STANDARD OPERATING PROCEDURE

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The definitive versions of all UHPNT RD&I Dept SOPs appear online, not in printed form, to ensure that up to date versions are used. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the Trust's website: https://www.plymouthhospitals.nhs.uk/research-sops

Randomisation & Blinding

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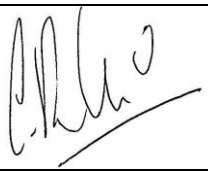
	APPROVED BY
Name:	Chris Rollinson
Job Title:	Research Governance Manager
Signature:	
Date:	21st Jan 2019

1 Purpose and Scope

To define procedure 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.

Randomisation is the process used for assigning subjects in a clinical trial to intervention groups without taking any similarities or differences between them into account. Random allocation ensures that any differences between the groups at trial entry are due to chance alone and that each individual has the same chance of receiving each intervention. An experienced statistician, or other appropriately qualified individual, should lead on the development of an appropriate randomisation method and ensure that the randomisation schedule is produced and documented.

Blinding is the process that keeps one or more parties involved in a trial (e.g. the sponsor, pharmacy, the investigator team and/or the subject) unaware of what treatment arm subjects have been randomised to. It is vital that the blind is maintained throughout the trial in order to prevent the unintentional biases of parties affecting subject data. Unblinding is however permissible for the urgent medical treatment of a subject, for safety reporting requirements e.g. reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Medicines and Healthcare products Agency (MHRA) or for any pre-specified protocol indication.

In scope: research sponsored by University Hospitals Plymouth NHS Trust (UHPNT) where there is a requirement to randomise or blind the study.

Definitions

CI	Chief Investigator
Code Break	Also known as breaking the blind. Is the mechanism that permits the rapid identification of the trial treatment received by a subject in the case of a medical emergency, pre-specified protocol indication or safety reporting requirement, but does not permit undetectable breaks of the blinding.
CTIMP	Clinical trial of an Investigational Medicinal Product.
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GCP	Good Clinical Practice - a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.
GCP	Good Clinical Practice

HRA	Health Research Authority
IMP	Investigational Medicinal Product
Interactive Voice Response System	A phone technology that allows a computer to detect voice and touch tones using a normal phone call. IVRS can respond with pre-recorded information to further direct callers on how to proceed with regards to a clinical trial
Interactive Web Response System	A Web technology that is designed to give adequate information for users to manage clinical trials.
IVRS	See 'Interactive Voice Response System'.
IWRS	See 'Interactive Web Response System'
MHRA	Medicines and Healthcare products Regulatory Agency; the Competent Authority in the UK
UHPNT	University Hospitals Plymouth NHS Trust
PI	Principal Investigators
RD&I	Research Development & Innovation
Randomisation Code	A unique number or code that is linked *via* a randomisation list to the treatment.
Randomisation Schedule	A list of intervention groups, randomly ordered, used to assign sequentially enrolled participants to intervention groups. Also termed the "randomisation list".
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction For CTIMPs, A Serious Adverse Reaction that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an Adverse Reaction, an Unexpected Adverse Reaction and a Serious Adverse Reaction
TMF	Trial Master File
Unblinding	Is the disclosure of the identity of blinded treatment

2 Who should read this document?

The Chief Investigator (CI) and study Statistician. All staff involved in setting up and conducting research would be advised to read.

3 Procedure to Follow

3.1. Responsibilities:

Chief Investigator (CI):

- Define randomisation (and unblinding arrangements) in protocol
- Where sub-contracting (e.g. for statistical expertise or for manufacturing/blinding/shipping/unblinding of Investigational Medicinal Product (IMP) ensure appropriate agreements are in place
- Ensure that the randomisation schedule is produced by a statistician or other appropriately qualified individual
- Develop appropriate documentation (e.g. randomisation form, unblinding record)
- Ensure procedures are implemented to control the randomisation schedule and related documents in order to prevent unnecessary unblinding throughout the lifetime of the trial
- Ensure that in circumstances where unblinding is permissible, e.g. emergency unblinding for urgent medical treatment, defined procedures are in place and clearly documented
- Maintain oversight of frequency of and reasons for unblinding
- Archive randomisation documentation in the Trial Master File (TMF) on completion of the trial

Note the CI may delegate specific tasks which must be documented in a trial delegation log or other formal agreement. The CI remains responsible and their input should be clearly visible throughout the duration of the trial.

Statistician:

Provide advice on the appropriate randomisation method for the trial and ensure that the schedule is produced and documented.

3.2. Randomisation

An experienced statistician, or other appropriately qualified individual, should lead on the development of an appropriate randomisation method for the trial and should have the responsibility of ensuring that the schedule is produced and documented.

3.2.1. Randomisation Methodology

- The type of method used will be trial specific and must reduce the chance of imbalance between treatment groups (e.g. simple, block, stratified, minimisation)
- The methods of preparing the randomisation schedule can be quite varied; including the use of random number tables, secure online randomisation programs and bespoke programs/macros. For the latter situation and for complex algorithms, where computer systems are used, there should be a documented validation of the program
- The randomisation methods and parameters of the randomisation process (e.g. stratification variables, inclusion and exclusion criteria) should be described fully in the protocol and in the final publication, according to CONSORT (Consolidated Standards of Reporting Trials) statement guidelines (http://www.consort-statement.org/).

3.2.2. Documentation of Design

- Once the design and type of randomisation has been established, a randomisation list with details of the randomisation codes should be produced
- The randomisation schedule may consist of a paper record only or also as an electronic version
- Typically the production of the randomisation schedule will be in collaboration with an appropriately qualified statistician. For trials managed outside of a clinical trials unit, it is strongly recommended that a third party source is used to generate the randomisation list (e.g. a clinical trials unit). The details of the service being provided and the roles and responsibilities of any third party should be documented and agreed *via* a signed contractual agreement.
- In the process of producing the randomisation schedule, all procedures should be documented with particular consideration given to the following details:
  - Method of generation of the randomised code list
  - Allocation of unique subject identifier (i.e. Trial Number) and methods in place to prevent same subject being randomised more than once
  - Person/people (and job title) responsible for preparing and checking the randomised code list / schedule. The system should be fit for purpose and perform reliably and consistently as intended
  - Distribution of electronic and paper copies of the schedule including storage and access control methods. The approach used to conceal allocation (e.g. password protected electronic format)
  - Method of implementation (e.g. web-based system, telephone based system)

- For blinded trials, method by which the emergency access to the unblinding code for individual subjects is to be organised during the trial
- For blinded trials, details on how the randomisation codes will be provided to IMP manufacturer to ensure the IMP(s) are packaged, coded and labelled in a manner that protects the blinding at the site and at the coordinating centre
- For blinded trials, interim analysis details (time points at which conducted)
- How the treatment allocated will be compared with the treatment received at the end of the trial
- Any changes to the randomisation schedule through the course of the trial, along with the date when the new scheme became active
- Computer software used to generate the randomisation list and perform randomisation and details on the validation of this system
- Details of the documentation to be completed prior to randomisation (e.g. signed informed consent form, randomisation checklist, eligibility criteria checklist)
- Details on how pharmacy (if applicable) will be informed of the randomised treatment allocation (e.g. e-mail sent to pharmacy)
- Procedures put in place to ensure the randomisation schedule is adhered to. It is strongly recommended to have a third party (independent of the trial) execute the randomisation, e.g. local pharmacy or by using a randomisation service provided by a clinical trials unit.

3.2.3. Pre-randomisation

It is important to ensure that randomisation of subjects only occurs once all other factors are in place:

- The site has been approved for randomisation (i.e. Regulatory approvals (HRA, REC, MHRA etc.) RD&I agreement has been obtained, the Clinical Site Agreement has been signed, site initiation has been performed, and for CTIMPs IMP is available and, where applicable, code-break envelopes are available on site)
- The patient is eligible and has been appropriately consented for the trial

3.2.4. Subject Withdrawal

Once randomised, subjects should remain in the trial unless they specifically withdraw consent. Methods should be employed so that once a subject has been randomised; the record of the subject's randomisation cannot be removed.

3.3. Blinding

All efforts should be made to maintain the blind throughout the trial, but under certain conditions it may become necessary to reveal the treatment assignment for medical reasons, safety reporting or for a pre-specified protocol indication.

3.3.1. Maintenance of the Blinding

Maintaining the integrity of the blind is a key consideration for all those involved in the trial. Compromising the blinding may have a significant impact on the interpretation of the results.

- Procedures should be implemented to control the randomisation schedule to prevent accidental or deliberate (unauthorised) unblinding. These procedures should include consideration of:
  - Documented access restrictions for the electronic/paper schedule to the code throughout the conduct of the trial
  - Processes for handling the master randomisation list and drug administration records
  - Processes being in place to protect the trial team from gaining access to unblinded data or the randomisation schedule in cases where data monitoring committees require interim unblinded analysis reports
  - Storage of any unblinded documentation separate to the rest of the trial documentation, either until the end of the trial or until the randomisation code has been broken for analysis

3.3.2. Circumstances for Unblinding

Examples of circumstances where unblinding may be required include:

- Unblinding in a medical emergency or pre-specified protocol indication
  - There must be the ability to unblind a subject immediately in the case of a medical emergency. For safety assessments, where there are unblinded personnel there should be clear documentation (for example on the site signature and delegation log) of who is authorised to request a code break and be unblinded to the treatment allocation in order to provide assurance that those performing efficacy and safety assessments remain blinded and, therefore, unbiased
  - For Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting there is a regulatory requirement to unblind prior to reporting to the competent authority
  - If the protocol pre-specifies that unblinding is performed when certain criteria are met (e.g. for oncology trials where subjects may be unblinded upon progression of their disease)

- Unblinding of the trial for analysis purposes
  - There should be a formal process to control the unblinding of the trial for analysis purposes and this should be documented
  - There should be documentation which confirms when the randomisation code was requested or provided and when the randomisation data were applied to the analysis datasets or database at final analysis

3.3.3. Unblinding

- Systems must be implemented to ensure that no unnecessary or unintentional unblinding occurs
- In the case of an emergency, there must be a system in place for providing 24 hour cover to access the code break
- Code break procedures for emergency situations must be clearly established and detailed in the trial protocol
- Options for access to code break information include: interactive response systems such as IVRS, IWRS, online or physical code breaks e.g. code break envelopes held at site
- Back-up systems should be available in the event that the IWRS, IVRS isn't functioning or if physical systems are unavailable
- If sealed code break envelopes are used for unblinding, the integrity of the envelopes should be checked during any routine on-site monitoring visits
- There should be a documented process for the reconciliation of physical code breaks (e.g. envelopes) at the end of the trial and a check made that they have not been tampered with
- When using an interactive response system it needs to be possible to demonstrate that the blinding has not been compromised
- If the code is unblinded (either inadvertently or on purpose) during the conduct of the study, this event must be fully documented in the TMF and in the statistical report.

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a Senior RD&I manager***, by the nominated author. These must be ratified by ***a Senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I intranet site. Internal Trust Staff are expected to use the RD&I intranet site to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given *via* the following routes:

- Inclusion in the Trust weekly e-bulletin Vital Signs
- Direct email to Trust Researchers and or teams

4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

CONSORT (Consolidated Standards of Reporting Trials) statement guidelines (http://www.consort-statement.org/) guidelines.

6 Amendment History

Version Number:	2.1
Date Of Amendment:	Jan 2019
Details Of Amendment:	Updated Trust and Dept. name; Reduce signature requirement to single senior RD&I Manager.

Version Number:	2.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	Updated SOP template and number system. Reviewed and updated SOP.

Version Number:	1.1 (minor amendment)
Date Of Amendment:	Mar 2012
Details Of Amendment:	Cover page - Change of SOP location address.