Royal Papworth Hospital
NHS Foundation Trust

Document Title: Code Breaking/Unblinding of Clinical Trials, Training and Procedure Testing

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Summary Amendments

Version Number:	Modification:
3.0	Administrative changes throughout
3.1	Administrative changes throughout
4.0	Administrative changes throughout
5.0	Administrative changes throughout

Key related documents:	Research and Development Standard Operating Procedures entitled: SOP018 Randomisation of Papworth sponsored clinical trials FRM029 Clinical Trial code break request FRM030 Code break test procedure

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. This SOP applies to all personnel that are conducting research at the Trust.

b. 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.

c. 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.

3 Policy

This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Procedure

4.1 General things to consider

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. 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.

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

e. The procedure must be well defined in the protocol and appropriate staff must have received training before the trial can commence.

f. 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.

g. 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.

h. Where code break access is not a physical envelope but an Interactive Response Technology (IRT) system, R&D and the Principal 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.

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

j. R&D are responsible for initiating an annual code break test on hosted studies and evidence of this must be filed within the trial master file.

k. For RPH sponsored / PTUC managed studies an out-of-hours code break test must be carried out as part of the sponsor green light process see FRM030 Code break Testing Procedure. This should be done after 18:00hrs. Evidence of this must be filed in the trial master file.

l. For RPH sponsored / PTUC managed studies an out-of-hours emergency contact test must be carried out at each site as part of the sponsor green light process see Appendix 1. This should be done after 18:00hrs. Evidence of this must be filed in the trial master file.

m. 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.

n. It is expected that the trial sites have the ability to unblind a subject within 2 hours in the case of a medical emergency.

o. 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 either the research or the clinical care team.

p. 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

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

r. 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.

s. 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.

t. 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. 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.

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 file.

e. 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.

f. 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).

g. 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.

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 must be documented and filed in the site file.

6 Code breaking testing procedures

a. For all RPH sponsored or managed blinded trials, testing of the unblinding procedures must be completed at least annually. This must also include at least one out of hours test and should follow the steps outlined below. 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 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 CPM should aim to complete the form Code Break Test Procedure (FRM030) 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 Code Break Testing Procedure.

f. The results of the testing procedure should be reported to the investigator for each trial, the Sponsor and RPH QA Team. 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.

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 (2023)

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

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Appendix I

Telephone guidance and form for the completion of an out of Hours test call prior to sponsor green light

a. Locate emergency out of hours contact number on the Patient Information sheet.

b. Call the out of hours number and ask receiver to locate the protocol for the study.

c. Ask the receiver to confirm the version number and date of the protocol.

d. Request the receiver to open a certain page of the protocol.

e. Ask a question in relation to that page e.g. page of the inclusion and exclusion criteria – choose an exclusion criteria number and request the receiver read back that exclusion criteria.

Complete and File in your site file:

- Name & role of person contacted
- Date & time called
- Name of study
- Protocol number and date
- Out of Hours Number to call
- Was the out of hours call answered at the first call?
- If not answered at the first call, how many times did you have to try?
- Was the receiver able to locate the Protocol?
- Could the receiver confirm the Version number?
- Could the receiver confirm the date of the protocol?
- Was the receiver able to answer the Question related to the protocol?

Test completed by:

Date and time test completed: