Humber Health Partnership

Randomisation SOP

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Authorized by		Sign	Date
R&D Director	Professor Thozhukat Sathyapalan	DocuSigned by: 4C017C4E8DDA44B...	13/5/2026
R&D Manager	James Illingworth	DocuSigned by: James Illingworth 3DDA0F96873F430...	13/5/2026

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This page details the version history and the main changes made for each new version.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, (24.05.2022)	L. Cox	First SOP approved by R&D Committee on 31.05.2022
Version 2, 27.04.2026	L. Cox	**Section 3.3** Added new wording on emergency unblinding, expanding to clarify that unblinding of one participant must not unblind all participants, and that investigators must be prepared to perform emergency unblinding without delay. All unblinding events needs to be documented and assessed on trial integrity along with a contingency plan for participants safety. **Section 3.3** Updated heading from "Blinding" to "Blinding and Unblinding" to reflect the new content. Minor editorial updates to ensure clarity and alignment with current R&D QA expectations. Update from HUTH to HPP incorporating both HUTH and NLaG.

Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs.

Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the HHPR&D GCP SOPs are available at:

https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps

1 Introduction, purpose and who should use this SOP

This SOP describes the procedures for producing a randomisation list for HHP Sponsored CTIMP Randomised Controlled Trials (RCTs).

Clinical trial randomisation is the process of assigning patients by chance to groups that receive different treatments. In the simplest trial design, the investigational group receives the new treatment and the control group receives standard therapy.

Randomised controlled trials help prevent bias. Bias occurs when a trial's results are affected by human choices or other factors not related to the treatment being tested.

Randomisation contains several key elements which are:

- the type of randomisation used (e.g. simple, block, stratification)
- the generation of the random allocation sequence
- allocation concealment
- the mechanism used to implement the sequence

The above elements will depend upon the type of trial:

- **Open label** - treatment is known by both research team and participant after randomisation.
- **Single blind** - the treatment is unknown to the participant but known to everyone else.
- **Double-blind** - The participants and clinicians / data collectors are all blinded to the allocated treatment.

This SOP is applicable to all randomised controlled trials sponsored by HHP.

This SOP should be used by:

- All research staff involved with HHP-sponsored CTIMPs – chief/principal investigator, co-investigators, research nurses, project managers, clinical trial coordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists
- All HHP R&D staff.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for trial set-up or the Trial Master File. HHP R&D SOPs are defaulted to in this case.
- Research staff involved with HHP-sponsored non-CTIMPs may find this SOP a useful guide for the set up of studies.

2 When this SOP should be used

This procedure should be consulted before starting a RCT to ensure that the correct procedures for randomisation are in place before the study commences.

3.1 Generation of the randomisation list

- Allocation using centralised or third party external involvement (e.g. Clinical Trials Unit or HYMS Statistician) is desirable to ensure allocation concealment, in the case of blinded trials, however in some studies this may not be practicable. For HHP sponsored CTIMP studies the approved trial protocol must detail how the randomisation list will be generated following the HHP Guide to writing a protocol for a HHP-sponsored CTIMP.
- Participants should be assigned to comparison groups in a trial on the basis of a random process that is unpredictable and cannot be tampered with. **Allocation methods such as alternation, hospital numbers, or date of birth are not considered robust allocation methods**. For HHP sponsored CTIMP studies, a statistician should be involved in the development and/or review of the method to generate the randomisation sequence to ensure that the system achieves these aims. This involvement must be documented in the Trial Master File using the HHP Randomisation Process File Note signed by the study statistician (see Appendix 1).
- Computer generated schemes (such as Sealedenvelope.com) is an acceptable method of sequence generation for randomisation.
- As a minimum, a documented check should be carried out prior to the randomisation going live. For more complex randomisation studies (such as with stratification) a dummy study should be run before the study is set up. These checks should confirm by examination that the proposed method of randomisation has been tested using the same requirements as the study, to ensure that it produces the correct number of randomisations and block sizes. Supporting documentation should be held securely in the Trial Master File.
- The person generating the randomisation list and / or allocation concealment should not be involved in the later implementation of the sequence, this would normally be carried out by the HHP R&D QA department, where necessary guidance will be sought from an independent statistician. Thus a list should be generated by a person who has no direct contact with the trial subjects or involvement with the assessment for eligibility in the trial. For large multi-centre trials it is recommended that the Chief Investigator considers using an external source to perform this task using either an IVRS, IWRS system or randomisation software.
- If the sequence is generated by computer, the seed used in the randomisation should be fixed and documented so that if necessary the sequence is repeatable; care should be taken to ensure that the same value does not result every time the computer is restarted
- If lists are generated manually, the details of the particular random number table used, which numbers correspond to which treatments and how the starting point in the tables was determined should be detailed, however we do not recommend lists are generated manually.
- The randomisation schedule/list should be version controlled so that it is clear which the final version is.
- Where possible, the R&D QA Team (for HHP sponsored single-centre CTIMPs) shall be the custodian and controller of the generated randomisation list but this will be discussed and agreed on a study-by-study basis.

3.2 Checking the randomisation list

The implementation of randomisation should be checked as follows:

- During monitoring randomisation for each study should be checked to determine that it has been followed. One method of doing this is to check whether patient ID numbers have been allocated in chronological order and ensure the allocated treatment is correct. The need for these checks should be assessed on a study by study basis and built into the study monitoring plan for HHP sponsored CTIMPs.
- **The importance of following the generated randomisation list should be emphasised. Failure to do so may introduce bias that cannot be accounted for in the data analysis.** If the randomisation has not been followed, the Sponsor should discuss any anomalies with the study team to determine the possible source of the problem and statistical input should be sought to attempt to assess and document the effect of this on the analysis of the data.
- Unusual patterns of randomisation may indicate fraud and the statistician or R&D QA Team may need to undertake a statistical examination of the data for results indicative of fraud.
- Computer randomisation systems should be thoroughly tested before use and monitored carefully throughout the trial to ensure they are working. For HHP sponsored CTIMP studies the initial testing of the system and all ongoing monitoring during the trial (as per monitoring plan) must be documented in the Sponsor Study File.
- If any subject is randomised twice, the first randomisation should be used. The second should be left in the database, indicating it is a duplicate.

3.3 Blinding and Unblinding

- It must be ensured in blinded trials that emergency unblinding of one participant does not unblind all participants in the trial. For example, in a more complex (for instance a multicentre double-blinded study) calling the treatments A and B is not sufficiently robust. In case of emergency unblinding, to protect participant safety, the investigator should be prepared and capable from the start of the trial to perform unblinding with undue delay and hindrance, this should be described within the Randomisation Process File Note.
- All unblinding events (planned or unplanned, including emergency) must be documented (who/when/why/how) and any unplanned unblinding must be assessed for impact on trial integrity and reported/escalated as required.
- A documented contingency procedure must be in place for randomisation/unblinding system failure (e.g., downtime process, secure fallback, accountability and later reconciliation), ensuring participant safety and preserving allocation concealment.
- Where interim analysis is to be carried out and requires unblinded data, an independent statistician or investigator should perform this; this should be fully explained in the protocol.

4 Close of Trial

For double-blind randomised trials where a 3rd party randomisation service holds the randomisation list, R&D QA will need to be in receipt of the complete set of trial data and then request release of the randomisation list. R&D QA will then forward the list to the statistician and Chief/Principal Investigator and document the order of events on the Data Timelines Log (WI 19). The randomisation service will be informed at the trial set-up phase that they can only release the list to the Sponsor when the trial has finished and that the request will come from the R&D QA staff.

5 Implementation

Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.

FILE NOTE
Trial Master File
Section 3

Date:

Regarding: Randomisation Process

Do all staff involved in recruitment have individual user name and password log-in details for the randomisation system?	
1) Who will be responsible for producing the randomisation list or envelopes containing the randomisation code?	
2) When will the list/envelopes be produced?	
3) How will list/envelopes be produced? Mention if applicable • Online software application used • Treatment groups • Block size • List length • Randomisation ratio • Strata	
4) Where will list/envelopes be held during the study?	
5) Who will inform investigators of the randomised treatment?	
6) Who will have access to the list/envelopes? In double-blind studies, the investigator allocating treatment must not have access to the randomisation list.	
7) How is a patient randomised? Mention if applicable • Who is contacted • Who allocates the next patient study number and treatment allocation • Is a prescription written • Who collects the study medication from pharmacy or theatre (as applicable)	

8) What are unblinding procedures, if? Mention if applicable • Who is responsible for unblinding? • When will it happen? • Who will remail unblinded?	
9) In double-blind studies, is there a code break procedure? Is there a clear procedure should the randomization code need to be broken for a patient?	

Name **(Chief/Principal/Co-Investigator)**

Sign …….. date ……

Name **(Pharmacy Technician)**

Sign …….. date ……

Name **(Statistician)**

Sign …….. date ……

Name **(Clinical Trials GCP monitor)**

Sign …….. date ……