

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 managed 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 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 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 be understood by the 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/FRM098 Trial Registration Form Sealed Envelope
- CCTU/FRM044 Randomisation User Acceptance Testing Form
- CCTU/FRM045 Randomisation Closure Form
- CCTU/TPL058A Delegation Log Coordinating Centre Roles, Responsibilities and Signature Log
- CCTU/SOP033 Database Locking
- CCTU/TPL028 Participating Site Activation letter
- CCTU/TPL009 Data Management Plan
- R&D/SOP008 Un-blinding Subjects in an Emergency Situation
- CCTU/GD038 Storage and access to Confidential Materials

6. Summary of Significant Changes

Modification of the approvals for the specification.
Warnings about possible errors to avoid at the UAT stage.
Removal of the requirement to take a copy of the audit trail at the start of a blinded trial.
Clarification as to a suggested point of closing the randomisation system.

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

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 the coordinators.

7.2. Specification

- Document an overview of the basic requirements of the system in human readable form use CCTU/FRM98 Trial Registration Form Sealed Envelope
- This will be approved and signed by the Statistician, Chief Investigator or delegate
- 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 questions that must 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 requires 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 created 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 will specify who should receive the randomisation list. This should be a named statistician unconnected with the trial. Considerations should be made regarding the blinding requirements of the trial

7.2.4. Archivist Role

The specification will need to provide a named archivist from the start of the trial. The role is required from the start of the trial to be able to rapidly download material, including audit trails, in the event of an inspection.

This should be a member of the Programming team who can manage folder permissions for the downloads of data.

The role can be assigned by an Administrator.

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 trial database. Any deviation must be explained in the DMP CCTU/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 and Final Analyses

Details of procedures to obtain the concealment list for interim analyses will need to be planned on a trial-specific basis. The concealment list will normally be retained locally (refer to CCTU/GD038) at the start of the trial.

Details of who will receive the list, to preserve blinding to statisticians or allow unblinding, should be documented in a data management plan or minutes or charters associated with DMC or TSC.

It is recommended that an initial version of the SAP be prepared in advance to finalise details of the primary analyses (incorporating any sequence of interim analyses). However these details are not required at the start of a trial.

The process to allow unblinding at the end of the trial, to facilitate 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. Reallocation of drug kits

Where expensive or limited drug supplies are used, with repeated and/or multiple allocation of drug kit numbers, if a participant withdraws before using some drug kits, to minimise waste that drug kit may be reallocated.

- Sealed Envelope has the functionality to allow re-allocation of drug kits. But this does incur a potential risk if emergency unblinding occurs that patients with a "shared" drug kit may both be unblinded, one in error
- Whilst this is rare, a risk-assessment should be carried out on a trial basis
- The information recorded on drug kits should be minimal, where and by whom, if re-allocation is needed
- Staff involved in any drug re-allocation must be given an Administrator role within Sealed Envelope and are considered as unblinded
- The unblinded status must be recorded on the delegation log (CCTU/TPL058A)

7.5.4. Unblinding Log

Do not unblind Trial personnel without explicit reasons.

The delegation log (CCTU/TPL058A) will capture who is unblinded and will distinguish between:

- 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 participant level where possible
- Entire database unblinding: those who do not need to remain blinded to the entire data, e.g. during interim analyses

7.6. Contracts

Sealed Envelope will provide a contract document 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

The CI or delegate, usually the clinical trial coordinator, perform user acceptance testing.

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

- Document the version number of the system set externally by Sealed Envelope (distinct from the version number recorded on internal documents).
- The external Sealed Envelope version number is always displayed in the footer of the test system e.g. "1.2.0-RC4".
- 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
- Steps outside of UAT should not be undertaken, as this may cause issues.
 - The UAT can be invalidated by creating spurious extra patients that take up assignments from the randomisation list
 - Fully deleting patients makes it very hard to demonstrate the correct sequence of assignments was followed. Rather they should be set to "assigned in error" or similar to be present in the data and handled correctly.

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 by using a

- Randomisation list provided to Sealed Envelope
- 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, perform a dummy run of treatment allocations.

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 the 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:

- 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 is written 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 is filed 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 a trial is ready to close the randomisation system, complete the Randomisation Closure Form CCTU/FRM045. For an open-label trial this may be after recruitment is complete, but for a blinded trial the emergency unblinding facility is likely to be required until follow-up is complete.

An archivist role will be assigned to a named member of staff from the start of the trial. This should be a member of the programming team who can manage folder permissions for managing downloads of data.

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 trial-close form provided by Sealed Envelope, which will be returned to conclude the trial 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/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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