York and Scarborough Teaching Hospitals NHS Foundation Trust R&D Unit
Standard operating Procedure
R&D/S05

Research Related Adverse Event Reporting Procedure for Trust Sponsored Studies (Including reporting a pregnancy)

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.research.yorkhospitals.nhs.uk/sops-and-guidance-/ and/or Q-Pulse

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This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date implemented	Reviewers	Details of significant changes
1.0	17th August 2005		
2.0	22nd May 2008		Updated to include signature at bottom of forms. Front page statement about Alliance SOPs. Page numbers reformatted.
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4.0	1st July 2010		Format of 'date implemented' changed. eSUSAR reporting incorporated. Clarification as to who should use this SOP.
5.0	22nd April 2013		Scheduled update. Minor clarifications to process.
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9.0	3rd January 2024	Monica Haritakis Jonathan Hawker Deborah Phillips	Change of author. Change of SOP to title. Merged with SOP R&D/S19 to document CTIMP and Non-CTIMP SAE requirements for Sponsored studies in one SOP.

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1 Introduction, Background and Purpose

The purpose of this SOP is to describe and standardise the adverse event (AE) reporting procedure that should be followed for all studies Sponsored by York and Scarborough Teaching Hospitals NHS Foundation Trust (the Trust). This SOP helps to safeguard that all systems are in place for the management of AEs for Trust Sponsored studies to ensure that during a study the participants' involvement in research is recorded and reported to ensure their continued safety.

To be compliant with GCP, Sponsors have a responsibility to record and report SAEs. The reporting requirements for each research project will differ, dependent on the nature of the study and the patient population. The individual study protocol will state clearly what events are expected to be reported and what exceptions there may be in safety reporting.

For CTIMP studies the Medicines for Human Use (Clinical Trials) Regulations specify the reporting requirements for research related adverse events. To breach these requirements constitutes a breach in criminal law. Additionally, non-CTIMP studies also have specific adverse event reporting requirements.

As well as research related adverse events, adverse incidents occur on research studies. It is important that research related adverse incidents are reported in the same way as non-research related adverse incidents (see Section 5.6).

2 Who Should Use This SOP

This SOP should be used by investigators involved in studies sponsored or co-sponsored by the Trust, or where the R&D Unit has contracted to provide pharmacovigilance services for a particular study.

This SOP does not describe the requirements for externally sponsored studies hosted by the Trust. For externally Sponsored studies SOP R&D/S19 should be followed.

3 When this SOP Should be Used

Recording and reporting of Adverse Events (AEs), including Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs), and Suspected Unexpected Serious Adverse Reactions (SUSARs) should be managed in line with the reporting procedure of the Sponsor of the research study.

Where the Trust is the Sponsor or co-sponsor, this procedure must be followed as a minimum standard.

4 Procedure(s)

4.1 Abbreviations

AI	Adverse Incident
AE	Adverse Event

AR	Adverse Reaction
CTIMP	Clinical Trial of an Investigational Medicinal Product
IMP	Investigational Medicinal Product
ISF	Investigator Site File
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

4.2 Definitions

The following definitions are taken from the Medicines for Human Use (Clinical Trials) Regulations 2004.

Adverse Event (AE)
Any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with the study treatment or procedure (e.g. abnormal laboratory findings, unfavourable symptoms or diseases) is classed as an ***adverse event (AE***). *Comment: An adverse event can therefore be any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with the use of the medicinal product/intervention, whether or not considered to be related to the medicinal product/intervention.* ***Note: the definition of adverse event given above is that used in the clinical trials regulations however, when the Trust is sponsoring a trial there may be additional requirements to collect AEs prior to administration of a medicinal product (e.g. to collect any adverse events that may occur during any screening procedures). Such a decision will made prior to the start of the trial and documented accordingly.***

Adverse Reaction (AR)
An ***adverse reaction (AR)*** is any untoward and unintended response in a subject to a product or study procedure where there is evidence or argument to suggest a causal relationship. ***Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a product or study procedure qualifies as an AR.*** Note: All adverse reactions are adverse events.

Unexpected Adverse Reaction (UAR)

An ***unexpected adverse reaction*** is an adverse reaction the nature and severity of which is not consistent with the information about the event or the medicinal product in question set out –

(a) in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC or SPC) for that product,

(b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

(c) in the study protocol (for non-CTIMP studies)

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. All unexpected adverse reactions are adverse events.

Serious Adverse Event (SAE)

An adverse event, adverse reaction, or unexpected adverse reaction is defined as ***serious*** if it:

(a) results in death,
(b) is life-threatening,
(c) requires hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity, or
(e) consists of a congenital anomaly or birth defect
(f) is otherwise considered medically significant

Comment: Life threatening in the definition of an SAE/SAR refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an SAE/SAR is serious in other situations. Important SAE/SARs 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 or the other outcomes listed in the definition above, should also be considered serious.

ALL AE/SAEs should be collected for all trial subjects <u>from the commencement of any study related procedures</u> (including screening procedures). This is the default position for all Trust sponsored studies and any deviation from this must be agreed by the Sponsor prior to the start of the study and documented accordingly.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A ***SUSAR*** is a suspected unexpected serious adverse reaction. A **suspected unexpected serious adverse reaction (SUSAR)** is an SAR which is also "unexpected", meaning that its nature and severity are not consistent with the information about the medicinal product in question set out: 1. in the case of a product with a marketing authorisation, in the summary of product characteristics for that product; 2. in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question. *Comment: All adverse events that are suspected to be related to an investigational medicinal product and that are both unexpected and serious are considered to be SUSARs.*

Investigational Medicinal Product
An ***Investigational Medicinal Product*** (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including a medicinal product which has a marketing authorisation but is, for the purposes of the trial, being used or assembled (formulated or packaged) in a way different from the approved form or being used for an unapproved indication or when used to gain further information about an approved use.

Non-Investigational Medicinal Product (NIMP)
Products that are not the object of investigation (for example drugs used as part of standard care) may be supplied to subjects participating in the study and used in accordance with the protocol. This might be, for example, medicinal products such as support/rescue medication for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. These medicinal products do not fall within the definition of investigational medicinal products (IMPs) in Directive 2001/20/EC and are called **non-investigational medicinal products** (NIMPs).

Adverse Incident (AI)
An ***adverse incident (AI)*** is any incident/accident, near miss or untoward event which had or may have had the potential to cause harm, dissatisfaction or injury to persons, loss or damage to property. This definition includes hazards, accident, ill health, dangerous occurrences and near misses**.**

5 Investigator responsibilities in the event of an AE/SAE

Delegation of Responsibilities

- For multi-site studies, the Chief Investigator (CI) has overall responsibility for Pharmacovigilance and Safety Reporting for Trust sponsored studies at all participating sites.

- Each Principal Investigator (PI) is delegated responsibilities for Pharmacovigilance and Safety Reporting for Sponsored studies at their site.
- Assessment of an adverse event is a medical decision and as such MUST be performed by a medically qualified team member. This may not be the PI if they are not medically qualified.
- If there is only one site in the study, the CI usually is also the PI.

5.1 All Adverse Events

The Investigator must ensure that the dignity, rights, safety and wellbeing of subjects are given priority at all times and must take appropriate action to ensure the safety of all staff and participants in the study. The Investigator will consider what actions, if any, are required and in what timeframe.

In the event of an *adverse event*, the investigator (or delegated member of research team) must review all documentation (e.g., hospital notes, laboratory, and diagnostic reports) relevant to the event. The investigator will make an assessment of intensity, causality, expectedness and seriousness. **Detailed guidance on making this assessment is given in section 6.**

Except where the protocol states otherwise, all *adverse events/reactions* should be recorded in detail to allow analysis at a later stage. A template for recording adverse events is provided (refer to Section 7 R&D/T02), alternatively AEs may be recorded in the case report form. It is advisable that adverse events are also recorded into the patient's medical notes where possible and that this includes the assessment of causality, severity and seriousness.

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.

The investigator should keep an ongoing log of adverse events on EDGE that must be made available to the Sponsor on request (see appendix B).

At the conclusion of the study all *adverse event/reactions*, recorded during a study must be subject to statistical analysis and that analysis and any subsequent conclusions included in the final study report.

5.2 Serious Adverse Events (SAEs)

Immediately on becoming aware of a reportable serious adverse event on a Trust Sponsored study (and within 24 hours) a member of the research team must notify the R&D Unit. Written reports should be made by completing a Research Related SAE/SUSAR Initial Report Form (R&D/F07) or study specific report form depending on the individual study. The initial report will include as much information as is available at the time and should be signed by a suitable qualified medical doctor, usually the CI, PI or delegated investigator, to confirm their review and assessment of the SAE .

This form must be emailed to the R&D Unit using yhs-tr.research.governance@nhs.net. This email address is checked every working day.

For the avoidance of doubt, the date that the initial notification is issued to the R&D Unit is day 0 of the reporting timescales.

The R&D Unit will acknowledge receipt of the SAE notification by noon of the following working day. If acknowledgement of the SAE is not received by the Investigator by this time, then it is the responsibility of the individual reporting the SAE to contact the R&D Unit immediately. For further details of what to do on receipt of a notification of SAE/SUSAR to the R&D Unit refer to the SOP R&D/S12 detailed in Section 7.

In addition the following bodies must also be notified in a timely fashion where applicable. It is strongly recommended that this be at the same time as notifying the sponsor:

- The host organisation R&D Department
- The Chief Investigator
- Any other persons or bodies specified in the protocol or clinical study agreement (e.g. Data Monitoring Committee).

The only exception is where the protocol or Investigator's Brochure identifies the event as not requiring immediate reporting. Laboratory parameters may also require reporting within the same timescales as SAEs and these should be specified in the protocol.

The investigator (or delegated person) will provide any information missing from the initial report within five working days of the initial report to the R&D Unit and the bodies specified above (where applicable).

After the initial report the investigator is required to actively follow up the subject until either (i) the SAE resolves, or (ii) the Sponsor and CI/PI agree that no further follow-up is required. This decision must be documented.

Investigators (or delegated persons) will provide follow-up information, each time new information is available, using a Research Related SAE/SUSAR Follow-up Report Form (R&D/F08) or study specific form.

For all studies the Chief Investigator will inform all Principal Investigators of relevant information about SAEs that could adversely affect the safety of subjects.

The investigator must maintain an up to date log of all SAEs on EDGE (see appendix B. This log will be reconciled with the R&D Unit's log during trial monitoring. The frequency of this reconciliation may be defined in the study monitoring plan. As a minimum, reconciliation will take place as part of the database check prior to database lock.

For SAEs that are deemed 'possibly, probably or definitely related' and 'unexpected' refer to section 5.3 below. Note: Although there is no requirement for onward expedited reporting to the Regulatory Authorities of SAEs that are not deemed to be related to the intervention *or* are expected, they must be documented in Development Safety Update Reports, Annual Progress Reports and Quarterly Progress Reports as detailed in the Reporting Requirements SOP (refer to section 7).

For non-CTIMP studies, although there is no requirement for onward expedited reporting for SAEs that are not deemed to be related to the intervention *and* unexpected, they must be documented in the Annual Progress Reports to the REC as detailed in the Reporting Requirements SOP (refer to section 7 R&D/S06).

In device studies, all serious adverse events, whether initially considered to be device related or not, involving a device under clinical investigation coming within the scope of the Medical Devices Directive and undergoing clinical investigation, should be reported immediately to the MHRA (devices) following the instructions on the MHRA website.

The Sponsor should retain a comprehensive list of all SAEs for each site in the TMF.

5.3 SUSARs

Where the SAE has been deemed by the investigator *or* Sponsor (taking advice from an independent medical expert where necessary) to be 'possibly, probably or definitely related' and 'unexpected' additional expedited onward reporting requirements exist.

For all multi-site studies, the Chief Investigator must inform all Principal Investigators of SUSARs occurring on the study. It is the responsibility of the CI to communicate all information to the PIs, in particular any information that could adversely affect the safety of subjects. This notification must be documented.

The R&D Unit will (on behalf of the Sponsor) notify the MHRA (CTIMP studies only) and ethics committee of SUSARs within the specified reporting timescales (refer to SOP in section 7 R&D/S13). However, the R&D Unit reserves the right to delegate this responsibility to the CI and this decision will be documented.

5.4 Events involving 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 and when considering patient safety ALL drugs used are of interest. All comparator drugs and placebos are therefore considered IMPs and are subject to the same local reporting requirements described in this SOP as the test drug. This is to eliminate any ambiguity with regards to the requirement to report adverse events to the Sponsor.

In blinded studies the initial expectedness assessment needs to be against both test and comparator RSIs. If the reaction is unexpected for either, then the blind should be broken and if the reaction is unexpected for the product the unblinding reveals, then the SUSAR reported appropriately. Procedures should be in place to protect the blind for the study team for those SARs unblinded by the sponsor for regulatory reporting purposes.

Non-investigational medicinal products (NIMPs) such as rescue medication or challenge agents, used in a trial may also be subject to formal reporting requirements and such details should be provided in the study protocol.

The following scenarios are examples of when an adverse reaction to a NIMP would require reporting:

- If the adverse reaction is suspected to be linked to an interaction between a NIMP and an IMP and is serious and unexpected

- 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
- 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 appropriate licensing authority.

In some circumstances trial subjects may experience an SAE which is clearly not related to the study product, but which is related to the research (such as a study procedure). Such SAEs must also be reported to the Sponsor using the SAE initial report form (R&D/F07).

5.5 Reporting a Pregnancy

The requirement to follow up a pregnancy reported in a female research subject, or in the partner of a male trial subject during the course of the study must be assessed during the risk assessment process prior to the study commencing.

For CTIMP studies the procedure to be followed in the event of a pregnancy being reported must be detailed in the protocol and approved by the Sponsor. As a minimum, the Investigator must ensure follow-up or the pregnancy and inform the Sponsor of the outcome of the pregnancy. It may be necessary to monitor the development of the newborn for an appropriate period post-delivery. Refer to Safety Reporting SOP (see Section 7).

A pregnancy should be reported to the Sponsor using R&D/F121.

5.6 Adverse 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 hosting Trust's own Adverse Incident Reporting Procedure/System (see SOP R&D/S112). An example of a research related adverse incident may be lost drugs. This is not an AE but should be reported as an AI.

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

All Adverse Incidents that are reported as occurring on research studies taking place in York and Scarborough Teaching Hospitals NHS Foundation Trust are reviewed by the R&D Unit and are assessed for trends quarterly.

6 Assessment of Adverse Events

6.1 Intensity

The assessment of intensity will be based on the investigator's clinical judgement using the following definitions:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

Comment: The term severity is often used to describe the intensity (severity) of a specific event. This is not the same as 'seriousness', which is based on patient/event outcome or action criteria.

6.2 Causality

The relationship between the drug/procedure and the occurrence of each adverse event will be assessed and categorised as below. 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 etc. will be considered. The Investigator will also consult the Investigator Brochure or other product information.

- Not related: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- Unlikely: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- *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, definitely related, the event is an **adverse reaction (AR)**.

6.3 Expectedness

Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined according to the reference safety information (RSI) as defined in the study protocol (e.g. a section of investigator brochure or marketing information).

- Expected: Reaction previously identified and described in protocol and/or reference documents e.g. Investigator Brochure, summary of product characteristics (SmPC).

- Unexpected: Reaction not previously described in the protocol or reference documents.

NB The protocol must specify the documentation that contains reference safety information for the trial. (e.g. specific section of an IB or SmPC).

6.4 Seriousness

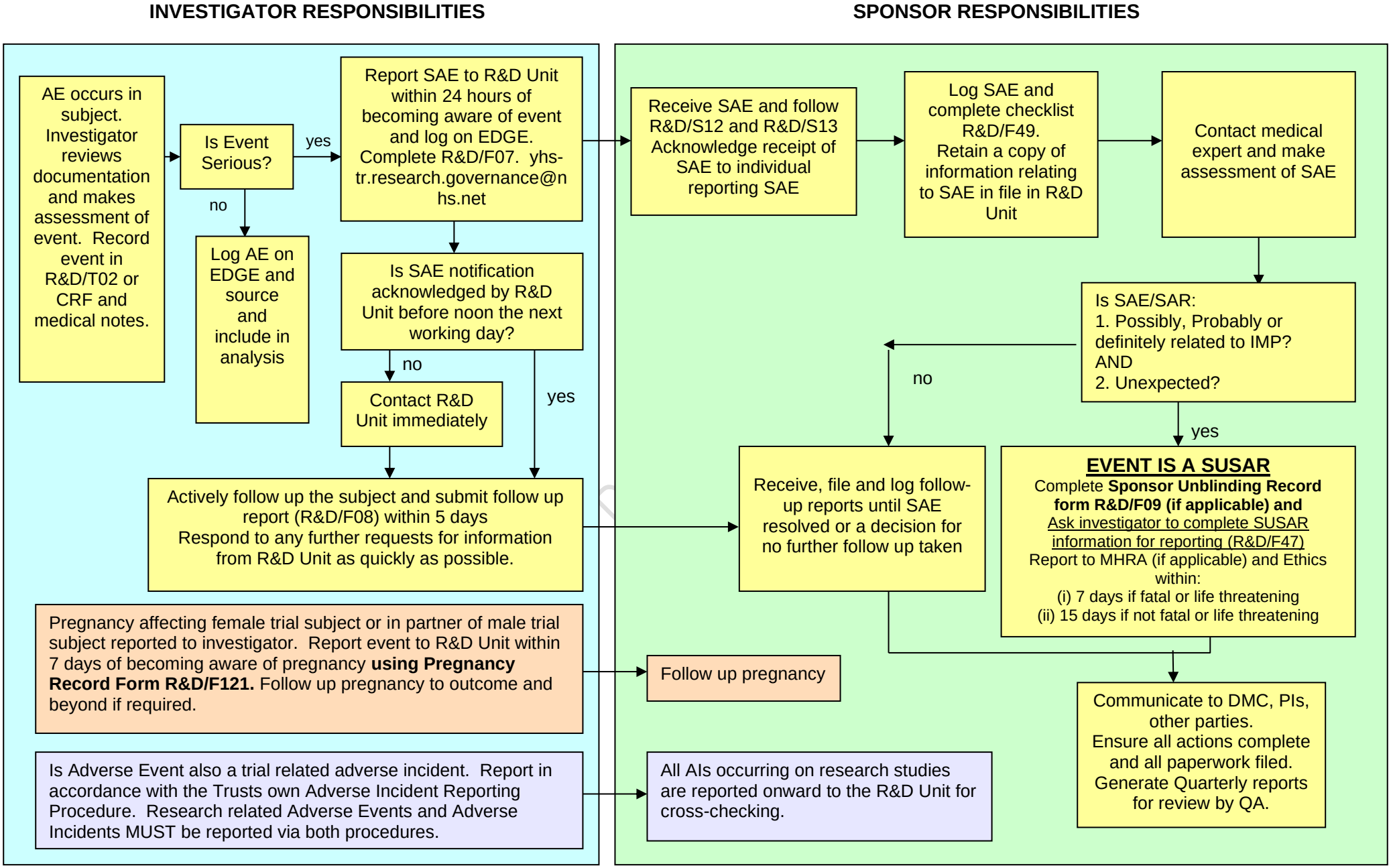
An event is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

7 Related SOPs and Documents

R&D/T02	Research Related Adverse Event (AE) Recording Template
R&D/F07	Research Related SAE/SUSAR Initial Report Form
R&D/F08	Research Related SAE/SUSAR Follow-up Report form
R&D/F09	SUSAR Unblinding Record
R&D/F46	AE/SAE Log
R&D/F47	SUSAR Data Collection Form
R&D/F121	Pregnancy Reporting Form
R&D/S112	Research Related Adverse Incident Reporting
R&D/S12	Receiving and Acknowledging Safety Notifications to the R&D Unit
R&D/S13	R&D SAE/SUSAR Handling Procedure
R&D/S19	Research Related Adverse Event Reporting for hosted studies
R&D/S06	Reporting Requirements During Studies

8 Appendix A


INVESTIGATOR RESPONSIBILITIES
SPONSOR RESPONSIBILITIES
AE occurs in subject. Investigator reviews documentation and makes assessment of event. Record event in R&D/T02 or CRF and medical notes.
Is Event Serious?
yes
no
Report SAE to R&D Unit within 24 hours of becoming aware of event and log on EDGE. Complete R&D/F07. yhs-tr.research.governance@nhs.net
Log AE on EDGE and source and include in analysis
Is SAE notification acknowledged by R&D Unit before noon the next working day?
no
yes
Contact R&D Unit immediately
Actively follow up the subject and submit follow up report (R&D/F08) within 5 days
Respond to any further requests for information from R&D Unit as quickly as possible.
Pregnancy affecting female trial subject or in partner of male trial subject reported to investigator. Report event to R&D Unit within 7 days of becoming aware of pregnancy using Pregnancy Record Form R&D/F121. Follow up pregnancy to outcome and beyond if required.
Is Adverse Event also a trial related adverse incident. Report in accordance with the Trusts own Adverse Incident Reporting Procedure. Research related Adverse Events and Adverse Incidents MUST be reported via both procedures.
Receive SAE and follow R&D/S12 and R&D/S13 Acknowledge receipt of SAE to individual reporting SAE
Log SAE and complete checklist R&D/F49. Retain a copy of information relating to SAE in file in R&D Unit
Contact medical expert and make assessment of SAE
Is SAE/SAR:
1. Possibly, Probably or definitely related to IMP?
AND
2. Unexpected?
no
yes
Receive, file and log follow-up reports until SAE resolved or a decision for no further follow up taken
EVENT IS A SUSAR
Complete Sponsor Unblinding Record form R&D/F09 (if applicable) and
Ask investigator to complete SUSAR information for reporting (R&D/F47)
Report to MHRA (if applicable) and Ethics within:
(i) 7 days if fatal or life threatening
(ii) 15 days if not fatal or life threatening
Follow up pregnancy
All AIs occurring on research studies are reported onward to the R&D Unit for cross-checking.
Communicate to DMC, PIs, other parties.
Ensure all actions complete and all paperwork filed.
Generate Quarterly reports for review by QA.

9 Appendix B

Logging Safety Reports on EDGE

1. Go to the applicable project site page (red bar) in which the patient was recruited.
2. From here navigate to the participant tab and click on the relevant participant's name.
3. To the left-hand side there will be multiple tabs starting with "Overview" and ending with "Documents", navigate to the tab labelled "Safety Reporting".
4. From here click on the 

Button to the right-hand side of the page.
5. Fill out all the relevant information when/if it is known to you. Make sure to return to the form if more information becomes available.
6. Once you have filled out the form, click **Save**.
7. Once saved you can **Edit**, **View** or **Delete** the event by clicking on the corresponding action to the right of the event.
8. A notification will then go out to all the people working on the study with clinical access.