ECTU Central Office SOP ECTU_ST_02: Randomisation and Blinding Procedures

Version No:	5.0
Effective Date:	11 February 2021

Authorship and Approval			
Name and Designation	Author/Reviewer/ Approval	Date	Signature
Linda Williams, Senior Statistician	V5.0 Author	21 January 2021	See Retained approval email dated 21 January 2021
Michelle Steven, Data Management & Programming Team Lead	V5.0 Reviewer	25 January 2021	See Retained approval email dated 25 January 2021
Catriona Keerie, Senior Statistician	V5.0 Reviewer	20 January 2021	See Retained approval email dated 20 January 2021
Steff Lewis, ECTU Statistics Team Leader	V5.0 Approval	25 January 2021	See Retained approval email dated 27 January 2021

Document Revision History		
Version No	Date	Summary of Revisions
ACCORD	29th June 2009	Previous version held by ACCORD
1.0	6th Aug 2012	Moved to ECTU format
2.0	27th March 2015	Minor updates following detailed review
3.0	26th June 2017	Updated at scheduled review. Changes to numbering throughout document. Reference to ECTU_WPD_ST_W2 and ACCORD SOP details updates in section 4
4.0	6th November 2018	Document updated due to the need for more statistical oversight of randomisation systems within ECTU. Extensive changes throughout document. Document moved to new template
5.0	11 February 2021	Addition of section on emergency randomisation. Clarification of responsibilities and other small matters

1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedures for randomisation and blinding in clinical trials and the documentation of these procedures. The aim of these procedures is to avoid the introduction of systematic bias into the conduct of the trial.

2. SCOPE

This SOP applies to all randomised trials run through ECTU. It applies in particular to the Trial statistician, and the senior software developer or REDCap developer of the randomisation system and database.

3. PROCEDURE

Randomisation and blinding procedures will be determined for individual research studies by discussion between the Trial Statistician (or designee), the Senior Software Developer or REDCap Developer (if applicable), and the Chief Investigator (CI).

The definition of randomisation will include all those procedures that are required to design, set up and run a randomisation scheme in accordance with the protocol, the principles of GCP and the applicable statutory and regulatory requirements. The definition of blinding will include all those procedures that are required to design, set up and conduct a trial using appropriate methods of blinding in accordance with the protocol, the principles of GCP and the applicable statutory and regulatory requirements.

3.1 Randomisation

3.1.1 Where applicable, for Clinical Trials of Investigational Medicinal Products (CTIMPs) the Trial statistician (or designee) should be aware of the relevant procedures used in drug packaging and drug distribution to ensure that the randomisation codes are applied correctly.

3.1.2 The interplay of unpredictability versus balance should be considered when designing the randomisation scheme.

3.1.3 To achieve better balance, consideration should be given to the use of stratified randomisation (or minimisation), to ensure balance for baseline prognostic factors. Care should be taken that there are not too many strata, and that they are reasonably independent of each other, so that they can be adjusted for in the final analysis.

3.1.4 To keep the randomisation scheme as unpredictable as possible, if minimisation is used, where possible, centre should not be included as a minimisation factor in a study that cannot be suitably blinded. Centres can be clumped into groups (e.g. within countries) if necessary. If minimisation is used, it should contain a random element to comply with the principles of GCP. For trials using blocking, the blocks should be of varying lengths if there are blinding issues.

3.1.5 As a further aid to unpredictability, clinical staff who randomise participants should not be informed of all details of stratification or minimisation variables unless necessary for the conduct of the study. Allocation concealment must be maintained for staff performing randomisation

3.1.6 For open label studies, only the allocation of the current patient should be released, and not the entire randomisation list.

3.2 Conduct

3.2.1 Once randomised, generally subjects should remain in the study unless they specifically withdraw consent for further follow up, and should be followed up whether or not they have treatment.

3.2.2 In computer randomisation systems, methods should be employed so that once a subject has been randomised, the record of the subject's randomisation cannot be removed. In manual systems, it is sensible to train staff in ensuring allocation concealment and not letting randomising clinicians change their minds once they have been given the randomisation code.

3.3 Generation of the randomisation scheme

3.3.1 The randomisation scheme should be reproducible. Various methods could be used. For instance, if the randomisation scheme is generated by a computer, the seed used in the randomisation procedure could be fixed (and documented), but vary from study to study, so that the scheme is repeatable. If lists are generated manually, the details of the particular tables used, which numbers corresponded to which treatments and how the starting point in the tables was determined should be detailed.

3.3.2 In computer generated schemes, care should be taken to ensure that the same value does not result every time the computer is restarted. If the seed is chosen to be something that varies over time, such as using the time of randomisation, the seed value should be stored, so that the scheme can be repeated.

3.3.3 Alternatively, lists of random numbers could be generated in advance.

3.4 Randomisation System Description and Confirmation – Electronic Systems

3.4.1 Where ECTU is responsible for both the statistical analysis and design, build and maintenance of the study database, the Trial Statistician or designee, with input from the senior software developer or REDCap developer, will be responsible for generating and documenting the system description.

3.4.2 The Randomisation and System Description and Confirmation process within ECTU will be followed. This is outlined in ECTU Central Office WPD ECTU_ST_W6 Randomisation System Description and Confirmation.

3.4.3 In cases where ECTU is responsible for the statistical analysis but the responsibility for the database lies elsewhere, this should be discussed with the Chief Investigator and a bespoke process put in place. This should be documented by the Trial Statistician or designee and retained in the Statistics Master File (SMF).

3.5 Paper-based Randomisation Systems

In paper-based systems, the randomisation schedule for each investigator, or other unit of randomisation, should be checked to determine that it has been followed. One method of doing this is to check whether code numbers have been allocated in chronological order.

3.6 Emergency randomisations

3.6.1 If applicable (for instance, in trials where randomisations are time critical), a description of the process for emergency randomisations for instances when the electronic randomisation system is unavailable , should be included in the trial protocol.

3.6.2 The process will vary on a trial-by-trial basis but similar considerations should be given as defined in section 3.3 when generating the randomisation scheme. Allocation concealment should be considered.

3.6.3 Details of the procedures for emergency randomisations will be included in the Randomisation System Description and Confirmation Document.

3.6.4 To provide clear instructions on the emergency randomisation process, a project specific Working Practice Document should be created. This might detail, for example:

- A process to ensure consent is taken prior to randomisation

- The minimum dataset that is required for confirmation of eligibility/randomisation, how this is to be recorded, and how it should be transferred to the database.
- Allocation and recording of the participant's trial number
- How the database will record whether randomisation were done using the emergency process

3.7 Blinding

3.7.1 The study protocol should define all individuals involved in the study who will be blinded to treatment, and those who will not be blinded to treatment (terms such as "double-blind" should not be used as they are ambiguous).

3.7.2 Individuals whose conduct could affect the interpretation of the results or the results themselves, should be blinded when it is practical to do so

3.7.3 In most studies, it is possible for outcome to be assessed blind to treatment allocation.

3.7.4 When carrying out interim analyses of blinded results, the integrity of the blinding of the study should not be compromised.

3.7.5 Only a person not directly involved in the running or conduct of the study should have access to the full randomisation code list.

3.7.6 If a single statistician is responsible for all statistical aspects of the trial, decisions on how the data will be analysed and presented should ideally be made before the unblinded analysis of the data. Several statisticians would be involved in each trial some of who will be blinded and some unblinded, with all decisions relating to the final analysis being made by the blinded statisticians.

3.7.7 Adequate steps should be taken to ensure that the treatments are indistinguishable in placebo-controlled trials.

3.8 Documentation of Unblinding

3.8.1 The circumstances for breaking the code must be clearly described in the protocol.

3.8.2 If the code is unblinded (either inadvertently or on purpose) during the conduct of the study, this event must be fully documented in the statistical report.

4. RELEVANT DOCUMENTS AND REFERENCES

ECTU Central Office WPD ECTU_ST_W6 Randomisation System Description and Confirmation (on shared drive)
ECT Unit/SOPs/Finalised SOP and WPD/ST/WPD/Current PDF versions for use

ECTU Central Office WPD ECTU_ST_W2 Statistical Input into Trial and Protocol Design (on shared drive)
ECT Unit/SOPs/Finalised SOP and WPD/ST/WPD/Current PDF versions for use

ACCORD SOP CR007 Study Documents, CR007-T01 CTIMP Protocol Template (on ACCORD website)
http://www.accord.scot/research-access/resources-researchers/sop