

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

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

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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.

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1.0	17 th August 2005	
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1 Introduction, Background and Purpose

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 and these are covered in a separate SOP (refer to section 7).

The purpose of the SOP is to describe the adverse event reporting procedure that should be followed for CTIMPs sponsored by York Teaching Hospital NHS Foundation Trust (the Trust).

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 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 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 a Suspected Unexpected Serious Adverse Reaction occurring in the Trust. 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.

This SOP does not apply when reporting Adverse Events in non-CTIMP or medical device studies. For these studies refer to the relevant SOP in section 7.

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.

4.2.1 Adverse Event

An **adverse event** is 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.

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 be made prior to the start of the trial and documented accordingly.

4.2.2 Adverse Reaction

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

Comment: Any adverse event judged by either the reporting investigator or the sponsor as having reasonable causal relationship to an IMP qualifies as an AR; there is evidence or argument to suggest a causal relationship.

Note: All adverse reactions are adverse events.

4.2.3 Unexpected Adverse Reaction

An **unexpected adverse reaction** is an adverse reaction the nature and severity of which is not consistent with the information about 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.

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.

4.2.4 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.

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.

4.2.5 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 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.

4.2.6 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.

4.2.7 Non-Investigational Medicinal Product

Products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to subjects participating in the trial 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).

4.2.8 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

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), 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 in the ISF that must be made available to the Sponsor on request (see SOP R&D/F46).

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 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). 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 to the R&D Unit.** In the event that the R&D Unit fax is unresponsive please email the completed form to research.governance@york.nhs.uk. The email notification must ONLY be used in the event that the R&D Unit fax is unresponsive or where there is written confirmation from the Sponsor that SAE reports may be submitted this way. 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 detailed in Section 7.

In addition, the Chief Investigator and any other persons or bodies specified in the protocol or clinical trial agreement (e.g. Data Monitoring Committee) should also be notified in a timely fashion.

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).

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 trial monitoring at each interim monitoring visit, unless the monitoring plan specifies differently. 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 *and* unexpected, 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).

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 and ethics committee of SUSARs within the specified reporting timescales (refer to SOP in section 7). 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.

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 of 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).

Although not by definition an SAE, 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. 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 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/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 non-CTIMPS
R&D/S06	Reporting Requirements During Studies

8 Appendix A

INVESTIGATOR RESPONSIBILITIES

SPONSOR RESPONSIBILITIES

