York Foundation Trust R&D Unit
Standard operating Procedure
R&D/S19

Research Related Adverse Event Reporting Procedure for Non-CTIMP Studies

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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.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.northyorksresearch.nhs.uk/sops.html and/or Q-Pulse

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	Date:	19th July 2017

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	Details of significant changes
1.0	22nd August 2017	

Contents

1 Introduction, Background and Purpose

The purpose of this SOP is to describe and standardise the adverse event reporting procedure that should be followed for all non-CTIMPs (non-drug trials) sponsored by York Teaching Hospital NHS Foundation Trust (the Trust). This SOP helps to safeguard that all systems are in place for the management of AEs for non-CTIMPS to ensure that during the course of a study the participants' involvement in research is recorded and reported to ensure their continued safety.

For each study the research protocol should document:

- which adverse events are to be recorded and reported
- how adverse events will be identified (e.g. by enquiry at study visits, from lab and radiology reports, medical records)
- how adverse events are to be recorded, e.g. in the CRF and/or patient records
- any type of event which is an expected occurrence and therefore excluded from the reporting

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. In all cases for non-CTIMPs the individual study protocol will state clearly what events are expected to be reported and what exceptions there may be in safety reporting.

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 5.4).

2 Who Should Use This SOP

This SOP should be used by investigators involved in non-CTIMP 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 non-CTIMP studies hosted by the Trust. In these circumstances, the Sponsor reporting procedure should be followed although there is an additional requirement to notify the R&D Unit in the event of an SAE that is both unexpected and thought to be related. This notification must be made in an expedited fashion.

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
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
NIMP	Non-investigational Medicinal Product
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

4.2 Definitions

4.2.1 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).

4.2.2 Adverse Event

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***)

4.2.3 Adverse Reaction

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.

4.2.4 Unexpected Adverse Reaction

An event where there is evidence to suggest a causal relationship and when that type of event is not listed in the study protocol as expected.

4.2.5 Serious Adverse Event

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

ALL AE/SAEs should be collected for all trial subjects from the commencement of any study related procedures (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.

4.2.6 Suspected Unexpected Serious Adverse Reaction

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 the type of event is not listed n the study protocol as expected.

All adverse events that are suspected to be related to non-investigational medicinal products or study interventions and procedures and that are both unexpected and serious are considered to be SUSARs.

4.2.7 Urgent Safety Measures

All urgent safety measure must be communicated to the CI and Sponsor ***IMMEDIATELY*** and discussed with the REC by telephone. (Please refer to section 7 R&D/S68).

4.2.8 Adverse Incident

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

The specific reporting requirements for non-CTIMPs may vary depending on the nature of the study being undertaken. Details must be included in a distinct section of the study protocol. Where reporting requirements exist the following will apply.

Delegation of Responsibilities

- For multi-site studies, the Chief Investigator (CI) has overall responsibility for Pharmacovigilance and Safety Reporting for Trust sponsored non-CTIMPs at all participating sites.
- Each Principal Investigator (PI) is delegated responsibilities for Pharmacovigilance and Safety Reporting for Sponsored non-CTIMPs 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 well being 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 also advisable that adverse events are 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 in the ISF that must be made available to the Sponsor on request.

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 after becoming aware of a reportable serious adverse event (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 PI or delegated investigator, to confirm their review and assessment of the SAE .

This form must be faxed or emailed to the R&D Unit to research.governance@york.nhs.uk. This email address is checked every 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 Investigator 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 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 identifies the event as not requiring immediate reporting. 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 to 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 report 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 using R&D/F46. This log will be reconciled with the R&D Unit's log during study 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 study database lock.

For SAEs that are deemed 'possibly, probably or definitely related' and 'unexpected' refer to section 5.3 below. Note: 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 REC of SUSARs within the specified reporting timescales (refer to 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.

The requirement to report a Pregnancy in a subject during the course of the study must be assessed during the risk assessment process. For non-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.

5.4 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.

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 Foundation Trust are reviewed by the R&D Unit and are reported

to the R&D Group for consideration where the R&D Unit deems this to be appropriate.

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 intervention/procedure/product 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.

- Not related: Temporal relationship of the onset of the event, relative to administration of the intervention/procedure/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 intervention/procedure/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 intervention/procedure/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 intervention/procedure/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 intervention/procedure/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 protocol or other reference documentation.

- Expected: Reaction previously identified and described in protocol and/or reference documents
- Unexpected: Reaction not previously described in the protocol or reference documents.

NB The protocol must identify the reference documentation used.

6.4 Seriousness

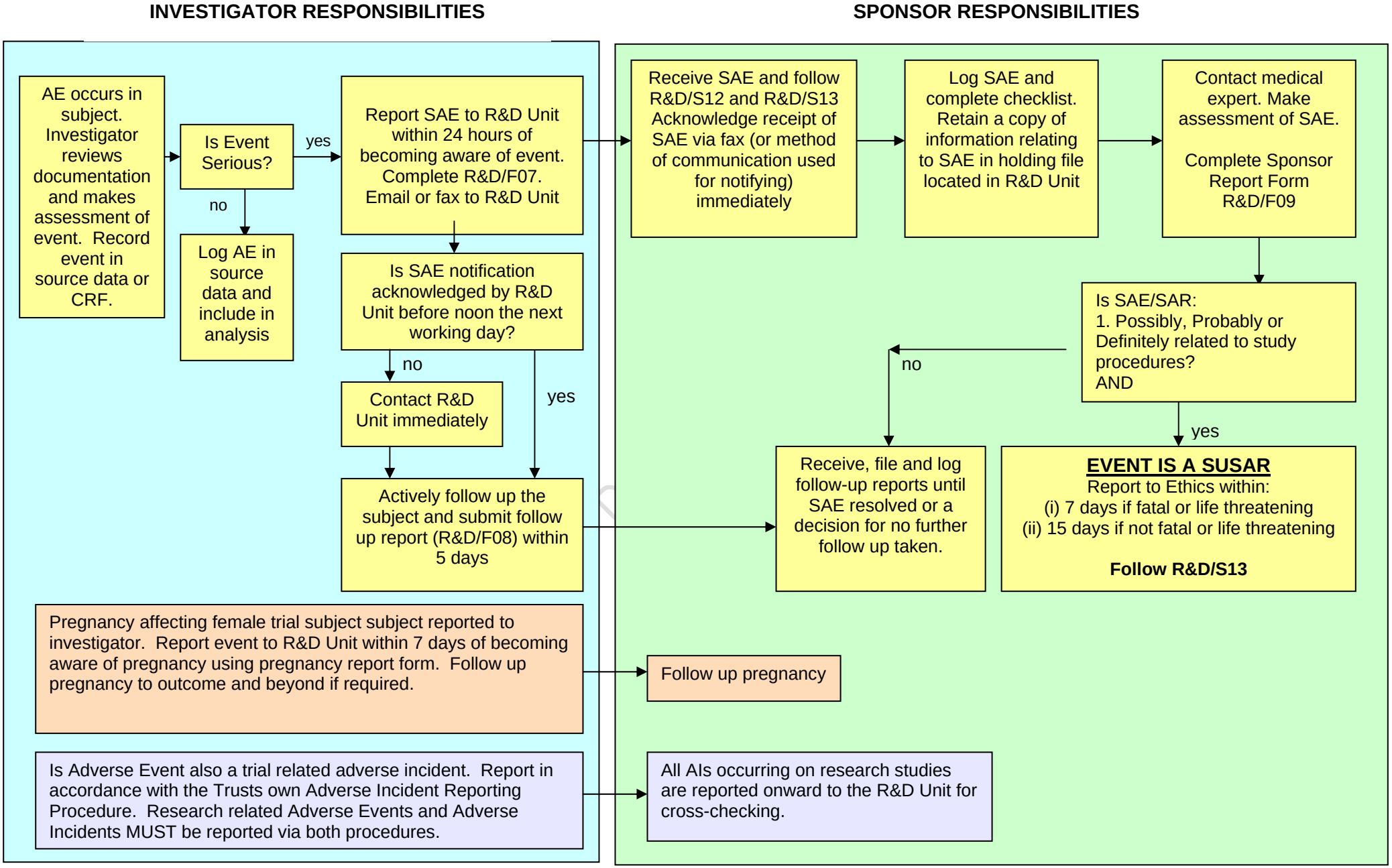
An event is considered serious if it meets one or more of the following criteria:

- 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	Research Related SAE/SUSAR Sponsor Report Form
R&D/F46	AE/SAE Log
R&D/F121	Pregnancy Notification Form
R&D/S12	Receiving and Acknowledging Safety Notifications to the R&D Unit
R&D/S13	R&D SAE/SUSAR Handling Procedure
R&D/S06	Reporting Requirements During Research Studies

8 Appendix A


INVESTIGATOR RESPONSIBILITIES
SPONSOR RESPONSIBILITIES
AE occurs in subject. Investigator reviews documentation and makes assessment of event. Record event in source data or CRF.
Is Event Serious?
yes
no
Log AE in source data and include in analysis
Report SAE to R&D Unit within 24 hours of becoming aware of event. Complete R&D/F07. Email or fax to R&D Unit
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
Pregnancy affecting female trial subject subject reported to investigator. Report event to R&D Unit within 7 days of becoming aware of pregnancy using pregnancy report form. 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 via fax (or method of communication used for notifying) immediately
Log SAE and complete checklist. Retain a copy of information relating to SAE in holding file located in R&D Unit
Contact medical expert. Make assessment of SAE.
Complete Sponsor Report Form R&D/F09
Is SAE/SAR:
1. Possibly, Probably or Definitely related to study procedures?
AND
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
Report to Ethics within:
(i) 7 days if fatal or life threatening
(ii) 15 days if not fatal or life threatening
Follow R&D/S13
Follow up pregnancy
All AIs occurring on research studies are reported onward to the R&D Unit for cross-checking.