Title: Adverse Event in CTIMPs

Effective Date: 1-6-18  
Review Date: 1-6-21

Author: Patricia Burns, Research Governance Manager  
QA Approval: Richard Cowie, QA Manager

Approver: Prof Maggie Cruickshank, R&D Director  
Approver: Prof Steve Heys, Head of School

1. **Scope**

1.1 This SOP applies to any individual delegated the task of identifying, recording and reporting an Adverse Event (AE), Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR) occurring in a Clinical Trial of Investigational Medicinal Products (CTIMP), sponsored or co-sponsored by University of Aberdeen (UoA) and/or NHS Grampian (NHSG). It also describes the procedure for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) via the eSUSAR online system.

For Medical Device Clinical Investigations see SOP-QA-39 - Adverse Events in Medical Device Clinical Investigations.

1.2 For other interventional studies please contact the Research Governance Office via researchgovernance@abdn.ac.uk for advice.

2. **Responsibilities**

Chief Investigator (CI)  
Report, assess and sign-off SAE/SUSARs occurring in Grampian.

Principal Investigator (PI)  
Report, assess and sign-off SAE/SUSARs occurring outside Grampian.

Sponsor  
Ensuring SUSARs are reported by the CI to the MHRA.

3. **Procedure**

**Protocol safety section**

3.1 The decision on what AEs to record and report should be determined during the trial protocol development and informed by the CI and Sponsor risk assessment. This should also be noted for SAEs (which are a subset of AEs) particularly in relation to whether any will be recorded as outcomes rather than as SAEs.
3.2 🟢 The trial protocol shall clearly define:

- How AEs shall be identified and the follow up period when they will be identified.
- Which AEs will be recorded.
- Whether any AEs will be recorded as outcomes, rather than AEs.
- Which AEs are expected as a result of the participant’s condition.
- Which AEs are expected following administration of the MP (reference should be made to the Reference Safety Information (RSI)).
- That AEs where the frequency and/or severity (see sections 4.2 and 4.3) are not in keeping with the RSI shall be recorded as unexpected events.
- The procedure for dealing with incidental findings (ie recorded as AEs or not).
- The procedure for dealing with abnormal measurements (eg laboratory results).
- Whether any auxiliary investigational medicinal products (AMPs) are to be supplied to participants in the trial (eg support/rescue medication or preventative, diagnostic or therapeutic treatments to ensure good medical care to participants).
- Whether the CI will review PI assessment of SAEs before or after reporting to Sponsor.
- The procedure for unblinding in blinded trials.
- If it is necessary to record pregnancy and whether it should be an exclusion.

⚠️ On review of data, the Data Monitoring Committee (DMC) may note events which could be relevant for the safety of trial subjects and may also require assessment as potential AE/ARs.

**Identifying the Adverse Event**

3.3 AEs shall be identified by, or notified to, the research team.

3.4 🟢 Unless stated in the protocol a member of the research team shall ask participants at each trial visit (or telephone contact) about hospitalisations, consultations with other medical practitioners, disabilities, incapacities, or if any AEs have occurred since the previous trial contact. In addition, participants may self-report AEs via direct contact to the trial team or by completion of research project questionnaires.

3.5 🟢 Potential AEs may also be identified during the assessment of trial outcomes by support departments, for example, clinical laboratories, and radiology. Where notification of abnormal values or measurements is not standard clinical practice, the procedure for notifying such out of range events to the CI or PI must be clearly documented in the trial protocol or study specific SOPs. Such out of range events may or may not constitute AEs.

**Assessment of Adverse Event**

3.6 AEs must be assessed according to Appendix 1 in conjunction with the definitions in section 4 and the trial protocol.

⚠️ AEs must be assessed for seriousness by the study team. If deemed serious then the PI or CI must be informed and a decision then made as to whether the event is related to the MP or not (see section 4 for definitions). If related to the MP the CI or PI shall determine if the event is expected or unexpected. The assessment must be recorded on an SAE Reporting Form (TMP-QA-10). For blinded studies, AEs shall be assessed as though the trial subject was taking the MP.

3.7 🟢 For all SAEs the CI or PI shall make an assessment of severity. The assessment shall be recorded on the SAE form according to the following categories:
**Mild:** an event that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.

**Moderate:** an event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe:** an event that prevents normal everyday activities.

⚠️ The term ‘severe’ used to describe the intensity of an event or reaction should not be confused with the term ‘serious’ which is a regulatory term used for trial participant/event outcome. For example, a headache may be severe but not serious, while a minor stroke may be serious but not severe.

### 3.8 ⚠️ The SAE form shall be completed by a member of the research team and signed by the PI/CI.

**Reporting SAEs to the Sponsor**

3.9 ⚠️ If the SAE/SUSAR occurs out with Grampian the CI must delegate the assessment and sign off of the SAE form to the local Principal Investigator (PI). This responsibility can be delegated by the PI to another Consultant at that site if required. This must be documented in the Site Delegation Log (TMP-QA-13). The local PI/Delegate must report SAEs/SUSARs in a timely manner (within 24 hours of knowledge of event) to the CI. All SAE/SUSAR which occur out with Grampian must be recorded on the Trial Log of SAEs (TMP-QA-11).

3.10 ⚠️ All SAEs must be reported to the Sponsor within 24 hours of the CI/PI or delegate’s awareness of the event. This is delegated to the CI by the Sponsor and is formally documented in the CI responsibilities letter issued by Sponsor. All reports must be on a study specific SAE Reporting Form (TMP-QA-10) emailed to pharmaco@abdn.ac.uk. The SAE form should be as complete as possible within the timeframe and signed and dated by the CI/PI, or medically qualified delegate. Documents shall be assessed by a Sponsor medic, checked for completeness, and a follow up requested if appropriate.

3.11 ⚠️ All SAEs must also be recorded on the Trial Log of SAEs (TMP-QA-11). This shall be forwarded to the Sponsor at the same time as the SAE Reporting Form.

3.12 ⚠️ The Sponsor shall review all reported SAEs. For blinded CTIMPs, SAEs shall be assessed as though the trial subject was taking the MP. The Sponsor shall email the outcome of the Sponsor assessment to the study team. The Sponsor may disagree with the CI or PI assessment and this shall be recorded by the study team in the Trial Log of SAEs (TMP-QA-11).

3.13 ⚠️ If the event has been considered by either the CI, PI or Sponsor as a SUSAR, the participant shall be unblinded, if a randomised trial, and the event reported to the MHRA if the participant was taking MP.

3.14 Due to the necessity to report SAEs within 24 hours it is anticipated that there may be additional information which will be submitted as a follow-up report. All follow-up reports shall be submitted to pharmaco@abdn.ac.uk along with an updated log and shall be reviewed by Sponsor as detailed in 3.12.

⚠️ Any follow-up to an SAE must be reviewed using the RSI that was approved and relevant at the time of the initial report. Any changes to this shall be documented and reported to Sponsor.

3.15 ⚠️ Should the CI become aware of a systematic issue or identify a factor in the SAEs being recorded (eg events occur at a higher than expected frequency, identify a risk factors in patient population or potential drug-drug interactions) they shall notify the Sponsor immediately (pharmaco@abdn.ac.uk).

3.16 All recorded AEs and SAEs shall be reported as part of an Annual Progress Report (APR) to the REC.
which provided the favourable opinion for the trial, and to the MHRA as part of the Development Safety Update Report (DSUR) (see SOP-QA-21 – APRs and DSURs). The DSUR shall also be forwarded to the REC.

**Reporting SUSARs to the Sponsor**

3.17 SUSARs shall be reported to the Sponsor using the same procedure as outlined above for SAEs.

3.18 It may be necessary to unblind the participant in order to make a definitive assessment of an SAR that is unexpected, and hence to confirm whether it is a SUSAR or not. If in doubt contact Sponsor.

3.19 The trial protocol shall set out the procedure for unblinding in such circumstances. Important point to note: Efforts should be made to ensure that any study team member involved in further study assessments of the unblinded participant remains blinded. In such cases, the Sponsor can be contacted for advice.

3.20 If all the required information is not available at the time of reporting a SUSAR to the Sponsor, the CI must ensure that any missing information is provided to the Sponsor as soon as this becomes available in a follow-up report (see 3.12). It shall be supplied using a new SAE reporting form (TMP-QA-10), with a clear indication that the new information is a follow-up report to a previously reported event.

**Filing**

3.21 All SAE forms and any follow-up communication with any information to/from the Sponsor or MHRA shall be retained in the Trial Master File (TMF) or Investigator Site File (ISF). The updated SAE log, and the SAE report for a SUSAR received by the Sponsor, together with any follow-up information, shall be kept in the Sponsor File. If stored electronically, the file path shall be clearly indicated.

**Expedited reporting of SUSARS to REC, MHRA and addition trial sites**

3.22 The CI is responsible for reporting SUSARs in writing to the MHRA and REC, which gave the favourable opinion about the trial, as soon as possible (see Appendix 1). For fatal or life threatening SUSARs this should be done no later than 7 calendar days of the study team’s awareness. All other SUSARs must be reported within 15 calendar days of the CI first becoming aware. This also applies to SUSARs occurring after the end of the trial.

3.23 The assessment of causality made by the investigator cannot be downgraded by the CI or Sponsor. Where the assessment of causality made by Sponsor and investigator differ, both assessments shall be recorded.

3.24 If an event has been considered by either the CI, PI or Sponsor as a SUSAR, the participant shall be unblinded, if a randomised trial, and the event reported to the MHRA if the participant was taking MP.

3.25 SUSARs shall be reported to the MHRA using the eSUSAR website (https://esusar.mhra.gov.uk) by the trial team. Appropriate trial team members shall be registered with the eSUSAR website by the Research Governance Team. Should trial team members require assistance in using the eSUSAR website they should notify the Sponsor of this need via pharmaco@abdn.ac.uk.

3.26 The CI shall report SUSARs to the REC which provided the favourable opinion for the trial. The eSUSAR report generated for the MHRA shall be downloaded from the eSUSAR website as a PDF document and used to report the event to the REC and sent along with a completed REC safety form http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting

3.27 For multicentre studies, the CI must forward details of all SUSARs reported in the trial to the PIs at all trial sites. Details must be forwarded to PIs within 14 days of the SUSAR being followed to resolution.

Uncontrolled when printed. Please ensure that you are working on the most up to date version of this SOP.

**Key to symbols**

- ✔ = Important point to note
- ⚠ = Warning
In addition to filing requirements (see 3.21) all relevant correspondence with MHRA/REC should be maintained in TMF/ISF.

**Reporting of Urgent Safety Measures to Sponsor, REC and MHRA**

3.28 🚨 The CI can deviate from the trial protocol or implement a change to the trial protocol to eliminate an immediate hazard to trial participants; without prior approval from the REC or MHRA. This shall be reported to the Sponsor immediately by email to pharmaco@abdn.ac.uk. The CI shall also contact and discuss the issue with a medical advisor at the MHRA, as detailed in the MHRA website.

3.29 The CI must then provide written notification to the MHRA, REC, Sponsor, PIs of additional sites (if a multi centre study) and relevant NHS Research and Development (R&D) offices within 3 days of the measures being taken and the reason(s) for the measures. A copy of the notification must be filed in the TMF and the ISF (as appropriate). This notification should be reported:

- To the Sponsor by email pharmaco@abdn.ac.uk
- To the MHRA by email clinicaltrialhelpline@mhra.gsi.gov.uk marked ‘Urgent Safety Measure’ and sent as a PDF on CD to Information Processing Unit, Area 6, MHRA, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ.
- To the REC who provided the favourable opinion for the trial by email marked ‘Urgent Safety Measure’.
- To relevant NHS R&D offices (email or hard copy) marked ‘Urgent Safety Measure’.

3.30 🚨 The CI must discuss the implications of the urgent safety measure on the conduct of the trial with the Sponsor as a matter of urgency.

**Pregnancy reporting (if required by the protocol)**

3.31 Pregnancy is not considered to be an AE or SAE. If required by the protocol, the CI or PI must collect pregnancy information for trial participants, or partners of trial participants who become pregnant.

3.32 The CI, PI or delegated medically qualified research team member shall record the information on a Pregnancy Notification Form (TMP-QA-12) and send this to the Sponsor within 14 days of being made aware (pharmaco@abdn.ac.uk).

3.33 Any pregnancy that occurs in a trial participant, or a trial participant’s partner, during a trial shall be followed to outcome. In some circumstances it may be necessary to monitor the development of the newborn for a period post delivery. This requirement must be specified in the trial protocol.

3.34 If the pregnant participant, or pregnant partner of a participant, does not agree to this information being collected their wishes shall be respected and a note to that effect made in the Clinical Research Form (CRF) and the patient’s medical records.

### 4. Abbreviations and definitions

**Adverse Event (AE)**

4.1 Any untoward medical occurrence in a clinical trial participant to whom a Medicinal Product (MP) has been administered, but which is not necessarily caused by or related to that product.

Only AEs that are identified in the protocol as critical to evaluations of safety in the trial should be recorded. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease.
Adverse Reaction (AR)
4.2 All untoward and unintended responses to the MP, related to any dose administered to that participant. ARs are all adverse events judged by the reporting PI, CI, or delegated Consultant, as having a reasonable causal relationship to the MP.

ARs may be classed as either:

**Expected**: the AR is consistent with the AR profile of the trial drug listed in the trial protocol, Investigator Brochure (IB) Reference Safety information (RSI) or Summary of Product Characteristics (SmPC/SPC).

**Unexpected**: the AR is not consistent with the AR profile in the trial protocol, IB, RSI or SmPC/SPC. Or the documented AR has occurred at a greater frequency or severity than expected.

Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)
4.3 The classification of serious is:

Any untoward medical occurrence, event or reaction that at any dose:
- Results in death.
- Is life-threatening.
- Requires hospitalisation, or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life threatening resulting in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above.

Life threatening, by definition, refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement by the CI/PI or delegate shall be exercised in deciding seriousness of an AE or AR.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
4.4 Any AR classed as serious and possibly, probably or definitely caused by the MP (see 4.5) (but not consistent with the known information on that product, as documented in either the trial protocol, SmPC/SPC, RSI or IB), is termed unexpected and is a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The trial protocol or IB should include a list of known side effects for each drug in the study. This should be consulted when a SAR occurs, to determine expectedness. If the event is not listed, or has occurred in a more serious form, or more frequently than expected, it should be considered to be a SUSAR. All deaths related to the MP should be considered to be SUSARs.

4.5 Relatedness (Causality)

**Unrelated**: where the AE is not considered to be related to the trial drug (MP).

**Possibly**: although a relationship to the trial drug (MP) cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
**Probably:** the temporal relationship and absence of a more likely explanation suggest the event could be related to the trial drug (MP).

**Definitely:** the known effects of the trial drug (MP) or its therapeutic class, or based on challenge testing, suggest that the trial drug (MP) is the most likely cause.

### 4.6 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AMP</td>
<td>Auxiliary Medicinal Product</td>
</tr>
<tr>
<td>APR</td>
<td>Annual Progress Report</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CTIMP</td>
<td>Clinical Trial of an Investigational Medicinal Product</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MP</td>
<td>Medicinal Product</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development (NHS)</td>
</tr>
<tr>
<td>RSI</td>
<td>Reference Safety Information</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SmPC/SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
</tbody>
</table>

### 5. Related documentation and references

- SOP-QA-22 Appendix 1 Identifying Adverse Events
- SOP-QA-3 Protocol guidance for high risk trials and CTIMPs
- SOP-QA-6 Study start-up
- SOP-QA-21 APR and DSURs
- SOP-QA-31 Research project closure
- SOP-QA-39 Adverse Events in Medical Device Clinical Investigations
- TMP-QA-10 SAE reporting form
- TMP-QA-11 Trial log of SAEs
- TMP-QA-12 Pregnancy notification form
- TMP-QA-13 Site delegation log
SOP-QA-22 Appendix 1 – Identifying, recording and reporting Adverse Events

Has an Adverse Event (AE) been identified?

An AE is defined as any untoward medical occurrence in a clinic trial participant, not necessarily having a causal relationship with a Medicinal Produce (MP)

Has an Adverse Reaction (AR) been identified?

An AR is defined as any untoward and unintended response to any dose of MP administered to that participant

Is the AE or AR serious?

A serious adverse event (SAE) or serious adverse reaction (SAR) is defined as any AE or AR which at any dose:

- Results in death of the clinical trial participant.
- Is life threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Consists of congenital anomaly or birth defect.
- Any other important medical event not immediately life threatening which may jeopardise the participant or require an intervention to prevent one of the outcomes listed above.

Is the SAE/SAR likely to be related to the MP?

Any SAE/SAR that is assessed as being possibly, probably or definitely related to the MP should be reported as being related to the MP.

This is a SAE therefore no requirement to assess expectedness. Report to Sponsor within 24 hours of the study team’s awareness of the event (see SOP section 3.9).

This is a SAR

Is the SAR expected?

Expected SARs are listed in the Summary of Product Characteristics, Investigator Brochure or trial protocol.

No

This is a SUSAR Report to sponsor within 24 hours of the team’s awareness of the event (see SOP section 3.16). After unblinding, if the participant was taking MP, there may be a requirement for expedited reporting to the MHRA within 7 or 15 days (see SOP section 3.21).

Yes

This is a SAR

Report to sponsor within 24 hours of the team’s awareness of the event (see SOP section 3.9).

This is a SAR

Report as per trial protocol

Yes

No

Uncontrolled when printed. Please ensure that you are working on the most up to date version of this SOP.

Key to symbols  ● = Important point to note  ▼ = Warning