Royal Papworth Hospital
NHS Foundation Trust

Document Title: Randomisation of Research Studies

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Summary of Amendments

Version No:	Modification:
5.0	Clarifying the processes and amendments throughout

Key Points of this Document

- This document sets out the procedures to be followed when designing clinical research studies sponsored by Royal Papworth Hospital NHS Foundation Trust or managed by Royal Papworth Trials Unit Collaboration (PTUC).
- This SOP provides guidance on randomisation to ensure compliance with the Trust's policies.

- The SPIRIT Statement (Standard Protocol Items: Recommendations for Interventional Trials, https://www.spirit-statement.org/) provides guidance for the conduct of clinical trials (Chan et al., 2013). Section 16 details recommendations on allocation, and Section 17 details recommendation on blinding. References to relevant SPIRIT statements are made in this SOP.

1. Purpose and Contents

a. This document defines the Trust's procedures for developing randomisation sequences, requirements for randomising patients and validation for research studies and clinical trials sponsored by Royal Papworth Hospital or managed by PTUC as described in Good Clinical Practice (GCP: 'a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected').

b. Statistical input into the study is outside the scope of this SOP and is described in PTUC SOP017: Statistical Input in Clinical Trials.

c. This SOP defines all stages in the registration of trial participants and the provision and use of a randomisation service.

d. The subsequent use and analysis of research study data is outside the scope of this SOP and is described in PTUC SOP021: Trial Closure and End of Trial Reporting.

e. The monitoring of study data to ensure validity of the data is outside the scope of this SOP and is described in PTUC SOP016: Monitoring Research Studies.

2. Roles & Responsibilities

a. This Policy applies to all personnel that are conducting research at the Trust including: full and part-time employees of the Trust, those working at the Trust with employment contracts funded partially or wholly by third parties including those within Cambridge University Health Partners (CUHP) Academic Health Science Centre (AHSC) and those seconded to and providing consultancy to the Trust, and to students undertaking training at the Trust.

b. Staff involved in randomisation must comply with the requirements set out in section 4 of this SOP.

c. It is the responsibility all research staff to ensure that they are familiar with and adhere to all current SOPs and have signed the relevant log in their training record.

d. Within PTUC, the people responsible for appropriately randomising patients in clinical trials are the chief investigator (CI), the principal investigator (PI), the statistical team (ST) and the trial statistician (TS). The randomisation service will be either commissioned via an external subcontractor, e.g. www.sealedenvelope.com, or developed in-house via electronic lists (not online). The use of an external sub-contractor that provides a randomisation system, blinding and code breaking mechanisms should be used, unless it has been documented during setup why this is not possible or adequate.

e. CI & PI: overall responsible for liaising with the trial statistician, recruitment, randomisation, and safety of participants, although tasks can be delegated to other team members.

f. PI: responsible for implementing allocation of treatments and unblinding if necessary. Tasks can be delegated.

g. Statistical Team: responsible for checking the integrity of the randomisation system. If the system is commissioned, then appropriate validation and testing documents will be obtained from the external sub-contractor.

h. Trial Statistician: under in-house randomisation, the TS is responsible for the choice of an appropriate randomisation scheme, training other team members, and recording and registration of the process. The TS is also responsible for setting up a Back-up Randomisation system if required (see section 4.5) and ongoing support throughout the trial. Ensuring blinding when required. The above responsibilities may be delegated to trial manager, data manager, another statistician or to the external sub-contractor when their services are used.

i. Trial Manager/Project Manager: responsible for setting up data recording systems, commissioning a randomisation service from an external sub-contractor if required and negotiating the costing of services and general management issues. Developing, in association with the TS and other appropriate trial members the details of the randomisation and testing procedures. Overseeing day-to-day implementation of registration and randomisation requests. Providing accrual figures in conjunction with the TS. Ensuring there is a Back-up Randomisation process in accordance with the trial needs.

3. Policy

a. This SOP is mandatory and as per the Trust's Information Governance and Records Management framework non-compliance with may result in disciplinary procedures.

4. Procedure

4.1. Preparation

a. Random allocation of a clinical trial's participants to the treatments under study aims to ensure that any differences between the treatment groups are due to chance alone. The randomisation procedure must be determined during the design phase of the trial and detailed in the trial protocol. Please see SPIRIT Statement 16 – Allocation (Chan et al., 2013). The trial statistician should be involved at this stage to ensure that the type of randomisation is appropriate for the trial design. The randomisation list should be produced and implemented once funding for the trial is confirmed and prior to patient recruitment. Consideration should be given to the following:

   1. Type of randomisation and a description of the randomisation process, allocation ratios, block sizes, and stratification variables and any other variables used in the randomisation procedure to be recorded. This detail must be included within the Statistical Analysis Plan and should include points (but not limited to) those detailed in Appendix 1.

   2. The level of blinding as required by the trial's protocol (e.g. unblinded, single-blind or double-blind) and how it will be implemented (e.g. through the use of an identical placebo). Please see SPIRIT Statement 17 – Blinding (Masking). The protocol should explicitly state who will be blinded to intervention groups – at a minimum, the blinding status of trial participants, care providers, and outcome assessors. Only in exceptional circumstances should breaking of the randomisation occur for unblinding

      a patient's allocated treatment (i.e. when essential for further management of the patient's treatment). See point d below.

   3. Allocation concealment**,** a technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment. Allocation concealment prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given

intervention group. Allocation concealment is possible with all types of trials, including unblinded trials, and is therefore universally recommended.

4. Unblinding/code breaking: for blinded trials, randomisation systems should include a mechanism that permits rapid identification of the allocated treatment in case of a medical emergency, but one that does not permit undetectable breaks of the blinding in order to protect the integrity and validity of the data. To ensure this, the code break procedures must be clearly established and the circumstances where unblinding can be performed should be detailed in the protocol, e.g. treating an individual for an adverse event or for the submission of trial data to the Data Monitoring and Safety Committees (DMSC).

   The procedures to follow in case of a code break are described in SOP069 : Emergency unblinding and code break.

5. Method of implementation (e.g. web-based, password protected lists).

6. Responsibilities for each stage of the process should be clearly defined, i.e. who is responsible for the timing of the final unblinding of all trial participants

b. The process of producing the randomisation list should be documented including the following:

   1. Method of producing the list and rationale for its choice.

   2. If the randomisation list is produced in house, the code for generating the sequence should be documented and stored.

   3. People responsible for preparing and checking the randomisation list. The preparation and checking of the randomisation list should be undertaken independently from one another (i.e. a different person is responsible for checking the randomisation list, from the person who created and prepared this).

   4. Person or people responsible for implementing and using the list. Contingency plans for staff absences (i.e. sick leave, annual leave) need to be established.

   5. Guidelines for the user (including storage and access control methods).

   6. Unblinding arrangements.

4.2. Methods of access

a. Internet access is needed for on-line randomisation. This is the preferred randomisation method, with the external sub-contractor recommended being www.sealedenvelope.com. On-line access is password protected. The unique password will be given by the provider to any appropriate research individuals, e.g. TS, trial manager, PI, research nurses, pharmacists.

b. If an in-house randomisation list is used, once produced by the TS, it can be made available on-line by an external sub-contractor, for example, creating a trial in www.sealedenvelope.com/simple-randomiser/v1/new and uploading a .csv file with the following headings: “block identifier”, “block size”, “sequence within block”, “treatment”. The first three fields must be numeric, e.g. 1,2,3…, and the last one can be alphanumeric, e.g. Group A, Group B…

c. Alternatively, an external sub-contractor can provide a randomisation list to be used. For example, you can export a list from www.sealedenvelope.com/simple-randomiser/v1/lists.

d. If web randomisation is not possible, a randomisation list and guidance document must be produced by the TS in accordance with the considerations of the trial design.

e. If in-house randomisation is used, e.g. the TS produces an electronic list, the records should be kept in the study’s private folder (with limited access to team members) and be password protected. The TS will send a copy of the randomisation list to any other team member as required, e.g. pharmacist, and will make arrangements to ensure that the password can be accessed in case of emergencies. Access to randomisation should be provided either through the web or via a password protected list.

f. Back-up Randomisation will be done either via telephone or email, and will be set up for each study – see section 4.4 below

g. The use of physical envelopes to randomise patients should be an ultimate, last resort, only when on-line randomisation methods are not feasible.

4.2.1. On-line randomisation

a. External sub-contractors such as sealedenvelope.com have their own testing system. The system must be tested to ensure reliability. Testing should include whether; (i) a final sequence is random (ii) the randomisation specification has been met, (iii)the backup system works, and (iv) the system is robust to wrong data input, and to ensure that the code can be broken in those circumstances identified as necessary by the protocol.

b. For in-house randomisation testing should include whether: a final sequence is random and the randomisation specification has been met. For details on how to do this see SOP guidance document "GD017 Randomisation Procedure".

4.2.2. Non-online randomisation

a. When a complete randomisation list is drawn once and stored for later use, the sequence generation (i.e. computer-generated random numbers) should be tested (i.e. checked to ensure there is no non-random, deterministic element). As for in-house randomisation, testing should also include whether; (i) a final sequence is random; and (ii) the randomisation specification has been met. Testing external services should also be performed when possible.

4.3. Participant registration in randomisation lists

a. Personal information. In order to randomize a participant, the following information should be recorded within the randomization database to ensure that they have not been previously randomized: initials; date of birth and study ID

b. Recording of treatment allocation. Treatment allocation will be recorded on the trial database and randomisation database, e.g. held by Royal Papworth pharmacy and the TS. Audit trails of Participant recruitment and treatment allocated should be established. If using sealedenvelop.com, there will be an email sent each time a patient is randomised, which should be retained in an appropriate location (digitally or in a paper record). With in-house randomisation the treatment allocation should be emailed (either free text or sent as a form, PDF is best as can't be edited), and this should be retained in a similar way.

4.4. Back-up Randomisation

a. Back-up Randomisation procedures should be in place, against events such as power cuts preventing access to web. A telephone number and email of someone with access to the full electronic, or paper, randomisation list should be available. Telephone randomisation can be provided by sealedenvelope.com at additional cost. Any instance of Back-up Randomisation should be recorded in the randomisation data set.

5. Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Investigator and Sponsor Master File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Appendix 1

Randomisation Details

Authorship, version and date

Method of generation of randomised list and necessary code

Individuals responsible for preparing and checking randomised list

Specification of stratification and blocking variables

Access to randomisation list

Rules for unblinding

Changes to the randomisation schedule

PTUC SOP018: Randomisation

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	[Current active version approved date]
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK policy framework for health and social care research (2018)
Key related documents:	Trust Research Policy

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	NO	NO	NO	NO	NO	NO	NO
Positive/Negative							

Review date:	July 2025

I certify the contents of this SOP has been reviewed and ratified

DocuSigned by:
31-Jul-2025 | Dr Patrick Calvert
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Signed by Dr Patrick Calvert, Clinical Director of R&D — Date

References

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