Standard Operating Procedure for Managing and Reporting Serious Adverse Effects for Studies Sponsored by the University of Bath

Contents page

1. Acronyms and Definitions
2. Purpose
3. Scope
4. Responsible Personnel
5. Procedure
   5.1 Managing the SAE
   5.2 Classifying the SAE
   5.3 Documenting the SAE
   5.4 Reporting related and unexpected SAEs
   5.5 Following up SAEs (where data missing or event not resolved)
   5.6 Notifying the TSC/IDMC
6. References
7. Referenced SOPs
8. Appendices
   Appendix I Process map
   Appendix II SAE Reporting flow diagram
   Appendix III Link to Example report of SAE Form (NRES website)
   Appendix IV Reporting Guidance
1. Acronyms and Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>ICH GCP</td>
<td>International Conference on Harmonisation – Good Clinical Practice</td>
</tr>
<tr>
<td>IDMC/DMEC</td>
<td>Independent Data Monitoring Committee / Data Monitoring &amp; Ethics Committee</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>Main REC</td>
<td>Main Research Ethics Committee</td>
</tr>
<tr>
<td>PI</td>
<td>Principle Investigator</td>
</tr>
<tr>
<td>RA/F</td>
<td>Research Associate/Fellow</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure; Specifies what should be done, when, where and by whom</td>
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<tr>
<td>SR</td>
<td>Safety Reviewer</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TM</td>
<td>Trial Manager</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UAR</td>
<td>Unexpected Adverse Reaction</td>
</tr>
<tr>
<td>UoB DH</td>
<td>University of Bath, Department for Health</td>
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</table>

Definitions

**Adverse Event (AE)**

Any untoward medical occurrence in a participant taking part in health care research, which does not necessarily have a causal relationship with the research.

The following do not need to be recorded as AEs, if they are recorded as medical history/concomitant illness on the CRF at the start of the study.

Planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the participant signed the consent form.

Pre-existing conditions found as a result of screening procedures.
Serious Adverse Event (SAE)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that -
(a) results in death,
(b) is life-threatening,
(c) requires hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity, or
(e) consists of a congenital anomaly or birth defect;

NB: Serious and severe are not synonymous. Serious refers to a specific definition for the outcome of an event (see above) whereas severe refers to the intensity of a reaction (e.g. mild, moderate, severe).

The term life-threatening in the definition of a SAE refers to an event in which the participant has a risk of death at the time of the event. It does not refer to an event which, hypothetically, might have caused death if more severe.

Any serious adverse events must be reported by the PI/CI to the Sponsor via the Executive Officer, Research (m.wells@bath.ac.uk) within 24 hours on the appropriate form. An initial report is sufficient at this stage, further details to be provided as soon as they are available.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
If an SAE is related and unexpected it is a SUSAR. Related means it resulted from administration of any of the research procedures. Unexpected is when the type of event is not listed in the protocol as an expected occurrence.

2. Purpose
The purpose of the SOP is to provide the necessary definitions, policies, principles and guidance to personnel involved in reporting and managing SAEs relating to non-IMP studies sponsored by the University of Bath.

This SOP has been written in accordance with ICH GCP; Medicines for Human Use regulations 2004 (including amendment, 2006); and Research Governance Framework for Health and Social Care in England 2005.

The events which may be exempt from being reported must be discussed and approved by the Trial Management Group (TMG) and noted in the protocol.

3. Scope
This procedure applies to all studies sponsored by the University of Bath studies that do not involve an IMP.

4. Responsible Personnel
The Investigator or Study Personnel is responsible for:
• Reporting details of all SAEs that occur by completing the study specific SAE Form within the specified time frames (see individual study protocol for details).

• Providing the follow up report (if required) to the University of Bath via the Executive Officer, Research (m.wells@bath.ac.uk).

• Providing any further information that has been requested to the University of Bath via the Executive Officer, Research (m.wells@bath.ac.uk).

The Chief / Principal Investigator is responsible for:

• Reviewing the SAEs for seriousness, causality and expectedness; classifying the SAE (related / unexpected) and signing off the SAE form.
• Reviewing and signing the NRES “Report of SAE Form”.

The Trial Management Group (or project group for qualitative studies) / supervisor for PGR studies are responsible for:

• Discussing all SAEs that have been received in between TMG meetings.
• When required: giving consensus to a SAE classification (consensus reached when at least 2-3 members replied and agreed.)

Trial Steering Committee/ Independent Data Monitoring Committee (TSC/IDMC):

• If agreed with either/both committee(s) before the study commences, the SAE should be sent to the appropriate body for their information within the agreed timeframe.

The Trial Manager/ Research Associate/Fellow (who will be designated in TMF within the Study’s data management information form) is responsible for:

• Scanning/typing and verifying the SAE on to the Study database and chasing missing information.
• Coordinating the NRES “Report of SAE Form” and obtaining the sign off, if necessary.
• Sending the reports to the main REC concerned (from which approval was given) within the specified guidelines.

The TM/RA/F can delegate scanning/typing of SAE form to other study personnel – this should be described within Delegation of Duties Log form.
5. Procedure

5.1 Managing the SAE
(a) When a SAE Form is received, the TM/RA/F logs receipt of the form by initialling and dating the form and also recording receipt of the form on the study database.

(b) The TM/RA/F should check the SAE form for missing information that is needed to determine whether the SAE is related or unexpected. If any information is missing they should request more details immediately from the local investigator e.g. if it is unclear as to what event has occurred, or the seriousness, causality and expectedness categories are missing.

5.2 Classifying the SAE
(a) All SAEs should be referred to the CI (or person(s) identified in protocol) for review. The CI should assess the SAE to determine whether they believe the SAE is related and unexpected based on the information provided and complete the University of Bath section of the SAE form. This should be done within 24 hours and returned to the TM.

(b) When required: the CI can decide to send details (totally anonymised) of the event to the TMG for a second opinion. Consensus of an SAE classification is reached when at least 2-3 members have replied and agreed.

5.3 Documenting the SAE
(a) The TM/RA/F scans/types and verifies the SAE data onto the database and files the SAE form in the patient file.

(b) If the event is not resolved or data is missing then TM/RA/F should follow procedures outlined in Section 5.5.

(c) If the outcome to Section 5.2 (classifying the event), is related and unexpected the TM should follow procedures in Section 5.4.

5.4 Reporting related and unexpected SAEs
(a) TM/RA/F should complete the NRES report of serious adverse event form in typescript (see appendix 3) using the information provided on the SAE form and send it to the CI for review.

(b) The CI should review the form and when happy with the content sign the form.

(c) The TM/RA/F should send the following to the ethics committee who gave favourable opinion and to the sponsor (PVC, Research);

   (i) A cover letter (always ensure the REC number is stated).
(ii) The NRES report of serious adverse event form (ensure a photocopy is taken)

(iii) A copy of the SAE form.

(d) The TM/RA/F should file the photocopy of the form and cover letter in TMF and if there is no missing data and the event has been resolved file the SAE form in the site file.

5.5 Following up SAEs (where data missing or event not resolved)

(a) Where there is missing data/queries or the event is not yet confirmed as resolved, the TM/RA/F must manage the event/chase the data until the form is complete.

(b) TM/RA/F should update the database with all new information received.

(c) When the SAE form is complete the TM/RA/F should file the SAE form in the site file.

5.6 Notifying the TSC/IDMC

If requested before the start of the study that the TSC or IDMC would like to be notified of all SAEs reported, the TM/RA/F should send a report of the SAE to the members within the specified timelines.

6. References

- ICH Topic E6 (E1) Guidelines for good clinical Practice (CPMP/ICH/135/95), July 2002
- The Medicines for Human Use (Clinical Trials) Regulations 2004. UK Statutory Instrument 1031
- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006. UK Statutory Instrument 1928
- www.nres.npsa.nhs.uk
8. Appendices

- Appendix I: Process map
- Appendix II: SAE Reporting flow diagram
- Appendix III: Link to Example report of SAE Form (NRES website)
- Appendix IV: Reporting Guidance
Appendix I  Process Flow Diagram

SAEs for Non-IMP Studies Process Flow

<table>
<thead>
<tr>
<th>TM / RA</th>
<th>SAE Received</th>
<th>Log Receipt</th>
<th>Able to Classify?</th>
<th>YES</th>
<th>SAE Ready for Review</th>
<th>Enter Details Onto Database</th>
<th>YES</th>
<th>Complete and Send NRES Report</th>
<th>Obtain all Outstanding Information and Update Database</th>
<th>All Data Resolved, Event Closed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td>Request information Immediately</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>Relaxed &amp; Unexpected?</td>
<td>Save SAE Form on Patient File</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd Opinion Needed?</td>
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<tr>
<td>TMG</td>
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<td></td>
<td></td>
<td></td>
<td>Classify SAE and Respond</td>
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<td></td>
</tr>
</tbody>
</table>
Appendix II: SAE Reporting Flow Diagram

Was the Adverse Event serious? Did the event result in any of the following?
• Death
• Is life-threatening
• Hospitalisation, or prolongation of existing hospitalisation
• Persistent/significant disability or incapacity
• A congenital abnormality or birth defect

- YES
- NO

Was the event Unexpected?

- YES
- NO

Is it possible that the event resulted from participation in the research?

- YES
- NO

Record as a unexpected, related SAE

Report within 15 days to the concerned Main or Local REC
Appendix III: Link to the University of Bath SAE Form

Appendix IV: Reporting Guidance

Suggested wording for Protocol

Serious adverse events

<<Detail the definition of both adverse events [AE’s] and serious adverse events [SAE’s] as they apply to the study/trial and outline procedures for collecting appropriate information and reporting to relevant persons>>

Adverse Event (AE): Any untoward medical occurrence in a study participant.

Serious Adverse Event (SAE): Any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening [refers to an event during which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death had it been more severe in nature]
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent/significant disability or incapacity
- Is a congenital abnormality or birth defect

Related AE:

The SAE resulted from administration of any of the research procedures. (Causal to the research process or intervention)

Unexpected AE:

The event is unexpected and is not one of the following:

<<List any expected events – e.g. disease progression or death due to the disease.>>

Reporting responsibilities of the centre:

Where the adverse event meets one of the serious categories <<the generic University of Bath SAE form / Study specific SAE form>> should be completed by the responsible clinician (the clinician(s) named on the signature list and delegation of responsibilities log) and faxed to the <<trial name>> Study/Trial Manager within 24 hours <<if no SAE form, written notification is sufficient>> upon becoming aware of the event.

Confidential Fax Number: <<xxx>>
Evaluating and Reporting:

The <<Study name>> Study Manager and/or the Chief Investigator will assess the nature of the SAE, for seriousness, causality and expectedness. Following the initial report, follow up data may be requested by the <<Study name>> Study Manager. Where the SAE is both related and unexpected the <<Study name>> Study Manager will notify the main REC within 15 days of receiving notification of the SAE.

Reporting guidelines

What needs reporting and whom to report to:

The University of Bath should keep detailed records of all SAEs, which are reported by the investigators for individual studies. Reporting is required for SAEs where in the opinion of the chief investigator the event was related to study participation and it was unexpected:

(1) ‘Related’ – that is, it resulted from administration of any of the research procedures; and

(2) ‘Unexpected’ – that is, the type of event is not listed in the protocol as an expected occurrence related and unexpected.

Related and unexpected SAEs should be reported to:

The REC that gave a favourable opinion of the study (the ‘main REC’ or ‘local REC’).

When to report

Immediate reporting: Reports of related and unexpected SAEs should be submitted within 15 days of the chief investigator becoming aware of the event.

How to report

Immediate reporting: Use the NRES report of serious adverse event form (for research other than CTIMPs). See appendix 2– download copy from NRES website). The form should be completed in typescript and signed by the chief investigator.

N.B. Reports of SAEs in double-blind trials should be unblinded.

The Co-ordinator of the main REC will acknowledge receipt of safety reports within 30 days.