Randomisation and Code Breaking

NJRO-REG-SOP-001

Contents

1. Background/Introduction

Randomisation is the process by which participants of a clinical trial are allocated to intervention groups. Random allocation ensures that any differences between the groups at trial entry are due to chance alone. The mechanism that is used to allocate participants to study groups must be truly random, non-deterministic and it should not be possible to change the allocation after randomisation.

Blinding is an important aspect of randomised controlled trials and refers to keeping trial participants or specific study team members unaware of treatment group assignment to prevent inadvertent biases affecting trial data. In order to protect the wellbeing and safety of the trial subject as required by the principles of Good Clinical Practice (GCP), the coding system for the Investigational Medical Product(s) in blinded Clinical Trials of Investigational Medicinal Products (CTIMPs) or Advanced Therapy Investigational Medicinal Products (ATIMPs) should include a mechanism that permits rapid identification of the product(s) 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, code break procedures must be clearly established.

At the start of any clinical trial the Chief/ Principal Investigator should have a written procedure on the randomisation, blinding and code break process as well as the details of authorised personnel who will have access to unblinded data.

2. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the process to be followed when establishing a randomisation procedure and for releasing the randomisation codes at the end of a study or in an emergency situation.

3. Scope of Document

This SOP is applicable to all personnel involved in randomised studies sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH FT), particularly those personnel acting as Chief Investigator (CI)

4. Definitions

ATIMPs	Advanced Therapy Investigational Medicinal Products
CI	Chief Investigator
CTIMPs	Clinical Trials of Investigational Medical Products
CTU	Clinical Trials Unit
DMSC	Data Monitoring and Safety Committee
GCP	Good Clinical Practice
IMP	Investigational Medical Product

IRT	Interactive Response Technology
PI	Principal Investigator
RCM	Regulatory Compliance Manager
SUSAR	Suspected Unexpected Serious Adverse Reaction

5. Roles & Responsibilities

The responsibility for the production and implementation of the randomisation schedule or list should be assigned to appropriate individuals. Typically the production of the schedule will be the responsibility of the Trial Statistician and its implementation will be the responsibility of the Trial Manager but these roles could be assigned to other qualified members of the study team if one or both of these posts does not exist.

6. Procedures

6.1. Randomisation

The randomisation procedure must be determined during the design phase of the trial and detailed in the trial protocol. The CI is responsible for determining the type of randomisation to be used (simple, blocked, stratification, minimisation, etc.) however a qualified statistician should be consulted to ensure that the type of randomisation chosen is appropriate for the trial. Methods that must not be used include: alternate allocation; day of the week; odd or even date; and odd or even last digit of hospital number.

Once the design and type of randomisation has been detailed in the protocol and funding has been confirmed (but before recruitment) a randomisation list or schedule with details of the randomisation codes should be produced in accordance with the protocol. It is best practice that the randomisation list is generated by a person without direct contact with the trial participants or involvement with the assessment for eligibility into the trial (e.g. trial statistician or data manager). The method of generating the randomisation list should be clearly documented and include the person responsible for its generation, the person responsible for checking the list and who accessed the list prior to database lock.

The randomisation list should be version controlled and dated to ensure that the correct version of the list is used at all times and by all relevant personnel. Checks should be performed by a qualified person (e.g. trial statistician) to ensure that the randomisation schedule has been followed. Unusual patterns of randomisation can be an indication of fraudulent activity and under such circumstances, a statistical assessment of the trial data must be undertaken to investigate this further.

In the event of a participant being randomised twice, the first randomisation should be used and the second recorded as a duplicate.

6.2. Blinding

The blinding of the trial must be maintained for the entire duration of the trial until database lock. The protocol should define the level of blinding required in the trial (e.g. unblinded, single-blind or double-blind) and how this blinding will be implemented (e.g. use of an identical placebo/comparator or sham treatment). In the case of double-blinded trials, consideration should be given to how the treatment under study and placebo will be packaged, coded and labelled in order to protect and maintain the blind for the duration of the trial until database lock.

For trials involving medicinal products, the master randomisation codes should be kept by the Pharmacy Department and the trial data management team with appropriate security measures and access control.

6.3. Unblinding/Code Breaking

The unblinding process should be detailed in the protocol including the circumstances where unblinding can be performed:

- Treatment of an individual in a medical emergency where knowledge of the treatment allocation is required.
- Treatment of an individual for an adverse event.
- In the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) the participant must be unblinded.
- In the event that the participant's study medication is accidentally taken by a member of their household e.g. a child.
- For the submission of trial data to the Data Monitoring and Safety Committee (DMSC) for the monitoring of safety and/or efficacy.

For double-blind trials the master randomisation codes should be retained by individuals not directly involved in the day-to-day management of the trial (e.g. Trust Pharmacy).

All individuals directly involved in the clinical management of participants in the trial must not be unblinded.

6.3.1. Unblinding/Code Breaks in NuTH FT-Sponsored Trials

When a code break occurs in a trial sponsored by NuTH FT, the Research & Development (R&D) team must be informed of the code break as the representative of the sponsor.

For those trials managed by a Clinical Trials Unit (CTU) it is the responsibility of the CTU to inform the R&D team of a code break. For trials not managed by a CTU, it is the responsibility of the CI to inform the R&D team.

For studies designated as High Risk (e.g. CTIMPs, ATIMPS, clinical investigations of non-CE marked devices, etc.), contact should be made by email directly to the Regulatory Compliance Manager (RCM), or appropriate delegate, copying in the Sponsor Management email address (tnu-tr.sponsormanagement@nhs.net). For all other studies, contact should be made to the appropriate Research Management and Governance Manager copying in the main R&D email address (nuth.genericqueries@nhs.net). This email must contain:

- Date and time of the code break
- The reason for the unblinding
- The actions taken
- Details of the person(s) involved in the code break
- Patient study number/trial identifier

6.3.2. Use of Code Break Envelopes

Although the use of code break envelopes is permitted, it is not the preferred method of providing the code breaking functionality. The use of code break envelopes instead of an Interactive Response Technology (IRT) must be considered during the initial risk assessment of the trial and specific Sponsor approval sought.
The envelopes should be based on the randomisation schedule (once finalised) and prepared by members of staff otherwise unconnected with the study. Points to consider when using code break envelopes include:

- The envelopes should be brown to ensure that the contents cannot be seen when held up to the light
- The envelopes must not have a window
- The envelopes should either be double sealed or have a perforated seal.
- The correct identification number should be written on the outside of the envelope and checked against the schedule by the second person
- The envelopes should be signed on both seals
- In the event of a code break the name and signature of the code breaker, date and time of the code break needs to be recorded on the outside of the envelope.

For trials involving medicinal products, code break envelopes should be held by the site Pharmacy Department and if unblinding is required outside of normal working hours, the on-call Pharmacist will be available to perform the code break. Within NuTH FT the on-call Pharmacist can be contacted via the hospital switchboard.

The relevant Pharmacy SOP will be followed to perform the code break.
All code break envelopes must be returned to the CI at the end of the study in order to document any decoding which may have occurred.

7. References

7.1. Guidelines for Standard Operating Procedures for Good Statistical Practice in Research – Statisticians in the Pharmaceutical Industry (PSI) Professional Standards Working Party
7.2. MHRA: Good Clinical Practice for Clinical Trials https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials
7.3. Newcastle Clinical Trials Unit: SOP ST-004 Randomisation and Blinding Procedures - http://www.ncl.ac.uk/nctu/activities/sop/library.htm
7.4. NuTH FT Pharmacy SOPs

8. Appendices

8.1. Not applicable