York Foundation Trust R&D Unit
Standard Operating Procedure
Pharm/S54

Managing Code Break Procedures

(Production and Receipt of Code Break Envelopes, Undertaking and Testing Code Breaks Procedures)

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&D Unit's website and R&D Newsletter 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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.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&D Unit 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&D Unit website: www.northyorksresearch.nhs.uk/sops.html

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	Date:	20th July 2015

This SOP will normally be reviewed every 2 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	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	

Contents

1 Introduction, Background and Purpose

This SOP is required to ensure that blinding of a clinical trial is maintained throughout the course of that trial. Study blinding is important to ensure that no bias – deliberate or unintentional – is introduced.

This SOP describes:

1. Procedures to ensure that the production of code break envelopes by Pharmacy is conducted to a defined standard to ensure blinding is robust.
2. Procedures to ensure that the distribution, receipt and return of code break envelopes is tightly controlled.
3. Unblinding procedures in the event that a code break is required.
4. How to test code break procedures.

Production of a randomisation schedule is covered in R&D/S62. Where Pharmacy has a responsibility in handling a randomisation schedule for a particular study, the above SOP should be referred to, together with guidance on the control of randomisation schedules contained within the MHRA Good Clinical Practice Guide. In these circumstances, Pharmacy should document the procedures being implemented to control the randomisation schedule in a study specific SOP or within the Pharmacy trial instructions, to ensure inadvertent or deliberate un-blinding is prevented.

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 in a similar manner to that described above.

2 Who Should Use This SOP

This SOP applies to all Pharmacists and members of the clinical trials team within Pharmacy at York and Scarborough hospitals, which form part of York Teaching Hospital NHS Foundation Trust.

3 When this SOP Should be Used

This SOP should be used when Pharmacy staff are required to:

1. Produce code break envelopes.
2. Receive and distribute code break envelopes.
3. Perform a code break.
4. Test the code break procedure.

4 Procedure(s)

4.1 Production of Code Break Envelopes

To produce code break envelopes for use during a Clinical Trial of an Investigational Medicinal Product (CTIMP) (where required), follow the process

detailed below and document the following information on a production of code break envelopes form (Pharm/F25):

- Study title
- Hospital site
- Principal Investigator
- Eudract number
- Protocol number
- R&D Unit reference
- Set number of code break envelopes produced
- Randomisation numbers covered by that set

A Clinical Trial Senior Pharmacy Technician should:

- Obtain the randomisation list for the trial and required number of plain brown envelopes
- Create adhesive labels to add one to the front of each envelope. Labels should be labelled 'code break envelope' together with the following information relevant to that trial:
    - Principal Investigators name
    - Study title
    - Protocol number
    - Randomisation number
- Create a second set of labels corresponding to the treatment allocated for each randomisation number and place one label inside each corresponding envelope. The labels produced should contain the following information:
    - Trial name
    - Patient randomisation number
    - Treatment allocation

The relevant sections of Pharm/F25 should be completed.

A Pharmacist (or nominated independent person) should then check that:

- The number of envelopes matches the number of subjects on the randomisation list.
- Each envelope is labelled correctly.
- The patient randomisation numbers correspond to those on the randomisation list.
- The information contained on the treatment allocation labels matches the randomisation list.
- The correct treatment allocation is placed in the correct envelope.

The Pharmacist (or independent delegate) should then securely seal the envelopes and sign over the seal of the envelope.

The quality control section of Pharm/F25 must be completed by the Pharmacist (or independent delegate) to confirm the code break envelopes meet the necessary criteria. The form should then be filed in the code break section of the relevant Pharmacy site file.

4.2 Receipt of Code Breaks by Pharmacy

When code break envelopes are delivered to Pharmacy the individual receiving the code breaks should:

- Sign and date the delivery documentation to acknowledge receipt of the code break envelopes (and provide an audit trail for their receipt).
- Complete the first section of the receipt of code break envelopes form (Pharm/F26) to clearly document receipt of the envelopes at site.
- File the delivery documentation in the relevant section of the Pharmacy site file.

For purposes of Quality Control, the envelopes should be checked to ensure the following criteria are met:

- Study title and/or protocol number should be on the envelope.
- The contents of the envelope should not be visible.
- There is a separate envelope for each randomisation number.
- The envelope is sealed and tamper proof.
- The envelope is clearly labelled 'code break envelope' or similar wording.
- The envelope is clearly labelled with a subject randomisation number.

Complete, sign and date form Pharm/F26 to confirm that the quality control check has been completed. If any of the above criteria are not met, contact the Sponsor. Store the code break envelopes and completed form (Pharm/F26) in the Pharmacy site file.

4.3 Distribution of Code Break Envelopes

Pharmacy may be required to distribute sets of code break envelopes to the Principal Investigator and/or Sponsor of a CTIMP. To ensure there is a documented audit trail for this, Pharm/F27- distribution of code break envelopes form must be completed. The person receiving the code break envelopes must sign and date the form to document that they have taken responsibility for the code break envelopes received.

File the completed form in the code break section of the Pharmacy site file. This form should also be completed to document return of code break envelopes to Pharmacy at the end of the study (see section 4.4), or return of code break envelopes to the Sponsor (if requested by them).

4.4 Return of Code Breaks to Pharmacy

Code break envelopes distributed by Pharmacy must be returned to Pharmacy following completion of the trial but prior to study close down. The Clinical Trial Senior Pharmacy Technician should request the return of the code break envelopes from the person they were issued to (which will be documented on Pharm/F27). Upon return of the envelopes, the remaining information in form Pharm/F27 should be completed.

File the completed form Pharm/F27 in the code break section of the relevant Pharmacy site file.

4.5 Undertaking a Code Break

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.

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).

4.5.1 In the event of a Medical Emergency

A request may be received from the treating physician or the CI/PI. A member of the Clinical Trials Team (or the on-call pharmacist if the request is made out of hours) must facilitate breaking the code by following the procedure outlined below:

- Locate the Pharmacy site file for the study for which code break is being requested.
- Document the name of the person requesting the information and the reason for the code break request.
- Follow the procedures detailed in the code break section of the Pharmacy file.
- Complete the code break record form (Pharm/F53), unless an alternative form is specified (this will be found in the code break section of the Pharmacy site file).
- File the completed form in the code break section of the Pharmacy site file.
- Notify all necessary parties that a code break has been undertaken (i.e. CI/PI, Clinical Research Associate (CRA) or Sponsor, R&D Unit, Research Nurse) and the reasons for the actions taken as soon as possible.
- If the code break took place out of hours the on-call Pharmacist must inform the Pharmacy Clinical Trials Manager (or delegate) that a code has been broken the next working day. The Clinical Trial Manager (or delegate) must then check that all necessary parties are aware of the code break.
- The 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.

4.5.2 At the request of the Sponsor (in the event of safety concerns where the Sponsor is the Trust)

A code break request may be received from the Sponsor of the trial in the event of safety concerns or in the event of a Serious Adverse Reaction (SAR) in a trial participant. A member of the Clinical Trials Team (or the on-call Pharmacist if out of hours) must facilitate breaking the code as soon as practically possible. Such a request is likely to be received in normal working hours (refer to R&D/S13 as to the format of this request) and should be actioned as described below:

- Locate the Pharmacy site file for the study for which code break is being requested.
- Follow the procedures detailed in the code break section.
- Document who broke the code and when.
- Complete the code break record form (Pharm/F53) unless an alternative form is specified.
- Scan the form and send via email to the Sponsor only (by replying to the Sponsors original email request to un-blind). This should be actioned as soon as possible on the same working day as the request.

The results of the code break must only be communicated to the Sponsor and not to any member of the investigative team in order to protect the integrity and validity of the data.

- File the completed form in the code break section of the Pharmacy site file.

4.5.3 At the end of a study (Trust sponsored studies only)

For Trust sponsored trials the R&D 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&D Unit and the trial database has been locked (see R&D/S29).

The Pharmacy Clinical Trials Manager (or delegate) should document the breaking of the code within the Pharmacy site file. This documentation should be in 2 parts; (1) A completed code break record form (2) A list of all trial subjects numbers and their respective treatment allocation.

4.6 Testing Code Break Procedures

Prior to initiating a blinded clinical trial at site, Pharmacy will test the code break (or un blinding) procedures to ensure they are robust. Pharmacy will confirm that this test has been undertaken on the Pharmacy readiness letter (See Pharm/T09). 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.
2. Complete the code break test form being sure to record the outcome of the test and any actions required to address any issues raised. Sign and date the form.
3. Inform the Principal Investigator & relevant Research Nurse that the code break procedure has been tested by sending them the completed form.

4. Request PI or Research Nurse signature on the form to acknowledge the test

5. Once the fully signed and completed form has been received back, complete any actions required by Pharmacy before filling 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 are robust. The following points may be useful when considering this:

- Could the Principal Investigator be contacted?
- How long did it take to do this?
- Were the contact details correct?
- Could the PI/Pharmacy contact the Telephone helpline/IVRS? Could US/Europe contact numbers be accessed?
- Were the contact details correct and correct forms in place for IVRS?
- Where code break envelopes were in use, could they be accessed?
- Was the on call Pharmacist aware of the process?
- Was the Trial status inventory list accurate and up to date with the correct code break information?
- Did the on call case contain all the required information?

5 Related SOPs and Documents

Pharm/F25	Production of Code Break Envelopes Form
Pharm/F26	Receipt of Code Break Envelopes
Pharm/F27	Distribution of Code Break Envelopes
Pharm/F53	Code Break Record Form
Pharm/F50	Code Break Test Form
R&D/S29	Data Management
R&D/S62	Production of a Randomisation Schedule for Randomised Controlled Trials (RCTs)
R&D/S13	R&D SAE/SUSAR Handling Procedure
Pharm/T09	Pharmacy Confirmation of Readiness

MHRA Good Clinical Practice Guide, 2012.