RDSOP28 Randomisation and Unblinding in Clinical Trials of an Investigational Medicinal Product (CTIMP’s)

Greater Manchester Mental Health NHS Foundation Trust
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<th><strong>Title of Standard Operating Procedure:</strong></th>
<th>RDSOP28 Randomisation and Unblinding in Clinical Trials of an Investigational Medicinal Product (CTIMPs)</th>
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<tr>
<td><strong>Document Summary:</strong></td>
<td>This document provides a general procedure for CTIMP randomisation and unblinding. Those CTIMPs that are not blinded do not fall within this procedure.</td>
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| **Target Audience:**                    | Trust-wide, Research Community, Internal and External Researchers |
| **Consultation:**                       | R&I Office, research community and R&I Committee members |
| **Approval Committee:**                 | R&I Committee |
| **Cross Reference Document(s):**        | Research Approval Policy  
All Trust R&I SOPs |
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<th><strong>Minimum Monitoring Requirement</strong></th>
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<th><strong>Process for monitoring</strong></th>
<th><strong>Evidence</strong></th>
<th><strong>Responsible Individual(s)</strong></th>
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1. Introduction

All clinical trials of an investigational medicinal product (CTIMPs) must adhere to The Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.

According to the ICH Guideline for Good Clinical Practice “In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.” Therefore procedures/systems must be in place to enable urgent code-breaks.

2. Purpose

This document provides a general procedure for CTIMP randomisation and unblinding. Those CTIMPs that are not blinded do not fall within this procedure.

3. Roles and Responsibilities

3.1 Duties within the Organisation

It is the responsibility of the Research & Innovation Office to make Trust R&I SOPs available to all research active staff working on Trust-approved research studies.

It is the responsibility of the study Chief Investigator (CI) or local Principal Investigator (PI) to ensure that up-to-date copies of Trust R&I SOPs are available to research staff.

It is the responsibility of the study Chief Investigator or local Principal Investigator to ensure up-to-date SOPs are filed in the Investigator Site File and are available to research staff, and to inform the Research Support Co-ordinator of the names of all research staff involved on a study so that copies of SOPs can be distributed appropriately.

It is the responsibility of the study Chief Investigator or Principal Investigator to designate if the SOPs of another organisation are to be followed for a study. For example those of a Clinical Research Network or commercial sponsor. If there is significant conflict between the external SOP and the Trust R&I SOP it is the responsibility of the CI or PI to resolve these with the Research Office prior to starting the study.

It is the personal responsibility of all staff to follow Trust (or the designated alternative organisations) procedural documents.
4. Procedure

4.1 Randomisation

Pharmacy Staff Producing a Randomisation List for a CTIMP

I. Use a statistical programme/randomisation website (for example, www.randomization.com) recommended by the trial statistician to generate a randomisation list.

II. Discuss the following information with the Chief Investigator (CI):
   a. Total number of participants to be recruited
   b. The number of participants expected to be recruited per month
   c. Recruitment rates experienced with similar participant groups
   d. Number of trial sites involved
   e. The proposed blinding and unblinding procedures.

III. If the method of randomisation involves ‘blocks’ and recruitment is expected to be slow, use a small block size, for example 4 or 6 depending on the total number of participants expected to be recruited into the CTIMP. If recruitment is likely to go well, use a larger block size of 10 for example. Produce a randomisation list with at least one more block than the expected number to allow for a higher than expected drop out rate.

IV. Print out the randomisation list, sign and date it, and file it in the trial pharmacy file.

V. Keep the randomisation list secure and ensure blinded staff are prohibited from viewing it until the end of the CTIMP.

VI. If asked to randomise more participants than originally agreed ensure the revised protocols and necessary approvals are in place (an increase in the total number of participants to be recruited into the CTIMP would constitute a substantial amendment).

VII. Ensure investigational medicinal product (IMP) packaging and labelling protects the ‘blind’. Where IMP is to be blinded, it must not be possible for the blinded staff to ascertain the contents of the IMP. In most cases the active and placebo IMP must look the same.

VIII. Ensure any documentation that contains reference to the participant’s treatment is removed prior to dispensing to the participant or research team.

IX. Ensure paperwork such as the trial prescription and drug accountability log protect the ‘blind’.

X. When communicating with Trust, research or pharmacy staff that are blinded, ensure no information is provided that could compromise the blind.
XI. If the monitor is blind, ensure all documentation that reveals the participant’s treatment arm is removed from site files before monitoring visits and ensure returned IMP is packaged and labelled in a manner that preserves the blind.

XII. At the end of the CTIMP, the investigator must send an email request stating that the trial data is locked in order to be given the randomisation list. Do not release the randomisation list to the investigator until all the necessary data has been collected. (If a statistician is performing an interim analysis, ensure the statistician emails to confirm all the data has been collected for the selected number of participants and requests the randomisation list just for those participants).

XIII. If data is being sent to a person outside of the Trust, the data should be anonymised before it is sent, for example no dates of birth or full names should be provided.

XIV. Site files containing unblinded information should not be shown to blinded staff members if they visit the R&I Office or pharmacy before the database lock has taken place.

4.1.2 Randomisation List and Procedures Provided by the CTIMP Sponsor

I. Trust, research and/or pharmacy staff must follow the sponsor’s randomisation procedures, as specified in the CTIMP protocol.

II. Randomisation codes/lists must be kept in a secure location as specified in the CTIMP protocol and only accessed by Trust, research and/or pharmacy staff with appropriate authorisation.

III. Ensure any documentation that contains reference to the participant’s treatment is removed prior to dispensing to the participant or research team.

IV. If the monitor is blind, ensure all documentation that reveals the participant’s treatment arm is removed from site files before monitoring visits and ensure returned IMP is packaged and labelled in a manner that preserves the blind.

V. At the end of the CTIMP, an investigator must send an email request stating that the trial data is locked in order to be given the randomisation list. Do not release the randomisation list to the investigator until all the necessary data has been collected. (If a statistician is performing an interim analysis, ensure the statistician emails to confirm all the data has been collected for the selected number of participants and requests the randomisation list just for those participants).

VI. If data is being sent to a person outside of the Trust, the data should be anonymised before it is sent, for example no dates of birth or full names should be provided.

VII. Site files containing unblinded information should not be shown to blinded staff members if they visit the R&I Office or pharmacy before the database lock has taken place.
4.1 Unblinding (also referred to as code breaking)

Unblinding should only occur when the identity of the trial drug must be known to the doctor in order to provide appropriate medical treatment to a patient in an emergency.

4.2.1 Trust Sponsored CTIMPs

I. The unblinding procedure must be stated in the trial protocol.
II. Unblinding must be authorised by the CI or PI. If pharmacy staff receive a request for unblinding ‘during normal working hours’, they should contact the site investigator for authorisation to break the code. If the site investigator is not available, then pharmacy staff should contact the CI to authorise unblinding.
III. There should be a procedure in place to deal with situations where neither the CI of PI are available and there is a request for unblinding.
IV. The procedure for unblinding will be kept in the CTIMP-specific pharmacy file or in a place dictated by the CTIMP protocol. (Usually, only the investigators and/or research nurses will be able to access code-break information via Interactive Voice Response Systems (IVRS) or Interactive Web Response Systems (IWRS)).
V. In the event of unblinding (whether accidental or deliberate) the CI/PI must document the following information and any action taken;
   a. CTIMP title and EudraCT number
   b. Participant’s identification number
   c. Name and title of person requesting the code-break
   d. Reason for unblinding
   e. Date and time of code-break
   f. Name of person authorising the code-break
   g. Signature of person performing the unblinding.
This information must be filed in the investigator site file. The information must also be emailed to GMMH’s R&I Office as soon as possible.

VI. If the clinical trials pharmacist/pharmacy staff break the blind, the information as specified in section V (a-g) must be recorded and filed in the pharmacy file for the trial. This information must also be emailed to GMMH’s R&I Office as soon as possible.
VII. There must be a system in place to manage requests for unblinding outside of ‘normal working hours’.
VIII. Details of any unblinding should be included in the annual report submitted to the Data Monitoring and Ethics Committee.
IX. Unblinding will not be routinely performed at the end of a CTIMP.

4.2.2 CTIMPs not Sponsored by GMMH
Trust, research and pharmacy staff must follow the sponsor’s procedures for unblinding, which will be documented in the trial protocol.

Additional Information (if appropriate)

5. References


ICH Topic E6 (R1) Guideline for Good Clinical Practice.