Standard Operating Procedure:

Randomisation and Blinding

# Purpose

This standard operating procedure (SOP) describes the randomisation and blinding procedures involved in clinical research conducted within the University of Birmingham (UoB).

# Scope

This SOP is applicable to all clinical research where the UoB is the sponsor or takes on sponsor responsibilities for randomisation and blinding procedures. Where clinical research is (co-)sponsored by another institution, this procedure should be followed as far as possible, and in line with the contractual agreement between the UoB and the other institution. This SOP also applies to clinical research approved by UoB Research Ethics Committee (REC) that is required to follow the UoB Principles of Good Clinical Practice (GCP) for Clinical Research (UoB-GCP-POL-001) and there is a requirement to randomise or blind. This SOP may be used as a guidance document in all other cases.

# Implementation plan

This SOP is implemented directly after its effective date for any clinical research that is in the set-up phase. For existing clinical research this SOP will be implemented within three months of the effective date.

# Stakeholders

Note that where the UoB takes on the sponsor responsibility for randomisation and blinding, the UoB will delegate the majority of these duties to the Chief investigator (CI) and/or to a clinical trials unit (CTU), who may delegate these duties further to their research project team(s). All delegation of duties will be documented e.g. using either the CI declaration and/or the Clinical Trials Task Delegation Log (UoB-SPO-QCD-001).

* CI: The CI may delegate activities to members of their research project team, although evidence of CI oversight and approval is still expected and may not be delegated where ‘no delegation allowed’ is indicated. The SOP will state where delegation is possible. For clinical research approved by UoB REC, the role of CI may be referred to as the principal investigator (PI), or the supervisor for postgraduate research students.
* Statistician: The statistician must possess the relevant statistical knowledge and experience. This may be the CI where they have sufficient knowledge and experience to advise on and/or perform the required statistical elements of the research project.
* Statistical advisor: The statistical advisor may contribute to some, but not all, aspects of the research project design, conduct, analysis and reporting. The statistical advisor may take on the responsibility of the ‘statistician’ for specific statistical aspects of the research project that they will perform, and will adhere to the relevant sections of this SOP. See the *Statistics SOP (UoB-STA-SOP-001)* for further information.
* Laboratory academic lead (LAL): The laboratory academic lead to the research project will lead the laboratory-based research and takes on the responsibility of the ‘lab manager’ and the ‘analytical manager’ as detailed in the Laboratory Set Up and Management SOP (UoB-CRL-SOP-001).

# Background and rationale

For the purposes of this SOP the terms ‘clinical research or ‘research project’ will cover clinical trials of investigational medicinal products (CTIMPs), other interventional trials (e.g. surgical trials, device trials and non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the sponsor), and clinical studies.

Randomisation is the process used for assigning participants in a clinical research project to intervention groups without taking any similarities or differences between them into account. Random allocation ensures that any differences between the groups at entry to the research project are due to chance alone. 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 research project (e.g. the sponsor, pharmacy, the investigator team and/or the subject) unaware of what treatment arm participants have been randomised to. Maintaining the integrity of the blind is a key consideration for all those involved in the research project. Compromising the blind may have a significant impact on the interpretation of the results so careful planning, communication and training are necessary to ensure robust processes are in place to maintain the blind. Unblinding is however permissible for the urgent medical treatment of a participant, for safety reporting requirements e.g. reporting of suspected unexpected serious adverse reactions (SUSARs) to the Medicines and Healthcare products Regulatory Agency (MHRA) or for any pre-specified protocol indication such as interim analysis.

Monitoring of blinded clinical research projects can be complicated, especially if the intervention is unblinded to some of the staff at the investigator site (for example the pharmacist). If the monitor is unblinded, there could potentially be bias introduced into the queries raised by monitors when conducting data verification on adverse events (AEs) or serious adverse events (SAEs) and they may risk unblinding the investigator team.

# Process map



# Procedure

## Randomisation

### Randomisation methodology

1. The CI (or delegate) will seek advice from a statistician or statistical advisor on the development of an appropriate randomisation and blinding method for the research project and the production of a documented randomisation schedule (or list). See *Statistics SOP (UoB-STA-SOP-001)* for further information.
* Evidence of the statistician’s or statistical advisor’s involvement in the design will be documented (e.g. emails, meeting minutes, comments on proposals/protocols).
1. The CI (or delegate) will ensure that the randomisation method used is appropriate for the research project and reduces the chance of imbalance between treatment groups (e.g. simple, block, stratified, minimisation).
2. The statistician will ensure that when user-written codes/macros and programs are used to prepare the randomisation schedule the program is appropriately validated, documentation to demonstrate the validation is retained and that the randomisation method can be verified and reconstructed at a later date.
* For example, where software using a random number generator is used to produce the randomisation schedule the seed used for the randomisation is documented and stored.
1. The CI (or delegate) will ensure that the randomisation method and parameters of the randomisation process (e.g. stratification variables, inclusion and exclusion criteria) are described fully in the protocol.
* For clinical trials, the randomisation method and process will be described in the final publication according to the [CONSORT (Consolidated Standards of Reporting Trials) Statement guidelines](http://www.consort-statement.org/). Also see [Extensions of the CONSORT Statement](http://www.consort-statement.org/extensions) for “non-standard” randomised trial with specific designs, data and interventions.

### Production and maintenance of the randomisation schedule

1. The CI (or delegate) will produce a randomisation schedule with details of the randomisation codes.
* The randomisation schedule may be produced in collaboration with the statistician.
* The randomisation schedule may consist of a paper record only or also as an electronic version.
* It is expected that the randomisation code is complex enough to ensure blinding is maintained; avoid simple coding such as labelling arms as ‘A’ and ‘B’, which means when one participant is unblinded the whole research project will be unblinded.
* For independent investigators running clinical research outside of a UoB CTU, it is strongly recommended that a third-party source is used to generate and execute the randomisation schedule, e.g. a local pharmacy or a randomisation service provided by a CTU.
* The details of the service being provided and the roles and responsibilities of any third party will be documented and agreed via a signed contractual agreement (for sources external to UoB) or a memorandum of understanding (for sources internal to UoB). See the Compliance Review SOP (UoB-CPR-SOP-001) for further information on third-party (vendor) assessment and management.
1. The CI (or delegate) will ensure the randomisation schedule has version-control applied. Where there are changes to the randomisation schedule through the course of the research project, version control will include the date when the new schedule became active. See the Essential Documents Development and Maintenance SOP (UoB-ESD-SOP-001) for further information on version control.
2. The CI (or delegate) will ensure that all procedures in the process of producing and managing the randomisation schedule are documented, with particular consideration given to the items listed below.
* Person(s) and job title(s) of those responsible for preparing and checking the randomisation schedule.
* Distribution of the randomisation schedule including storage, access control methods and approach used to conceal allocation (e.g. password protected electronic format).
* Method of implementation (e.g. web-based system, telephone-based system).
* Details on how the pharmacy or investigational medicinal product (IMP) supplier will be informed of the randomised treatment allocation (e.g. email sent to pharmacy), if applicable.
* Procedures put in place to ensure the randomisation schedule is adhered to.

**Randomisation of participants**

1. The CI (or delegate) will ensure that randomisation of participants only occurs once the following are in place:
* The site has been approved for recruitment (e.g. HRA approval has been obtained and, if applicable, R&D approval has been obtained, the Clinical Site Agreement has been signed and site initiation has been performed). See also the Investigator Site Management SOP (UoB-SMA-SOP-001).
* The participant is eligible, has been appropriately consented for the research project and the required documentation has been completed (e.g. signed informed consent form, randomisation checklist, eligibility criteria checklist).
* For CTIMPs, IMP is available and, where applicable, code-break envelopes are available on site.
1. The CI (or delegate) will ensure the allocation of a unique identifier for each participant (i.e. a trial/study number) and that methods are in place to prevent the same participant being randomised more than once.
2. The CI (or delegate) will ensure that if a participant withdraws post-randomisation the record of the participant’s randomisation is retained.

## Blinding

### Maintenance of the blind

1. The CI (or delegate) will ensure that procedures are implemented to control the randomisation schedule to prevent accidental or deliberate (unauthorised) unblinding. These procedures will include those listed below.:
* Access restrictions for the electronic/paper schedule and processes for handling the master randomisation schedule throughout the conduct of the research project.
* If there are unblinded staff, clear documentation (e.g. in the delegation log) of who is authorised to perform unblinded duties.
* Processes in place to protect the research project team from gaining access to unblinded data in cases where data monitoring committees require interim unblinded analysis reports.
* Storage of any unblinded documentation separate to the rest of the research project documentation, either until the end of the project or until the randomisation code has been broken for analysis.
* For CTIMPs, processes for managing drug administration records and the IMP. See the Medicinal Product Management SOP (UoB-MED-SOP-001) for more information.
1. Where sub-contracting (e.g. for blinding/shipping/unblinding of IMP), the CI (or delegate) will ensure appropriate agreements (external to UoB) or a memorandum of understanding (internal UoB sources) are in place.

**Unblinding**

1. The CI (or delegate) will risk assess the need for providing 24-hour cover to access the code break in the case of emergency unblinding, and document where 24-hour cover is not required in the study/trial master file (S/TMF).
2. Where applicable, the CI (or delegate) will ensure that code-break procedures for emergency unblinding situations are clearly established prior to the commencement of treatment/intervention and detailed in the protocol, including those listed below.
* Details of who can request that unblinding take place and who will assess the need for unblinding.
* The system used to access the code-break information including interactive response systems such as interactive voice response systems (IVRS), interactive web response systems (IWRS), online or physical code breaks e.g. code-break envelopes held at site.
* Ensure staff who are delegated code-break activity have the correct access to the interactive response system prior to the commencement of treatment.
* Back-up systems will be available in the event that the IWRS/IVRS is not functioning or if physical systems are unavailable.
* When using an interactive response system, it needs to be possible to demonstrate that the blinding has not been compromised, e.g. via an audit trail.
1. If the code-break procedure involves a number of steps or staff, or may occur out of hours, the CI (or delegate) will ensure that the code-break process has been tested prior to the commencement of treatment and that documented evidence of the process being tested and deemed satisfactory is retained.
2. The CI (or delegate) will document a process for unblinding for safety reporting requirements e.g. prior to reporting a suspected unexpected serious adverse reaction (SUSAR) to the competent authority. See the Adverse Event Reporting SOP (UoB-AES-SOP-001) for further information.
* There will be clear documentation of who is authorised to request a code break, who needs to authorise the unblinding and who must remain blinded.
1. The CI (or delegate) will document a process to control unblinding for analysis purposes.
* Where interim unblinded analysis is required, ensure the research project team cannot gain access to unblinded data or the randomisation schedule.
1. The CI (or delegate) will ensure there is documentation which confirms when the randomisation code was requested or provided and when the randomisation data were applied to the analysis datasets at interim and final analysis.
2. Where analytical laboratories are required to unblind samples for analysis, the LAL (or delegate) will have a documented procedure detailing how data will be communicated in a blinded manner, how samples will be re-blinded and how information that allows samples to be unblinded will be stored. See the Laboratory Set-Up and Management SOP (UoB-CRL-SOP-001) for further information.
3. The CI (or delegate) will consider clarifying under which circumstances unblinding may be feasible following a request from a participant, including whether it is practical and ethical to do so without harming data integrity.
* Circumstances could include, for example, the research project having to be completed.
* If applicable, the CI (or delegate) will ensure these circumstances are documented in, for example, the protocol.
1. The CI (or delegate) will ensure that if the code is unblinded (either inadvertently or on purpose) during the conduct of the research project, this event is fully documented in the S/TMF and in the end-of-research-project report, including the reason for unblinding.

## Monitoring

1. The CI (or delegate) will consider the allocation of unblinded monitors for the intervention aspects of a research project, along with how any communication will be documented, reviewed and approved during the project without compromising the blind.
2. The CI (or delegate) will ensure that where sealed code-break envelopes are used for unblinding, the integrity of the envelopes are maintained and where electronic systems are used, a check to confirm the integrity of the system is performed during a routine on-site monitoring visit.

## Archiving

1. The CI (or delegate) will document a process to reconcile physical code breaks at the end of the research project to confirm they have not been tampered with or where electronic systems are used a process to confirm the integrity of the system and the integrity of the blind was maintained.
2. The CI (or delegate) will archive all documentation related to randomisation and blinding, both paper and electronic, along with the rest of the S/TMF at the end of the research project. See the *Archiving SOP (UoB-ARC-SOP-001)* for further information.

# List of expected outputs

* Evidence of the statistician’s or statistical advisor’s involvement in the randomisation and blinding design.
* Documented agreements where third parties are used for randomisation/blinding/unblinding.
* Where applicable, documented validation of the programme, macro or algorithms used to generate the randomisation schedule.
* Randomisation methods and parameters of the randomisation process described in the protocol, and in the final publication for CTIMPs and trials according to [CONSORT](http://www.consort-statement.org/extensions).
* A documented randomisation schedule (or list) and documented procedures to control the randomisation schedule.

### Where blinding is used

* Documented procedures to maintain the blind.
* Documentation in the S/TMF where 24-hour emergency unblinding is not required.
* Documented procedures for emergency unblinding, prior to the commencement of treatment, where applicable.
* Documented evidence of the emergency code-break procedures being tested and deemed satisfactory, where applicable.
* Documented procedures for unblinding in the case of safety reporting.
* A documented process to control the unblinding of data for analysis purposes, if applicable.
* A documented procedure to maintain the blind’s integrity where analytical laboratories are required to unblind samples for analysis in the laboratory, if applicable.
* Documented evidence of any instances of unblinding.
* A documented process for the reconciliation of physical code breaks at the end of the research project and a check made that they have not been tampered with.

# Related documents

* UoB-AES-SOP-001 Adverse Event Reporting
* UoB-ARC-SOP-001 Archiving
* UoB-CPR-SOP-001 Compliance Review
* UoB-CRL-SOP-001 Laboratory Set Up and Management
* UoB-ESD-SOP-001 Essential Documents Development and Maintenance
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-MED-SOP-001 Medicinal Product Management
* UoB-SMA-SOP-001 Investigator Site Management
* UoB-SPO-QCD-001 Clinical Trials Task Delegation Log
* UoB-STA-SOP-001 Statistics

UoB QMS documents can be found on the [Clinical Research Compliance Team (CRCT) website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT (crct@contacts.bham.ac.uk) and/or from the Research Governance Team (RGT) (researchgovernance@contacts.bham.ac.uk).

# References and frameworks

* CONSORT (Consolidated Standards of Reporting Trials) Statement guidelines: [http://www.consort-statement.org/](http://www.consort-statement.org/%22%20%5Co%20%22Website%20for%20the%20CONSORT%20%28Consolidated%20Standards%20of%20Reporting%20Trials%29%20Statement%20guidelines)
* Health Research Authority (HRA) Information for participants at the end of a study: Guidance for Researchers/Sponsors/Chief Investigators/Principal Investigators v4.1 20-Aug-2015: <https://www.hra.nhs.uk/documents/322/hra-guidance-end-study-pis-v4-1_20-august-2015.pdf>
* Medicines and Healthcare products Regulatory Agency (MHRA). *Good Clinical Practice Guide*, London: The Stationery Office, 2012.

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| Blinding | Blinding is the process that keeps one or more parties involved in a clinical research project (for example, the sponsor, the investigator team, and/or the participant) unaware of what treatment arm participants have been randomised to. In relation to an investigational medicinal product, blinding is the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. |
| Code break | Also known as breaking the blind. This is the mechanism that permits the rapid identification of the intervention/treatment received by a participant 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 | A clinical trial of an investigational medicinal product(s). |
| Interactive voice response system (IVRS) | 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 research project. |
| Interactive web response system (IWRS) | A web technology that is designed to give adequate information for users to manage clinical research projects. |
| Randomisation | The process of assigning participants to an intervention/treatment or control groups in order to reduce bias. |
| Randomisation code | A unique number or code that is linked via a randomisation list to the intervention/treatment. |
| Randomisation schedule  | A list of intervention groups, randomly ordered, used to assign sequentially enrolled participants to intervention groups. Also termed the "randomisation list". |
| Statistical advisor | A qualified statistician or experienced researcher who may contribute to some, but not all, aspects of the clinical research design and analysis, but takes responsibility for the statistical aspects of the tasks they perform. |
| Statistician | A qualified statistician who contributes to the design, analysis and interpretation throughout the clinical research life cycle and takes responsibility for the statistical aspects of the project. The statistician may be unblinded to the allocation and evolving results whilst performing interim analyses, but will not disclose these to the rest of the research team. There may be a senior statistician supervising a more junior statistician. |
| Study/trial master file (S/TMF) | The study/trial master file consists of essential documents kept at the sponsor (or delegate) site, which enables both the conduct of a clinical study/trial and the quality of the data produced to be evaluated. The filing system can be in the form of a single file or a number of files as deemed most appropriate. |
| Suspected unexpected serious adverse reaction (SUSAR) | 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. |
| Unblinding | The disclosure of the identity of blinded intervention/treatment. |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).