Standard Operating Procedure CCTU/SOP58

Randomisation using Sealed Envelope

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 trials coordinated by the CCTU.

2. Purpose

To describe the steps required in setting up a randomised treatment allocation system in collaboration with Sealed Envelope. This document covers both blinded and open-label trials.

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 OR Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Randomisation	The act of allocating a treatment to a trial subject using an element of chance to determine which treatment is to be allocated.
Blocked Randomisation	A method of randomisation where a short sequence of treatments e.g. AAABBB, is repeatedly permuted at random e.g. ABBABA, to define a list of treatments, and a new trial subject receives the next treatment in the list.
Sealed Envelope	An external provider of trial-specific randomisation systems.
Human Readable	An electronic document that can both be understood by a user of the document and be processed directly by a computer.
Minimisation	A family of methods of treatment allocation where each new patient is allocated to a treatment in a manner that attempts to minimise the degree of imbalance in treatment allocations within stratification factors.

3.2. Abbreviations

Abbreviation	Meaning
TMF	Trial Master File
CI	Chief Investigator
CCTU	Cambridge Clinical Trials Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
URL	Uniform Resource Locator: a website address
FDA	Food and Drugs Administration
EMA	European Medicines Agency

4. Undertaken by

Coordinators
Randomisation Manager
Statisticians
Chief Investigator or Delegate

5. Items Required

- Signed Contract with Sealed Envelope
- CCTU/FRM98 Trial Registration Form Sealed Envelope
- CCTU/FRM091 Randomisation Specification Overview Approval From
- CCTU/FRM044 Randomisation User Acceptance Testing Form
- CCTU/FRM045 Randomisation Closure Form
- CCTU/FRM104 Unblinding log
- CCTU/SOP033 Database Locking
- CCTU/TPL028 Participating Site Activation letter
- CCTU/TPL009 Data Management Plan

6. Summary of Significant Changes

Additional details about trial close processes and what info is collected on the CRF.

7. Method

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

7.1. Overview

Sealed Envelope is an external supplier of a web-based randomisation system that must meet the requirements of:

- "General Principles of Software Validation; FDA"
- "Reflection paper on expectations for electronic source data; EMA"
- "Data transcribed to electronic data collection tools in clinical trials; EMA".

Sealed Envelope requires a complete specification template that provides the overall requirements, as part of a trial-specific contract.

- Documentation must be provided to:
    - Specify the requirements of the trial – Use CCTU/FRM098 Trial Registration Form Sealed Envelope
    - Approve the specification document – Use CCTU/FRM 091 Randomisation Specification Overview Approval From

An equivalent set of documents is required for any general software used to provide the framework for building the randomisation system.

The system is built by Sealed Envelope. User acceptance testing on a test version of the system is carried out by coordinators.

7.2. Specification

An overview of the basic requirements of the system is documented in human readable form use CCTU/FRM98 Trial Registration Form Sealed Envelope.

This will be approved by the Statistician, Randomisation Manager, Chief Investigator or delegate, use CCTU/FRM091 Randomisation Specification Overview Approval Form.

When complete, the specification will provide sufficient documentation to lead directly to a corresponding set of individual tests with desired outcomes, as components of user acceptance testing.

7.2.1. Details of the questions that need to be collected at the point of randomisation

Method of identifying the subject to which the randomisation applies:

- Subject ID number, Month and Year of Birth are the default. Collecting further patient identifiable data, such as initials, or full date of birth, would need trial-specific approval
- What question values would stop a subject from being randomised
- Stratification or Minimisation factor levels

7.2.2. Method of Randomisation

- Blocks; block size or range of block size if random block size
- Minimisation; a full description of the algorithm
    - How to measure imbalance in each treatment arm across the sample of patients recruited
    - How to determine the probability of allocation to each treatment based on the measures of imbalance
- Details of any other method of randomisation if not contained within the scope of blocked randomisation or minimisation
- The randomisation section from FRM98 Trial Registration Form Sealed Envelope should be completed/checked by a statistician
- Created within the system are details of which roles and associated permissions are allocated to access information, randomise new subjects, or enter data

7.2.3. Randomisation List

- The randomisation list is created either outside of the system and uploaded or by Sealed Envelope; the choice is made on practical grounds
- These lists should be stored according to CCTU/GD038 Storage and access to Confidential Materials
- The trial team should specify who should receive the randomisation list and should be a named statistician not otherwise connected with the trial. Considerations should be made regarding the blinding requirements of the trial

7.3. Blinding

For blinded trials the following information should be included in the specification:

- How blinding will be implemented
- Who will generate the concealment list
- Whether an unblinding facility will be required

7.4. Concealment List

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

- 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 drug kit label provides no information regarding the contents of the drug kit
- The concealment list can be generated within Sealed Envelope, or generated externally 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 drug kit with a unique label
- The drug kit number should be recorded in the CRF and main study database. Any deviation must be explained in the DMP TPL009
- 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
- Unless otherwise stated the concealment list should be stored in a password-protected manner and not included in any TMF until the end of the trial after all unblinding has occurred. Refer to CCTU/GD038 Storage and Access to Confidential Materials

- A named statistician not otherwise connected with the trial should handle receipt of the concealment lists and their subsequent storage

7.5. Unblinding an Individual Participant

Sealed Envelope can be programmed to allow specific users to become unblinded and reveal a participant's treatment allocation.

Refer to R&D/SOP008 Un-blinding Subjects in an Emergency Situation which details:

- Who has the authorisation to request and/or perform unblinding
- The information required to carry out the process
- The information to be retained and recorded
- A backup unblinding procedure should the system fail

7.5.1. Unblinding all participants for Interim Analyses

Details of procedures to obtain the randomisation list for interim analyses.

The process to allow unblinding at the end of the trial, before the final analyses will normally include:

  - Completion of the Randomisation Closure Form CCTU/FRM045
  - Completion of the Database Lock refer to Database Locking CCTU/SOP033

- Details of which roles or specific personnel in the trial will need to be unblinded throughout the trial to implement the randomisation system should be provided
- These choices will be made on a trial-by-trial basis based on a risk assessment of the potential to bias the trial results versus practical considerations
- Any further details should be added to the specification document as necessary to provide sufficient documentation to allow the replication of the randomisation process, for example the use of a double-dummy system

7.5.2. Trial Specific Blinding and/or Drug Supply Considerations

Further details of drug management may need to be considered on a trial by trial basis. This may include, but is not limited to:

  - Expiry dates
  - Temperature excursions
  - Monitoring of the frequency and quantity of repeat doses
  - The format of the labels or numbers used in the Concealment List.
  - How labels will be produced and applied to individual drug kits, where, when and by whom
  - If relevant details of any drug re-supply steps following a subject's initial randomisation

7.5.3. Unblinding Log

Trial personnel should not be unblinded without explicit reasons to do so.

An unblinding log CCTU/FRM104 will record:

- For single-case unblinding: those who can have access to a single-case of unblinding in an event of safety e.g. SUSAR. These individuals have authority to unblind without further approval of the CI/TSC. This should be done on an individual patient level where possible
- For entire database unblinding: those who do not need to remain blinded to the entire data, e.g. during interim analyses

7.6. Contracts

A contract document will be provided by Sealed Envelope once the specification form has been received and any queries resolved.

The official signatory will sign on behalf of the sponsor, and should be the R&D manager or delegate.

The Randomisation Manager is a representative of CCTU. CCTU will remain the primary contact with Sealed Envelope and process invoices and payments relating to the research project.

Upon finalisation of the contract, Sealed Envelope will commence work on the randomisation system.

7.7. User Acceptance Testing

User acceptance testing is performed by the CI or delegate(s), usually the clinical trial coordinator.

For each role within the system a script of tasks will be created using CCTU/FRM044 Randomisation User Acceptance Testing Form. This script will:

- Cover all the tasks that the role should be able to perform
- Test the tasks where the role does not have the requisite permissions
- Be annotated by the person performing user acceptance testing to record the results
- Retain an audit trail
- Be signed at each iteration by the CI and Randomisation Manager to provide overall approval of the system
- Be stored within the randomisation folder and optionally the TMF

The statistician should run a sequence of randomisations to check that the results are consistent with the randomisation list.

This can be done with either a randomisation list provided to Sealed Envelope or, using a dummy list provided by Sealed Envelope.

It is important to ensure that a different randomisation list is used for the test system than for the final build.

For a trial that uses minimisation, it is recommended that a sequence of minimising covariates is provided, and a dummy run of treatment allocations performed.

In parallel the probabilities of the allocations can be calculated for each new allocation in turn, and any "impossible", or low probability, allocations detected.

Generally a set of test cases and desired outcomes will be produced. The details will correspond to the specification document in terms of:

1. Identification questions
2. Question values that prevent treatment allocation

3. Stratification or minimisation questions

- A set of test cases representing all possible acceptable values and scenarios of unacceptable values will be built up, along with the desired outcomes.
- Once user acceptance testing is complete and signed off by the Randomisation Manager, Statistician and Chief Investigator the system is ready to go live.

7.8. Client Acceptance Form & Trial Opening

Upon notification that the user acceptance testing is complete, Sealed Envelope will provide a Client Acceptance Form which must be signed to indicate that the randomisation criteria have been tested and agreed. Return of the form will trigger the system to go live.

- The sequence of documentation needed to open the randomisation system depends largely if the trial is open-label or blinded drug supply:

Blinded trials

May need drug supply to be set up within the system before site activation

Where this is the case the Client Acceptance Form may be returned to Sealed Envelope and the web-interface made live. At this point only the persons and roles performing drug management (Pharmacy, Coordinator) will be assigned access to the system.

- Once a copy of the lead site activation letter TPL028 is received, and a copy of the Sealed Envelope audit trail taken. Access will be granted to the roles/persons delegated to perform randomisation
- Where drug supply does not need to be set up in advance of site activation follow the procedure for open label trials

Open-label trials

Open label trials require a copy of the lead site activation letter TPL028. The Client Acceptance Form will then be returned to Sealed Envelope and the trial opened for randomisation

Variations on these steps may be permitted if justified and explained in a File Note.

7.9. Trial Specific User Manuals

Trial-specific guidance should be produced to allow a new user of the system to perform their role without further training. Consider if a more than one set of guidance is required according to role e.g. one for site staff and one for the system administrator. User guidance for randomisation using Sealed Envelope should contain:

- Details of how to access the system (webpage, phone number)
- A backup procedure in the event of the web-page being inaccessible

User guidance should be kept in the randomisation section of the TMF or elsewhere, if documented with a file note.

7.10. Change Control

If any aspect of the system requires amendment, the sequence of specification and validation (7.2-7.7) will be repeated.

7.11. Trial Close

When recruitment to a trial is closed complete the Randomisation Closure Form CCTU/FRM045.

An archivist role will be assigned to a named member of staff. This should be a member of the programming team who can manage folder permissions for managing downloads of data. A form will be provided by Sealed Envelope to effect and record assignment.

The archivist will then download and save a copy, according to SOP033, of the archived data provided, which will include, but not limited to:

- The data recording the treatment allocation
- Any questions /values
- The concealment list for blinded trials
- The audit trail
- Data dictionary

Checksum hash values will be generated on the saved files and compared to the reference values provided by Sealed Envelope, to ensure that an accurate version of the data have been received.

Once the archive is downloaded to the satisfaction of the Randomisation Manager, the Randomisation Manager will then complete, sign and date a study-close form provided by Sealed Envelope, which will be returned to conclude the study and allow deletion of the local files held by Sealed Envelope.

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"

Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, EMA/INS/GCP/454280/2010

General Principles of Software Validation, Version 2, January 2011 2002, FDA.

10. Associated Documents

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.

Review date	2 years (or earlier in light of new evidence) from approval date
Owning department:	CCTU QA
Supersedes:	CCTU/SOP058 V3
Local reference:	CCTU/SOP058 V4