Standard Operating Procedure CCTU/SOP036

Open Label 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 steps required in setting up a randomised treatment allocation system that is open-label or unblinded.

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 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.
Tenalea	A web-based randomisation system.
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.
Human readable	An electronic document that can both be understood by a user of the document and be processed directly by a computer

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	Federal Drugs Agency
EMA	European Medicines Agency

4. Undertaken by

This process involves:

- The Programmer or Randomisation Manager
- The Statistician
- The Chief Investigator or delegate

5. Items Required

1. CCTU/TPL035 Tenalea Randomisation System Requirements
2. CCTU/GD031 Tenalea Browser Requirement Guidelines
3. CCTU/FRM091 Randomisation Specification Overview Approval From
4. CCTU/TPL013 Randomisation Functional Specification Template
5. CCTU/FRM040 Randomisation Approval Form
6. CCTU/TPL016 Randomisation Functional Testing Template
7. CCTU/FRM044 Randomisation User Acceptance Testing
8. CCTU/TPL 036 Tenalea Trial Specific User Manual
9. CCTU/FRM045 Randomisation Closure Form

6. Summary of Significant Changes

The audit trail of the randomisation system will be downloaded as an electronic file when the trial closes

7. Method

Clarification regarding what information is transferred into the CRF.

7.1. Overview

Any electronic system used to perform randomisation or treatment allocation 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".

Each trial that requires randomisation must provide documentation to:

- Specify the requirements of the trial
- Validate that the specifications are met

- An equivalent set of documents is required for any general software used to provide a framework for building the randomisation system for any trial
- Tenalea a web-based system is used along with templates for specification and validation. If a trial team wishes to use an alternative system the equivalent documentation must be provided
- An open-label or unblinded trial is one where the investigator allocating treatment is provided with the explicit name of the treatment. Therefore there are no requirements to ensure the treatment cannot be identified (blinding) or provide a mechanism for emergency un-blinding
- A randomisation system should not be considered as means to record data. Outputs from the randomisation should be recorded in the CRF, including the treatment assigned for open-label studies. Deviations from this practice need to be noted and explained within the Data Management Plan TPL009

7.2. Specification Template

- An overview of the basic requirements of the system is documented in human readable form using CCTU/TPL35 Tenalea Randomisation System Requirements
- This will be approved by the Statistician, Programmer, Chief Investigator or delegate, using CCTU/FRM091 Randomisation Specification Overview Approval From
- The Randomisation Functional Specification Template CCTU/TPL013 supplies the comprehensive technical details required as input for the Tenalea system
- Both parts of the specification documentation will be approved by the Statistician, Programmer, Chief Investigator or delegate, using CCTU/FRM040 Randomisation Approval Form

The following elements of this specification must be documented in full before the system can be used to randomise subjects either in:

- The trial protocol
- The Tenalea Randomisation Functional Specification template CCTU/TPL013
- The Tenalea Randomisation System Requirements template CCTU/TPL035

Details of what questions need to be collected at the point of randomisation:

  - Method of identifying the subject to which the randomisation applies: Subject ID number, Date of Birth and Initials as a minimum
  - What question values would stop a subject from being randomised
  - Stratification or Minimisation factors levels
- 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 the amount of 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

- Details of which roles and associated permissions to access information, randomise new subjects, or enter data are created within the system
- Details of who will be allowed to login to the system, under which roles, including the details of delegates representing investigators: email addresses, institution and department addresses. This information may be amended as the trial progresses
- Details of how to access the system (webpage, phone number)
- A backup procedure to be used in the event of the web-page being inaccessible. This will detail who will be the CCTU contact with appropriate permissions to override the system if required, and how they would perform a treatment allocation
- Trial-specific guidance documents for each role created should be produced to allow a new user of the system to perform their role without further training. The template (CCTU/TPL 036 Tenalea Trial Specific User Manual) can be used to produce a trial-specific manual for use by the end users

7.3. Building of the Randomisation System

- The specification documentation provided should enable the system to be built directly, or alternatively an existing system could be copied and amended to the trial specification
- The system will be built by the Programmer

7.4. Validation Specification and Testing using Tenalea

- In this section and 7.5 words in italics (Development, Test, Acceptance, and Production) have a specific technical meaning within the Tenalea randomisation system that determines which users can access and use the system for a particular trial
- When the system is under development by the Programmer the system will be published to Development
- For functional testing by the Trial Statistician or delegate, the system will be published to Test to be accessed by the Trial Statistician and Data Manager for functional testing
- The system will be published to Acceptance for the final User Acceptance testing stage involving the Chief Investigator or delegate and any other parties involved as desired

7.4.1. Functional Testing

The method of randomisation or treatment allocation can be classified as either Static or Dynamic which will require different methods of testing.

Static Randomisation

- Lists of treatment allocations, one list for each combination of strata levels, are created at the start of the trial and each subsequent patient recruited within a particular combination of strata levels will be allocated to the next treatment on the list
- Blocking is a case of static randomisation. This list will be generated in advance by the Programmer or Trial Statistician and provided to another member of staff with suitable statistical expertise for checking

- The static randomisation list will be stored separately within the TMF

Dynamic Randomisation

- For dynamic randomisation, it is impossible to produce a static list of treatment allocations at the start of the trial as the allocation may depend upon the history of allocations and stratification factors observed
- Minimisation is a case of dynamic randomisation. A sequence, or multiple sequences, of stratification factors will be specified in advance
- The Trial Statistician or delegate will use the system to generate associated sequences of treatment allocations and record the implied allocation probabilities for each treatment at each patient

Other Testing

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

  - Identification questions
  - Question values that prevent treatment allocation
  - 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
- The system will be tested to check that all desired outcomes are achieved. In the case of static randomisation, a further check will be made that the correct sequence of treatment allocations is made
- The exercise will be repeated with all the roles to be used within the trial

Functional Testing Approval

When all tests and associated documents (Randomisation Functional Testing CCTU/TPL016) have been completed the documents will be signed off by the Programmer and the Trial Statistician and stored within the TMF.

7.4.2. User Acceptance Testing

- For each role within the system a script of tasks to perform will be created (Randomisation User Acceptance Testing CCTU/FRM044)
- This script will cover all the tasks that the specified role is able to perform as explained within the trial-specific guidance notes, it will also check that tasks where the role does not have permission cannot be performed
- The script will be annotated by the person performing user acceptance testing to record what happened, and an audit trail created within the system will be retained
- Each user role will be tested by the CI or delegates. The CI and Programmer will sign each user acceptance testing script to provide overall approval of the system. The approved scripts will be stored within the TMF

7.5. Trial Opening

When all user acceptance testing is approved and the copy of the CCTU/FRM012 Trial Initiation Form has been received by the Trial Statistician the system will be published to Production (using Tenalea) and the system opened to allow trial subjects to be randomised.

7.6. Change Control

- If any aspect of the system is amended, then the sequence of specification, building and validation (7.2-7.4) will be repeated
- Within the Tenalea framework, to build the revised system and perform functional validation a copy of the system will be created and amended
- After the functional validation is approved the following will be performed in order:
    - The live system's status changed to Suspended to stop any subjects being randomised
    - The changes implemented to the system
    - User acceptance testing repeated and approved
    - The live system's status changed to Open and randomisation resumed

7.7. Trial Closure

- When recruitment to a trial is closed and CCTU/FRM045 Randomisation Closure Form signed by the Chief Investigator or Delegate and the Trial Statistician and Programmer/Randomisation Manager. The randomisation system will be closed to prevent any further randomisation
- The following steps should be taken:
    - The final treatment allocation data set will be downloaded as an electronic file and treated as source data in accordance with the requirements documented within Database Locking CCTU/SOP033
    - The trial definitions will be downloaded as an electronic file as a record of any coded questions/values
    - The audit trail of the randomisation system will be downloaded as an electronic file and treated as source data in accordance with the requirements documented within Database Locking CCTU/SOP033
- These documents ideally should be printed and stored in the TMF but may be too large or unreadable, in which case a clear explanation and statement of the relevant file path should be placed in the TMF

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/FRM012 Trial Initiation Form

CCTU/TPL09 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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