responsibility	Undertaken by	Activity
1	Sponsor/CI	CI/PI/ Delegated Individual	Ensure prior to study commencement that responsible individuals are identified and delegated the responsibility for SUSAR reporting. Ensure cover for planned/unplanned leave.
	Sponsor/CI/PI	PI/Delegated Individual	Check access to and randomisation/unblinding systems prior To study commencement and at time points during the study lifetime.
2	Sponsor/CI	Statistician or suitably qualified individual	Produce/manage the randomisation schedule
3	PI/ Delegated Individual	PI/ Delegated Individual	Implement procedures to control the randomisation schedule. Maintain the integrity of the blind to prevent accidental/deliberate unblinding throughout the lifetime of the study.

13. Who Guideline Applies To

All staff within UHL and external to UHL who are delivering research.

14. Education and Training

The SOP is detailed so the process can be clearly followed. No flowchart is provided / required.

15. Education and Training

None

16. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Sponsor Audit	Randomly chosen for audit	Carolyn Maloney	As and when	A report will be produced

17. Supporting Documents and Key References

None

18. Key Words

Research, Innovation, EDGE, Randomisation, Blinding, Unblinding, IRT, SUSAR

19. Contact and Review Details

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Lisa Wann R&I manager	**Executive Lead** **Medical Director**
Details of Changes made during review: **Review and update**	

20.

This line signifies the end of the document

20.1)

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

20.2)

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Julie James / Carolyn Maloney	**Job Title:** Clinical Trial Monitor / Head of Research Operations
Reviewed by:	UHL R&I Governance Meeting	
Approved by:	Professor Nigel Brunskill	**Date Approved:**

REVIEW RECORD			
Date	**Issue No.**	**Reviewed By**	**Description Of Changes (If Any)**
April 2021	1	CM,LW,JJ	Update to new trust template

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