DIRECTORATE OF RESEARCH AND INNOVATION

Document Number: GOSH/ICH/SOP/R/037	Version Number: 2
Title: Managing Blinding and Unblinding	
Effective Date:	*Same as implement by date.*

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1. Scope

This SOP is applicable to

- All Great Ormond Street Hospital for Children (GOSH) or UCL Great Ormond Street Institute of Child Health (GOS-ICH) staff who will be involved in the set-up and/or conduct of research studies that involve blinding. This includes studies where GOSH and/or UCL are the Sponsor (and where these studies are managed through the Joint R&D Office for GOSH/ICH) or where there is an external Sponsor (hosted studies).

Further to the requirements listed in this SOP, personnel must also comply with:

- Any additional study-specific requirements mandated by the CI, PI, Sponsor or R&I.

2. Purpose

The purpose of this SOP is to outline the process to ensure that blinded studies are appropriately managed, so that the blind is maintained while ensuring that participants are protected and can be unblinded in an emergency, as well as the documentation that is necessary to demonstrate this.

3. Definitions/Abbreviations

Blinding – The process by which one or more parties (e.g. the investigator team and/or the participant and/or the data analysts) are kept unaware of what intervention the participant has been allocated to. The blind should be maintained throughout the study to ensure that there is no bias of expectation influencing the research findings, particularly when making safety and/or efficacy assessments.

- Open-label – All parties are aware of the intervention the participant has been allocated to.
- Single-blinded – Either the participants or the researchers don't know which study group the participants are in.
- Double-blinded – Neither the participants nor the researchers know which study group the participants are in.
- Triple-blinded - Neither the participants, the researchers, nor the people carrying out the statistical analysis know which study group the participants are in.
- Blinded and unblinded teams – in some studies, it might not be possible to blind the whole study team (e.g. if the research nurse needs to make up the study drug in the ward). In this case, some of the team may be unblinded (aware of the intervention allocation) and the rest will be blinded (see section 5.1).

CI – Chief Investigator

CRF – Clinical Research Facility

EPR – Electronic Patient Record

GCP – Good Clinical Practice

IMP – Investigational Medicinal Product

IRT – Interactive Response Technology

ISF – Investigator Site File

PI – Principal Investigator

PSF – Pharmacy Site File

Research – As per UK Framework for Health and Social Care Research and HRA/MRC 'Is my study research?' tool.

Unblinding (or code-break) – The process by which the treatment or allocation of the intervention are unmasked. This may be necessary in an emergency where knowledge of the allocation is necessary for the treatment of an adverse event, or in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) needing expedited reporting (see SOP/R/005 - Reporting and Escalation for Clinical Research Studies). Note that unblinding may result in the participant being withdrawn from the study.

4. Responsibilities

Duties may be delegated but the responsibility always remains with those listed.

4.1 The Sponsor is responsible for:

- Ensuring that blinded studies and interventions are designed to robustly preserve the blind while protecting participants.
- Reconciling the blinding arrangements at the end of study to ensure the blinding has not been compromised and any cases of unblinding have been appropriately documented.

4.2 The study Principal Investigator (PI) is responsible for:

- Ensuring that their study complies with the requirements detailed in this SOP and Trust processes (e.g. the use of EPR).
- Ensuring a documented unblinding procedure (including appropriate contingencies) is in place and has been checked prior to the first participant visit, and that all staff involved in the study and process are aware of the arrangements.
- Ensuring that any processes put in place to preserve the blind will not compromise, hinder or delay the care of the participant. This includes ensuring that the study team would be able to unblind a participant immediately in the case of an emergency. If they have concerns about the blinding, then these must be discussed with the Sponsor as soon as possible.
- Ensuring that if they become aware of any aspect of the study design which may compromise the blind, they let the Sponsor know as soon as possible.
- Ensuring that if deliberate or accidental unblinding occurs, the unblinding procedure is followed and appropriately documented in the Investigator Site File (ISF) and participant's EPR.

4.3 Unblinded Staff are responsible for:

- Maintaining the study blind in accordance with the protocol and study-specific blinding/unblinding procedures.
- Only reveal intervention allocation if instructed to do so by the study medical monitor/ PI or CI.

4.4 All staff are responsible for:

- Being aware of the specific blinding arrangements for their studies and preventing accidental or premature unblinding.
- Being aware of the specific unblinding arrangements for their studies and ensuring they would be able to unblind a participant immediately if required.
- Ensuring that if they become aware of any aspect of the study which may compromise the blind, they raise this as soon as possible (see section 5.2).
- Ensuring their practice meets the requirements of this SOP, the study protocol, GCP and any applicable legislation, policies, procedures or guidelines.

5. Procedure

5.1 Managing the Blind

Procedures to manage blinded studies must be put in place before the study starts and will define which people and/or roles (if any) have access to unblinded information (e.g. pharmacy staff if a randomisation list is used, lab staff performing PK analysis, a nurse who has to prepare and/or administer an infusion from labelled medication, a data manager entering dosing information).

Those who are unblinded must take particular care that they do not inadvertently unblind others. Any processes put in place to protect the blind must be

documented in FRM/R/014 Managing Blinding and Unblinding. These may involve setting up physical barriers such notices on doors to keep blinded people out of a room where drug is being checked, or use of sealed envelopes for essential documents in the site file.

The study team must think about how records will be stored to protect the blinding while maintaining appropriate documentation and access. They must also think about how to ensure communication links exist within the team, between the study team and supporting departments (such as imaging, pharmacy and labs), and between the study team and Sponsor that allow for the effective transfer of information whilst also protecting the blind.

The study team may also want to consider discussing with participants/families that they limit talking about the study (e.g. on social media or in patient forums) in case this jeopardises the blind. Such conversations with participants must be documented in their EPR.

If Pharmacy are managing the blinding, their controls will be detailed in the Pharmacy Site File (PSF) and access will be restricted to unblinded study personnel including an unblinded monitor. Pharmacy may manage the blind when:

- The IMP allocation is from a paper-based randomisation list, or
- Pharmacy masks the IMP allocation at dispensing, after they have used unblinded IRT allocation e.g., IMP is aseptically reconstituted in Pharmacy.

However, it should never be assumed that pharmacy are managing the blind, even if they are unblinded, unless this has been specifically agreed.

5.2 Concerns About the Blinding

During the study, blinded members of the study team may suspect that they know which intervention a participant/group of participants has been allocated. For example, certain properties of an IMP (such as smell or how well it can be drawn up into a syringe), or from adverse events that participants experience (such as injection site reactions or more frequent urination).

If this happens then it might mean that the blind is/could be at risk, and this should be escalated as soon as possible to avoid the study being compromised. The person must be very careful when talking about their concerns to ensure they don't accidentally unblind others. Concerns should be raised to the unblinded lead or PI in the first instance so that they can support further investigation/escalation to the Sponsor as required. The R&D department (Research Governance Manager or Head of Governance, Clinical Trials and Contracts) can support from a governance perspective.

5.3 Written Unblinding Procedure

Blinded studies must have a defined process to allow the investigator site to unblind a participant immediately if required (e.g., in the case of a medical emergency). Unblinding must be secure, always readily available during the study, and not allow breaks of the blinding to go undetected. Emergency breaking of the blind may be done using physical code breaks (e.g., code-break envelopes kept in the PSF or ISF) or via an interactive response technology (IRT) system. The

unblinding process, and how/when the Sponsor should be notified of unblinding, should be described in the protocol or associated document. If it isn't, the PI must discuss this with the Sponsor as soon as possible.

Before the start of the study, the study team must complete FRM/R/014 Managing Blinding and Unblinding to ensure the local site step-by-step instructions are documented (see 5.5).

Consideration must be given to what would happen if unblinding was required out-of-hours, particularly if out-of-hours cover is provided by non-study staff.

If an IRT system is used, consideration must be given to what the back-up system for managing the unblinding will be if this is not working (this will need to be discussed with the Sponsor/owner of the system) or if key staff are unavailable.

5.4 Unblinding Procedure Preparation and Testing

The unblinding system should be in place before the study starts to make sure the intervention is not given before the study team can unblind (e.g. code break envelopes or IRT login details need to be sent to site before or together with the intervention).

The PI must ensure that the unblinding process is tested before the first participant visit. This means that the system is available (e.g., physical code breaks are in the designated place, or working and appropriate access codes for the IRT have been provided) and that all staff involved in the study and process are aware of the arrangements.

Any testing must be documented in FRM/R/014 Managing Blinding and Unblinding along with if the testing was satisfactory, or if not, that corrective action has taken place.

5.5 Documenting the Blinding and Unblinding Management

FRM/R/014 Managing Blinding and Unblinding is used to document the local site processes for managing the blinding and unblinding for the study, including any testing.

This form must be drafted during study set up and must be finalised before the first participant is recruited to make sure that all the necessary steps to manage blinding and unblinding are in place in good time.

If there are any changes to managing the blinding or unblinding, a new version of the form must be completed. The previous version(s) must be retained and marked as 'superseded'.

All finalised versions of the completed form must be stored in the ISF.

5.6 Unblinding During the Study

The study randomisation and blinding procedures must be followed and unblinding should only occur if necessary (e.g. to clinically treat a patient). Any premature unblinding (e.g., accidental or emergency unblinding) must be promptly

documented in the ISF and EPR and explained to the PI, R&D and Sponsor at the earliest opportunity (evidence of this communication must also be filed in the ISF).

To avoid introducing bias into the study, care should be taken to limit the knowledge of the randomisation arm the unblinded participant was assigned to.

If there is premature unblinding, the impacted participant(s) and/or staff may need to be withdrawn from the blinded part of the study to prevent bias. This will need to be decided on a case-by-case basis by the PI depending on the degree of unblinding, the likelihood and/or consequence of bias, and the study processes. There may need to be a discussion with the Sponsor. All decisions must be documented and filed in the ISF (and EPR for participants).

A Sponsor may request to be contacted before unblinding, however, the safety of the participant is paramount and so delays, or a Sponsor's refusal to unblind a participant in an emergency is not acceptable.

5.7 Support and Escalation

If a staff member has questions or queries, they can ask for support from a more experienced colleague or their line manager. If the query is related to a specific study, then the study research nurse, PI, Governance officer, and/or CRA may also be able to help.

If a staff member becomes aware of an issue or has any concerns, then this must be escalated to the appropriate person(s) in a timely manner (see SOP/R/005 Reporting and Escalation for Research).

5.8 Compliance

Compliance with this SOP will be reviewed during routine monitoring/audit.

At the end of the study, the Sponsor is responsible for reconciling the blinding arrangements to ensure that the blinding has not been compromised and any cases of unblinding have been appropriately documented.

Systematic or persistent failure to comply with the study procedures and/or this SOP will be seen as non-compliance to GCP and must be bought to the attention of the Head of Governance, Clinical Trials and Contracts who will decide the appropriate action.

6. Related Documents

- GOSH/ICH/SOP/R/005: Reporting and Escalation for Clinical Research Studies
- GOSH/ICH/FRM/R/014: Managing Blinding and Unblinding

7. References

- MHRA Good Clinical Practice Guide (Grey Guide) chapters 6.6, 11.4.9, 12.7.3
- MHRA Phase I Accreditation Scheme Requirements
- MHRA Phase I Accreditation Scheme Guidance Document

- ABPI (2012) Guidelines for Phase I Clinical Studies