# Standard Operating Procedure CCTU/SOP046

# Blinded Randomisation

## 1. Scope

This Standard Operating Procedure applies to staff of the Cambridge Clinical Trials Unit, Chief Investigators and their trial teams working on Cambridge-Sponsored CTIMPs or clinical studies coordinated by the CCTU.

## 2. Purpose

To describe the extra steps required, in addition to those described in CCTU/SOP036 General Principles of Randomisation, to set up a blinded randomised treatment allocation.

- Concealment lists & labelling
- Drug supply, re-supply and shipping
- Unblinding: emergency and end-of-study

## 3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

### 3.1. Definitions

| Term | Definition |
|---|---|
| Cambridge Sponsored | Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC<br>or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge |
| Randomisation | The act of allocating a treatment to a study subject using an element of chance to determine which treatment is to be allocated |
| Blinded | The concept of concealing the treatment that is assigned from the staff and patients to prevent biases occurring |
| Concealment List | A set of unique labels or numbers applied to identify the individual drug kits that are otherwise visually identical across different treatments without revealing the identity of the treatment contained in the individual drug kit. |
| Randomisation seed | Numerical algorithms used to generate random numbers can be made exactly replicable by the specification of a starting number: the randomisation seed. |
| Trial steering committee | A committee responsible for overall supervision of a trial and to ensure that it is conducted to rigorous standards. |

### 3.2. Abbreviations

| Abbreviation | Meaning |
|---|---|
| TMF | Trial Master File |
| CI | Chief Investigator |
| CCTU | Cambridge Clinical Trials Unit |
| CRF | Case Report Form |

## 4. Undertaken by

The roles involved in the process are:
Programmer
Statistician
Chief Investigator or delegate

## 5. Items Required

1. CCTU/TPL035 General Randomisation System Specifications
2. CCTU/FRM044 Randomisation User Acceptance Testing Form
3. CCTU/FRM045 Randomisation Closure Form
4. R&D/SOP008 Un-blinding Subjects in an Emergency Situation
5. CCTU/GD038 Storage and Access to Confidential Materials
6. Master Treatment Coding Document
7. Log of password protected documents

## 6. Summary of Significant Changes

Simplification of signatures for specification.

## 7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

### 7.1. Processes and Documentation

The processes and documentation described in CCTU/SOP036 General Principles of Randomisation must all be applied and completed in full for any blinded study. The same framework of specification, building and testing, and the associated documentation is to be used for a blinded study, but further details must be included. These extra details are described in this SOP.

- An equivalent set of documents is required for any general software used to provide a framework for building the randomisation system for any study.
- If a study team wishes to use an alternative system to the CCTU default (Sealed Envelope) the equivalent documentation (see CCTU/SOP036) must be provided
- In the majority of cases blinded trials apply to drug treatments, although it is not impossible for other modes of treatment to be blinded by using a

'double-dummy' method whereby multiple modes of treatments are given to all subjects, but only one of the modes are an active treatment and all the rest are 'dummy' or placebo versions

- This document will use the terms "drug" and "treatment" interchangeably
- A randomisation system should not be considered as means to record data. Outputs from the randomisation should be recorded in the CRF, including the drug kit number for a blinded study. Deviations from this practice need to be noted and explained within the Data Management Plan TPL009

## 7.2. Additional Blinding Practices and Concepts

### 7.2.1. Master Treatment Coding

A Master Treatment Coding document should be produced. This will contain a set of anonymised labels for each treatment in the study. For example:

  - A = Paracetamol
  - B = Ibuprofen
  - C = Placebo
  - D = Aspirin

- The Master Treatment Coding Document should be stored in a password-protected manner and not included in any TMF until the end of the study after all unblinding has occurred
- The processes outlined in CCTU/GD038 Storage and Access to Confidential Materials should be followed.
- The programmer should have the only access to this document and is responsible for its maintenance and security
- Any subsequent documentation of the randomisation should then use these anonymised labels instead of the direct names of the treatment, to help preserve blinding during the specification, building and testing phases

### 7.2.2. Concealment List

During a blinded trial it is not sufficient to label each drug kit with an anonymised label stating a code for the treatment as any emergency unblinding of any single patient will unblind the entire treatment arm and the entire study in the case of a two-armed study.

- Each drug kit should be labelled with a unique label or number that is linked to the anonymised treatment labels in a concealment list along with any other information required, for example batch number
- Ensure that the label provides no information on the treatment contained in the drug kit
- The concealment list can be generated internally by CCTU statisticians, or generated externally, e.g. drugs manufacturer, and up-loaded into the system; the choice is made on practical grounds
- At randomisation, and possibly at repeat dosing, each patient will be assigned to a unique label of a drug kit
- If a treatment is prepared locally in pharmacy contemporaneously with dispensing it may be acceptable to have a single kit number assigned to

each patient at randomisation. The concealment list can be held by the pharmacy to allow the pharmacists to look-up the treatment for dispensing

- Other contexts may require repeated allocation of distinct kit numbers at each repeat dosing. If blinding is adequately preserved then the choice can be made on practical grounds
- The concealment list should be stored in a password-protected manner and not included in any TMF until the end of the study after all unblinding has occurred. The processes outlined in CCTU/GD038 Storage and Access to Confidential Materials should be followed.

### 7.2.3. Record of Unblinded Personnel

In general study personnel should not be unblinded without explicitly needing to do so.

The study delegation log will record:

- Which specific people and roles have been unblinded during the course of a trial along with the date, scope and reason for unblinding
- Which people or roles must never be unblinded without further approval from the Chief Investigator or Trial Steering Committee

### 7.2.4. Password Protected Documents

To guarantee blinding documents will be generated that must be password-protected.

- The processes outlined in CCTU/GD038 Storage and Access to Confidential Materials should be followed
- Standard software tools can be used to protect individual documents
- Files can be grouped together into a single compressed document, such as a zip file, that is then password protected
- It is the responsibility of the programmer(s) to ensure that the password(s) is kept and retained as appropriate or transferred and changed should the personnel in the role of Programmer change
- A log should be kept of which documents are password-protected and their network location recorded in the TMF if it is not readily apparent which documents exist but are password protected. See CCTU/GD038
- Generally, password protected documents should not be kept in a paper TMF until the end of the study

## 7.3. Specification Template

The extra components that should be included in the Randomisation Specification documents (CCTU/TPL 035 General Randomisation System Specifications) are:

- Management of drug supply may need to be incorporated into the randomisation system to help ensure that the system assigns subjects to drug kits that are genuinely available and suitable for use (e.g. within expiry date) at local sites and that local sites do not run out of drug supply. The steps could be designed to record and confirm the occurrence of the following:
    - A local site requesting drugs from a central supplier

  - The central supplier sending out the drugs to a local site pharmacy
  - Confirmation that the drugs have been received and can be used in the study
- These three steps should be documented as to how they will proceed in reality.
- Document any rules that determine what event will trigger a drug shipping request, such as a site opening or a site's drug supply falling below a cut-off, and how much drug will be requested.
- Specify which documents need to be provided to keep an audit trail of this process.
- As required on a study-by-study basis further details of drug management may be specified, potentially including but not limited to:
  - Expiry dates
  - Temperature excursions
  - Monitoring of the frequency and quantity of repeat doses
- Specify the format of the labels or numbers used in the Concealment List. Specify how the labels will be produced and applied to individual drug kits: where, when and by whom
- Details of any drug re-supply steps following a subject's initial randomisation if relevant

**Unblinding an individual participant**

- Refer to R&D/SOP008 Un-blinding Subjects in an Emergency Situation
- This details:
  - Who has the authorisation to request and/or perform emergency unblinding
  - What information will need to be provided to perform it
  - What information will subsequently be retained and recorded
- A backup procedure will need to be outlined to describe how emergency unblinding may be performed if the system fails
- Optionally further details may subsequently be provided in additional documents specific to local sites

**Unblinding all participants for interim analyses**

- Details of procedures to obtain the randomisation list for the interim analyses.
- Details of what steps have to occur to allow the unblinding at the end of the study to perform the final analyses. These will normally include:
  - Completion of Randomisation Closure Form CCTU/FRM045
  - Completion of the Data Base Lock as per CCTU/SOP033 Database Locking

**Unblinding Study personnel**

- Details of which roles or specific personnel in the study will need to be unblinded throughout the study to implement the randomisation system and recorded on the delegation log.

- These choices need to be made on a study-by-study basis based on a risk assessment of the potential to bias the study results versus practical considerations. Any further details needed to provide enough documentation to allow the replication of the randomisation process in theory, for example the use of a double-dummy system

## 7.4. Building of the Randomisation System

As per CCTU/SOP036 General principles of Randomisation

## 7.5. Validation Specification and Testing

- Refer to CCTU/SOP036 General Principles of Randomisation; the same steps will be taken to test the system (User Acceptance Testing) with the same documentation and approval forms
- User Acceptance Testing may require a mock concealment list and randomisation list to be provided
- Such mock lists should be retained to document the testing but new lists will need to be generated for the live study
- The process of generating these lists should be documented, either in terms of the code used to create and/or randomisation seeds
- Generally the documentation should provide details that would allow exact replication of the lists so the documents must be password protected as per section7.2.4.

## 7.6. Study Opening

Refer to CCTU/SOP036 General Principles of Randomisation

## 7.7. Change Control

Refer to CCTU/SOP036 General Principles of Randomisation

## 7.8. Study Close

In general, in a blinded study there will be a need to maintain the capacity to perform emergency unblinding during the follow-up phase. The randomisation system is expected to close when follow-up is completed, unlike an open-label study, which may close once recruitment is completed.

Refer to CCTU/SOP036 General Principles of Randomisation

# 8. Monitoring Compliance with and the Effectiveness of this Document

### a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

### b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

# 9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.
MHRA, Good Clinical Practice "Grey Guide"

# 10. Associated Documents

CCTU/SOP036 General Principles of Randomisation
CCTU/SOP033 Database Locking
CCTU/TPL009 Data Management Plan Trial Specific

# 11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

# 12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

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