Standard Operating Procedure for the Preparation of a Study Specific Randomisation, Blinding and Code Break Standard Operating Procedure

SOP ID Number: JBRU/INV/S06/01
Effective Date: 10/01/2010

Version Number & Date of Authorisation: V01, 06/01/2010
Review Date: 10/01/2012

SOP eDocument kept: S:\CLINICAL_TRIALS\SOPs\EFFECTIVE_SOPs_Guides\Investigator SOP\INV_S06_SOP preparation for randomisation, blinding and code breaks V01.doc
Revision Chronology:

<table>
<thead>
<tr>
<th>SOP ID Number</th>
<th>Effective Date</th>
<th>Reason for Change</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>JBRU/INV/S06/01</td>
<td>28/12/09</td>
<td>NA</td>
<td>Anne Marie Downey</td>
</tr>
</tbody>
</table>

ACRONYMS:

- **JBRU**: Joint Biomedical Research Unit
- **GCP**: Good Clinical Practice
- **SOP**: Standard Operating Procedure
Standard Operating Procedure for the Preparation of a Study Specific Randomisation, Blinding and Code Break Standard Operating Procedure

1. PURPOSE

This Standard Operating Procedure (SOP) has been written by the JBRU to describe the procedure that the investigator must follow for Preparation of his trial Specific Randomisation, Blinding and Code Break Standard Operating Procedure.

2. JOINT UCLH/UCL BIOMEDICAL RESEARCH UNIT POLICY

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

3. BACKGROUND

Clinical trials are often blinded to hide the treatment group assignment from participants and Investigators (in double-blinded studies) in order to prevent the unintentional biases of either parties affecting subject data.

In order to protect the well being and safety of the trial subject as required in the principles of GCP, the coding system for the Investigational Medical Product(s) in blinded trials 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 process for rapidly identifying a blinded Investigational Medicinal Product(s), as well as the details of authorised personnel who will have access to unblinded data.

Definitions

Allocation concealment: Is where the person randomising the patient 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.

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

Interactive Web Response System (IWRS): A Web technology that is designed to give adequate information for users to manage clinical trials.

Randomisation: The process of assigning trial subjects 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.

Simple Randomisation: is a subset of individuals (a sample) chosen from a larger set (a population). Each individual is chosen randomly with equal chance of receiving each treatment.

Single-Blind: Where the subject(s) are unaware of the 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.

Unblinding: Is the disclosure of the identity of blinded treatment.

4. SCOPE OF THIS SOP

The scope of this SOP is to describe the procedure for the investigator to write a study specific Standard Operating Procedure on randomisation, blinding and code break procedures (if applicable) for all randomised controlled clinical trials sponsored by UCL.

This SOP applies to all randomised, controlled clinical trials that are registered on the ReDA database after the effective date of this SOP, and trials which are in the set-up phase and have also not yet been initiated.

The investigator’s SOP should be drafted in conjunction with setting up the randomisation process and drafting of the protocol in accordance with the JBRU Protocol template and SOP on Protocol writing. The format of the study specific randomisation/ blinding / code break SOP can be done in accordance to the format of this SOP by using the UCL SOP template (and to the JBRU SOP for the preparation, review and approval of SOP for UCL sponsored clinical trials).

It is recommended that for double-blind, randomised controlled trials, the Chief Investigator considers using an external supplier that provides an interactive voice/web response system (IVRS or IWRS) for randomisation, blinding and code breaks. Appendix 1 lists some examples of external suppliers.

5. RESPONSIBLE PERSONNEL

Any researcher or member of a study team who has been given the responsibility for writing an SOP on randomisation, blinding and code breaking in a clinical trial should follow this SOP. The Chief Investigator of the trial must review, correct as necessary, sign and date the SOP. The SOP must also be authorised by a representative of the Sponsor.
The Chief Investigator is responsible for training all staff personnel in the trial team to ensure their SOP on randomisation, blinding and code breaking is well understood and complied with. The CI should document the SOP training for each member of the research team by ensuring that a SOP training log is part of the SOP as it is the case section 12 of this SOP.

6. PROCEDURE

6.1 Randomisation Procedure

The Chief Investigator needs to determine what type of method will be used to reduce the chance of imbalance between treatment groups. The design and type (simple, block, stratified, minimisation) should be detailed in the protocol and in the SOP. The Chief Investigator must consults with a JBRU qualified statistician to determine the type of randomisation needed and refers to the JBRU's SOP for producing randomisation lists for trials.

Once the design and type of randomisation has been established in the protocol, a randomisation list with details of the randomisation codes should be produced in accordance with the protocol and JBRU's SOP for producing randomisation lists for trials. The list should be generated by a person who has no direct contact with the trial subjects or involvement with the assessment for eligibility in the trial. It is recommended that the Chief Investigator considers using an external source to perform this task using either an IVRS or IWRS system (see Appendix 1). In cases of trials that are single site involving small numbers, and depending on the complexity of the randomisation required, a qualified statistician or data manager may perform this task.

The process used to produce the randomisation list and how randomisation will be implemented should be documented in the SOP with the following considerations made:

- A brief description of the randomisation process
- Variables used in the procedure to be recorded
- The name and job title of the person generating the randomisation list
- Computer software that will be used to generate the list and perform randomisation (if applicable) and details on the validation of this system before it is used.
- What approach will be used to conceal allocation (e.g. password protected electronic format), and details on location of the randomisation list and how it will be stored securely.
- Historically, small non complex single site trials have used a system of sealed envelopes. This is NOT a system we recommend. However, as such UCL sponsored trials are still running we need to recommend that the PIs ensure that all seals of these envelopes are signed and dated, and that the PI collects the envelopes at the end of the trial to ensure that the seals have not been broken.
- The name and job title of the person who will have access to the randomisation list and will be responsible for randomisation (NB for double blinded trials the
randomisation list should not be made available to the Chief Investigator and their trial team until database lock and the codes is officially broken at the end of the trial).

- For blinded trials, will need to provide details on 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.

- Details on the randomisation process (include telephone numbers and or web links) and should include open times for randomisation and procedure to be used out of hours if applicable (i.e. randomisation hours between 9-5 Monday to Friday).

- Details of the documentation to be completed for randomisation (e.g. signed informed consent form, randomisation checklist/ CRF or eligibility criteria checklist CRF)

- Details on how pharmacy will be informed of the randomisation treatment code allocation (e.g. fax sent to pharmacy).

- Should include the provision of a study specific patient card with contact details (including out of hours contact details) for emergencies.

6.2 Blinding

The protocol and SOP should define the level of blinding e.g. unblinded, single-blind or double-blind and how the blinding will be implemented (e.g. through the use of an identical placebo).

For double blinded trials the SOP should include the following:

- How the IMP will be packaged, coded and labelled in a manner that protects the blinding (NB labelling should not make reference to group allocation). Refer to Sponsor’s SOP on IMP labelling.

- The statement “The blinding of the trial must be maintained throughout the trial until all data entry and processing are complete and the database has been locked.”

6.2 Code Breaking

The code break process should be detailed in the protocol and the procedure thoroughly documented in the SOP and needs to include the following considerations:

- **Circumstances** where unblinding of individual can be broken such as in a medical emergency where knowledge of the blinded treatment is necessary, for the treatment of an adverse event, where a child in a participants household accidentally takes an IMP, in the event of a SUSAR (Suspected Unexpected Serious Adverse Reaction) needing expedited reporting, or if requested by a Data Safety Monitoring Committee (DSMC).

- Details on the format of the code break (i.e. 24 hour telephone number, scratch cards, tear off labels, IVRS or IWRS system).

- Although not recommended, sealed code break envelopes could be considered for small non complex single site trials. However, the Chief Investigator will need to detail in the SOP that the envelopes are to be signed on both seals, and in the event
of a code break the name of the code breaker, the signature, date and time needs to be recorded on the outside of the envelope.

- If code break envelopes are used, the SOP should give details on the collection of envelopes by the PI at the end of the study and provide information on where the code break envelopes will be held.

- It is essential that, in the case of an emergency, there is a system in place for providing 24 hour cover to access the code break. It is recommended that the Chief Investigator uses either an IVRS or IWRS system and examples of external suppliers for this can be found in Appendix 1. The SOP needs to provide the step by step instructions on how to code break in an emergency.

- Specify what needs to be documented and how for any emergency code break. The SOP should request this to be documented fully on a study specific code break form or file note and should contain: The date & time, reason for unblinding, name & signature of the person requesting the code break, name & signature of the person breaking the code.

- Detail where the written documentation of the code break should be filed.

- For single site trials, the SOP needs to state that the Investigator will notify the Sponsor in writing following a code break, detailing the reasons for unblinding.

- For multicentre trials, the SOP needs to state that the CI must inform the JBRU and other Investigators in writing following a code break, with the reasons for unblinding.

- Provide details on circumstances where patients will be able to remain on the trial following unblinding.

- Provide details of unblinding after study completion, all data collected and queries resolved and the database locked, including the role of the DSMC and Statistician.

- Consider the method of informing participants of their blinded treatment allocation, if applicable.

7. REFERENCES


Sponsor’s Standard Operating Procedure for the Preparation, Review and Approval of Standard Operating Procedures for UCL Sponsored Trials;

Sponsor’s Standard Operating Procedure for Standard Operating Procedure For IMP Labelling;

Sponsor’s Standard Operating Procedure Standard Operating Procedure SOP for the Preparation of a Study Specific Randomisation, Blinding and Code Break SOP.
for writing a Protocol for CTIMPs

Sponsor’s Standard Operating procedure for producing randomisation lists for trials
8. APPENDICES

APPENDIX 1: Recommended External Sources that provide IVRS and or IWRS:

The Sealed Envelope is a web based online service for randomisation, blinding and 24 hour code break services: http://www.sealedenvelope.com/

Emergency Scientific & Medical Services at Guy’s and St Thomas’ provide services such as clinical trials emergency unblinding, emergency medical response, and adverse event management and reporting: http://www.guysandstthomas.nhs.uk/services/ambulatory/pathology/medtox.aspx

9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UCL SOP template</td>
</tr>
</tbody>
</table>

10. SOP DISSEMINATION & TRAINING

This SOP will be provided to the PIs at the time they are drafting their protocol and their trial specific SOP on randomisation, blinding and nblinding. All staff trial team concerned by this SOP will sign the SOP training log (12. SOP TRAINING LOG) part of this SOP. In addition each PI trial team member should have an “Individual staff SOP and courses log” which will need to be updated once trained on this SOP. These documents should be filed in the ISF.

Existing trials “in progress”: This SOP will be emailed to the PIs and their teams having existing trials “in progress”. These investigators will be requested to read the new SOP and email back to acknowledge receipt and understanding of this new SOP. The email sent to the PIs and their email acknowledging receipt and understanding of the SOP should be printed out and filed in the JBRU SOP folder.

11. SIGNATURE PAGE

<table>
<thead>
<tr>
<th>Author and Job Title:</th>
<th>Anne Marie Downey, Clinical Trial Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td>Anne Marie Downey</td>
</tr>
<tr>
<td>Date:</td>
<td>06/01/2010</td>
</tr>
<tr>
<td>Authorised by:</td>
<td>Helen Cadiou, Quality Assurance Manager</td>
</tr>
<tr>
<td>Name and Job Title:</td>
<td></td>
</tr>
<tr>
<td>Signature:</td>
<td>Helen Cadiou</td>
</tr>
<tr>
<td>Date:</td>
<td>06/01/2010</td>
</tr>
</tbody>
</table>
### 12. SOP TRAINING LOG:

<table>
<thead>
<tr>
<th>Name of Staff (Capital letters):</th>
<th>Job Title:</th>
<th>Department:</th>
<th>Training Date</th>
<th>I confirm that I understand &amp; agree to work to this SOP</th>
<th>SIGNATURE</th>
<th>Name of Trainer (if applicable)</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of Staff (Capital letters):</td>
<td>Job Title: Department:</td>
<td>Training Date</td>
<td>I confirm that I understand &amp; agree to work to this SOP SIGNATURE</td>
<td>Name of Trainer (if applicable)</td>
<td>Signature</td>
<td>Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-----------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>