STANDARD OPERATING PROCEDURE 9
Randomisation in Research Studies

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Revision Chronology:	Effective date:	Reason for change:
Version 3.0	13 December 2022	Biennial review. Change to new format. Minor update to 4.3.1 for emphasis. Addition of new section 4.3.2 on site setup pre-randomisation checklist, previous text moved to 4.3.3. Addition of section 4.3.4 on end of recruitment. Removal of Appendix 1. Contingency procedures moved to SOP 40.
Version 2.0	21 July 2020	Removal of information on blinding studies, change of title (new blinding SOP 41 created). Addition of IVR information in 4.3.2. Addition of emergency procedures for remotely accessing handsets to transfer the randomisation phone line. Change to new format.
Version 1.5	5 December 2016	Biennial review: Minor amends to SOP text and details in the emergency procedure information.
Version 1.4	17 September 2014	Biennial review: Minor text changes and change of fax number.
Version 1.3	6 August 2012	Format change. Additional sections added: confirmation of allocation, procedures for emergency randomisations and unblinding procedures
Version 1.2	14 May 2010	Addition of definition of blinding
Version 1.1	9 April 2008	Format change
Version 1.0	March 2006	

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Randomisation in Research Studies

1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to explain the role of randomisation in research studies and to detail potentially suitable methods of treatment allocation.

This SOP is applicable to all University of Warwick personnel involved in studies which randomise participants, and/or are involved in the WCTU randomisation service, unless external Sponsor or other agreed SOPs are to be followed.

2. Definitions

Randomisation	Defined by International Conference of Harmonisation (ICH) Good Clinical Practice (GCP)as: "The process of assigning study participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias".
Randomisation subject	May be individuals (unit) or groups (clusters).
Allocation ratio	The proportion of subjects in one allocation group versus the other group.
Allocation concealment	The procedure when the randomisation system is set up such that it is not possible to know or guess what the next allocation in the sequence will be.
Stratification	A component of a randomisation procedure used to ensure important pre-specified factors are balanced across groups. Factors may include gender, age, or other demographic/clinical factors such as biomarker status.
Randomisation methods:	
Simple	Randomisation using a single sequence of random numbers to assign intervention allocation to subjects.
Minimisation	A method of ensuring balance between groups for several prognostic factors. Allocation of the next participant enrolled in the study depends (wholly or partly) on the characteristics of those participants already enrolled. The aim is that each allocation should minimise the imbalance across multiple factors whilst preserving balance between allocation groups. *Minimisation with a random factor* is used to make minimisation a randomisation technique. This gives both allocation groups a non-zero probability of being given, with a higher probability given to the allocation group which minimises imbalance.

Blocking	A randomisation procedure where a "block size" is specified, and subjects are allocated randomly within each block. It maintains balance across randomisation strata. *Random permuted blocks* is a type of blocking when multiple block sizes are used. The choice of block size is often also randomly chosen from a pre-specified set of choices.

3. Background

Random allocation of participants in a research study ensures that any differences between the groups at study entry are due to chance alone. The mechanism that is used to allocate participants to study groups will depend on the study design and must satisfy the following criteria:

- The sequence of allocations must be random.
- It must be based on random number generation or some other random process.
- Non-random processes such as alternate allocation, allocation based on days of the week or hospital numbers are not acceptable.

Allocations must be concealed in advance of randomisation. This means it must not be possible to know or predict in advance what the next allocation in the sequence will be. Failure to conceal the allocation means that the study is open to bias, because it could be possible to select participants to receive a specific intervention.

It must not be possible to change the allocation after randomisation. Again, if intervention allocations can be changed after they have been assigned, the study will be open to bias.

The randomisation method to enrol study participants should be determined by the study statistician in consultation with the Chief Investigator (CI) and details of the full randomisation method must be clearly described in the protocol and in the final publication, in accordance with CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement guidelines: http://www.consort-statement.org/.

4. Procedure

4.1 Responsibilities

Chief Investigator (CI)	• Jointly with the study statistician, determine and document the study randomisation procedures in the protocol
Principal Investigator (PI) at recruiting sites	• Ensure that study staff at PI's site are trained in the randomisation procedure • Ensure all patients have met the requirements of study/trial eligibility before performing randomisation • Ensure all randomised participants receive the correct study treatment/intervention allocation.
Study statistician	• Jointly with the study CI, determine the method used for randomisation and document this in the protocol • Produce any emergency randomisation lists

	• Be aware of location/custodian of unblinded randomisation list and liaise with custodian to obtain a copy when required for interim or final statistical analyses • Develop or test/validate the randomisation procedure as appropriate. • Retention of documentation to demonstrate appropriate QC or validation of the program.
Randomisation service provider	• Develop and test the randomisation system • The quality control (QC) or validation of the program, especially where complex computer algorithms are used and document the checks • Retention of documentation to demonstrate appropriate QC or validation of the program.
Study manager	• Ensure Investigational Medicinal Product (IMP) supplier receives a copy of the unblinded randomisation list (if applicable) • Ensure that sites are trained in the randomisation procedures • Ensure (with the randomisation service manager*) that all staff completing randomisations are fully trained • Ensure access permissions to the randomisation database are granted and revoked in a timely way as required, and lists of site staff delegated to randomise patients are similarly maintained.

* the QA Support Officer acts as the randomisation service manager within WCTU.

4.2 When?

The randomisation procedure should be determined during the design phase of the study and clearly documented in the protocol.

The method of randomisation should be developed and tested before a study is open to recruitment.

4.3 How?

4.3.1 Methods of randomisation

The method used for randomisation will be specific to each study and is usually determined by the study statistician with input from the study chief investigator.

The chosen method of generating the randomisation schedule should be clearly documented and should include who was responsible for its generation, approval and who had access to the schedule before database lock. The randomisation schedule should then be filed in the Trial Master File (TMF).

The methods of preparing the randomisation schedule (or randomisation list) can vary and include random number tables, online randomisation programs and/or bespoke programs/macros.

Where computer programs are used, there should be a documented method of quality control or validation of the program which states who was responsible for its generation and who had access to the schedule (or list) before database lock.

For WCTU studies, the programming team has developed a formal process for validation of the system developed which must be completed and subsequently reviewed and signed off by the study statistician.

For studies which are blinded (concealed intervention allocation), additional considerations should be made to ensure the robustness of the chosen method of randomisation. Procedures to control the randomisation schedule to prevent accidental or deliberate unblinding should be implemented and enforced for blinded protocols e.g., access restrictions for electronic schedules. See SOP 41 'Blinding in Research Studies' for further details.

Using a chosen randomisation method may involve either a manual or computerised process. Computer based randomisation systems generally use a web application or an Interactive Voice Response (IVR) telephone program. Where computer systems are used, there should be documented validation of the program and contingency measures to mitigate any risks resulting from the computer randomisation system being unavailable. This may consist of a central telephone-based service that allows the study arm to be allocated from a pre-determined list which has been created as an emergency backup to the computerised system.

For studies managed by WCTU or make use of the WCTU randomisation service see SOP 40 'WCTU Business Continuity Plan' for emergency procedures in case of the computer randomisation system being unavailable.

4.3.2 Site setup pre-randomisation checklist

It is important to ensure that randomisation of participants only occurs once all other factors are in place. This includes:

- The site randomising is fully approved to start recruitment
- Site delegation/training log (as applicable) has been completed correctly and confirmed by the trial team
- Staff members confirming eligibility and performing randomisation must have correct responsibility codes on the delegation log and are authorised to carry out randomisations

For studies using a WCTU Programming team bespoke database the following should also be completed:

- Ensure the trial has requested via the WCTU IT Support Helpdesk for the correct delegated staff user access roles, which are described in the study Functional Requirement Specification (FRS)
- Trial team have assigned site staff the correct roles on the trial database for confirming eligibility and performing randomisations

Requests can be made via the WCTU IT Support Helpdesk.

4.3.3 Pre-randomisation checklist (eligibility confirmation)

A pre-randomisation check should be performed by the person(s) recruiting a new study participant and the checks should ensure that:

- All eligibility criteria are met
- Informed consent has been obtained (if the study doesn't recruit using a waiver of consent e.g., in emergency situations)
- Interventions are prepared e.g., study manuals have been developed, study drugs have been ordered
- All pre-randomisation documentation is completed (e.g., consent form)
- The participant has not already been randomised (it happens!)

4.3.4 End of Recruitment

When a study is approaching the end of recruitment, the closure timeframe must be considered. Once the timeframe has been agreed, the following actions should be taken to prevent incorrect recruitment:

- All recruiting sites should be informed of the timeframes for closing recruitment, and confirmation received from sites that the timeframes have been understood.
- If the WCTU Randomisation Cover Team is performing a support role for recruitment to the study, then they will need informing of the date recruitment is closing. The Cover Team can ensure they do not perform any recruitment on behalf of a study site after this date. The WCTU QA team's resource account can be contacted for this purpose via wctuqa@warwick.ac.uk.
- If the study is using a WCTU-managed database to perform recruitment a request will need to be made to the WCTU programming team via WCTU IT Support Helpdesk, requesting that access to the recruitment systems is closed.

List of abbreviations

CI	Chief Investigator
CONSORT	*Cons*olidated *S*tandards *o*f *R*eporting *T*rials) statement guidelines (http://www.consort-statement.org/)
FRS	Functional Requirement Specification
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IVR	Interactive Voice Response
IMP	Investigational Medicinal Product
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
R&IS	Research & Impact Services
SOP	Standard Operating Procedure
TMF	Trial Master File
WCTU	Warwick Clinical Trials Unit