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SOP 206 Adverse Events: Identifying, Recording and Reporting adverse events for Non-CTIMP Non-Device Healthcare Research Studies

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

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SOP 206 Adverse Events: Identifying, Recording and Reporting adverse events for Non-CTIMP Non-Device Healthcare Research Studies

1. Contents

2. Definitions of Terms Used / Glossary

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRFs	Case Report Forms
GDPR	General Data Protection Regulations
HRA	Health Research Authority
ICH GCP	International Conference on the Harmonisation of Good Clinical Practice
IDMC	Independent Data Monitoring Committee
JRGC	Joint Research Governance Committee
Non-CTIMP	Trial which does not involve an investigational Medicinal Product
NCTU	Norwich Clinical Trials Unit
PI	Principal Investigator
R&D	Research and Development
REC	Research Ethics Committee
RES	Research Ethics Service
SAE	Serious Adverse Event (See below for definition)
SAR	Serious Adverse Reaction
SI	Statutory Instrument
SOP	Standard Operating Procedure

A Serious Adverse Event (SAE) is defined as any untoward occurrence that:

- Results in death
- Is life-threatening*
- Requires hospitalisation, or prolongation of existing in-patients' hospitalisation.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

* Life-threatening, in the definition of an SAE, 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 is serious in other situations. Important adverse events 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.

3. Objectives

To describe the process which ensures that systems are in place for the recording, managing, and reporting of adverse events (AEs) in Clinical Research Studies in line with ICH GCP E6 / SI 2004/1041

4. Scope

This SOP applies to all research studies **other than** CTIMPs / Medical Device Trials sponsored by NNUH and UEA. With prior agreement of the sponsor, the process may be modified to meet the needs of individual studies.

5. Purpose

It is essential that all adverse events which occur during a study are recorded and reported appropriately, to ensure that patient safety is maintained.

6. Rules

Failure to Report

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

Reporting Timelines

- Adverse events are reportable from the time of participant study enrolment unless study specific exclusions are detailed in the protocol.

Unblinding (blinded studies)

- Systems for SAE reporting must, as far as possible, maintain blinding of individual clinicians and of local trial staff involved in the day-to-day running of the study.
- It is important that the details of the unblinding process are included in the study protocol. However participant safety should be the priority.
- The Sponsor may require the participant treatment to be unblinded.

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 NNUH sponsored study, NNUH may delegate the safety reporting responsibilities to the NCTU. This decision will be documented in the protocol and sponsor agreement.
- When safety reporting is managed by the NCTU for NNUH sponsored studies copies of SAEs need to be provided to the R&D office (rdsae@nnuh.nhs.uk) to ensure review by the Joint Research Governance Committee.

7. Study Protocol Content

	• The protocol should document expected disease-related and treatment related Adverse Events which will **not** then need to be reported as SAEs
	• A detailed explanation of SAE reporting procedures must be included in the protocol (**SOP 320 Developing a Research Protocol**)
	• The CI/PI can decide on the scope of recording and reporting adverse events, whether expected or not. It may be decided that all, or only some, non-serious AEs are to be recorded, depending on how critical they are to evaluation of the safety of the study. This decision and justification must be clearly documented in the protocol.
	• It must be documented in the protocol that the CI must notify the Sponsor of an SAE within 24hrs of the CI becoming aware of the event.
	• Where the Sponsor or Funder deems it is necessary an Independent Data Monitoring Committee (IDMC) shall be appointed to review safety data regularly throughout the study and when required, recommend to the Sponsor whether to continue, modify or terminate the study (this procedure must be defined in the protocol).

8. Event Evaluation Procedure

The PI holds responsibility for the initial assessment and reporting of an event to the CI. Each AE must be evaluated as follows:

For Intensity
• **Mild**: an event easily tolerated by the patient, 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

For Causality
Adverse reactions should be assessed for relationship to the intervention using the definitions below: • **Unrelated -** there is no evidence of any relationship to the intervention • **Unlikely -** there is little evidence to suggest there is a relationship and there is another reasonable explanation for the event • **Possible -** there is some evidence to suggest a relationship, however the influence of other factors may have contributed to the event • **Probable** - there is evidence to suggest a relationship and the influence of other factors is unlikely • **Definitely -** there is clear evidence to suggest a relationship and other possible contributing factors can be ruled out • **Not assessable -** there is insufficient or incomplete evidence to make a clinical judgement of the relationship

For Expectedness
• **Criteria for expectedness must** be documented in the Protocol - see section 7.

9. Recording & Reporting Procedure

Once the CI / PI has evaluated the AE in terms of intensity, causality and expectedness, the following guidelines should be followed:

As with all recording and reporting, subject confidentiality and adherence to the General Data Protection Regulation 2018 (GDPR) must be maintained on all reports.

9.1 AE Recording Procedure

	• Document on the relevant case report forms (CRFs) and / or AE log, and participant's hospital notes.
	• Record of AE must be available for Sponsor review (e.g. during audit or Sponsor Oversight Visits)

9.2 SAE Recording and Reporting Procedure

- Every SAE must be assessed for relatedness to the study and expectedness.

- A SAE form or agreed alternative is completed by the investigator for all AEs considered to be serious.
- The most current SAE reporting form is available on the NNUH website (**SOP 206 Appendix 1**)
- The role of safety reporting may be delegated to a member of the research team (and this must be recorded on the study delegation log).
- The completed SAE form must be signed by the investigator.

- The SAE form must contain records of the event with the PI's assessment of causality and expectedness
- The SAE form is to be kept in the Investigator Site File.
- A copy of the SAE form must be sent to the CI and the Sponsor.
- The event must be followed up to a satisfactory resolution.

- **Any SAE assessed as related and unexpected must be reported to the CI and the Sponsor within 24 hours of being made aware of the event**

- Where not all information is available, the initial report must contain the following as a minimum: Identifiable Event, Participant ID & Reporter
- This must be followed with a detailed follow-up report

- An entry of the event must be made in the study SAE log for the site.
- The record of the SAE must be available for Sponsor review (e.g. during audit or Sponsor Oversight Visits)

<u>Completed SAE forms received by CI from site PIs</u>

- Must be re-assessed by the CI for relationship to the study procedure
- The CI will decide if they agree with the PI's classification or whether the event should be upgraded
- The CI must not down-grade an event
- An entry of the details of the event must be made in the main study SAE Log

9.3 SAE Reporting to REC

- **The CI must notify any SAE <u>that are assessed as related to the study and are unexpected</u> to the REC within 15 days of the CI becoming aware of it**
- **This will be done using the "Non-CTIMP safety report to REC form" available on HRA website.**

- The CI will report all logged events to the Sponsor or delegate as agreed within the standard terms and conditions for conducting research at the NNUH, which are signed by the CI as part of study set up.

9.4 SAE Follow up and Further Reporting

- All SAEs must be followed up by the CI/PI until satisfactory resolution, and this should be recorded as a Follow Up report on the SAE form, and on the SAE log
- At each stage of follow up the CI/PI should sign and date the form
- In single site or multi-site studies, the CI should send a copy to the Sponsor

<u>Multi-Centre trials</u>

- CI must inform all PIs of an SAE as soon as possible - this does not have to be within the 15-day deadline.
- All PIs must be sent a summary of SAEs approximately every 3 months. This timeframe may vary between trials depending on the rates of recruitment and/or SAEs.
- When safety reporting for NNUH sponsored studies is managed by NCTU, copies of SAEs need to be provided to the R&D office (<u>rdsae@nnuh.nhs.uk) to ensure review by Joint Research Governance Committee.</u>
- If the study has a Data Monitoring Committee, they must ensure that they regularly review SAEs, looking for possible trends. The review sessions must be minuted as having taken place, with a note of the attendees and the SAEs that have been reviewed.

10. Contact Information

NNUH R&D

- Send an email and attach a copy of the SAE form to: rdsae@nnuh.nhs.uk
- Include the R & D study reference numbers or IRAS numbers
- For documents that require the CI's signature, if an electronic copy of the signed document is not available for email, please follow up the email by sending a signed copy of the document to rdsae@nnuh.nhs.uk

UEA Research and Innovation Services (RIN)

- Send an email and attach a copy of the SAE form to: researchsponsor@uea.ac.uk
- Include the study reference number for externally funded studies

11. References and Related Documents

References
ICH GCP E6 / SI 2004/1031
General Data Protection Regulation 2018 (GDPR)

SOP No.	**SOP Title**
SOP 205	Adverse Events: Identifying, Recording and Reporting for CTIMPs Sponsored by the NNUH
SOP 206 App 1	NON CTIMP SAE Form
SOP 207	Adverse Events: Identifying, Recording and Reporting Adverse Events for Device Trials
SOP 230	Urgent Safety Measures
SOP 320	Developing a Research Protocol

12. Approval

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13. Reason for new version and Training Implication

This SOP replaces the previous version number v2

Changes made	
Reason	• New layout • Clarifying recording and reporting procedures • Addition of possible study suspension for failure to report • Addition of NCTU rules – use of local forms permitted • Record of AE must be available for Sponsor review • SAE to be kept in ISF • Significant amendment of REC recording section
Training Implication	**No**
Actions required	• None