Title: Unblinding

1. Scope

1.1 This SOP is applicable to Sponsor staff and research staff undertaking randomised blinded projects sponsored by the University of Aberdeen (UoA) and/or NHS Grampian (NHSG).

1.2 This includes Clinical Trials of Investigational Medicinal Products (CTIMPs) covered by the UK Medicines for Human Use (Clinical Trials) regulations, as amended, or equivalent local legislation outside the UK.

1.3 This Standard Operating Procedure (SOP) details the procedures to:

- Unblind a subject in an emergency situation.
- Unblind data for the purpose of notification to the Data Monitoring Committee (DMC).
- Manage accidental unblinding.
- Unblind a research project for analysis purposes at the end of the trial.
- Unblinding due to other purposes

2. Responsibilities

Trial team

Ensure no unnecessary unblinding occurs.

Chief Investigator

Ensure the emergency unblinding process is in place, including out-of-hours access, and that all of the trial team are aware of the procedure.
3. Procedure

3.1 For the purpose of this SOP, ‘Unblinding’ is synonymous with ‘Code Breaking’ and with ‘Unmasking’; all terms that are frequently used in research protocols.

3.2 Treatment codes shall be broken before reporting a Suspected Unexpected Serious Adverse Reaction (SUSAR) to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC).

3.3 ⚠ Where appropriate, participants in CTIMPs shall be issued with ‘In case of emergency’ cards to be carried at all times. Minimum details on the card shall include the trial emergency contact number, study identifier and details of the potential IMP (eg Bisoprolol 5mg or Placebo) and participant study number.

3.4 ⚠ The Unblinding system shall be tested, including contact with the system, prior to recruitment of the first participant. The process shall be documented and reviewed at the Study Initiation Visit.

3.5 ⚠ If the trial or a single subject is accidentally unblinded or unblinded due to a serious adverse event (SAE) the CI, or delegate, is responsible for promptly documenting the series of events and notifying the Sponsor (TMP-QA-26).

3.6 The details of all unblinding shall be included in the statistical report.

Emergency unblinding of individuals

3.7 Any member of the trial team, or a health care professional involved in the care of a participant, may unblind or request unblinding in an emergency situation. Following such a request, the information shall be transmitted to the requesting party. If emergency unblinding is not required, this shall be documented in the protocol.

3.8 ⚠ All care shall be taken to ensure that the study team are kept blinded.

3.9 If the Clinical Trials Pharmacy, or an individual as named on the Delegation Log, has performed the procedure, they shall inform the Sponsor (via pharmaco@abdn.ac.uk) of the trial identifier, subject number and name and title of the person making the request, but not the result.

3.10 ⚠ Details of any emergency unblinding shall be documented fully in the Sponsor file, Investigator Trial Master File (TMF), Pharmacy File and Site File(s), as appropriate (see TMP-QA-26). This includes, but may not be limited to:

- Date
- Subject details
- Reason for unblinding
- The result of the unblinding (when required)
- Name and role of the individual requesting the unblinding
- Name and role of the individual carrying out the unblinding
- Details on the CI’s decision for the subject to remain in the trial, or be withdrawn.
3.11 ⚠️ The Sponsor may instruct the CI, or delegate, to unblind an individual in an emergency situation. In this event the Research Governance Team or Sponsor Quality Assurance Manager (QAM) shall be provided with the unblind. However, on a case-by-case basis a decision to unblind a wider team may be necessary.

**Unblinding for DMC**

3.12 A named statistician (ideally not involved with the final data analysis or with the study) shall receive the relevant codes, perform the interim analysis and prepare an unblinded report for the DMC if this is requested. A record shall be kept in the Investigator TMF of the name of the statistician, the date they were supplied with the relevant code breaks and the location of the results. The unblinded data and the results supplied to the DMC shall **not** be accessible to the CI or trial staff (see SOP-QA-17 - Project committees).

**Accidental unblinding**

3.13 ⚠️ Details of any accidental unblinding shall be documented fully. This includes, but may not be limited to:

- Date
- Subject details
- Reason for accidental unblinding
- Name and role of the individual responsible for the unblinding
- Action taken to prevent recurrence
- Details on the CI's decision for the subject to remain in the trial, or be withdrawn

The unblinding template should be completed (TMP-QA-26) and forwarded to Sponsor at pharmaco@abdn.ac.uk.

**Unblinding at the end of trial**

3.14 The Statistical Analysis Plan shall be provided in the protocol, or be finalised prior to the release of the randomisation codes. Any changes to the statistical analysis plan shall be version controlled.

3.15 A record shall be kept in the Investigator TMF to confirm when the randomisation code was requested and when provided.

**Other Unbinding**

3.16 There may be other cases where patients may be unblinded, for example:

- Real time unblinding for DMC
- Legal instruction
- Participant/GP request to know treatment allocation for planning future treatment.

Sponsor approval should be sought prior to unblinding. If approval is given, information should be provided to the requesting party and the unblinding template should be completed (TMP-QA-26) and forwarded to Sponsor at pharmaco@abdn.ac.uk. All care shall be taken to ensure that the study team are kept blinded.
4. Abbreviations and definitions

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CI</td>
<td>Chief Investigator</td>
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<tr>
<td>CTIMP</td>
<td>Clinical Trial of an Investigational Medicinal Product</td>
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<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<tr>
<td>QAM</td>
<td>Quality Assurance Manager</td>
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<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse reaction</td>
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<tr>
<td>TMF</td>
<td>Trial Master File</td>
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<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
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Definition

4.1 A ‘blind’ study is a clinical trial in which the subject or the Investigator (or both) are unaware of which trial product/drug the subject is taking.

4.2 When only one is blinded to the treatment allocation this is a ‘single blind’ study. When both do not know the treatment, the study is ‘double-blind’.

4.3 Studies in which the participant takes part in three arms, such as placebo, active drug and comparative drug remain as double blind.

4.4 Unblinding is the process by which the allocation code is broken so that the CI and/or a clinician managing the patient and/or trial statistician and/or Sponsor delegate becomes aware of the intervention.

5. Related documentation and references

| SOP/QA-15 | Management of Medicinal Products used in research |
| SOP/QA-17 | Project committees |
| SOP/QA-18 | Randomisation and blinding for controlled trials |
| SOP/QA-22 | Adverse Events in CTIMPs |
| TMP/QA-26 | Emergency Unblinding Form |