York and Scarborough Teaching Hospitals NHS Foundation Trust R&I Department
Standard Operating Procedure
Pharm/S54

Managing Code Break Procedures (Unblinding)

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&I Department's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&I Department SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&I Department website: https://www.research.yorkhospitals.nhs.uk/sops-and-guidance-/ and/or Q-Pulse

SOP Reference:	Pharm/S54
Version Number:	6.0
Author:	Poppy Cottrell-Howe
Implementation date of current version:	1st July 2025

Approved by:	Name/Position:	Kate Nixon Deputy Chief Pharmacist
	Date:	23rd June 2025
	Name/Position:	Sarah Sheath, SOP Controller
	Date:	30th June 2025

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Reviewers	Details of significant changes
1.0	1st February 2011		
2.0	12th September 2013		Removal of references to the North and East Yorkshire R&D Alliance. Change of SOP Controller. Updated to include Scarborough hospital as a site using this SOP. Addition of requirement to write study specific SOP (or include procedures in trial instructions) for handling of a randomisation schedule in Pharmacy to ensure maintenance of study blinding.
3.0	20th August 2015		
4.0	19th December 2017		Change of author, removal of reference of pharmacy green light letter.
5.0	3rd September 2020		Change of link to R&D website.
6.0	1st July 2025	Poppy Cottrell-Howe	Removal of outdated methods, updated process to reflect the modernised methods used by sponsors.

Contents

1 Introduction, Background and Purpose

Unblinding is the process by which the treatment allocation code is broken, revealing the intervention allocated to a trial participant. Sponsors of clinical trials have strict unblinding procedures, and study sponsors must provide documentation of the unblinding procedure their clinical trial as part of the regulatory requirements.

It is important to keep in mind while reading this SOP that all studies will have their individual unblinding requirements specific to the individual trial. This SOP is to ensure that all code break requests are carried out and documented in line with study specific requirements and that an audit trail is maintained to avoid inadvertent or deliberate unblinding.

In circumstances where Pharmacy is unblinded to a patients' treatment allocation, and will handle documents containing treatment information, particular care should be taken to ensure the process to maintain blinding is robust and clearly documented.

2 Who Should Use This SOP

This SOP applies to all Pharmacists that have on call responsibilities and members of the Pharmacy clinical trials team at York and Scarborough Teaching Hospitals NHS Foundation Trust. Research Nurses/Members and those acting as Principal/Sub Investigators responsible for blinded studies and clinical trials.

3 When this SOP Should be Used

This SOP describes circumstances of when code breaking/Unblinding may be needed and the commonly used methods of code breaks.

- Testing the code break procedure prior to the trial opening at site.
- Unblinding procedure during standard open hours performed by the Pharmacy Clinical Trials Team
- Emergency unblinding out of hours – supported by the on-call pharmacist and Principal Investigator or delegate.

4 Procedure(s)

4.1 Undertaking a Code Break/Unblinding

Code break procedures must be clearly established to ensure that no unnecessary or unintentional un-blinding occurs and to protect the integrity and validity of the data. If unblinding of participants is allowed during the conduct of a clinical trial other than for an emergency situation, the protocol must state the procedures for obtaining permission to break the blind.

It may be necessary to break a trial code for the following reasons:

1. In the event of a medical emergency in a trial participant and by request from the physician responsible for the patient or the Chief Investigator (CI)/Principal Investigator (PI) for the trial.

2. In the event of a Serious Adverse Reaction (SAR) in a trial participant and by request from the Sponsor where the Sponsor is the Trust.

3. In the event of concerns over trial safety (e.g. for review by a Data Monitoring Committee) and by request from the Sponsor where the Sponsor is the Trust.

4. At the end of the study and only with agreement of the Sponsor where the Sponsor is the Trust.

5. In the event of a SUSAR (Suspected Unexpected Serious Adverse Reaction) needing expedited reporting

6. Where a child in a participant's household accidentally takes an IMP

Note: A medical emergency in a trial participant may occur either during normal pharmacy working hours or out of hours. In the event that a code break is requested out of hours the on-call pharmacist must be contacted via switchboard (or as per local policy).

Methods of code break/unblinding

Each clinical trial may use a different format for unblinding participants treatment allocation outlined in the study protocol. This procedure will be detailed in Trial Summary within the pharmacy site file and in the individual study protocol.

Methods of the code break include:

- 24-hour telephone number
- IWRS
- Tear off labels.
- Code break envelopes.
- Sealed envelope website.
- Or any other methods which the sponsor deems suitable for their clinical trial.

4.1.1 Unblinding procedure during standard open hours

The Principal Investigator (PI) or Sub-PI should always be informed and must follow the instructions specific to the study in question to unblind the participant. The Principal Investigator (PI) or Sub-PI can find the unblinding information in the study specific protocol.

A member of the Pharmacy Clinical Trials Team) can facilitate the breaking the code by following the procedure outlined below depending on the method used to preform unblinding

- Notify all necessary parties that a code break has been undertaken (i.e. CI/PI, Clinical Research Associate (CRA) or Sponsor, R&I Unit, Research Nurse) and the reasons for the actions taken as soon as possible.

- The PI/Sub PI is responsible for documenting the breaking of the code and the reasons for doing so on the Case Report Form (CRF) and in the Investigator Site File (ISF).
- The PI is responsible for notifying the Research Ethics Committee (if applicable) and follow up with the sponsor on the actions to complete following the unblinding of the participant.

4.1.2 Unblinding procedure for out of hours performed supported by the on-call pharmacist.

An unblinding request may be made for any of the above-mentioned reasons in section 4.1. However, it is important to inform the requestor (if it is not the CI or PI) that they should only unblind the participant if they feel it is necessary.

In the majority of cases the on-call pharmacist is not performing the unblinding but assisting in passing on information to the treating physician out of hours about the trial and how the unbinding can be performed if required. This is primarily because pharmacy have an on-call service so can access clinical trials protocols out of hours. The prevalent used method (especially for commercial sponsors) is to use IWRS/IRT (a web-based programme which access is only granted to those with direct association to the individual trial) meaning a PI, SubPI or delegate will have to perform the unblinding via this system. This is why it is essential this process is confirmed with the PI prior to opening by testing their access.

- Either locate the physical Pharmacy site file for the study for which code break is being requested. These files are in the Pharmacy clinical trials dispensary at the York site. **Or** locate the electronic folder on the pharmacy x: drive X:\Clinical Trials\Studies\3. Open to recruitment (patients receiving treatment) chose the York or SGH depending on where the study is based. Select the study and find the current version of the trial summary in the 1. Pharmacy Trial Instruction folder.
- In the trial summary it will have an unblinding section follow the procedure outlined in this section.
- Confirm the name and role of the person requesting the information and the reason for the code break/unblinding request.
- Confirm the participants name and trial ID number.
- Complete the code break/unblinding record form (Pharm/F53) printed from R&I website https://www.research.yorkhospitals.nhs.uk/sops-and-guidance-/pharmacy-sops-forms-and-templates/if a code break form is supplied by the sponsor (this will be found in the code break section of the Pharmacy site file) this must be completed in conjunction with Pharm/F53.
- You can contact the Pharmacy clinical trials manager or the Deputy chief pharmacist on the PANDO app if you need support with this process.
    - Inform a member of the Pharmacy Clinical Trials team the next working day so they can ensure the process is completed by informing all relevant parties and completion of paperwork.

The results of the code break/unblinding must only be communicated to members of staff/ research members and sponsor staff if it is necessary. order to protect the integrity and validity of the data.

4.1.3 Trust sponsored studies

Creating a code/binding system for a Trust sponsored Trial

There may be a need to create a randomisation list or blind the trial for a Trust sponsored trial, the most suitable method will be agreed upon while the Trial is in its early design stages. This process must be documented in the trial protocol, and pharmacy manual. The method, randomisation list and contact details will need to be documented in a trials specific SOP for the Trust sponsored trial.

At the end of a Trust sponsored study

For Trust sponsored trials the R&I Unit must be contacted for permission to release the code break envelopes/randomisation list to the CI/PI. Such information can only be released once written confirmation has been received from the R&I Unit and the trial database has been locked.

A full detailed procedure of the method of code break/unblinding will be discussed prior to the trial opening and this will be documented in a trials specific SOP and trial protocol for the Trust sponsored study.

4.2 Testing Code Break/Unblinding Procedures

Prior to initiating a blinded clinical trial at site, the Pharmacy Clinical Trials Team will test the code break (or unblinding) procedures to ensure they are robust. They will confirm that this test has been undertaken on the Pharmacy Study Set Up Form. Therefore, Pharmacy readiness should not be issued without this test having been conducted.

1. To perform the test, follow the procedures below; Follow the documented code break procedure/s within the code break section of the Pharmacy Trial Instructions, which has been created from the trial specific protocol/pharmacy manual supplied by the sponsor.
2. Complete the code break/unblinding test form (Pharm/F50) being sure to record the outcome of the test and any actions required to address any issues raised. Sign and date the form.
3. Request PI or Research Nurse signature on the form to acknowledge the test or attached an email to the back of the code break test form to indicate they are aware that the code break/unblinding test is complete.
4. Once the code break test form is complete file the form in the relevant section of the Pharmacy site file.

The testing process should not unblind the study. The aim of the test is to ensure that the procedures for code breaking/unblinding are robust. The following points may be useful when considering this:

- Could the Principal Investigator be contacted?
- Can the PI or delegate be contacted out of hours to access IWRS?
- Is the IWRS website accessible?
- Are the contact details correct?
- Could the PI/Pharmacy contact the Telephone helpline/IWRS? Could US/Europe contact numbers be accessed?
- Are the contact details correct and correct forms in place for IWRS?

5 SOPs and Documents

Pharm/F53	Code Break/Unblinding Record Form
Pharm/F50	Code Break/Unblinding Test Form