NIHR | Lancashire Clinical Research Facility

STANDARD OPERATING PROCEDURE

Unblinding in Clinical Trials

AUTHOR.	AUTHORISED BY	DATE AUTH	RISK MANAGEMENT PROCEDURE NUMBER
NAME **Dr David Cameron** **LCRF Senior Clinical Research Fellow**	NAME **Dr Dennis Hadjiyiannakis** **LCRF Medical Director**	04-09-2025	**LCRF SOP 29**
SIGNATURE *David Cameron*	SIGNATURE *Dennis Hadjiyiannakis*	**REVIEW DATE** 04-09-2027	

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RESEARCH AND DEVELOPMENT

LCRF

BACKGROUND

The National Institute of Health & Care Research (NIHR) Lancashire Clinical Research Facility (LCRF) is a purpose-built unit within Lancashire Teaching Hospitals NHS Foundation Trust (LTHTr), providing access to Early Phase Experimental Medicine research trials to the local population.

Clinical Trials of Investigational Medicinal Products (CTIMPS) may employ (single or double) blinding, wherein the treating team and/or the participant is unaware of the precise treatment administered. Blinded trials often involve the use of placebo treatment. It is possible that treatment may need to be revealed for safety or other reasons during the trial. This process is known as “unblinding”, “breaking the blind”, or “code break(ing)” and under normal circumstances must be avoided if possible, to avoid compromising the integrity of the trial. It is essential that a robust process for unblinding (where appropriate) is in place. This process must allow for unblinding both in and out of regular working hours.

Some CTIMPS include both blinded and unblinded delegated staff. In these circumstances some delegated staff may be aware of the treatment used (for example if unavoidable due to the practicalities of administration) whilst others remain blinded.

PURPOSE/OBJECTIVE

The purpose of this Standard Operating procedure (SOP) is to provide guidance to principal Investigators (PIs) and research study teams on best practice for ensuring a robust mechanism is in place for unblinding study treatment where required.

SCOPE

This SOP applies to Principal Investigators and members of research teams conducting clinical trials employing any form of blinded treatment which may require unblinding for any reason (both in and out of hours).

PROCEDURE

1. WHO?

• The PI is ultimately responsible for all aspects of a trial and must read and understand this SOP. As likely the most senior member of the study team involved in the trial and with an in-depth knowledge of the investigational medicinal product they are often the "decision maker" with responsibility for deciding to unblind a blinded treatment.
• This SOP is also for the benefit of Sub-Investigators and other team members who may be involved in the process of unblinding treatment.

2. WHEN?

• This SOP must be referred to during the lifespan of any clinical trial involving the LCRF for any clinical trial that employs blinded treatments.

3. HOW?

Maintaining the blind

Under usual circumstances blinding in clinical trials must be maintained for any blinded trial. It is important when designing the trial to consider how the blinding will be maintained. The specifics of maintaining blinding (for example through the use of split teams and responsibilities for blinded and unblinded delegated staff) must be assessed during the feasibility stage of study setup and must be agreed to by the PI. This will ensure that inadvertent unblinding is avoided.[1]

The trial protocol must define the level of blinding and how this will be implemented.[2] This includes which trial staff must be blinded and which (if any) may be unblinded.

The sponsor must implement procedures to control the randomisation schedule, or documents containing treatment information, to prevent accidental or deliberate unblinding. This must be strictly enforced for blinded protocols.[1]

For double blinded trials procedures, there must be documentation on how the IMP will be packaged, coded and labelled in a manner that protects the blinding.[4]

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Unblinded team members must take all precautions to avoid accidentally revealing information to blinded team members which may compromise the integrity of the blind.

Participant trial details must be appropriately recorded to ensure straightforward access for all staff. This includes the recording of the specific site ID number and participant trial number to be readily accessible via the EVOLVE/Harris Flex electronic health record (EHR) system, or other EHR as appropriate. A short synopsis should also be uploaded to the EHR to cover the procedure for unblinding. Responsibility for this lies with the Research nursing team/Clinical Research Fellow.

In order to maintain the blind, unblinded documentation must be stored separately as per the blinding plan for each individual study.

Please ensure that the blinding plan for any study is referred to in the event of unblinding.

For Oncology trials, site specific ID and participant trial numbers are to be recorded on the iQEMO notes system in a readily accessible fashion and must also include a short synopsis to cover the procedure for unblinding. Responsibility for this lies with the Research nursing team/Clinical Research Fellow.

Unblinding procedures

The process for unblinding a participant's treatment must be detailed in the protocol and the procedure thoroughly documented in the trial specific instructions/procedure. The exact unblinding procedure may vary from trial to trial (e.g. through the use of paper envelopes or electronic systems) but must include at a minimum the points detailed below. This must be agreed as part of feasibility.

- The procedure must document the circumstances in which unblinding of the participant can be undertaken.[2]
- The investigator or delegate must have a written procedure for rapidly identifying a blinded IMP and how to unblind it in an emergency.[3,4]
- The procedure must be secure, and readily available at all times during the trial.[2,4]
- Breaks of the blinding must be appropriately recorded and must not be permitted to go undetected.[4]
- An Investigator should be able to unblind a participant's treatment allocation immediately, without having to first contact any trial staff or the sponsor.[4]
- The procedure must instruct what needs to be documented and how for any emergency unblinding.[4]
- The procedure for unblinding participant treatment must be tested as soon as possible during study setup and prior to participant enrolment. This trial run must incorporate the involvement of the PI.

Out of hours considerations

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It is essential that, in the case of an emergency, there is a system in place for providing 24-hour cover to access the code break.[4] It is recommended that the study employ an electronic method for unblinding study treatment.

The unblinding process (be this via telephone ,email or digital system) should be tested (including out of hours) periodically (e.g.6-monthly) . Documentation of the testing should be recorded.[4] Responsibility for this lies with the Clinical Fellow and must include the Principal Investigator and all staff who may take responsibility for unblinding.

If a telephone number or other outside contact system is involved in the unblinding process, this must be clearly documented in the participants EHR (including Evolve and, where appropriate, iQEMO or other systems relevant to the speciality) so as to be readily available in the event of an emergency.

Inadvertent unblinding

Study protocols should include the procedure to follow in the event of accidental/inadvertent unblinding.

Inadvertent unblinding of trial staff should be reported to the Sponsor immediately. Trial staff who become unblinded to trial treatment should not thereafter participate in trial related activities that require staff to be blinded.

4. References:

1. MHRA Good Clinical Practice Guide 2012
2. UCL Standard Operating Procedure for the Preparation of a Trial Specific Randomisation, Blinding and Code Break Standard Operating Procedure V05 12/02/21
3. UKCRF Framework for Conducting Highest Risk Phase I and Experimental Medicine Studies within NIHR Clinical Research Facilities and wider NHS acute Trusts Version 1.0 – November 2020
4. ABPI Guidelines for Phase I clinical trials 2018 edition

OTHER RELATED PROCEDURES:

LCRF SOP 28_Out of Hours Cover For clinical Trials.
RDCLI08_Safety reporting

CONSULTATION WITH STAFF AND PARTICIPANTS

Name	Role
Dr Dennis Hadjiyiannakis	Medical Director, LCRF
Jacqueline Bramley	Head of Clinical Research Operations/NIHR Lancashire Clinical Research Facility Lead
Dr Kina Bennett	Head of Research & Development
Rebecca Davenhall	Quality Assurance Lead
Early Phase Committee	Review and Approval
LCRF Operational Group	Review and Approval

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Sign Off Lancashire Teaching Hospitals			
Lead Author:			
Name and Position	Dr David Cameron, LCRF Senior Clinical Research Fellow		
Signature	*David Cameron*	**Date**	04-09-2025
Reviewed and approved by:			
Name and Position	Dr Dennis Hadjiyiannakis, LCRF Medical Director		
Signature	*Dennis Hadjiyiannakis*	**Date**	04-09-2025
Authorised for release by:			
Name and Position	Rebecca Davenhall, Research Quality Lead/Research Access Project Manager		
Signature	*Rebecca Davenhall*	**Date**	04-09-2025

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