Document Title: Code Breaking/Un-blinding of Clinical Trials, Training and Procedure Testing

Document Number: PTUC SOP069

Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Operational Manager, Clinical Project Manager
Document author/owner:	Senior R&D Manager
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For use by:	NHS Staff Trust-Wide
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Summary Amendments

Version Number:	Modification:
3.0	Administrative changes throughout

Key Points of this Document

- To describe the process for identifying clinical trial code breaking procedures and ensuring all delegated research staff have appropriate training
- To establish a procedure for routine testing of clinical trial code break procedures

1 Purpose and Contents

a. To ensure that code breaking is discussed at the early stages of protocol development/ trial set up.

b. To ensure that all requests for the unblinding of a clinical trial are appropriate.

c. To ensure the correct documentation is completed for all code-breaks and appropriate members of the research team and the trial sponsor are informed.

d. To ensure research and pharmacy staff are aware of the different methods of code breaking and how to identify these within the specific trial protocol.

2 Roles and Responsibilities

a. The Principal Investigator (PI) is responsible for ensuring appropriately trained staff members are available to action code breaks when required for medical emergencies which may be required out of normal working hours. Cover must be provided 24 hours a day by the research team or by pharmacy by prior agreement where physical code breaks are kept within pharmacy only.

b. The PI may delegate code breaking responsibilities to other members of the research team or the pharmacy depending on the nature of the code break i.e. envelopes or IVRS /IWRS (Interactive Voice/Web Response System) and the availability of staff. The investigator should always be made aware when a code break is requested.

c. For Royal Papworth sponsored studies, R&D should have oversight of this procedure and should ensure that the procedure is robust prior to approving the study.

d. For non-Royal Papworth sponsored studies the procedure should be well defined in the protocol and appropriate staff have received training before the trial can commence.

e. Where physical code break envelopes exist and are stored in pharmacy, the pharmacy clinical trials team are responsible for providing accurate information and procedures to the on call pharmacy staff to ensure out of hours code breaks are available.

f. Where physical code break envelopes exist and are stored outside of pharmacy it is the responsibility of the research team to approve the storage area and disseminate appropriate information on how to access the code breaks in and out of hours.

g. Where code break access is not a physical envelope but an Interactive Response Technology (IRT) system, R&D and the Chief Investigator should ensure that out of hours access is available within the research team. Pharmacy staff will not be available to cover these code break requests.

h. The PI will be responsible for ensuring the Sponsor has been notified of the code break within 24 hours or the request.

i. The Sponsor, in conjunction with R&D and pharmacy, are responsible for ensuring investigators and their delegated representatives have appropriate training

j. R&D are responsible for initiating an annual code break test on blinded PTUC sponsored/ hosted studies.

3 Policy

a. All research active staff should be aware of this SOP at the commencement of their research study. Failure to follow this SOP may result in disciplinary procedures.

b. This SOP should be read in conjunction with other R&D SOPs on Clinical Trial Investigational Materials, sourcing and supply. Research staff should also be aware of SOP018 Randomisation of Research Studies, if Royal Papworth is the sponsor or co-sponsor.

4 Procedure

4.1 General points to consider

a. The protocol or another document accessible to the study team should state how the code breaks will be accessed and how 24 hour access will be made available.

b. It is expected that the investigator site has the ability to unblind a subject within 2 hours in the case of a medical emergency.

c. Emergency treatment unblinding in a clinical trial must only be broken where knowledge of the treatment is necessary to provide acute medical care or where there is safety/clinical concern from the research team.

d. The protocol should state who will have access to the treatment randomisation codes throughout the trial and this should be reflected in the delegation log. All staff involved in code breaking should have appropriate trial specific training

e. Up to date contact numbers for research team members who have code break access should be maintained in the trial master file.

f. Where access is Investigator Only, there must always be a member of the research team on call and contactable out of hours (this can be the same consultant as is on call for clinical duties as long as they are on the delegation log as an investigator or sub-investigator).

g. Investigators and delegated members with unblinding responsibilities are responsible for maintaining their own access to any IRT system used for unblinding. A backup system should be available to the site should the IRT system not be functioning – this should be described in the trial protocol.

h. Where pharmacy has physical access to envelopes stored in the pharmacy department, the pharmacy clinical trials team will produce a document detailing each trial's code break procedures and how to access the appropriate information should a request be made out of hours to the on call pharmacist.

i. Where possible, all code break requests should be discussed with the Investigator, Sub Investigator or Sponsor before unblinding. In all cases the Investigator and Sponsor must be notified by the next working day of the code break request, although it is not necessary to inform the sponsor of the result of the request. All communication should be documented in the trial master file.

j. All care should be taken to ensure that no unnecessary unblinding of the study team occurs when they are not the requesting party of the code break.

4.2 Completing the Unblinding request form:

a. Requests for unblinding should be accompanied with adequate subject details and reasons for requesting the code break. This information should be documented on the form Clinical Trial Code Break Request (FRM029) and should include the following:

1. Patient information and trial information
2. Identity of the person requesting the code break
3. Reason for the code break request
4. Bottle or box number of the trial medication (if available to hand)

b. Do not break the code unless all the information marked with a * on the form has been obtained from the requester.

c. If the requesting doctor is unable to answer all the questions appropriately or there is concern that the request is unnecessary please refer to a senior member of the research team, pharmacy clinical trials team or the Investigator.

d. If all the above criteria are satisfied, access the code break according to the protocol, pharmacy manual or equivalent. Details on physical code breaks held in pharmacy will be held in the pharmacy trial file.

e. If the code break is not an envelope, written documentation will be required of the unblinding by email.

f. Attach the unblinding information to the 'Clinical Trial code break request' form (FRM029) and ensure the form and any additional trial specific documentation is completed as per the trial protocol.

g. The requesting clinician should be informed immediately of the treatment allocation - if requested written documentation should be provided (a copy of the code break request would be suitable)

h. If the request for unblinding was made to the on call pharmacist, the pharmacist must inform the pharmacy clinical trials team on the next working day.

i. If the research team is to remain blinded the person requesting the code break should ensure that any unblinding data is kept separately and restricted until the end of the trial.

j. For trial close down, when the randomisation list is opened for analysis the code break procedure is not required – SOP021 Trial Closure and End of Trial Reporting, should be followed.

5 Training of Staff

a. All staff who are delegated to undertake responsibilities for unblinding/code breaking should undergo training before the trial can begin to ensure they are familiar with the procedures and risks associated with code breaking in clinical trials. This training should form part of the IMP training provided by Pharmacy.

6 Code breaking testing procedures

a. Annually the code break request procedure should be tested on a PTUC sponsored study. The testing procedure should include one out of hours test and follow these steps:

b. At least once a year, a CPM, in conjunction with the R&D QA team, should identify at random the trial(s) to be tested from the active trials inventory.

c. The relevant research team members should be informed of the planned code break test but not the timing.

d. The CPM should initiate the testing procedure by obtaining the trial protocol and delegation log and identifying the person responsible for code breaking. Where this is not explicit in the protocol or delegation log the lead investigator should be contacted.

e. The CMP should aim to complete the form Code Break Test Procedure and deem whether the code break attempt was successful. In no circumstances should the CPM actually request the researcher to access the code break, instead they should be asking what procedures would be followed and if the person

responsible would be capable of accessing the information in a timely manner. See (FRM030) for Form: Code Break Testing Procedure

f. The results of the testing procedure should be reported to the investigator for each trial and to the Sponsor. Where failures occur R&D should initiate an action plan to rectify any issues identified. This plan should be reviewed after 6 months.

7 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

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Further Document Information

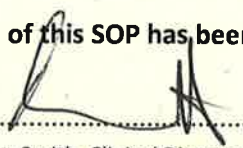
Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current active version approved date
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2018)
Key related documents:	Trust Research Policy Research and Development Standard Operating Procedures entitled: SOP018 Randomisation of Papworth sponsored clinical trials SOP021 Trial Closure and End of Trial Reporting FRM029 Clinical Trial code break request FRM030 Code break test procedure

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	No	No	No	No	No	No	No
Positive/Negative	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Review date:	November 2022

I certify the contents of this SOP has been reviewed and ratified



Signed by Dr Ian Smith, Clinical Director of R&D

10th November 2019

Date

SOP release date: 20th November 2019