STANDARD OPERATING PROCEDURE

SOP 206

IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR HEALTHCARE RESEARCH STUDIES THAT ARE NOT CTIMPS

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1 ABBREVIATIONS

AE	Adverse Event
ASR	Annual Safety report
CI	Chief Investigator
CRF	Case Record Form
CTU	Clinical Trials UnitDMC Data Monitoring Committee
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PI	Principal Investigator
REC	Research Ethics Committee
R&D	Research & Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group.
TSC	Trial Steering Committee.
UEA	University of East Anglia

2 INTRODUCTION

This SOP is for the Staff members of the NNUH Research and Development Department, Research and Enterprise Services at UEA and Research Teams at the NNUH and the UEA who are involved in healthcare research (other than those governed by the Medicines for Human Use (Clinical Trials) Regulations 2004) to ensure that systems are in place for the recording, managing and reporting of adverse events in clinical research studies other than CTIMPs.

The Chief Investigator (CI) /Principal Investigator (PI) must be aware of the Trust and UEA systems for reporting adverse events and should read and agree to adhere to this SOP to comply with the conditions of approval for studies sponsored in accordance with the Joint Research Governance Policy between NNUH and UEA.

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Adverse events affecting Trust patients must continue to be reported into the Trust's clinical risk systems in addition to those identified as a requirement through Research Governance and other regulatory frameworks as stated in this SOP.

The CI/PI must ensure at the start of the study that out of hours procedures are in place in the event that a study participant needs to make contact. The CI/PI should test the emergency contact arrangements and document in the Trial Master File that such a test has taken place. As part of the Trust's monitoring arrangements, regular testing of the emergency contact information will take place.

The Research Governance Framework for Health and Social Care requires all healthcare research to have a sponsor legally responsible for the conduct and monitoring of the study. The NNUH Research & Development Office will be responsible for monitoring all healthcare

research for which the Trust or University acts as Sponsor unless there is an explicit monitoring arrangement to the contrary.

It is essential that all adverse events which occur in patients or healthy volunteers during the course of their involvement in a research study are appropriately recorded and reported in order to ensure the continuing safety of study participants.
The Department of Health's Research Governance Framework for Health and Social Care and the National Research Ethics Service set out specific requirements for the managing of adverse events (AE). Of particular importance is the assessment of any event for *causality* and *expectedness*.

3 SCOPE

This SOP applies to all healthcare research sponsored by NNUH or UEA which falls within the scope of the Research Governance Framework (2nd edition 2005). Where additional legislation applies, for example the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amendments) or the Medical Devices Regulations 2002 SOP 205 must be followed. External sponsors may require use of their own SOPs and this will be specified in site agreements. It is the responsibility of the local PI to ensure that study specific SOPs can be operated without conflict to this SOP and in accordance with all organisational polices related to research.

4 DEFINITIONS

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

- results in death
- is life-threatening
- requires hospitalisation, or prolongation of existing inpatients' hospitalisation.
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is otherwise considered medically significant by the investigator
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Comment: 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.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious”, which is based on participant/event outcome or action criteria.

5 RESPONSIBILITY

There are a number of responsibilities when managing adverse events. A list of responsibilities for both the Investigator and the Sponsor are included as appendix 1 and 2 respectively.

The Chief Investigator (CI) on behalf of the Sponsor has overall responsibility for the conduct of the study. In a multi-site study, the CI has co-ordinating responsibility for reporting adverse events to the Medicines and Healthcare products Regulatory Agency (MHRA) and to the relevant Research Ethics Committee (REC).

The Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person. The PI is responsible for informing the CI, or the organising research team, of all adverse events that occur at their site following the guidelines below.

The Joint Research Governance Committee undertakes the Research Governance functions for healthcare research involving the NNUH and UEA according to its Terms of Reference.

The Clinical Trials Unit (CTU) may be formally delegated Sponsor responsibilities recorded in the Delegation of Sponsor Responsibilities form.

6 PROCEDURES

6.1 Study Planning

The protocol should include expected disease-related Adverse Events, which will not then need to be reported as SAEs. Treatment-related Adverse Events should also be described where these are expected. They may be recorded as secondary end points. A detailed explanation of SAE reporting procedures should also be included in the protocol.

A generic SAE reporting form is available in Appendix 1

6.1.1 Which AE to Record?

The CI can decide how to record and report adverse events, whether expected or not, in accordance with the protocol. Adverse events are usually described on case report forms (CRFs), unless they are classified as serious, in which case, these should be reported on the

generic SAE form (see Appendix 1 for an example). It should be clearly stated in the study protocol (and the local SOP if applicable) what will be recorded and how the reporting is to be managed. 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.

6.1.2 Which SAE to Report?
For each study, the Sponsor should agree with the CI the timeframe during which SAEs must be notified. It should state in the protocol which SAEs can be defined as disease-related and therefore not subject to expedited reporting. The procedures for managing and reporting SAEs must be clearly defined in the protocol.

Where the Sponsor or Funder feel it is necessary an Independent Data Monitoring Committee (IDMC) should be appointed in order to review safety data regularly throughout the study and when necessary, recommend to the Sponsor whether to continue, modify or terminate the study. Again, this procedure must be defined in the protocol. As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (1998) must be maintained on all reports.

6.2 During the Study

Each AE must be evaluated according to the definitions in Section 4 for **seriousness, causality** (also see 6.2.1)**, and expectedness**. The responsibility for this evaluation can be shared between the CI and PIs and this must be stated in the delegation of responsibilities between the Sponsor, the CI, the PI and his Trust. 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 protocol **(**and the local SOP if applicable) who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. This SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.

The flowchart in Appendix 2 is designed to enable Investigators/research personnel to assess AEs and SAEs should they occur during the study.
If an AE occurs that that is likely to affect safety of the subjects the CI must take appropriate **urgent safety measures** to protect the participants against immediate hazard. (see SOP 230)

6.2.1 Causality
Adverse reactions should be assessed for causality using the definitions below.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probable There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely There is clear evidence to suggest a causal 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 causal relationship.

6.3 Reporting Guidelines

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

6.3.1 AEs

AEs that are not considered serious should be included on the relevant case report forms (CRFs). The completed form should be filed along with the other CRFs for the study and a copy provided to the Sponsor as agreed. Frequency will be decided by the Sponsor based on a risk assessment of the study.

6.3.2 SAEs

6.3.2.1 Procedure to be followed by Study CI in single site studies

a) An event is identified by the CI and assessed for seriousness.

b) All non-serious AEs will be recorded in the participant's CRF.

c) An SAE Form (Appendix 1) is completed by CI for all AEs considered to be serious. This role may be delegated to a member of the research team (and this should be recorded on the study delegation log). However, the completed form must be signed by the CI.

d) The completed SAE Form must contain records of the event with the CI's assessment of causality and expectedness.
e) An entry of the details of the event must be made in the study SAE log. This log should be available to the Monitor for review during monitoring visits. Keep the completed SAE form in the Trial Master File with the SAE log and ensure that the event is followed up to satisfactory resolution.

f) An SAE occurring to a research participant must be notified by the CI to the Sponsor (see 6.5) within 24 hours of the CI becoming aware of the event. This must be followed within 48hrs of becoming aware of the event by a detailed, written report.

g) An SAE occurring to a research participant must be notified by the CI to the REC where in the opinion of the CI it was possibly, probably or definitely related, within 15 days of the CI becoming aware of it.

h) The CI must in addition ensure that all local Trust safety policy rules are followed.

j) The CI will report all logged events to the REC annually as a Safety Report, on the anniversary of the favourable opinion.
The CI will report all logged events to the Trust as required in the letter of permission.

g) If the study has a Trial Management Group, they must ensure that they regularly review SAEs, looking for possible trends etc. The review sessions must be minuted as having taken place, with a note of the attendees, and the SAES that have been reviewed.

6.3.2.2 Procedures for multi-centre studies.
Site reporting procedure
a) Every adverse event identified by the PI must be assessed for seriousness.

b) All non-serious AEs will be recorded in the participant's CRF.

c) An SAE Form (Appendix 1) is completed by PI for all AEs considered to be serious. This role may be delegated to a member of the research team (and this should be recorded on the study delegation log). However, the completed Form must be signed by the PI

d) The completed SAE Form must contain records of the event with the PI's assessment of causality and expectedness Keep the completed SAE form in the site Trial Master File and send a copy (scan and email, or fax) to the CI and ensure the event is followed up to satisfactory resolution. This log should be available to the Monitor for review during monitoring visits.

e) The PI must report the event to the CI within 24 hours of being made aware of the event. Where not all information is available while the SAE Form is being completed, the initial report must contain the following as a minimum:
- Identifiable Event
- Identifiable Patient
- Identifiable Reporter.

This must be followed within 48hrs of being made aware of the event by a detailed, written report.

f) The PI must in addition ensure that all local Trust safety policy rules are followed.

g) An entry of the event must be made in the study SAE log for the site.

h) The PI will report all logged events to the Trust as required in the letter of permission.

Chief Investigator and Trial Management Group procedure

a) Completed SAE Forms from sites are re-assessed by the CI for relationship to the study procedure. The CI will decide if he/she agrees with the PI on the classification or whether the status of the event should be upgraded. The CI may not downgrade an event.

b) An entry of the details of the event must be made in the main study SAE log.

c) An SAE occurring to a research participant must be notified by the CI to the Sponsor (see 6.5) within 24 hours of the CI becoming aware of the event. This must be followed within 48hrs of becoming aware of the event by a detailed, written report.

d) An SAE occurring to a research participant must be notified by the CI to the main REC where it was possibly, probably or definitely related, within 15 days of the CI becoming aware of it.

e) The CI will report all logged events to the main REC annually as a Safety Report, on the anniversary of the favourable opinion.
The CI will report all logged events to the lead Trust as required in the letter of permission.

d) If the study has a TMG, they must ensure that they regularly review SAEs, looking for possible trends etc. The review sessions must be minuted as having taken place, attendance and the SAEs that have been reviewed.

6.3.3.1 Unblinding

Systems for SAE reporting should, as far as possible, maintain blinding of individual clinicians and of local trial staff involved in the day-to-day running of the trial. It is important that the details of the unblinding process are included in the study protocol.

The Sponsor may require the participant treatment to be unblinded.

6.3.3.2 Reporting to PIs involved in Study

For multi-centre trials all PIs within the trial concerned should also be informed of the SAE, as soon as possible, although this does not have to be within the 15-day deadline. All PIs should

also 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.

6.4 Follow up and further reporting of SAEs

All SAEs must be followed up by the PI/CI 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 PI/CI should sign and date the form.

The PI in a multi-site study should send a copy of the revised SAE form to the CI.
In single site or multi site studies, the CI should send a copy (scan and email, or fax) to the Sponsor (see 6.5).

6.5

What safety information must be sent to the Sponsor

- Details of the SAE recorded on the appropriate form (Appendix 1)
- Follow up information on each SAE
- Quarterly Line-listing of all SAEs from the study or as decided following risk assessment.
- Copy of all safety reports sent to the REC for a UEA or Trust-sponsored Study.

How to send information to NNUH R&D
Send an **email** and attach a **copy** of the document to: rdoffice@nnuh.nhs.uk. Please include R&D study references wherever possible.

For documents that require the CI's signature (e.g. annual safety reports, SAE form), 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 by **Fax** to: **01603 289800.** Please mark the fax cover for the attention of Clare Dawdry, Research Governance Administrator.

How to send information to UEA Research and Enterprise Services (REN)

Send an **email** and attach a **scanned copy** of the document to researchsponsor@uea.ac.uk
Please include the study R reference for externally funded studies.

6.6 Urgent Safety Measures

Urgent Safety Measures are covered in SOP 230

7. REFERENCES

a) Detailed guidance on the collection, verification and presentation of adverse

b) National Research Ethics Service guidance on safety reporting:
http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports/
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-ctimps/

http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf

c) Norfolk and Norwich University Hospitals NHS Foundation Trust and University of East Anglia Joint Research Governance Committee Terms of Reference, Membership and Standing Orders 01/08/2012.

8. RELATED DOCUMENTS

SOP 230 Urgent Safety Matters

SOP 815 Data Management: Locking and Unlocking Trial Databases

9. LIST OF APPENDICES

Appendix 1 SAE Report Form

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Appendix 1: SAE Report form

Note: this form is available to download separately from the NNUH R&D website.

SOP Change Control Form

SOP Change Control Form			
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Version No	**Page No**	**Effective date**	***Section Change details***

REVISION SHEET

REVISION HISTORY:		
Version No	Change Date	Reason for Change

	NAME *(PRINT)*	SIGNATURE	DATE *(DD MMM YYYY)*
REVIEWED BY ROLE			
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