STU-SOP-DMS-002– Standard Operating Procedure on Blinding and Unblinding

1. Purpose

The purpose of this SOP is to describe the standard operating procedure (SOP) for blinding and unblinding within all randomised controlled trials adopted or managed by Swansea Trials Unit (STU) where the allocation arrangement is managed in house.

For externally managed allocations, the process for unblinding will be detailed in an appropriate contract.

2. Background

Blinding is a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s) to remove the potential of bias arising from the influence of knowing the assignment(s). Unblinding is the process by which the treatment allocation code is broken, revealing the intervention allocated to a trial participant. Unblinding may take place:

1) in medical emergencies;
2) for the purpose of notification to the Data Monitoring Committee (DMC);
3) in error;
4) for analysis purposes at the end of the trial.

The trial protocol must define the level of blinding (e.g. single blind or double blind) and the process to manage emergency unblinding. Measures should be agreed during the design phase of the trial to prevent unblinding the entire treatment arm and the entire study in the case of a two-armed study when the treatment allocated to a trial participant has to be revealed for clinical and safety reasons.

3. Roles and Responsibilities

Chief Investigator (CI) is responsible for ensuring arrangements for blinding and unblinding are in place and to liaise with the DMC and Sponsor as required.

Trial Statistician (TS) ensures the delivery of the randomisation list and is responsible for liaising with a suitably qualified peer, herewith referred as the Additional Statistician, for blinding and unblinding.

Independent Statistician (IS) is independent of the trial team and will liaise with the TS to generate allocation sets, safeguard the integrity of blinding, log the location of all documentations relevant to blinding and unblinding, and carry out necessary independent analysis requested by the DMC.

Trial Manager (TM) is responsible for overseeing that randomisation and allocation systems work properly e.g. packaging, coding and labelling of treatments to protect blinding; delivery of randomised treatments to trial participants; ensure unblinding logs are properly kept and transmitted to the relevant parties.

Data Manager (DM) is responsible for ensuring the database is designed to help preserve blinding and to ensure that the entire randomisation list, as available, is covered, unique trial participant identifiers are generated and transmitted to IS for mapping to allocation sets.

External use of SOP: this SOP and Associated Documents (AD) may be used for research projects not adopted by STU where Swansea University (SU) staff and associated NHS organisations require guidance. In such instances, oversight responsibility for any associated tasks will not be the responsibility of STU.

4. Procedure

Research team personnel should remain blinded as appropriate during the trial. Key steps to implement blinding and manage unblinding are summarised in this section. Adequate steps should be taken to ensure that all trial interventions are indistinguishable from each other.

4.1 Coding of treatments

After generating the randomisation list, the TS should liaise with the IS to produce a Treatment Coding Document. The Coding Document will contain a set of codes for each treatment in the study. For example:

- 1 = Paracetamol
- 2 = Ibuprofen
- 3 = Placebo
- 4 = Aspirin

Any subsequent documentation of the trial should then use these codes instead of the direct names of the treatment, to help preserve blinding. IS should have the only access to the Treatment Coding Document and is responsible for its maintenance and security. The Coding Document should be stored electronically in a password-protected manner and as a hard copy in a secure and confidential area with restricted access. Location details will be held in the TMF.

4.2 Produce Allocation Sets

During a double blinded trial, it may not be sufficient to anonymise treatments delivered to individual participants with a treatment code. Any unblinding of a single participant may unblind the entire treatment arm and the entire study in the case of a two-armed study. To mitigate against this risk, the IS should produce sets of allocation identifiers (IDs mapping back to specific treatment code. The associated document Recommendations for Generating Allocation Identifiers (STU-AD-GDN-004) should be used as a reference.

Details of randomisation and allocation will be documented in the protocol to protect blinding. Where applicable, how treatments should be packaged, coded and labelled will be outlined in the protocol as required.

The IS will verify that the Allocation Sets maps to the randomisation list using the Allocation to Randomisation Checklist (STU-AD-TMP-013).

4.3 Manage unblinding

Circumstances for breaking the randomisation code must be clearly described in the protocol, and the trial procedure for unblinding documented. The unblinding request log (STU-AD-FRM-012) should be completed. The method to be used for office and out of hours unblinding must be tested, documented and filed in the Trial Master File.

The details of all unblinding, including the revealed codes, shall be included in the statistical report at the end of the trial.

4.3.1 In medical emergencies

Any member of the medical team, or a health care professional involved in the care of a participant, may request unblinding in an emergency situation.

Arrangements for 24 hour emergency unblinding should be made before the trial commences. Details of the revealed allocation will be transmitted to the requesting party by the IS or delegate. Details of the request must be documented using the Unblinding Log (STU-AD-FRM-012) and stored in a confidential section within the Investigator Site File.

The trial office will be informed about all unblinding requests.

4.3.2 For the purpose of requested notification to relevant safety committees

The IS shall request and receive copies of the relevant unblinding log(s) and perform any interim analyses described in the protocol or subsequently requested for safety purposes. The IS shall prepare an unblinded report which should include the date of code breaking and the reasons for the unblinding request.

The unblinded data and the results supplied shall not be accessible to the CI or trial staff.

4.3.3 Erroneous unblinding

Details of any erroneous unblinding shall be documented using the Unblinding Request Log (STU-AD-FRM-012) and completing a file note where relevant.

4.3.4 For analysis purposes at the end of the trial

The Statistical Analysis Plan must be finalised prior to the release of the allocation IDs. A record shall be kept in the TMF detailing who requested and when the allocation IDs were provided.

5. References

- Health Research Authority website (HRA) - http://www.hra.nhs.uk/
- Medicine and Healthcare products Regulatory Agency website (MHRA) - https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency#page=DynamicListMedicines
- UK Policy Framework for Health and Social Care Research (2017) - https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/
- UK Medicine for Human Use (Clinical Trials) Regulations 2004 - http://www.legislation.gov.uk/uksi/2004/1031/contents/made
- ICH Guideline Statistical Principles for Clinical Trials - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

It is assumed that by referencing the principal regulations that all subsequent amendments are included in this citation.

6. Associated Documents

Number	Title	Location
STU-AD-GDN-004	Recommendations for Generating Allocation Identifiers	Q-Pulse
STU-AD-TMP-013	Allocation to Randomisation Checklist	Q-Pulse
STU-AD-FRM-012	Site Unblinding Request Form	Q-Pulse

7. Abbreviations

List of Abbreviations	
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DM	Data Manager
DMC	Data Monitoring Committee
IDs	Identifiers
IMP	Investigational Medicinal Product
IS	Independent Statistician
PI	Principal Investigator
SOP	Standard Operating Procedure
STU	Swansea Trials Unit
SU	Swansea University
TM	Trial Manager
TS	Trial Statistician

8. Appendices

Appendix 1: Document History

Version No:	3	**Effective Date:**	22-Apr-2024
Description of changes:	Updated to SOP Template v5		

Appendix 2: Blinding and Unblinding Flowchart