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SOP 205 Adverse Events: Identifying, Recording and Reporting for CTIMPs Sponsored by the Norfolk and Norwich University Hospitals NHS Foundation Trust

For Use in:	Research
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
Key words:	AEs, SAEs, Severity, Causality
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This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

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1. Contents

2. Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRGC	Joint Research Governance Committee
MAH	Marketing Authorisation Holder
NCTU	Norwich Clinical Trials Unit
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
R&D	Research and Development
RGC	Research Governance Coordinator
RSI	Reference Safety Information
RSM	Research Services Manager
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics

SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UEA	University of East Anglia
USAR	Unexpected Serious Adverse Reaction

3. Scope

The aim of this SOP is to describe the process for Identifying, Recording and Reporting of Adverse Events for Clinical Trials of an Investigational Medicinal Product (CTIMPs) for all health care research activities within the UEA and NNUH.

4. Introduction

This SOP applies to all CTIMPs **sponsored** by NNUH. With prior agreement of the sponsor, the process may be modified to meet the needs of individual studies.

It is essential that all adverse events which occur during the course of a study are recorded and reported appropriately, in order to ensure that participant safety is maintained.

5. Purpose

The purpose of this SOP is to ensure participant safety is maintained. Adverse events are reportable from the time of participant study enrolment unless study specific exclusions are detailed in the clinical trial protocol.

6. Rules

Reporting
Failure to report incidents, or deal with incidents adequately, can result in, study suspension, regulatory approval being withdrawn from an individual project, or, in extreme cases, from all research conducted by an individual investigator.

7. Responsibilities

Chief Investigator

- The Chief Investigator (CI) has overall responsibility for the conduct of the study.
- The Chief Investigator (CI) /Principal Investigator (PI) must be aware of the NNUH systems for reporting adverse events by complying with this SOP.
- All CTIMPs must have a sponsor legally responsible for the conduct and monitoring of the trial.
- The Research & Development (R&D) Office will be responsible for ensuring monitoring is conducted for all CTIMPs for which the Trust acts as Sponsor.
- It is the responsibility of the local PI to ensure that study specific SOPs can be operated without conflict with this SOP and in accordance with all organisational polices related to research.

Norwich Clinical Trials Unit (NCTU)

- Where NCTU has been delegated sponsor activities, local forms and reporting instructions may be followed as described in study documentation, providing they are not in breach of this SOP
- If the NCTU is delegated the management of a trial, NNUH may delegate the safety reporting responsibilities to the CTU trial manager. This decision will be documented in the protocol and clinical trial agreement.
- NCTU will form a Trial Management Group to support the review of SAE / SUSAR report forms for trials where NCTU have been delegated the safety reporting responsibilities.
- When safety reporting is managed by NCTU, copies of SAEs for NNUH sponsored studies need to provide to the R&D office (rdsae@nnuh.nhs.uk) to ensure review by the Joint Research Governance Committee.

8. Procedures

8.1 Assessment and Recording of all Adverse Events

- All AEs should be recorded for all trial subjects from the time of their enrolment into the study, whether an IMP has been administered to this subject or not
- In the event of an AE the investigator or delegate member of the research team should review all documentation (e.g. hospital notes, laboratory and diagnostic reports) relevant to the event

- The event and relevant comments should be recorded in the subject's medical notes, Case Report Forms (CRF) and/or AE log
- An assessment of intensity, and seriousness must be made by the investigator. Please refer to Appendix 1 Event Assessment and Appendix 2 Definitions to complete assessment process.

- Except where the protocol states otherwise, all AEs that are not considered serious should be recorded in detail on the CRF and / or AE log to allow analysis at a later stage. Causality (relatedness to trial treatment) and expectedness do not need to be assessed for AEs unless explicitly required by the sponsor. These assessments are only undertaken for events classified as serious (SAEs).

- Adverse events and/or laboratory abnormalities identified in the protocol as critical to the evaluations of the safety of the study **shall be reported to the Sponsor** in accordance with the reporting requirements documented in the protocol

- If the administered product is a comparator the event will be assessed for expectedness as per the RSI.

- Any SAE must be reported to the Sponsor. Please refer to section 8.3 for details on reporting SAEs
- If the adverse reaction is considered serious, unexpected and related to the event then it will be subject to expedited reporting as a potential SUSAR. Please refer to section 8.3 for reporting SUSARs
- Refer to SOP 230 for urgent safety measures

8.2 Reference/Comparator Drugs and Study Procedures

Often more than one drug is used in a clinical trial in order to meet the objectives of the trial. When considering patient safety ALL drugs used in the trial are of interest.

Non-investigational medicinal products (NIMPs) used in the trial may also be subject to reporting requirements and details should be provided in the study protocol.

The following scenarios show when an adverse reaction to a NIMP would require reporting:

a) If the adverse reaction is suspected to be linked to an interaction between a NIMP and an IMP and is serious and unexpected
b) If a SUSAR is reported and it might be linked to either a NIMP or an IMP but cannot be attributed to only one of these
c) If an adverse reaction associated with the NIMP is likely to affect the safety of the trial subjects

SARs associated with a NIMP should be reported to the Marketing Authorisation Holder (MAH) in order that this information may be used in the MAH's ongoing safety monitoring procedures.

A SAR associated with a NIMP which does not have a Marketing Authorisation in the UK must be notified to the licensing authority. In some circumstances trial subjects may experience a SAE which is not related to the study product but which is related to the research (such as study procedure). Such SAEs must be reported to the sponsor using the SAE report form.

If unblinding reveals that the participant is taking placebo, the investigator should be asked whether they think the serious adverse reaction could have been caused by an excipient in the placebo. If they agree it is possible and the event is not listed as expected, it should still be reported as a SUSAR to the MHRA but it must be made clear in the report that this is a suspected reaction to an excipient in the placebo and that the participant was not on active treatment. Correspondence regarding this must not risk unblinding of other team members, so it must be communicated and filed separately according to the usual procedures for a blinded trial.

8.3 Serious Adverse Event Reporting

Any SAE must be reported to the Sponsor immediately. No later than **24 hours** of becoming aware of an SAE event any member of the research team must notify the Sponsor, as documented in the protocol. The only exception is where the protocol or IB identifies the event as not requiring immediate reporting.

↓	• The investigator or delegated member of the research team will complete the NNUH SAE report form. The initial report will include as much information as is available at the time.
↓	• Within 24 hours the report should be emailed to rdsae@nnuh.nhs.uk
↓	• The CI must be copied into the notification
↓	• If the SAE report is an initial report it must include as much information as is available at the time. A follow up report must be submitted to R&D as soon as all information is available.
↓	• R&D will send an acknowledgement of receipt of the SAE report form to the sender by noon of the following working day.
↓	• If acknowledgement of the SAE report form is not received it is the responsibility of the investigator or delegated member of the research team to contact R&D immediately.

8.4 SUSAR Reporting

Any AE that the PI evaluates as serious, is suspected of having a causal relationship to the IMP and is unexpected will require **expedited** reporting to:

- rdsae@nnuh.nhs.uk
- MHRA, REC and to other organisations as required under the terms of the individual contracts (e.g. relevant pharmaceutical companies, other NHS Trusts)

Timeframes for expedited reporting

Fatal or life threatening SUSARs
• CI must inform the NNUH R&D Office as Sponsor immediately • The Sponsor, or delegated individual, must inform the MHRA and main REC as soon as possible but not later than 7 days after becoming aware of the reaction • Follow up information should be reported within an additional 8 days

Non-fatal and non-life threatening SUSARs
• The CI must report all other SUSARs to the Sponsor • The Sponsor, or delegated individual, must inform the MHRA and main REC as soon as possible, but no later than 15 days after becoming aware of the incident. Further relevant information should be given as soon as possible.

8.5 eSUSAR Reporting

⇩	• The sponsor, or delegated individual, is responsible for the reporting of SUSARs.
⇩	• From 01 October 2022 SUSARs must be submitted via the Individual Case Safety Reports (ICSR) Submissions Portal. For NNUH RSM and RGC are account holders and will be responsible for making the submission. If safety reporting is delegated to a CTU, nominated members of the CTU will be added by the RGC or RSM under the NNUH account.
⇩	• With ICSR Submissions you will receive acknowledgement that the MHRA has received the report. You will have access to live submissions status giving you visibility of your reports. You will also benefit from the data validation checks within ICSR Submissions portal, which will help with submitting ICH e2B compliant data.
⇩	• Once a report has been submitted it cannot be altered and any amendments will need to be included in follow-up reports.

8.6 Procedure for Multi-centre studies

The responsibility for evaluation of events can be shared between the CI and PIs and this must be stated in the delegation of responsibilities between the Sponsor, CI, and PI. It may be most appropriate for the treating PI at each local site to evaluate each event, before reporting it to the CI. It must be stated in the clinical trial protocol who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. As expedited reporting may be required, this SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.

⇩	• Completed SAE report forms from sites are re-assessed by the CI. The CI will decide if he/she agrees with the PI on the classification or whether the status of the event should be upgraded to SUSAR. The CI must not downgrade an event graded by a PI as a SUSAR
⇩	• Causality is assessed by both the PI and CI. If the CI is not in agreement with the "causality" decision of the PI, they cannot overrule the PI's decision. Both opinions should be recorded on the SAE report form.
⇩	• Reporting of events to Sponsor should follow process described in 8.3 & 8.4.
⇩	• An entry of the details of the event must be made in the SAE log in the TMF. All logged events will be reported to the REC and competent authority annually in the DSUR. If an event is identified as a SUSAR, expedited reporting is required as detailed in Section 8.4
⇩	• The CI, or delegated individual, will send a monthly study update report to the Sponsor for review by the Joint Research Governance Committee (JRGC)
⇩	• **Reporting SUSARs to PIs involved in a multi-centre Study -** For all multi-centre studies where NNUH is the sponsor, the CI, or delegated individual, must inform all PI's of SUSARs occurring on the study, although this does not have to be within the 7/15 day deadline. This notification must be documented in the TMF. • The same will apply where other trials are being undertaken within the Trust of the same study drug. If the CI is informed of SUSARs from other trials by a pharmaceutical company, the CI, or delegated individual, should inform PIs as above.

8.7 Urgent Safety Measures

Urgent Safety Measures are covered in SOP 230.

8.8 Trust Reportable Incidents

In the same way that adverse incidents, including clinical, non-clinical and near misses can involve patients, staff and visitors during routine care, adverse incidents can also occur during research related activities. It is important that research related adverse incidents are treated in the same way as non-research related adverse incidents.

Research related adverse incidents must therefore be reported in accordance with the Trust's own Incident Reporting procedures.

8.8.1 For Studies being carried out within NNUH

The Lead Nurse and Research Services Manager and RGC should be alerted to all reportable incidents relating to research that take place at the NNUH

Events that are both Adverse Incidents and Adverse Events MUST be reported independently following both processes and procedures.

8.8.2 For Studies being carried out outside of the NNUH

For NNUH sponsored studies being carried out outside of the NNUH, sites will follow this SOP unless agreed otherwise at the study set up.

The NNUH, as sponsor, should be notified of all reportable incidences relating to research that it Sponsors via Rdsae@nnuh.nhs.uk.

8.9 Pregnancy Reporting

Should a study participant become pregnant whilst participating in a CTIMP, or aid in the conception of a child whilst they are participating in a CTIMP, the pregnancy and resulting child should be followed up for a period of no less than 18 months to verify whether a congenital anomaly or birth defect is present. This will be subject to guidance from the relevant pharmaceutical company.

Investigator responsibility - Pregnancy occurring in a participant or a female partner of a male participant in a CTIMP, while not considered an adverse event or serious adverse event must, be reported to the sponsor and CI **within 7 days** of the investigator becoming aware of the event. The PI/CI must collect all information required regarding the pregnancy.

Guidance on the procedure for recording and reporting pregnancy should be included in the study protocol.

Any occurrence that results in a SAE/SUSAR should also be reported as detailed in section 8.3 and 8.4.

Sponsor responsibility - The Research Services Manager, or delegated individual, is responsible for reporting the event to the Marketing Authorisation Holder or for non-licensed products to the licensing authority, within 15 days of receiving the report.

9. References and Related Documents

References	
ICH GCP E6 / SI 2004/1041	
SOP No.	**SOP Title**
SOP 230	Urgent Safety Measures

10. Approval

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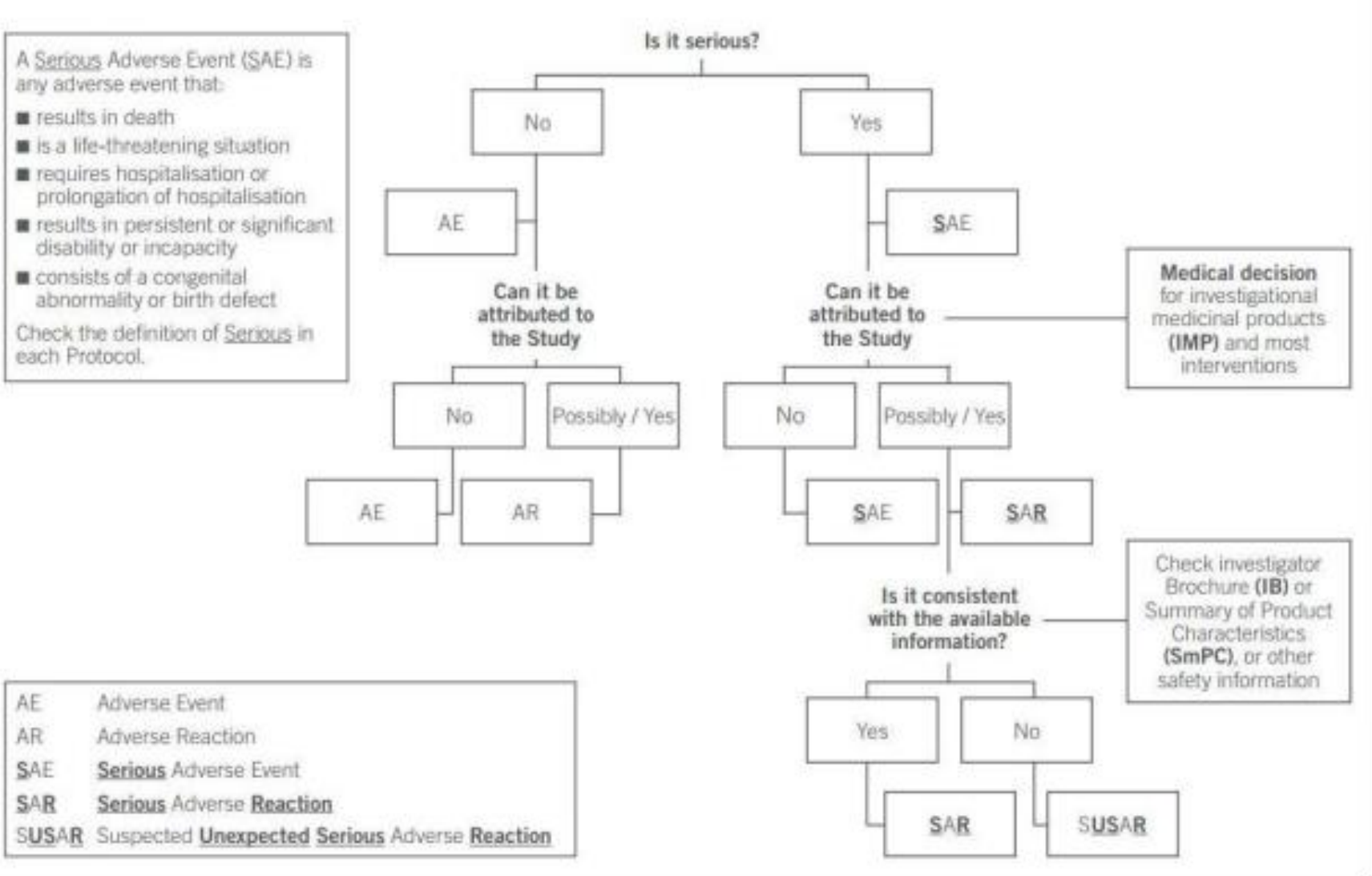
11. Reason for new version and Training Implication

This SOP replaces the previous version number V2.4

Changes made	What changes have been made to the contents of the document
Reason	• New layout • Revision in procedure • Moving 'Definitions' to Appendix 2 • Change in process regarding SUSAR reporting to ICSR
Training Implication	**Yes**
Actions required	• Additional training may be required

Appendix 1 – Event Assessment



Appendix 2 - Definitions

Adverse Event (AE) - An AE is defined as any untoward medical occurrence in a study participant who has been administered a medicinal product, as an Investigational Medicinal Product (IMP) or comparator. The event does not necessarily have a causal relationship with this product.

An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Adverse Incident – An adverse incident can be defined as an event or circumstance that could have or did lead to unintended or unexpected harm, loss or damage.

Adverse Reaction (AR) - An AR is defined as an untoward and unintended response in a participant to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the IMP qualify as ARs.

Not all adverse events are adverse reactions but all adverse reactions are adverse events.

Causality
The relationship between an IMP and the occurrence of an event. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, will be considered.

- **Not related** - Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can itself explain the occurrence of the event
- **Unlikely -** Temporal relationship of the onset of the event, relative to administration of the product, is doubtfully related, or the event could have been due to another, equally likely cause
- ***Possibly related -** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another equally likely cause
- ***Probably related -** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely explained by the product than any other cause
- ***Definitely related -** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive

***Where an event is assessed as possibly related, probably related or definitely related, the event is an adverse reaction.**

Expectedness - The approved Reference Safety Information (RSI) must be used to assess the expectedness of an adverse reaction.

Reference Safety Information (RSI) - The MHRA approved RSI is a list of medical events that defines which reactions are expected for the Investigational Medicinal Product (IMP), being administered to study participants, and so do not require expedited reporting to MHRA. It will be one single definitive document or a list contained within the Summary of Product Characteristics (SmPC) for a product with a marketing authorisation, Investigator's Brochure (IB) for any other investigational medicinal product, or protocol.

The RSI must be checked against each event that occurs in terms of expectedness to determine which Serious Adverse Reactions (SARs) require expedited reporting to the MHRA and which are exempt. Ensure that only the currently approved version of the RSI is referenced to determine expectedness, even if a newer but unapproved version exists.

Serious Adverse Event / Reaction (SAE/SAR) - An adverse event or adverse reaction is defined as serious if it:

- Results in death; or
- Is life-threatening*; or
- Requires hospitalisation or prolongation of existing hospitalisation; or
- Results in persistent or significant disability or incapacity; or
- Consists of congenital anomaly or birth defect; or
- Other: e.g. is otherwise considered medically significant by the investigator

* Life-threatening, in the definition of an SAE or SAR, refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

A planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without a serious deterioration in health, is not considered to be a serious adverse event unless specified in the clinical trial protocol.

Severity – can be described as:

- **Mild –** An event easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- **Moderate –** An event sufficiently discomforting to interfere with normal everyday activities
- **Severe –** An event that prevents normal everyday activities

Trials may use a different coding system, described in study documentation, but that severity is different to seriousness and may not need to be assessed for every trial. Refer to the trial protocol.

Suspected Serious Adverse Reaction (SSAR) - Any adverse reaction that is classed as serious and is consistent with the information about the IMP listed in the SmPC or IB.

Suspected Unexpected Serious Adverse Reaction (SUSAR) - A SUSAR is any adverse reaction that is classed as serious **and** suspected to be caused by the IMP that is **not** consistent with the information about the IMP in either the SmPC or IB i.e it is suspected and unexpected.

An SAE that is unexpected and thought to be related to an investigational medicinal product where the CTIMP is blinded will only be considered a SUSAR after the treatment code is unblinded and active treatment is confirmed. The reaction only becomes an Unexpected Serious Adverse Reaction (USAR) if the SAR is unexpected.

For blinded trials using a placebo, seriousness, causality and expectedness must be evaluated as though the subject was on the active drug.