Document Title: Randomisation of Research Studies

Document Number: PTUC SOP018

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Summary of Significant Change(s) (for this version only)

Section(s):	Modification:
4	Clarifying the randomisation process
4.3	Moved to a Guidance document

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).
    - It provides guidance on randomisation to ensure compliance with the Trust's policies.

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 its 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 CUHP 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 the 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 on-line service, e.g. www.sealedenvelope.com, or developed in-house via electronic lists (not online). The use of an external supplier that provides a randomization system, blinding and code breaking mechanisms should be used, unless it has been documented during set-up why this is not possible or adequate.

e. CI: 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 treatments and unblinding if necessary. Tasks can be delegated.

g. ST: 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 randomisation provider.

h. TS: 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 an emergency randomisation system if required (see section 4.5) and trouble shooting in conjunction with IT and pharmacy if required. Ensuring blinding when required. Tasks may be delegated to trial manager, data manager or another statistician or to the external supplier when its services were used.

i. Trial Manager/PTUC Manager: responsible for setting up data recording systems, commissioning a randomisation service 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 emergency randomisation 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. The trial statistician should be involved at this stage to ensure that the type of randomisation is appropriate for the trial design. The randomisation schedule should be produced and implemented once funding for the trial is confirmed and prior to patient recruitment. Consideration should be given to the following:

   a. 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, See Appendix 1.

   b. 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). The level of the blinding must be maintained for the entire duration of the trial.

   c. 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.

   d. 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.

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

f. Responsibilities for each stage of the process should be clearly defined.

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

a. Method of producing the schedule and rationale for its choice

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

c. Person responsible for preparing and checking the schedule

d. Person responsible for implementing and using the schedule

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

f. Unblinding arrangements

4.2. Methods of access

a. Internet access is needed for on-line randomisation. This is the preferred randomization method, with the external randomisation provider 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. Alternatively, if an in-house randomisation is used, once produced by the TS, it can be made available on-line by an external provider, 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 in-house randomisation procedure can provide a randomization 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 list randomisation must be produced by the TS in accordance to trial design considerations.

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.

f. Access to randomisation should be provided either through the web or via a password protected list.

g. Emergency randomisation will be done either via telephone or email, and will be set up for each study.

h. Physical envelopes should not be used.

4.3. Testing

4.3.1. On-line randomisation

a. External providers such as SealedEnvelope.com have their own testing system. However, the system must be tested to ensure reliability. Testing should include whether: a final sequence is random, a backup system works and the system is robust to wrong data input, and ensure that the code can be broken in those circumstances identified as necessary by the protocol.

b. For in-house randomization testing should include whether: a final sequence is random. For details on how to do this see guidance document GD017.

4.3.2. Non-online randomisation

a. When a complete list is drawn once and stored for later use, the mathematical algorithms should also be tested if randomisation is done within PTUC. Testing external services should also be performed when possible.

b. Access and blinding / allocation concealment must be considered, passwords and authorisations should be established and emergency procedures should be in place.

4.4. Participant registration in randomisation lists

a. Recording eligibility information. All potential participants will be given a study number. The total of ineligible or non-consenting patients will be registered as total counts in non-identifiable format so that a CONSORT diagram can be filled.

b. Personal information. Initials and date of birth should be kept next to the study id on the same randomisation database. Other personal identifiable information should be kept separately in a primarily administrative database held on site.

c. Recording consent and treatment allocation. Written and/or electronic records of consent will be kept. Treatment allocation will be recorded on the trial database and randomisation database, e.g. held by Royal Papworth pharmacy and the TS.

4.5. Emergency randomisation

a. Emergency 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, list should be available. Telephone randomisation can be provided by sealedenvelope at additional cost. Any instance of emergency 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 code list and necessary code

Individuals responsible for preparing and checking randomised code list

Specification of stratification and blocking variables

Access to randomisation code 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
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							

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Version Control

Version	Date effective	Valid to	Approved by	Date of approval
1.0		July 2011		5 August 2009
2.0		September 2014		8 November 2011
3.0	28 December 2012	December 2015	RDD	14 December 2012
4.0				

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

....23rd January 2019

Signed by Dr Ian Smith, Clinical Director of R&D Date

SOP release date: 31 January 2019

GD017

Randomisation Procedure Testing

Randomisation procedure testing is the process whereby a randomisation algorithm is shown to have been generated at random and therefore have the required properties for it to be a suitable randomisation procedure.

There are two types of randomisation methods that may be used:

1. Provided by an external provider, with online access or through a password protected list.
2. In-house, developed by the TS and/or the statistical team.

The testing procedure is different depending on which method has been used.

Externally provided randomisation sequence

a. External providers such as SealedEnvelope.com have their own testing system. However, the system must be tested to ensure reliability. Testing should include whether: a final sequence is random, a backup system works and the system is robust to wrong data input, and ensure that the code can be broken in those circumstances identified as necessary by the protocol.

b. If SealedEnvelopes.com is to be used the following testing must be completed on the test system which is an identical copy of the live randomisation system except it will use a dummy randomisation list or code list (where appropriate). To test it, take the following steps (see also http://sealedenvelope.com/help/faq/#how-do-i-test-a-randomisation-system):

   i) Add at least one site

   ii) Check the specification page and make sure it matches your requirements

   iii) Check the randomisation form. If detailed inclusion and exclusion criteria are listed make sure these are consistent with the approved protocol. If there are validation checks on fields (e.g. an age range on the date of birth field) make sure these operate correctly.

   iv) Perform some randomisations. Check that these are conforming to the randomisation protocol (blocks, minimisation etc). Ask Sealed Envelope for the dummy list or code list if necessary to help you check this. You may find the statistician for your trial can help, particularly if you have strata or are using minimisation.

v) Create an investigator account using another email account you have. Log in as an investigator and try randomising. This will show you the simplified interface investigators see.

vi) Check you have received the email notifications for the randomisations. Make sure they contain the correct information.

vii) Try marking a randomisation as in error. Check the reports now exclude this record.

viii) If relevant, try unblinding a randomisation. Check the treatment group matches the dummy code list.

ix) Try downloading the randomisations as a CSV file. Check the data is consistent with the randomisations you have performed

In-house randomisation sequence

For in-house randomisation we mainly need to test whether a sequence is random or not. This includes:

a) testing for no auto-correlation (significant patterns/similarities between randomization outcomes over time which could considerably reduce the unpredictability of the sequence).

b) Testing if the number of switches between treatments and the longest run without switches are as expected for a random sequence (Lunn et al. 2013).

c) The R program H:\SOP\Randomisation\testingrandomisation.R can be used. In addition and if relevant, vii) and viii) form above, should be implemented.

d) Details of the randomization code used to generate a sequence should be documented so that these testing can be re-done if necessary. Details of the seed used to generate the randomization in use should be stored.

1. References

a. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D (2013) The BUGS book: a practical introduction to Bayesian analysis. CRC Press. Example 8.4.2. p150