Standard Operating Procedure for Randomisation, Blinding and Code Break

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Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JBRU/INV/S06/01	28/12/09	NA	Anne Marie Downey
JRO/INV/S06/02	11/01/12	Due for review. No changes beside JBRU replaced by JRO	Anne Marie Downey
JRO/INV/S06/03	12/01/15	Due for Review. Changes to update the content in the SOP	Nimrita Verma
JRO/INV/S06/04	16/01/18	Due for Review. Changes to update the content in the SOP	Nimrita Verma
JRO/INV/S06/05	12/03/21	Due for Review. - Updated definition for interactive voice/web system and used the more commonly used term IxRS to include both IVRS and IWRS. - Added use of the Code Break (Unblinding) Log for documenting code breaks on the trial. - Added prompt to test the code break / emergency contact telephone number & use of Testing Log template	Samim Patel
JRO/SPON/S34/01	12/09/24	Converted Investigator SOP for Preparation of a Trial Specific Randomisation, Blinding and Code Break SOP (JRO/INV/S06/05) into Sponsor SOP for Randomisation, Blinding and Code Break. Modified the associated Trial Specific Randomisation, Blinding and Code Break SOP template to be a Trial Specific Randomisation, Blinding and Code Break Manual template	Catherine Maidens / Samim Patel

ACRONYMS:	
CI	Chief Investigator
COA	Compliance Oversight Advisor
CRF	Case Report Form
CTR	Clinical Trial Regulation (EU 536/2014)
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
IMP	Investigational Medicinal Product
IxRS	Interactive Voice / Web Response System
JRO	Joint Research Office UCLH/ UCL
PI	Principal Investigator
PIS	Participant Information Sheet
PV	Pharmacovigilance
RM (ATMP)	Regulatory Manager for Advanced Therapy
RMP	Regulatory Manager for Pharmaceuticals
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SUSAR	Suspected Unexpected Serious Adverse Reaction
UCL	University College London

DEFINITIONS

Allocation Concealment: Is where the person randomising the participant does not know what the next treatment allocation will be.

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).

Block Randomisation: Is the arranging of treatment allocations in groups (blocks) that are similar to one another.

Code Break: is also known as breaking the blind. It is the mechanism that permits the rapid identification of the trial treatment in case of a medical emergency, but does not permit undetectable breaks of the blinding in order to protect the integrity and the validity of the data.

Double-blinding: Where the participants, Investigators, monitor and in some cases, data analyst(s) are unaware of the treatment assignment(s).

Interactive Voice / Web Response System (IxRS): An Interactive Response System, which can be accessed via telephone or web. It can be configured and customised to allow trial teams

to manage key aspects of their clinical trials including enrolment/randomisation, dosing/drug dispensing, clinical supplies, drug inventory management and unblinding.

Randomisation: The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation Code: A unique number or code that is linked via a randomisation list to the treatment.

Single-Blind: Where the participants are unaware of their treatment assignment(s).

Stratification: A sampling procedure in which the population is divided into homogeneous subgroups or strata and the selection of samples is done independently in each stratum.

Un-blinding: Is the disclosure of the identity of blinded treatment.

Standard Operating Procedure for Randomisation, Blinding and Code Break

1. PURPOSE

This Standard Operating Procedure (SOP) describes the processes that the Chief Investigator (CI) and Sponsor must follow for setting up the systems for **Randomisation, Blinding and Code Break**, and the drafting of a trial specific manual.

2. JOINT UCLH/ UCL RESEARCH OFFICE POLICY

All JRO SOPS are produced, reviewed and approved in accordance with the JRO SOP on SOPs.

All SOPs produced from the JRO must be used in conjunction with local NHS Trust and UCL policies and procedures.

The JRO acts as the representative of the Sponsor and will be the official name used on all SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in SI 2004/1031, SI 2006/1928 and subsequent amendments. Where applicable, it incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, as UCL sponsors trials with EU and Northern Ireland sites, the SOPs are written to be compliant with EU Clinical Trials Regulation No. 536/2014 (CTR).

Clinical trials are often blinded to hide the treatment group assignment from participants and/ or Investigators in order to prevent the unintentional biases of either party affecting participant data.

Clinical trials comparing one or more treatments or placebo may be randomised such that participant treatment allocation occurs at random.

In order to protect the wellbeing and safety of the trial participant as required in the principles of GCP, the coding system for the Investigational Medical Product(s) (IMP(s)) in blinded trials should include a mechanism that permits rapid identification of the IMP(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.

Circumstances where code break / unblinding of the participant can be undertaken include:

- In a medical emergency where knowledge of the blinded treatment is necessary, for the treatment of an adverse event, or where a child in a participant's household accidentally takes an IMP,
- In the event of a SUSAR needing expedited reporting,
- If a report including unblinded data is requested by a Data Safety Monitoring Committee (DSMC) or Independent Data Monitoring Committee (IDMC),
- End of trial after database lock.

For double-blind, randomised controlled trials, an external supplier that provides an interactive voice/web response system (IxRS) for randomisation, blinding and code breaks should be used.

4. SCOPE OF THIS SOP

The scope of this SOP is to describe the procedure for the CI and Sponsor to set up the systems for **Randomisation, Blinding and Code Break**, and the drafting of a trial specific manual (using the associated template) for all randomised controlled clinical trials sponsored by UCL and managed by the JRO.

When an external Clinical Trials Unit (CTU) / Contract Research Organisation (CRO) has been appointed by the JRO to perform the trial management activities on behalf of the Sponsor; this SOP will be used in conjunction with the relevant CTU/CRO SOP.

5. RESPONSIBLE PERSONNEL

Responsibilities are outlined in Section 6.

6. PROCEDURE

6.1 Randomisation Process

Responsible Person	Task
Sponsor Regulatory Advisor (SRA) / Regulatory Manager – Advanced Therapies (RM (ATMP))	Provide CI with the **Randomisation, Blinding and Code Break Manual template** (associated template), and **24 Hour Contact Card template**, if applicable (associated template). The manual should be prepared for all randomised controlled clinical trials, including open label trials.
CI / trial team / statistician	Determine what type of randomisation will be used in the trial to reduce the chance of imbalance between treatment groups (refer to JRO SOP for Producing Randomisation Lists for Trials (JRO/SPON/S05)). The method of randomisation will then be translated to a computer code to provide a randomisation list or a minimisation algorithm. The program may be

	written by a statistician or the randomisation may be handled through an external randomisation service (e.g., Sealed Envelope). The type of randomisation must be detailed in the protocol, and the details of the randomisation process and implementation should be documented in the **Trial Specific Randomisation, Blinding and Code Break Manual**. Ensure all trial team members involved in enrolling/randomising participants have access to the external randomisation system, if used.
CI / trial team	*For blinded trials:* The protocol and trial specific manual should describe the level of blinding (e.g. open label, single-blind or double-blind) and how the blinding will be implemented. Consider how the randomisation codes will be provided to the IMP manufacturer to ensure the IMP are packaged, coded and labelled in a manner that protects the blinding, and how pharmacy will be informed of the randomisation treatment code allocation. Refer to JRO SOP on IMP labelling (JRO/SPON/S09). In some cases, the manufacturer might request for kit codes to be set up in a specific manner e.g. in a sequential manner and quantity of kit codes should account for overages. It is essential that there is a system in place for providing 24 hour cover to access the code break. Step by step instructions on how to code break in an emergency must be included in the manual. Ensure all trial team members and JRO personnel with **unblinding responsibilities** have access to the randomisation system with the appropriate user account: - Investigator / delegate – for emergency code break; - JRO Pharmacovigilance (PV) Manager / delegate – for safety reporting purposes; - JRO Regulatory Manager for Pharmaceuticals (RMP) – for facilitating IMP management between manufacturer, study team and pharmacy where treatment allocation is based on kit codes. Prepare the **24 Hour Contact Card** for trial participants, if applicable.
CI / trial team	Send draft manual and 24 Hour Contact Card (if applicable) to SRA / RM(ATMP) for review.
SRA / RM(ATMP) / RMP / PV Manager	Review the trial specific Randomisation, Blinding and Code Break Manual. Return to CI for any updates, finalisation and signature.
CI / PI / Site trial team	All members of the trial team **must be trained** on the Trial Specific Manual prior to commencing work on the trial. Training should be documented on the training log which is located at the end of the manual. In multicentre trials the CI is responsible for ensuring all Principal Investigators (PIs) and trial teams at participating sites are trained and familiar with the Randomisation, Blinding and Code Break Manual.

6.2 Code Breaking (Unblinding)

Responsible Person	Task
Emergency code break	
CI / PI / Delegate	All emergency code breaks should be documented fully on the trial specific **Code Break (Unblinding) Log** (associated template) and should contain: • participant's trial ID; • reason for unblinding; • date of unblinding; • name of the person who requested the code break; • name of the person breaking the code; • date the Sponsor was informed of the code break. In multi-site trials the CI should also be informed of the code break at the site. The **Code Break (Unblinding) Log** should be filed in the **Investigator Site File (ISF)**. Any additional information on the code break can be documented on a file note.
Compliance Oversight Advisor (COA)	The Patient Information Sheet (PIS) should be requested, on a regular basis from the site and the emergency number should be tested to ensure the PI can be reached. Documentation of the testing should be recorded on the **Emergency Contact Testing Log** (associated template) and saved in the Sponsor File.
PI and team	The PI should test the unblinding process on a regular basis. This involves regularly logging into the randomisation system to ensure the unblinding facility is readily available. The first test should be carried before Site Initiation Visit (SIV). JRO should be informed when the test has been carried out.
Unblinding for SUSAR reporting	
PV Manager / delegate	If a Serious Adverse Reaction is reported on the trial the JRO PV manager (or delegate) will assess expectedness of the event against the approved **Reference Safety Information** for the trial. If the event is assessed as unexpected the treatment allocation will be unblinded. If the participant was on active treatment the **Suspected Unexpected Serious Adverse Reaction (SUSAR)** will be reported to the regulatory authorities. The treatment allocation will not be shared with blinded members of the trial team, including the CI/PI. All SUSAR documentation will be filed in the **JRO Sponsor File**.
Unblinded data for trial oversight committee	
Unblinded trial statistician / delegate	Where **reports containing unblinded data** will be prepared for Data Safety Monitoring Committee (DSMC) or Independent Data Monitoring Committee (IDMC), the CI must have an unblinded member of the trial team, preferably an unblinded statistician. The process and personnel involved in preparing the unblinded reports should be documented in the trial specific Randomisation, Blinding and Code Break Manual. The required access to the randomisation system should be provided for this unblinded member of the trial team by the CI / delegate.
Unblinding at the end of the trial	

CI / trial team / statistician	The randomisation list should not be made available to the CI and their trial team until the database has been locked and analysis has been completed by the statistician. Consider the method of informing participants of their blinded treatment allocation.

7. REFERENCES

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), implemented on the 1st of May 2004 and as amended (SI 2006/1928);

EU Regulations 536/2014, (CTR)

8. APPENDICES

Not Applicable

9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP:

1	Trial Specific Randomisation, Blinding and Code Break Manual template
2	Code Break (Unblinding) Log
3	24 Hour Contact Card template
4	Emergency Contact Testing Log

10. SOP DISSEMINATION & TRAINING

SOPs relevant to the JRO only, will be distributed to the concerned JRO staff. Staff involved by the SOP will sign the SOP training log (Section 12. SOP TRAINING LOG) which is part of each SOP.

The training will constitute of the person reading the SOP and asking specific questions to the author of the SOP.

SOPs relevant to JRO staff and investigators or investigators only will be provided to the investigators during trial set-up where applicable and at the time of the trial initiation.

11. SIGNATURE PAGE

Author and Job Title:	Catherine Maidens, Pharmacovigilance Manager
Signature:	DocuSigned by: Catherine Maidens 6A859A9CF4EB497...
Date:	12 August 2024 | 11:39 BST

Authorised by: **Name and Job Title**	Helen Cadiou, Head of Quality Assurance
Signature:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5...
Date:	12 August 2024 | 13:59 BST

12. SOP TRAINING LOG:

	Name of Staff (Capital letters)**:**	**Job Title:** **Department:**	**Training Date**	**I confirm that I understand & agree to work to this SOP SIGNATURE**	**Name of Trainer** **(if applicable)**	**Signature**	**Date**
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