University of Hertfordshire

ADVERSE EVENT REPORTING

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for
Identifying, Recording and Reporting Adverse Events/Serious Adverse Events in Clinical Trials

SOP Number: gSOP-02-02	**Effective Date:** 28th July 2022
Version Number: 2	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire (UH) standard operating procedure (SOP).

It provides guidance on the responsibilities delegated to the Chief Investigator (CI) or delegated individual (DI) by the Sponsor regarding adverse event reporting.

This document sets out the procedures to be followed by all University of Hertfordshire (UH) staff who are involved in the identifying, recording and reporting adverse events/serious adverse events in research projects sponsored/co-sponsored by UH and/or adopted by the CTSN. Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

If a study is adopted by the CTSN, the Sponsor may delegate some or all responsibilities to the CTSN. These will be documented in the delegation of responsibilities document.

2.0 PURPOSE

- To outline responsibilities for assessment of seriousness, causality, severity and expectedness of safety events by the Sponsor and investigator.
- To outline procedures for Adverse Event (AE)/Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR) recording and reporting requirements for UH sponsored/co-sponsored clinical trials.
- To outline the Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting process to the Sponsor, the Medicines and Healthcare products Regulatory Agency (MHRA), ethics and participating sites (for multicentre trials).
- To outline Development Safety Update Report (DSUR) submission.
- To outline details of safety event trend analysis and monitoring by Sponsor and/or investigator.

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including, but not limited to: Chief Investigators (CI), Principal Investigators (PI), Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers and Students.

4.0 RESPONSIBILITIES

For UH sponsored drug trials, the responsibility for pharmacovigilance is delegated to the CI. The CI should ensure the pharmacovigilance responsibilities are delegated to appropriately trained and qualified individuals and is recorded in a delegation log (gSOP-06).

The CI shall also ensure that all study personnel involved in conducting sponsored trials attend SOP training sessions provided by the CTSN and evidence of this is maintained with the study personnel training files (gSOP-07).

5.0 PROCEDURE

5.1 Recording and Reporting Adverse Events (AEs) and Adverse Reactions (ARs)

5.1.1 All AEs/ARs should be recorded in the source data (medical records, unless the protocol states particular AEs/ARs are exempt from recording or reporting).

5.1.2 For Clinical Trials of Investigational Medicinal Products (CTIMPs) AEs/ARs should be reviewed by a clinician.

5.1.3 The severity of AEs and ARs should also be graded according to the criteria defined in the protocol.

5.1.4 For multicentre trials, the CI/Delegated Individual (DI) may not always agree on the grading of an event. Please ensure that the highest grading is used for reporting purposes.

5.1.5 Events considered serious, should follow procedures outlined in 5.2.

5.2 Recording and Reporting Serious Adverse Events

5.2.1 A SAE or SAR must be recorded and reported according to the protocol.

A SAE/SAR is any adverse event or adverse reaction that at any dose or stage in the research participation of a study:

- 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.

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.
Should a study participant become pregnant whilst undertaking 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 at least 6 months to verify whether a congenital anomaly or birth defect is present.

5.2.2 Any research personnel who observe an SAE is responsible for notifying the CI/DI within 24 hours of knowledge, unless the protocol states this event is exempt from immediate reporting. If this is the case, the SAE should be recorded in the participant's Case Report Form (CRF) and the relevant SAE log.

5.2.3 Seriousness Assessment

For a CTIMP seriousness must always be assessed by a medically qualified doctor.
The CI or DI should review whether the event is classed as serious, i.e., if the event results in one or more of the criteria listed above or has been identified within the protocol or reference document (e.g., Investigator's Brochure (IB) or Summary of Product Characteristics (SPC)) as an SAE.

5.2.4 The CI/DI should record the classification of the seriousness as per protocol recording requirements (e.g., CRF/SAE form).

5.2.5 Causality Assessment

For a CTIMP causality must always be assessed by a medically qualified doctor. The Sponsor may also make an independent assessment of causality.

The CI/DI should assess the causality of the event, by considering whether the event has any relationship to the administered study medication, as follows:

- Events which are Definitely, Probably or Possibly related are SARs.
- Events which are Unlikely or Unrelated are SAEs.

This assessment should be recorded as per protocol requirements.

All AEs judged by either the investigator or Sponsor as having a reasonable suspected causal relationship to an investigational Medicinal Product (IMP) qualify as ARs.
The investigator's decision should be independent of the Sponsor. In the case where the Sponsor assessment differs from that of the investigator's assessment under no circumstances should the Sponsor downgrade the investigator's assessment. If the Sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the Sponsor should be provided on the report. This disagreement should also be fully documented.

5.2.6 Expectedness Assessment

For SARs, the CI/DI should carry out the expectedness assessment using the reference information (SPC) or (IB) as stated in the protocol. If the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information for the IMP, they should be considered unexpected.

The Sponsor's representative will review the expectedness of all SARs against the Reference Safety Information (RSI).

5.2.7 Expectedness decisions must be based purely on the content of the RSI in either the IB or SPC; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease.

5.2.8 Current versions of the SPC should be printed and a hard copy kept in the Trial Master File (TMF). The Research Team should check periodically for updates to the SPC. If the SPC has not been updated since the last check, then the previous copy can be kept in the file, with a file note listing the dates of update checks.

5.2.9 IBs should either be kept in the TMF or in a central file with a file note stating the current version and its location.

5.2.10 When IBs are updated with no change to the safety information, please send a copy to the CTSN for notification.

5.2.11 When IBs are updated with a change to the safety information, this should be treated as a substantial amendment (see gSOP-09). An electronic copy of the IB should also be forwarded to the CTSN.

5.2.12 Where electronic copies are not available, a hard copy of the front sheet should be forwarded to the CTSN.

5.2.13 The CI/DI should ensure that the seriousness, causality, expectedness and severity assessments are documented according to the protocol.

5.2.14 All SAEs should be followed-up until resolution and this must be documented in the source information and/or study specific documents.

5.2.15 The SAE flow chart (appendix 2) can be used to assess SAEs and decide if the event requires further expedited reporting.

5.2.16 All SAEs should be followed up until resolution and subsequent follow-up reports submitted as per protocol requirements.

5.2.17 Events listed as expected and not requiring expedited reporting in the protocol do not need reporting but will need to be recorded according to the protocol and included in the annual line-listing (see gSOP-16).

5.3 Recording and Reporting SUSARs

5.3.1 Events identified as serious, related (or possibly/probably related) and unexpected, should be classed as Suspected Unexpected Serious Adverse Reactions (SUSARs).

5.3.2 For UH sponsored studies, the CI/DI is responsible for reporting SUSARs to the regulatory authorities and any participating sites according to the protocol and site agreements.

The Decision Tree for Adverse Event Reporting (Appendix 3) illustrates adverse event reporting definitions for CTIMPs and non-CTIMPs.

5.3.3 For CTIMPs SUSARs must be reported to:

- The Medicines and Healthcare products Regulatory Agency (MHRA): eSUSAR database.

  The CTSN will liaise with the sponsoring/co-sponsoring Trust R&D to access the eSUSAR database. SUSAR details need to be entered into this database and a copy filed in the TMF.
- The Health Research Authority (HRA): Safety Reporting Form (CTIMPs).
- The CTSN: SUSAR Reporting Form (Appendix 4).

5.3.4 For Non-CTIMPs interventional studies with a procedure SAEs that are related to the procedure and unexpected (the type of event is not listed in the protocol as an expected outcome) (Unexpected Related Serious Events- USREs) should be reported to:

- the Sponsor immediately,
- the REC using the HRA Non-CTIMP Safety Reporting Form within 15 days of the CI becoming aware of the event.

5.3.5 The timelines for SUSAR reporting purposes starts at day '0', which is the day that the Sponsor actually receives the information containing the minimum reporting criteria and not the day the Sponsor picks up and processes this information.

5.3.6 Initial reports for fatal or life-threatening SUSARs must be reported to the MHRA and the Research Ethics Committee (REC) within 7 calendar days from knowledge. Any follow-up reports must be reported and submitted within a further 8 days. The CTSN must also be notified as soon as the Research Team are aware of the SUSAR.

5.3.7 For all other SUSARs, the initial report should be submitted within 15 calendar days to the MHRA, REC and CTSN. Follow-up reports should be submitted as soon as available or as per protocol.

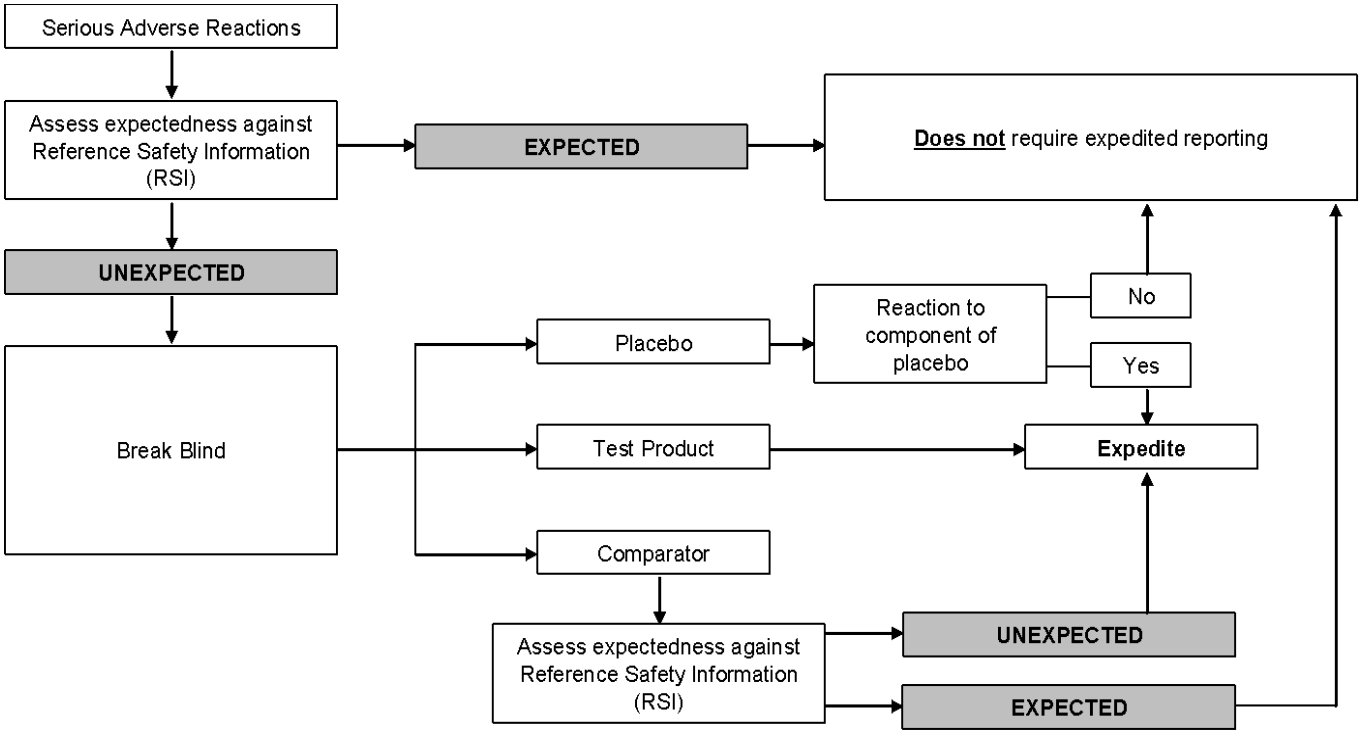
5.3.8 If there is any suspicion that a SAR is caused by a non-IMP interacting with an IMP, then this should be reported as a SUSAR.

5.3.9 As a general rule treatment codes should be broken by the Sponsor before reporting a SUSAR to the MHRA and REC. The unblinding of a single participant should only be carried out if it is important to the participant's safety. For further guidance, refer to the European Commission (EC) Guidance.

5.3.10 If the CI/DI decides not to unblind a SUSAR during the expedited reporting process, appropriate documented justification for this decision should be made. A copy of the documentation should be filed within the TMF and a copy provided to the CTSN with the SUSAR report form.

5.3.11 Completed SUSAR report forms should be sent in the first instance, as Word documents or a PDF file to the CTSN. Signed hard copies of completed SUSAR forms should also be sent to the CTSN as soon as possible.

Unblinding in relation to SUSAR Reporting:



5.3.12 Reporting Timeframes

The table below specifies the reporting timeframes during which the CI should respond to any SAEs, SARs and SUSARs.

Event	Reported by	Report to	Time
All SAEs/SARs/USREs (not identified in the protocol as expected) and SUSARs Follow-up reports	Researchers /DI	Chief Investigator	within 24 hours ASAP
All fatal/life-threatening SUSARs Follow-up reports	CI or DI	MHRA, HRA & CTSN. For co-sponsored studies to R+D office also.	within 7 days Further 8 days
All other SUSARs Follow-up reports	CI or DI	MHRA, HRA & CTSN. For co-sponsored studies to R+D office also.	within 15 days As soon as information is available
All SAEs, SARs and SUSARs per IMP for UH sponsored trials (both expected and unexpected), with a summary of any issues affecting safety of participants.	CI or DI	MHRA, HRA & CTSN. For co-sponsored studies to R+D office also.	Development Safety Update Report (gSOP-16)

5.4 Pregnancy

5.4.1 Pregnancy in itself is not regarded as an AE unless there is suspicion that the study medication may have interfered with the effectiveness of the contraceptive or that it might be harmful to the foetus.

5.4.2 Should a pregnancy occur, it should be recorded and reported in accordance with the procedures described in the protocol.

5.4.3 A pregnancy report form should be completed with the CI/PI's signature (attached as Appendix 5).

5.4.4 The mother should be followed-up during the course of the pregnancy and the baby should be followed-up for a minimum of six months after birth.

5.4.5 The mother should give consent for additional follow-up during the course of the pregnancy and once the baby is born.

5.4.6 Similarly, if the partner of a participant on a clinical trial becomes pregnant, the baby should be monitored for at least six months after birth. Consent needs to be obtained for this additional follow up.

5.4.7 Any event meeting the serious criteria (death, life-threatening, congenital abnormality, birth defects) should be reported as an SAE. This should be reported accordingly (see section 5.2).

5.5 Sponsor's Review of Safety Events

5.5.1. The CI should review all SAEs, SARs and SUSARs on an ongoing basis; however independent review by the CTSN and members of the Advisory Group on Research Governance for Clinical Studies (AGRGCS) will also take place. Annual reports will be submitted and reviewed by the CTSN.

5.5.2 A log of all safety events (SAEs/SARs/SUSARs) should be maintained in a chronological order from study commencement. The CTSN will monitor safety trends on an ongoing basis based on study risk. Compliance with safety recording and reporting timeframes will also be routinely assessed as part of the trial monitoring plan however separate pharmacovigilance audits may be performed where necessary.

5.5.3 A DSUR is required to be submitted annually to the MHRA and REC (see gSOP-16).

5.5.4 It is the responsibility of the CI to ensure a DSUR is submitted per drug on the anniversary of the Development International Birth Date (DIBD) (see gSOP-16).

5.5.5 A DSUR template is available from the CTSN and will be prepared in conjunction with the CTSN.

5.6 Urgent Safety Measures (USMs)

5.6.1 USMs are actions which need to be taken to protect participants from any immediate hazard relating to the conduct of the trial or new developments with the IMP, which may affect the safety of the participants.

5.6.2 USMs may be taken without prior notification to the MHRA. However, the CI/DI must inform the MHRA, the REC and the CTSN of the new events, the measures taken and the plan for further action as soon possible. (See gSOP-29-01 Urgent Safety Measures).

5.7 Safety Reporting Requirements for nIMPs

5.7.1 nIMPs are products that are used in accordance with the trial protocol, but which fall outside the IMP definition (e.g., medicines used to assess clinical trial end points such as a radiopharmaceutical used to measure organ function after administration of an IMP, concomitant medication given as part of standard of care for a condition that is not the indication for which the IMP is being tested).

5.7.2 SUSARs related to nIMPs, where there is a possibility of an interaction between a nIMP and IMP, must be reported as SUSARs.

5.7.3 If a SUSAR occurs which may be linked to either a nIMP or an IMP, but cannot be attributed to only one of these, the SUSAR must be reported.

5.7.4 If an AR associated with the nIMP is likely to affect the safety of the trial participants, the Sponsor must report this to the MHRA/REC as an Urgent Safety Measure, a substantial amendment or via a notification to terminate the trial, as applicable.

6.0 RELATED DOCUMENTS

- RE01 Research involving the use of human participants
- RE02 Misconduct
- gSOP-01- SOP on SOPs
- gSOP-06- TMF
- gSOP-07- Research Staff Training
- gSOP-09- Amendments
- gSOP-10- Serious Breaches (Sponsored/Co-sponsored)
- gSOP-16- DSURs (Sponsored)
- EC Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3) (2011/C 172/01)
- Detailed guidance on the request to the competent authorities of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end-of-trial (CT-1) (2010/C 82/01)

7.0 APPENDICES

- Appendix 1 - Definitions
- Appendix 2 - SAE Reporting Flowchart
- Appendix 3 - Decision Tree for Adverse Event Reporting

8.0 VERSION HISTORY

Revision History		
Version Number	**Effective Date**	**Reason for Change**
02	28th July 2022	Regular review and new separate SOP on USMs.

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date 16th June 2022**

Vice Chancellor (Research & Enterprise) Approval

Signature  **Date 16 June 2022**

Professor J M Senior

10.0 AGREEMENT

I have read and understood the contents and requirements of this SOP (gSOP-02-01) and accept to follow by UH policies implementing it.

Recipient

Signature:... .... Date:.....

Name & Position:..... ... ...

Please retain copy of the signed form for your reference in your training file

Appendix 1: Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Chief Investigator (CI)

An authorised healthcare professional who takes primary responsibility for the conduct of the trial. For UH sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of investigational Medicinal Product (CTIMP)

A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Delegated Individual (DI)

An individual delegated by the PI to carry out their task(s).

Pharmacovigilance: The regulations outline procedures for the recording and reporting of safety events (adverse events or suspected unexpected serious adverse reactions) arising from clinical trials

Principal Investigator (PI)

Authorised health professional (doctor, dentist, registered nurse, pharmacist) responsible for the conduct of the trial at the site.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any untoward medical occurrence or effect that at any dose that 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

* "life-threatening" refers to an event in which the patient 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.

Sponsor's Representative

The Director/ Assistant Director of R&D will appoint an appropriate staff member to act as the Sponsor's Representative.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
All suspected adverse reactions related to an investigational medicinal product (IMP) that is both unexpected and serious.

Unexpected Adverse Reaction
An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g., investigator's brochure (1B) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

Unexpected SAE/SAR
An adverse event that meets the definition of serious and is not listed in the protocol, 1B, SmPC or the most recent informed consent document for the study (list of unexpected SAE will be trial specific).

CTSN Safety Contact details
Email: ctsnsafety@herts.ac.uk

Appendix 2: SAE reporting flowchart

If an Adverse Event occurs during a clinical trial, what do I do next?

Was the event serious?

An Adverse Event is considered serious if the event:

- resulted in death
- is life-threatening
- required hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- is considered medically significant by the PI/delegate

Non IMP Study — **Yes**

1. Complete the SAE reporting form for this **Serious Adverse Event (SAE)** (from the UH CTSN) with as much detail as possible, using the term dictionary as specified in the study protocol
2. Fax or email a scanned copy of this form to the CTSN **as soon as possible but at least within 24 hours**
3. Follow up the event and report any additional information to the CTSN
4. File original SAE and follow-up information in the investigator site file
5. All SAEs should also be recorded as a corresponding AE on the relevant study eCRF

No

1. Record the **Adverse Event (AE)** on the relevant eCRF within the trial specific database, the source documents, i.e. medical records, as stated in the protocol.
2. Follow up the adverse event until resolved (if applicable)

IMP Study Yes

Is the event likely to be a reaction to the investigational medicinal product (IMP)?
Defined as events judged to have a reasonable expected causal relationship to an IMP i.e. those described as having a causal relationship this is "definitely", "probably" or "possibly" linked to the IMP.

No

1. This is a **Serious Adverse Event (SAE)**. Complete the SAE reporting form from the UH CTSN with as much detail as possible, using the term dictionary as specified in the study protocol
2. Fax or email a scanned copy of this form to the CTSN **as soon as possible but at least within 24 hours**
3. Follow up the event and report any additional information to the CTSN
4. File original SAE and follow-up information in the investigator site file
5. All SAEs should also be recorded as a corresponding AE on the relevant study eCRF

Yes

Is the Serious Adverse Reaction expected?
Reactions are considered **un**expected if they add significant information on the specificity or severity of an expected adverse reaction. Expected reactions are listed in the approved RSI found either in the Investigators Brochure (IB), Summary of Product Characteristics (SmPC) as stated in the Protocol.

No

This event is a SUSAR (Suspected Unexpected Serious Adverse Reaction)

1. Complete the SUSAR reporting form (from the UH CTSN) with as much detail as possible, using the term dictionary as specified in the study protocol.
2. Fax or email a scanned copy this form to the CTSN **as soon as possible but at least within 24 hours**
3. Follow up the event and report any additional information to the CTSN at the latest **6 or 12 days** after the initial event*
4. File original SUSAR reports and follow-up information in the investigator site file
5. All SUSARs should also be recorded as a corresponding AE on the relevant study eCRF

***The Sponsor has a legal requirement to report SUSARs to the MHRA (and the Ethics Committee) within 7 days if life-threatening/death, and within 15 days for all other SUSARs**. CTSN will undertake these duties on behalf of the Sponsor.

Yes

1. This is a **Serious Adverse Reaction** (SAR). Complete the SAE reporting form (from the UH CTSN) with as much detail as possible, using the term dictionary as specified in the study protocol
2. Fax or email a scanned copy of this form to the CTSN **as soon as possible but at least within 24 hours**
3. Follow up the event and report any additional information to the CTSN
4. File original report form and follow-up information in the investigator site file.
5. All SARs should also be recorded as a corresponding AE on the relevant study eCRF

Appendix 3 Decision Tree for Adverse Event Reporting

Introduction to Good Clinical Practice

NHS National Institute for Health Research

Decision Tree for Adverse Event Reporting