York and Scarborough Teaching Hospitals NHS Foundation Trust R&I Department
Standard Operating Procedure
R&D/S62

Production of a Randomisation Schedule for Randomised Controlled Trials (RCTs)

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

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SOP Reference:	R&D/S62
Version Number:	6.0
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Implementation date of current version:	13th May 2026

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	Date:	16th April 2026
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	Date:	15th April 2026

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Reviewers	Details of significant changes
1.0	1st March 2012		
2.0	4th April 2014		Removal of references to the North and East Yorkshire R&D Alliance.
3.0	15th June 2017		Change of Author. Review with one minor amendment to location of documentation.
4.0	2nd October 2019		Change of author. Change of link to R&D website. Further detail on allocation concealment
5.0	24th April 2023	Tom Szczerbicki Deborah Phillips	Three year review, no changes required.
6.0	13th May 2026	Liz Johnson	Change of author. Minor updates

Contents

1 Introduction, Background and Purpose

This SOP describes the procedures for producing a randomisation sequence for Randomised Controlled Trials (RCTs). This SOP is based on current thinking about the design of RCTs and follows the advice of the CONsolidated Standards of Reporting Trials (Consort) Group. This group has issued a series of statements to help authors improve the reporting of randomised controlled trials (RCTs). Many journals have adopted the Consort Statement and will only publish reports of RCTs that meet the requirements specified in the relevant Consort Statement.

The Consort Statement (2025) states 'Randomised controlled trials, when appropriately designed, conducted, and reported, represent the gold standard in evaluating healthcare interventions. However, randomised trials can yield biased results if they lack methodological rigour'. Randomisation is one element of a study that can introduce bias if not carried out appropriately. The principal purpose of randomisation is to distribute the characteristics of trial participants that may influence outcome randomly between the treatment groups. This allows any differences seen in the outcome of the trial groups to be attributed to the intervention that has been received and not to some demographic or clinical characteristic such as disease severity (Roberts and Torgerson, 1998).

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

There are specific legal obligations for clinical trials of investigational medicinal products (CTIMPs) to be run in compliance with the UK Clinical Trial Regulations. In addition, in York and Scarborough Teaching Hospitals NHS Foundation Trust, all studies, CTIMP and non-CTIMP, should be run to GCP-equivalent standards to ensure consistent practice and scientific quality. ICH-GCP states "The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design" and that the trial design should include a description of the measures taken to minimise/avoid bias, including randomisation and blinding.

2 Who Should Use This SOP

This SOP applies to randomised controlled trials sponsored or co-sponsored by the Trust.

This SOP applies to the personnel responsible for the design of the study e.g. chief investigator and/or individuals who have a pivotal role in the production of the randomisation scheme e.g. statistician, programmer.

3 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.

It should be applied when planning to conduct a RCT sponsored or co-sponsored by York and Scarborough Teaching Hospitals NHS Foundation Trust unless otherwise specified in a trial site agreement.

It should be used in conjunction with the other related SOPs listed in section 5. *Note: This SOP does not cover the procedure for breaking a blinding code and availability of code break information within Pharmacy (refer to Section 5).*

4 Procedure(s)

4.1 Type of randomisation

- The interplay of unpredictability versus balance of participant characteristics should be considered when choosing the type of randomisation for a trial.
- For larger sample sizes (several hundred participants) simple randomisation should generate comparable trial groups in terms of their numbers and characteristics. However there are exceptions where block randomisation may be more appropriate for larger trials where simple randomisation may result in groups of different sizes.
- For smaller sample sizes, block randomisation may be more appropriate to ensure that similar numbers are allocated to each of the groups. Consideration should be given to the use of blocks of varying lengths so the sequence cannot be predicted. Clinical staff involved in the research study should not be informed of the block size unless it is necessary for study conduct.
- To achieve better balance between the baseline characteristics of participants in the randomised groups, especially for prognostic factors, consideration should be given to the use of restricted randomisation such as stratification or minimisation. The number of strata should be limited to ensure a reasonable sample size – strata sizes of less than 20 are not recommended. The strata must be independent of one another so they can be adjusted for in the final analysis. In small studies, particular care must be taken as it is not practical to stratify on more than one or two variables.
- If there are several important prognostic factors, minimisation may be preferred to stratification. The centre should not be included as a minimisation factor in a study that cannot be suitably blinded (where possible). If minimisation is used it should contain a random element.
- To ensure the integrity of the randomisation methodology and sequencing chosen, the randomisation model and allocation tables should always be checked for accuracy by a statistician or person with equivalent statistical knowledge.

4.2 Generation of the randomisation list

- For CTIMP studies the approved trial protocol must detail how the randomisation list will be generated.
- 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 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 Sponsor file (refer to section 5 for template form).

- Acceptable methods of sequence generation include the use of a random number table or computer generated schemes.
- As a minimum, documented checks should be carried out for each randomisation undertaken. 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 Sponsor File.
- The person generating the randomisation list and / or allocation concealment should not be involved in the later implementation of the sequence.
- If the sequence is generated by computer, the seed used in the randomisation should be fixed and documented but vary from study to study so that the sequence is repeatable.
- In schemes such as minimisation, 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.
- If lists are generated manually, the details of the particular random number table used, which numbers corresponded to which treatments and how the starting point in the tables was determined should be detailed.
- For CTIMP studies individuals involved in the generation of the randomisation scheme must document every stage of the procedure followed for inclusion in the Sponsor file.

4.3 Implementation of sequence and allocation concealment

- The generated allocation sequence should be applied using allocation concealment. Allocation concealment aims to prevent selection bias by concealing the allocation assignment until enrolment, thus removing potential selection bias due to knowledge of treatment assignment. Allocation concealment shouldn't be confused with blinding and should always be implemented.
- Allocation using centralised or third party external involvement (e.g. Clinical Trials Unit or HYMS Statistician) is desirable to ensure allocation concealment however in some studies this may not be practicable.
- In blinded studies, clinical research staff should not be informed of the details of the stratification or minimisation variables or block sizes unless absolutely necessary for the conduct of the study or it is unavoidable.
- Once randomised, participants 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.
- In computer randomisation systems, methods should be employed so that once a subject has been randomised, the record of the participant's randomisation cannot be removed. In manual systems, staff should be trained in ensuring allocation concealment and not letting randomising

clinicians change their minds once they have been given the randomisation code.

4.4 Checking the randomisation sequence

The implementation of randomisation should be checked as follows:

- In paper-based systems, the randomisation scheme 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. The need for these checks should be assessed on a study by study basis and built into the study monitoring plan for CTIMPs.
- The importance of following the generated randomisation schedule 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 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 CTIMP studies the initial testing and all ongoing monitoring of the system during the trial must be documented.
- 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.

4.5 Documentation

The following information should be documented in the Sponsor file and archived with the essential documents at the end of the study (a template Form is available for use – refer to Section 5):

- Method of generation of the randomisation scheme, including any allocation concealment.
- Method of implementation e.g. sealed envelopes, web based system, telephone based system.
- Person/people (and job title/s) responsible for preparing and checking the randomisation scheme.
- Precise details of blocking and stratification variables, including exact specification of any cut-offs or algorithms used.
- The randomisation ratio if participants are allocated to groups in unequal numbers.
- Person/people (and job title/s) who will have custody of and/or access to the randomisation list throughout the conduct of the study and where data on treatment codes will be stored.
- Changes and/or extensions to the randomisation schedule and date/s when new scheme/s become active.

The R&I Office has links with the University of York and could work with staff to obtain appropriate access to statistical support if required. In addition the Trust also has access to statistical software. If you wish to discuss statistical support for your research please contact the R&I Office for further details.

5 Related SOPs and Documents

Pharm/S54	Managing code break procedures
R&D/F45	Sponsor details of randomisation procedure

Acknowledgements

SOP for randomisation and blinding procedures, Academic and Clinical Central Office for Research and Development, University of Edinburgh / NHS Lothian