SOP-QA-22 V7

Title: Adverse Event in CTIMPs

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Document History

Version	Description of update	Date Effective
6	Reformatted and Removal of APR's 3.31 - Addition of statement re pregnancy reporting 4.4 – Addition of reference to MedDRA preferred term 4.5 - Addition of 'Unlikely' to the criteria	16-10-25
7	Updated terminology throughout and removal of references to REC Updated assessment of AE process at 3.6 Updated reporting requirements at 3.9 – 3.16 Reference to blinded trials at 3.18 Updated AR reporting requirements at 4.2 Reference to trial drug in SUSARs at 4.4	28-04-26

1. Scope

1.1 This SOP applies to any individual delegated the task of identifying, recording and reporting a **Pregnancy**, **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 ICSR submissions portal.

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 at any site/location.
Principal Investigator (PI)	Report, assess and sign-off SAE/SUSARs occurring at their site/location.
Sponsor	Review and assess SAE/SUSARs. Ensure 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 process. 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 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) and any associated safety reporting requirements.
- 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 and report pregnancy and associated follow up. Whether pregnancy is an exclusion or grounds to stop giving an intervention to a participant.

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 expectedness will be determined by Sponsor and, if instructed by the protocol, the CI or PI may be asked to 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 local PI. In exceptional circumstances, to be agreed with Sponsor, the CI may be asked to sign off the SAE form in place of the PI.

Reporting SAEs to the Sponsor

3.9 The SAE/SUSAR should be assessed and the SAE form signed off by the local PI. This responsibility can be delegated by the PI to another investigator where this is in their normal remit, Consultant (or medical doctor of equivalent grade) at that site/location if required. This must be documented in the **Site Delegation Log** (TMP-QA-13). The local PI/Delegate must report SAEs/SUSARs immediately (**not later than 24 hours** of knowledge of event) to the CI, or delegate.

3.10 All SAEs must be reported to the Sponsor immediately (**not later than 24 hours**) of the CI/PI or delegate's awareness of the event. All reports must be on an approved study specific SAE Reporting Form (eg TMP-QA-10) emailed to pharmaco@abdn.ac.uk. The SAE form should be as complete as possible within the time frame and signed and dated by the PI, or qualified delegate. The PI or delegate should not delay reporting the event if the report is incomplete or not signed. 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 delegate) 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 factor in participant population, or potential drug-drug interactions) they shall notify the Sponsor immediately (pharmaco@abdn.ac.uk).

3.16 All SUSARs shall be reported to the MHRA, alongside all recorded SARs and SAEs, as part of the Development Safety Update Report (DSUR) (see SOP-QA-21 –DSURs).

Reporting SUSARs to the Sponsor

3.17 SUSARs shall be reported to the Sponsor using the same procedure as outlined above for SAEs. However, the CI is also required to sign off the SAE reporting form in the case of a SUSAR.

3.18 In a blinded trial it will be necessary to unblind the participant in order to make a definitive assessment of a 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. 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, Sponsor can provide 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 3.14). It shall be supplied using a new SAE reporting form (eg TMP-QA-10), with a clear indication that the new information is a follow-up 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) and 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 additional trial sites/locations

3.22 The CI is responsible for reporting SUSARs in writing to the MHRA, 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 delegate) or Sponsor as a potential 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 For trials taking place within the UK: SUSARs shall be reported to the MHRA using the ICSR submissions portal (https://icsrsubmissions.mhra.gov.uk/login) by the trial team. Appropriate trial team members shall be registered with the ICSR submissions portal by the Research Governance Team. Should trial team members require assistance in using the ICSR submissions portal they should notify the Sponsor of this need via pharmaco@abdn.ac.uk.

3.26 For trials conducted in other states of the European Economic Area: SUSARs shall be reported to the competent authorities for each of the countries where the trial is taking place using EudraVigilance. Reports shall also be made to the local REC as per their procedures.

3.27 For multicentre studies, the CI must forward details of all SUSARs reported in the trial to the PIs at all trial sites/locations. Details must be forwarded to PIs within **14 days** of the SUSAR being followed to resolution. In addition to filing requirements (see 3.21) all relevant correspondence with MHRA should be maintained in TMF/ISF.

Pregnancy reporting (if required by the protocol)

3.28 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.

3.29 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).

3.30 Unless otherwise stated in the protocol, any pregnancy that occurs in a trial participant, or, where defined in the trial protocol, 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. The trial protocol should define whether it is a requirement to follow up pregnancy in a trial participant's partner.

3.31 If the pregnant participant, or pregnant partner of a participant, does not consent 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 participant's medical records.

4. Abbreviations and definitions

4.1 Adverse Event (AE)

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.

4.2 Adverse Reaction (AR)

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 qualified delegate, 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 approved Reference Safety Information (RSI), which may be the trial protocol, Investigator Brochure (IB) or Summary of Product Characteristics (SmPC/SPC).

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

4.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

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.

4.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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 the RSI (which may be the trial protocol, SmPC/SPC or IB), is termed unexpected and is a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The RSI should include a list of known side effects for each drug in the study. The terms in the RSI should be coded to preferred terms. This should be consulted when a SAR occurs, to determine expectedness. If the event is not listed (matching the preferred term), or has occurred in a more serious form, or more frequently than expected, it should be considered to be a SUSAR (where the participant has been confirmed to be taking trial drug). 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).
Unlikely*: there is little evidence to suggest is a causal relationship; there is another reasonable explanation for the event (*only applicable to studies approved after 2025).
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

AE	Adverse Event
AMP	Auxiliary Medicinal Product
AR	Adverse Reaction
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
IB	Investigator Brochure
ICSR	Individual Case Safety Reports
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
REC	Research Ethics Committee
R&D	Research and Development (NHS)
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC/SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
USM	Urgent Safety Measure

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	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

MHRA Inspectorate Blog – RSI for Clinical trials I

MHRA Inspectorate Blog – RSI for Clinical trials II

MHRA Inspectorate Blog – RSI for Clinical trials III

6. SOP-QA-22 Appendix1 – Identifying, recording and reporting Adverse Events