

**Adverse Events/Adverse Reactions/Serious Adverse Reactions/  
Serious Adverse Events and Suspected Unexpected Adverse  
Events**

SOP Title	AE/AR/SAE/SAR/SUSAR
SOP No.	SOP 3
Author	Julia Farmery
Consulted Departments	Lincolnshire Clinical Trials Unit, Research and Development, Trust consultants and research staff.
Lead Manager  Sign and Print Name	Dr. Tanweer Ahmed Director of LCRF and Research and Development Manager
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**Tracked Changes to SOP 3 – Adverse Events/Serious Adverse Events and Suspected Unexpected Adverse Events**

Paragraph	Changes
1 - Purpose	<ul style="list-style-type: none"> <li>Detailed information of what the SOP is for and how staff should deal with this. It sets out the principles by AE/AR SAE/SAR/SUSARS will be recorded and methods by which they are categorised. It has detailed instructions that are to be followed that are in line with statutory law and regulations.</li> </ul>
2 - Adverse Events	<ul style="list-style-type: none"> <li>Included Medicine for Human Use Regulation at the beginning.</li> <li>Added a detailed explanation about AR, ADR.</li> <li>More detail on what determines an event as a SAE, SAR and SUSAR.</li> <li>Included Medicines for Human Use (Clinical Trials) Regulations (2004)</li> </ul>
3 - SUSAR	<ul style="list-style-type: none"> <li>Replaced definition with UK Clinical Trials Regulations with Medicines for Human Use (Clinical Trials) Regulations</li> <li>A brief explanation of what a SUSAR is.</li> <li>Replaced <u>adverse events</u> with <u>reactions</u></li> </ul>
4 - IMP	
5 - NIMP	
6 - SOP title	<ul style="list-style-type: none"> <li>SOP applies to all staff within ULHT.</li> <li>SOP defines responsibilities for trials sponsored and hosted by ULHT.</li> </ul>
7 - Relevant SOP documentation	<ul style="list-style-type: none"> <li>Added Ethics forms for SAEs/SARs and SUSARs for Sponsored Studies to the list.</li> <li>Added ULHT Serious Adverse Event/Serious Adverse Reactions Reporting Form to the list.</li> </ul>
8 - Definitions	<ul style="list-style-type: none"> <li>Included AR, ADR and SAR</li> </ul>
9 - Policy	
10- Procedure (Sponsor) Host	<ul style="list-style-type: none"> <li>A more detailed explanation of the Sponsor responsibilities.</li> <li>Added more detail to Host's responsibility about delegation.</li> </ul>
Adverse Event	<ul style="list-style-type: none"> <li>Included Medicine for Human Use</li> </ul>
11- Responsibilities of AE, AR and ADR for Sponsored and Hosted studies	<ul style="list-style-type: none"> <li>Included more detailed information on who can evaluate adverse events and time period.</li> <li>Added more on whom to inform after documenting in patient notes.</li> <li>Added statement about importance of Adverse events reports.</li> <li>Explanation on follow up to be done on SAE/SUSAR by the Investigator.</li> </ul>
12 – Responsibilities for SAE/SAR/SUSAR	<ul style="list-style-type: none"> <li>In depth explanation on what needs to be done from the time an SAE/SAR occurs up until the follow up is complete.</li> <li>Detailed explanation of what needs to be done if the SAE/SAR is a SUSAR.</li> </ul>

	<ul style="list-style-type: none"> <li>• Detailed explanation on what needs to be done if a patient or partner in a trial becomes pregnant.</li> <li>• IRI form needed for all SUSARs and where a copy of this needs to go.</li> </ul>
<b>13 – Timeline of events</b>	
<b>14 – Urgent Safety Measures</b>	<ul style="list-style-type: none"> <li>• Detailed explanation of the urgent safety measures to protect the subjects of a clinical trial against any immediate hazard and what needs to be done as soon as they are aware of the event.</li> </ul>
<b>15 - Responsibilities</b>	<ul style="list-style-type: none"> <li>• In depth explanation for the Host's responsibilities and the reporting time period in line with legislation.</li> </ul>
<b>16 – Forms</b>	<ul style="list-style-type: none"> <li>• Inserted the ULHT Serious Adverse Event Reporting Form (Version 1, July 2011)</li> <li>• Inserted NRES Safety Report Form (CTIMPs) (Version 4, April 2007))</li> <li>• Inserted NRES Safety Report Form (non-CTIMPs) Version 3, 2007</li> <li>• Insert ULHT Acknowledgement of SAE/SUSAR, )Version 2, July 2011)</li> </ul>

## **1 - Purpose**

This Standard Operating Procedure (SOP) applies to ALL Trust sponsored studies and details the requirements that the Chief Investigator, researchers team, and the Research & Governance department will handle :

- Adverse Events (AE)
- Adverse Reactions(AR)
- Unexpected Adverse Reactions (UAR)
- Serious Adverse Events (SAE)
- Serious Adverse Drug Reactions (SADR)
- Suspected Unexpected Serious Adverse Reactions (SUSAR).

It sets the principles by which they will be recorded and details the methods by which they are categorised. Moreover in this SOP it will state the Sponsors legal responsibilities in conjunction with the Chief Investigator in reporting the adverse events to the regulatory authorities.

For hosted studies this SOP will give guidance on the Trusts policy for the internal reporting of SAEs, SARs, SADR and SUSARs, in relation to the 24hr R&D notification and SUSAR IR1 reporting.

For sponsored studies, this SOP will set out detailed written instructions to follow, to achieve uniformity and pharmacovigilance safety, within the performance of the statutory law and regulations.

## **2 - Adverse Events**

The Medicines for Human Use (Clinical Trials) Regulations (2004) as amended, interpret an adverse event to be “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”.

In general an example of an AE can be any incident that happens to an individual that is different from previous; this maybe a fall or a headache, nausea or an abnormal lab finding. Moreover it is dependant of what the trial specific protocol classifies as an AE.

An adverse reaction (AR) is any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. (The Medicine for Human Use (Clinical Trials) Regulations (2004) as amended.

An Adverse Drug Reaction (ADR) is stated in the ICH Guideline E6 as, In the pre-approval clinical experience with a new medicinal product or it's new usages, particularly as the therapeutic dose(s) may not be established : all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR), or Suspected Unexpected Serious Adverse Reaction (SUSAR), means any AE, AR, SUSAR, respectively, that :-

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolonged or existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Consists of a congenital anomaly or birth defect, or
- Anything the Investigator deems to be of Clinical significance

The Medicine for Human Use (Clinical Trials) Regulations (2004) as amended; and the European Clinical Trials Directive 2001/20/EC

A SAE refers to an event where the individual subject/s was put at risk of harm at the time of the event. It is not an SAE if it has not occurred, yet might occur. A hypothetical situation is not a SAE.

## **3 - A suspected unexpected serious adverse reaction (SUSAR)**

The Medicines for Human Use (Clinical Trials) Regulations (2004) as amended state that an unexpected adverse reaction is “unexpected” if its nature and severity are not consistent with the information about the medicinal product.

(a) "In the case of a product with a marketing authorization, in the summary of the products characteristics for that product."

(b) "In the case of any other investigational medicinal product, in the investigational brochure relating to the trial in question."

Therefore, a SUSAR is a :

- (Assessment) : Assessment of event
- (Causality) : Possible related or related
- (Seriousness) : Classified as a Serious Adverse Reaction....yet it becomes a SUSAR as it is.....
- **(Expectedness) : Unexpected**

**All adverse reactions that are suspected to be related to an investigational medicine product that are both serious and unexpected are considered to be SUSAR's.**

#### **4 - Investigational Medicinal Product – IMP**

This is an active substance or placebo being tested or used in a medical trial. This could be a licensed drug which has marketing authorisation, but for purposes of the trial is being used for different means.

#### **5 - Non Investigational Medicinal Product – NIMP**

NIMPS are not the products of investigation; however they may be supplied to participants in the trial, in accordance with the protocol. Within the EU Directive 2001/20/EC a NIMP is not the tested product, placebo or active comparator. A NIMP may be a medicinal product, used as a rescue medication; for a preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject.

#### **6 - Applies to: (SOP title)**

All staff working with Clinical Trials within United Lincolnshire Hospitals NHS Trust.

This SOP defines the responsibilities held for trials we sponsor and trials we host.

#### **7 - Relevant SOP documentation :**

AE/SAE/SUSAR Flow chart

SAE R&D reporting form

Ethics forms for SAEs (6monthly) and SUSARs for Sponsored Studies.

United Lincolnshire Hospitals Serious Adverse Event Reporting Form United Lincolnshire Hospitals Trust Incident Reporting procedure. (IR1 – Datix reporting form).

## **8 - Definitions:**

AE – Adverse Event  
AR – Adverse Reaction  
ADR – Adverse Drug Reaction  
SAE – Serious Adverse Event  
SAR – Serious Adverse Reaction  
SUSAR – Suspected Unexpected Serious Adverse Event

MHRA – Medicines and Healthcare Products Regulatory Agency  
ULHT – United Lincolnshire Hospitals Trust

## **9 - Policy:**

The UK Clinical Trial Regulations No. 1031, No. 2754, No. 2759, No. 1928, No. 2984, No. 941, No. 1164.

Policy for Developing and Implementing Clinical Guidelines – United Lincolnshire Hospitals Trust- Intranet website and Trial Master File

Code of Good Research Conduct/Misconduct Policy – United Lincolnshire Hospitals Trust- Intranet website and Trial Master File

Policy for the development of Written Patient Information – United Lincolnshire Hospitals Trust- Intranet and Trial Master File

Incident Reporting Forms (IR1) Datix Incident Forms – United Lincolnshire Hospitals Trust- Intranet and Trial Master File.

Risk Management Strategy – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go Search . . .Risk management strategy

Risk Assessment Policy – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go Search. . Risk Assessment Policy

Risk Assurance Framework – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go Search. . Risk Assurance Form

Risk Assessment form – United Lincolnshire Hospitals Trust – Intranet

(<http://Intranet/applications/documents/>) then go Search. . Risk Assessment Form

Confidentiality Code of Practice for the United Lincolnshire Hospitals Trust – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go to Search. .Confidentiality also available in Trial Master File

Policy on Fraud, Corruption, Theft and other illegal acts – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go Search. .Fraud and misconduct.

Investigational Procedure – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go to Search. .Investigational Procedure. Copy is also available in the SOP template folder under R&D shared documents.

Mental Capacity Act – United Lincolnshire Hospitals Trust – Intranet (<http://Intranet/applications/documents/>) then go to Search. . Mental Capacity Act. Copy is also available in the SOP template folder under R&D shared documents.

European Commission – Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. (2006). . .Copy available-Trial Master File.

## **10 - Procedure :**

The procedure to follow will detail the responsibilities under :

**HOST:** and  
**SPONSOR:**

### **Sponsor responsibilities :**

The Chief Investigator is ultimately responsible for the reporting of any adverse events, as detailed above, to the relevant competent authorities and sponsor within the set timelines. However, Chief Investigators may delegate the day to day reporting of any events to any member of the research team, as detailed in the study delegation log. It is important to note, that the Chief Investigator does hold ultimate responsibility for this task, yet individuals will hold their own accountability under the knowledge and training they hold. This is why it is pertinent, that the delegation of duties is appropriately tasked to all members of the research team.

### **Host responsibilities :**

The Principal Investigator is ultimately responsible for the reporting of any AE/SAE/SUSAR's to the Chief Investigator and R&D, however the task maybe delegated to the research officers/nurses. Similarly, it is important that appropriate delegation takes place and is recorded on the delegation log.

## **1. Adverse Events**

- All staff are responsible for reporting AE/SAE/SUSAR's

All staff and clinicians involved with clinical trial subjects are responsible for noting adverse events, reported by the patient or their legal guardian/carer. Under Article 16 (1) and (2) of the EU Directive 2001/20/EC. Also regulated by ethics - General Medical Council Code of Conduct (2008) and the Nursing and Midwifery Council Code of Conduct (2008) also Mental Capacity Act (2005) – Best Interests/Duty of Care.

All staff have a duty under the Good Clinical Practice (GCP) guidelines and the UK Medicine for Human Use Regulations (2004) as amended and its statutory bodies to make them known to the appropriate medical staff and sponsor of the trial.

## **11 - Responsibilities for Adverse Events (AE), Adverse Reaction (AR) and Adverse Drug Reactions (ADR) for Sponsored and Hosted studies :**

- Individual adverse events should be evaluated by the Investigator or a delegated member of the team and reported to the sponsor for evaluation, if specified in the protocol, and at the appropriate time period.

- All AEs must be documented very clearly-with an explanation of the patient's definition of the event.

I.e. How, Where, When, Specific Duration, Symptoms, severity alleviating/attributing factors. A clear detailed history to be obtained.

- All documentation connected to the study is to be reviewed
- Document any change/ reduce increase in dose of study drug, etc. Any change in action taken regarding the study. Document down dates. Collaborate a concise history.
- Document any treatment/medication/therapy/intervention given for the event.
- Document the event outcome
- Document in patients notes, inform the Principal Investigator for hosted studies, or as deemed necessary the Chief Investigator for Sponsored Studies; and any other bodies specified in the protocol.
- The sponsor must retain detailed records of all adverse events reported by the investigator(s) and perform an evaluation with respect to seriousness, causality and expectedness. (Appendix 1). These reports perform a collection of safety data, which is pertinent to the safe and effective running and management of Clinical Trials.



After the initial report the investigator is required to actively follow up the subject either until:

- a) The SAE / SUSAR resolves
  - b) The sponsor and CI/PI agree that no further follow up is required.
- R&D department reserves the right to suspend or withdraw approval for a study. This may be considered if the safety of the public, staff and patients is put at risk from the trial.

Patients entered into clinical trials, must be encouraged from the outset to contact the 24hr contact person/use the emergency card if a SAE/SAR/SUSAR occurs. Or contact the research team/clinician if any AE occurs.

## **12. Responsibilities for Serious Adverse Events and Suspected Untoward Serious Adverse Events**

- As detailed above, yet with the addition of the following :.
- All serious adverse events/ reactions/ suspected unexpected serious adverse reactions must be documented as above. It is the responsibility of the Principal Investigator to classify the above and report to the sponsor, for hosted studies. The Sponsor will then also classify the event. Please note, the sponsor will not be able to down grade the event once classified, only upgrade the event. However, the sponsor is able to ask for any further details relating to that event to be supplied to aid in their evaluation of the incident.

For Sponsored studies, all serious adverse events/ reactions/ suspected unexpected serious adverse reactions must be documented as above, however ULHT require the following :

- The event to be recorded and classified under expedited reporting on ULHT SAE recording form. (Exceptions are made to this rule for on-going studies, prior to the production of this SOP).
- The event must be reported by a member of the research team to the Chief Investigator or Principal Investigator/Co-collaborator at the site and R&D office within a 24hr period. This must be documented in writing.
- R&D must notify acceptance and awareness of this SOP and ask for any further follow up or classification of the event/reaction, in-order to satisfy the expedited reporting arrangements set out in the regulations.

- R&D and the individuals involved in the SAE/SAR/SUSAR must follow up the event until resolved. R&D will stipulate the timeline and reporting information on their acceptance slip and detail any further requirements needed from the team, in-order to fulfil their sponsor responsibilities.
- In the event of a SUSAR occurring, the research team MUST inform R&D within the 24hrs period and R&D will assist in the process for gathering all data required.
- The Research Governance Manager or R&D manager for ULHT will report any SUSARs to the MHRA with cooperation from the research team, within a set time frame 7 days fatal, and 15 days, non fatal. This is a requirement as per the MHRA eSUSAR website. The above persons are registered on the MHRA eSUSAR system for electronic reporting for ULHT.
- Ethics Committees only need to be made aware of SUSARs via their expedited report form. The Research Governance Manager or R&D manager require full over site of this process if any SUSAR was to occur.
- The responsibility lies with ULHT to report whether or not the SAE/SAR is a SUSAR. If it is a SUSAR, as ULHT is the sponsor they must report this to the Medicines Healthcare Regulatory Agency and Research Ethics Committee. If fatal or life threatening, this should be done within 7 days of the event. Or 15 days, if the event was non-fatal and non-life threatening. Any further information regarding the SUSAR's, requested from the authority bodies must be reported within 8 days of request.
- ULHT Research Governance team must be made aware of any SUSARs and will be actively involved and will report in conjunction with the Chief Investigators and his teams assistance; to the relevant competent authorities.

In general for all Serious Adverse Events/Reactions; the following pertains:

- Inform the research co-ordinating body within 24hrs of the Investigators knowledge of the event. (See individual study protocols for there specific requirement if a SAE / SUSAR was to occur)
- Ensure a timeline of events is recorded, from initial reporting of the SAE / SUSAR
- All reports should be documented, a verbal report is valid as long as it is followed by appropriate documentation (Adverse Events reporting form) and a clear timeline of events displaying the process and procedures.
- Follow up reports are required to document the process of the event and additional information maybe asked for from the sponsor or R&D.

- All correspondences, emails, letters, summaries of telephone conversations and documents relating to the SAEs/SARs/SUSARs should be retained in the master site trial file with the patient's records.
- A communication log is needed
- Pregnancy in either a patient or the partner of the patient in a trial taking trial medication should always be reported to the trial centre or sponsor. (See protocol for preferred method). This must be followed up within 7 days from initial reporting. ULHT require this information to be reported on the Trust 1R1 system for internal risk management reporting. For Sponsored studies, ULHT R&D department, need to be made aware as soon as practically possible, so appropriate steps and measures can be put into place.
- It is the Chief Investigator's responsibility to inform all Principal Investigators if a SUSAR occurs. This must be documented in the Investigator Site File, signed and dated by the Principal Investigator and R&D informed.
- A AE/SAE reporting form must be completed for SAEs and SUSARs which is provided by the sponsor of the research study
- The R&D department will need to be notified of all SAE/SUSARs with 7 days if we are not the sponsors. If ULHT is acting as a sponsor – R&D to be notified within 24hrs. Best Practice is to notify R&D within 24hrs of any SAE/SUSAR, regardless of whether or not we are the sponsor.
- The R&D department can either be faxed/emailed/hand delivered the AE/SAE form reporting form (01522 543783). It will include as much information as what is available at the time.
- Where ULHT is the sponsor, or where no form has been provided, the investigator will use the ULHT SAESafety Reporting Form. (Appendix 2) Otherwise please use the forms provided within the protocol.
- The R&D department will acknowledge receipt of the AE/SAE notification, within the working week. If acknowledgement of the AE/SAE has not been forwarded by this time, it is the responsibility of the Investigator to contact the R&D department immediately.
- A document of receipt for notifying SAEs to the R&D department can be found in (Appendix 3)
- The investigator or delegated person will provide any missing information from the initial report within 5 working days of the initial report to the Sponsor and R&D department and the relevant bodies as in the protocol.
- Adverse events identified in the protocol as critical to the evaluations of safety of the study shall be reported to the sponsor in accordance with recording requirements documented in the protocol.

- All SUSARs for hosted and sponsored studies require an IR1 form completing and a copy of the form sending to the Research Governance Manager.

**All of the above decisions must be clearly documented.**

### **13 - Time line the events**

- At the conclusion of the study all AE/SAE/SUSARs that occurred during the study must be subject to statistical analysis and the analysis and subsequent conclusions included in the final study report.

### **14 - Urgent Safety Measures**

The sponsor and Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

If measures are taken to protect the subject from immediate hazard, the sponsor shall do the following :

- For a pandemic; or serious risk or potential risk to human health, the sponsor will take and make the appropriate urgent safety measures, as defined in their protocol and sponsoring body to prevent harm or suffering.
- Where ULHT are the sponsor, the Risk Manager, R&D Director, R&D Manager and Research Governance Manager, alongside the Chief Investigator and his team; and all other appropriate professionals, will meet as soon as aware of the event. An appropriate strategy will be put in place to prevent/deter any risk to human health; unless otherwise detailed in the protocol.
- When ULHT is a sponsor, as soon as an individual is aware of a risk, no later than 3 days from when the measures are taken, written notice to the licensing authority and relevant Ethics committee will be detailed; giving rise to actions taken.
- Advise would then be sought and followed up as advised and coordinated via the Trust and R&D.
- For hosted studies, ULHT will arrange a meeting, as above, and take the advice sought from the Chief Investigator, however the proportionality and risk to the patients and Trust will be assessed internally to ensure we are adhering to the Research Governance Framework (2005).

### **15. Responsibilities**

### **Hosted Studies :**

- A Principal Investigator is ultimately responsible for the study conducted at United Lincolnshire Hospitals NHS Trust. He may delegate safety reporting duties to team members, however this must be clearly described in the description of duties in the delegation log.
- All SAEs/SARs/SUSARs that occur must be reported to the sponsor within a 24 hour period, unless dictated otherwise in the individual sponsors protocol.
- All AE must be reported to the sponsor as dictated in the protocol. (If clinical recorded or specific for the particular trial).
- All SAE/SARs that occur at ULHT must be reported to the Research Governance Manager/R&D manager within a 7 day period.
- All SUSARs must be reported to the Research Governance Manager/R&D manager within 24hours.
- All SUSARs require internal IR1 reporting.
- It is the Principal Investigator's responsibility, or delegated duty; to complete a yearly R&D report, sent out by R&D, to alert R&D to the number of SAEs/SARs/SUSARs and recruitment figures/problems, as this allows R&D to comply with Research Governance Framework, as we need to proportionately audit 10% of projects on a risk based process.

### **Sponsored Studies :**

- The Chief Investigator is ultimately responsible for the expedited reporting of adverse events at United Lincolnshire Hospitals NHS Trust. However, the individual may delegate safety reporting duties to team members, however this must be clearly described in the description of duties in the delegation log. Collectively, R&D and the Chief Investigator will work together to ensure safety reports meet the standards and requirements set out as above. R&D, with the Chief Investigators or research team members assistance, will report SUSARs to the competent authorities.
- If ULHT has any contractual responsibilities with any commercial companies, this must be highlighted to the Research Governance Manager/R&D manager, to ensure the compliance with safety reporting is adhered to, as detailed in any contracts.
- All SAE/SAR/SUSARs must be reported to R&D within a 24hr period. R&D must respond within a 24hour period acknowledging receipt of the event.
- All SUSARs require internal IR1 reporting.

- All yearly Annual Progress and Annual Safety Reports need to be completed by the Chief Investigator, in collaboration with R&D, as detailed in SOP 8.
- It is the Chief Investigator's responsibility to complete a yearly R&D report; sent out by R&D, to correlate figures with R&D to the number of SAEs/SARs/SUSARs and recruitment figures/problems, as this allows R&D to comply with the Research Governance Framework, as we need to proportionately audit 10% of projects on a risk based process.
- **It is the responsibility of the ULHT, if the Trust is acting as a sponsor to ensure that all the regulatory bodies are informed if a SAE/SUSAR occurs within the set time frame.**

**24hrs initial R&D reporting, then 7 days SUSAR, 15 days non fatal SAR/SAE/SUSAR. Followed by 8 day set time limits; with requests from the MHRA for information.**

- **For our sponsored studies,**  
It is the Chief Investigator's responsibility to make a clinical decision based on expedited reporting, to classify the AE/ADR/AR/SAE/SAR/SUSAR.

#### **References and acknowledgements:**

Safety reports for CTIMPs (2011) accessed on 19/07/2011 @ <http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-ctimps/submitted-safety-reports-to-the-rec/>

Safety Reporting for all other research – REC form links. (2011) accessed on 19/07/2011 @ <http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/>

EU Clinical Trial Directive (2001/20/EC) accessed on 13/11/2009 available at [http://www.wctn.org.uk/downloads/EU\\_Directive/Directive.pdf](http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf)

Medicine Healthcare Regulatory Agency (MHRA) website. Accessed on 16.06.2011 @ <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials>

Hutchinson, D. (2010) Key Requirements affecting clinical trials in Europe. Canary Ltd : Surrey.

Hutchinson, D. (2009) The UK Clinical Trial Regulations – Indexed and Consolidated. Canary Ltd : Surrey.

United Lincolnshire Hospitals NHS Trust – Trust intranet site – Accessed on 05/11/2009.

**This SOP will be reviewed every two years, a more updated revision of the SOP will be implemented if new local, national or international regulations change. This would therefore replace the existing document. All SOP's can be located on the Research and Development's shared file and a hard copy of all SOP's are kept in the SOP Trial Master File**

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## Appendix 1

### Assessment of Adverse Events

#### Intensity

Based on Principle investigators judgements: based on the following –

- Mild – An event that does not affect the activities of daily living. It is easily tolerated; the effect is mild and does not impact on the individual.
- Moderate – Affects normal activities of daily living. Affects the ability of one to carry out tasks which they normally do. It causes discomfort and distress to the individual.
  - Severe – An event that prevents normal daily activities.

#### Causality

The relationship between the patient and the Investigational medicinal product is categorized in this section by the principle investigator. Alternative causes are considered, such as patients' past medical history, current treatment regime, and underlying diseases. The investigator is to consult the investigator's brochure for any other product information, regarding the Investigational medicinal product as a causal relationship.

- Not related – Temporal relationship with the event, relative to the administration of the product. It is not reasonable that any other product or relationship/cause can have caused/formulated this event. Must be onset related.
- Unlikely – Relationship to the onset of the event, due to administration of the product. It is likely to have another cause, which can by itself explain the occurrence of the event.
- Possibility related - to the onset of the event. Due to the administration of the product, however it is reasonable that the event could have been due to another, equally likely cause.
- Probably related – Temporal relationship of the onset of the event. It is reactive to the administration of the product, it is reasonable and realistic – the product can explain the outcome/adverse event.



- Definitely related – Relationship with the adverse event. There is no other cause reasonable to explain the event. It is more than feasible that the event occurred due to the product.

NB. Where an event is assessed as possibly related, probably related, definitely related, the event is an adverse reaction. The investigator's judgement then requires one to source whether or not an adverse reaction is serious. Report within 24hrs!

### **Expectedness**

Adverse reactions must be considered serious if :

Protocol based serious reactions list – Expected – follow rules for SAR/SAE

Protocol based unexpected serious reaction – not expected – reaction is not previously described in investigator's brochure, trial master file, or marketing information for investigational medicine product. Report to sponsor – they will grade it as SUSAR.

**This information has been adapted, with kind permission from York Hospitals NHS Foundation Trust 2009. Thank you.**

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## SERIOUS ADVERSE EVENT REPORTING FORM

When completing this form please refer to **“SOP 3 – Adverse Events/Serious Adverse Events and Suspected Unexpected Adverse Events”**

### 1. Project Identifiers: (where applicable)

NAME OF STUDY	Ethics No.
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EudraCT No.	R&D
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### 2. Project Title:

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### 3. Sponsor Organisation:

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### 4. Subject Identifiers:

Initials:	Date of Birth:	Age:	Sex:	Male <input type="checkbox"/>	Female <input type="checkbox"/>
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5. Date first became aware of event: .....

### 6. Event/Reaction Information:

Date of Onset:	Time of Onset:
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(Version 1, July 2011)

**SOP 3 Adverse Events/Serious Adverse Events and Suspected Adverse Events**

**6. Seriousness:**

**Result: (Please tick one)**

- Death       Hospitalisation/Prolonged or Existing Hospitalisation
- Congenital anomaly       Persistent or Significant       Life   
 Threatening  
 Or birth defect      Disability or Incapacity
- Anything the Investigator deems to be Clinical Significance

**7. Suspected Medicinal Product Information (tick if not applicable)**

Name of Medicinal Product (s):	Daily Dose (s):
Indication (s) for use:	Route of Administration:
Start/End Date of Therapy:	Was Medicinal Product Discontinued: Yes <input type="checkbox"/> No <input type="checkbox"/>

**7.1 Causality**

- Definite       Probable       Possible       Unlikely       Unrelated

**7.2 Severity of the event**

- Mild       Moderate       Severe       Life Threatening

**7.3 Expectedness**

- Expected (As seen in SmPc or 1B)       Unexpected

Has Unblinding Occurred? (Please tick one, if yes please provide details below) Yes  No

(Version 1, July 2011)

**8. Concomitant Medications and Relevant Medical History:**

Concomitant Meds: State Dose, Route and Start/End Dates (exclude those used to treat reaction)

Other Relevant Medical History:

**9. Event/Reaction Outcome**

1)	Recovered:	Yes: <input type="checkbox"/>	No: <input type="checkbox"/>	If yes, date of recovery:
2)	Improved:	Yes: <input type="checkbox"/>	No: <input type="checkbox"/>	If yes, date:
3)	Ongoing:	Yes: <input type="checkbox"/>	No: <input type="checkbox"/>	If yes, details:
4)	Worsened:	Yes: <input type="checkbox"/>	No: <input type="checkbox"/>	If yes, date:
5)	Subject Died:	Yes: <input type="checkbox"/>	No: <input type="checkbox"/>	If yes, date of death



# National Patient Safety Agency

## National Research Ethics Service

### CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

#### SAFETY REPORT TO MAIN RESEARCH ETHICS COMMITTEE

Please indicate which type(s) of safety report you wish to notify with this cover sheet (tick all that apply). Use a separate sheet for notifications relating to different trials. Please only send this to the main REC. For further guidance see:

<http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/safetyreports/safety-reports-for-ctimps/>

1. **Expedited report(s) of SUSAR in the UK**   
*Notify only Suspected Unexpected Serious Adverse Reactions occurring in the concerned trial at a UK site.*
  
2. **6-monthly safety report**   
**Include a global list of all SUSARs related to the investigational medicinal product (IMP) and occurring in the reporting period.**
  
3. **Annual safety report**   
**Include a global list of all SSARs (Suspected Serious Adverse Reactions) related to the IMP and occurring in the reporting period.**
  
4. **Other**   
*For example, report of Data Monitoring Committee or other safety review.*

Full title of study:	
EudraCT number:	
Research sponsor:	
Name of Chief Investigator:	
Name of main REC:	
Main REC reference number:	

#### Contact details for person making this notification

Name:	
-------	--

Address:	
Telephone:	
Fax:	
Email:	
Date of this notification:	
Signature:	

**List of enclosed documents**

Please list each report submitted with this notification (insert extra rows in table as required).

**1. Expedited SUSARs (UK only)**

Sponsor's report no./reference	Trial site	Date SUSAR first reported to sponsor	Is this a 7 or 15 day report?

**2. Other reports**

Type of report	Date of report

**Acknowledgement of receipt by main REC (please insert name):**

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back only to the sponsor (or other person submitting the report)  
Copy to be kept for information by main REC.



# National Patient Safety Agency

## National Research Ethics Service

### REPORT OF SERIOUS ADVERSE EVENT (SAE) (For all studies except clinical trials of investigational medicinal products)

*The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event.*

#### 1. Details of Chief Investigator

Name:	
Address:	
Telephone:	
Email:	
Fax:	

#### 2. Details of study

Full title of study:	
Name of main REC:	
Main REC reference number:	
Research sponsor:	

### 3. Type of event

Please categorise this event, ticking all appropriate options:

Death <input type="checkbox"/>	Life threatening <input type="checkbox"/>	Hospitalisation or prolongation of existing hospitalization <input type="checkbox"/>
Persistent or significant disability or incapacity <input type="checkbox"/>	Congenital anomaly or birth defect <input type="checkbox"/>	Other <input type="checkbox"/>

### 4. Circumstances of event

Date of SAE:	
Location:	
Describe the circumstances of the event: <i>(Attach copy of detailed report if necessary)</i>	
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	

### 5. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	



**6. Acknowledgement of receipt by main REC (please insert name):**

The [                      ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

*Signed original to be sent back to Chief Investigator (or other person submitting report)  
Copy to be kept for information by main REC.*

*This is a controlled document, when printed this document is no longer controlled.*

Appendix 3

Acknowledgement of SAE/SAR/SUSAR

<u>Patient ID</u>	<u>Trial/Study No.</u>	<u>Sponsor Site Informed</u>
<u>Date and Time of Form sent</u>		
<u>Acknowledged as process within 24hrs</u>		
<u>Action</u>		
<u>Review needed</u>		

## Withdrawal Form

Trial Name .....

Subject Name .....

Subject (CRF ID) .....

Visit Date .....

Date of Withdrawal .....

1. Please establish what the patient wants to do ...

	Yes	No
Withdraw completely from the trial – yet allow all information gathered to be used for future research purposes.	<input type="checkbox"/>	<input type="checkbox"/>
Withdraw Completely	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>

2. Primary Reason for Withdrawing ...

Death	<input type="checkbox"/>
Adverse Event	<input type="checkbox"/>
Lost to follow up	<input type="checkbox"/>
Failure to comply with protocol	<input type="checkbox"/>
Unable to tolerate Trial medications	<input type="checkbox"/>

Treatment failure	<input type="checkbox"/>
Withdrew consent	<input type="checkbox"/>
Administration Problems	<input type="checkbox"/>
Other	<input type="checkbox"/>

**3. Study medication . . .**

Date of last dose of study medication .....
Study Drug returned ? Y / N Medical Kit number(s) .....
Number .....
Will the subject continue follow up ? Y / N If no, complete end of trial form
Unblinding (code break) information, if appropriate
Date and time of code break .....
Reason for code break .....

**4. Other . . .**

--

**5. Confirmation of the above . . .**

I confirm that the information kept in this CRF is accurate and to the best of my knowledge.
Name of person recording withdrawal from trial .....
Patient consent from withdrawal of trial .....
Signature of Investigator .....
Date .....

**All staff are responsible for reporting Adverse Events(AE)/Adverse Reactions/Serious Adverse Events (SAE) and (SUSAR) Suspected Unexpected Serious Adverse Events**

**Always adhere to the trial or study protocol for their classification of AE/AR/SAE/SUSARs**

### **An Adverse Event (AE) Not Serious**

AEs can be any incident that happens to an individual that is different from previous. E.g. A fall, headache or abnormal lab result.

### **An Adverse Reaction (AR) Not Serious**

ARs relate to an expected reaction caused by the study medication or intervention. e.g. Nausea



**Not serious.** Does not meet the criteria of an SAE/SAR.

Report to trial centre as per protocol guidelines. R&D do not need to be informed of AEs/ARs. Annual Safety Report by Sponsor will detail their occurrence for all sites.

**No deadline**

### **SAEs and SARs**

#### **Seriousness**

**Report within 24hrs once initially aware**

- Death
- Disability
- Admission into hospital
- Overdose
- Malignancy
- Prolongation of treatment
- Birth defect
- Any other event the investigator deems to be of clinical significance.



#### **Causality –**

Not related to the study drug or intervention

#### **Causality –**

Possibly, likely or definitely related to the study drug or intervention.



**Expectedness –** Expected = SAE/SAR (As detailed in the SmPc or Investigator's Brochure)



**Unexpected =** (Not described in the SmPC or Investigator's brochure) **SUSAR** – e.g. Not a previously known side effect of the drug. A serious, related, unexpected event.

### **What to do for a SAE/SAR**

1. Inform all members of the team & Principal Investigator.
2. Complete SAE/SAR reporting form.
3. Contact Sponsor site within 24hrs.
4. Contact R&D within that period.
5. Complete SAE/SAR safety reporting form for R&D.
6. Address any requested remaining issues by the sponsor.
7. Follow up the event until the matter has resolved.
8. Timeline events = 15 day reporting procedure
9. Ensure the sponsor has classified the event.
10. If the Trust is acting as the Sponsor, inform R&D immediately, for classification of the event, the Chief Investigator or Medical Director is appropriate.
11. R&D will then work with the Chief Investigator, if ULHT is the sponsoring site, to aid with the submission of Progress and Annual Safety reports, to ensure all SAE/SARs are reported annually to the relevant competent authorities.

### **What to do for a SUSAR**

1. If ULHT are the sponsor – R&D – The Research Governance Manager will need to have all available information by day 7 of being made aware of the event.
2. The Research Governance Manager will report the SUSAR with a member of the clinical team, via the MHRA eSUSAR online reporting system. The Ethics Committee will also be notified.
3. A timeline of 7 days for fatal and 15 days non-fatal will be employed.
4. For hosted studies, R&D will need to be made aware of the SUSAR as soon as practically possible. All information available pertaining to the event will need to be given to R&D.
5. A IR1 form for both hosted and sponsored studies will need to be completed for SUSARs.
6. R&D will acknowledge all forms and give a final closure acknowledgement slip.