

**STANDARD OPERATING PROCEDURE:
Safety Reporting in Externally Sponsored Clinical Trials**

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SOP SUMMARY		
This policy covers procedures for safety reporting and notification to the appropriate bodies for Clinical Trials of Investigational Medicinal Products (CTIMPs)		
The Trust monitors the implementation of and compliance with this policy in the following ways:		
Monitoring of implementation and compliance with this procedure will be undertaken by the Executive Medical Director, Research manager, Research lead, R&D department staff and R&D group.		
Services	Applicable	Comments
Trustwide	✓	
Essex MH&LD		
CHS		

**STANDARD OPERATING PROCEDURE:
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CONTENTS

1. ADVERSE EVENT REPORTING

1.1. Definitions

1.1.1. Adverse Events (AE)

1.1.2. Adverse Reaction (AR)

1.1.3. Serious Adverse Event (SAE)

1.1.4. Suspected Serious Adverse Reaction (SSAR)

1.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

2. REPORTING PROCEDURES

2.1. Responsibilities of the person discovering a Serious Adverse Event Incident

2.2. Risk Management's Responsibilities

2.3. Reporting Requirements for SUSARS

2.4. Principal Investigator's Responsibilities

2.5. Evaluation of AEs for Causality

2.6. Evaluation of AEs for Severity

2.7. Recording of AEs

2.8. Reporting Of Medical Device Incidents To The Medical Devices Agency (MDA)

3. CONTACTS

4. APPENDICES

Appendix A: Responsibilities Following a Serious Adverse Event/SUSAR

5. REFERENCES

1. ADVERSE EVENT REPORTING

This policy aims to ensure that arrangements are in place to protect patient safety in all research involving human subjects, that investigators are aware of the safety implications of their research, and that the appropriate bodies are notified of safety information relating to medicines and devices.

The reporting arrangements below apply for all subjects taking part in research. Events or incidents should be reported even if they occur when the subject was not on Trust premises. For commercially-funded research or research sponsored by an external non-commercial body (e.g. the Medical Research Council) any reporting process established by the sponsoring body must be followed in addition to the procedures outlined below.

Adverse events must be recorded in the health records of the patient in accordance with GCP. If the adverse event fulfils the requirements of the Trust's Incident Reporting Policy then those procedures should be followed as usual. A reportable clinical incident is defined as:

"any unplanned or unexpected event in which a patient has been, or could have been, injured, or put in a position which could have compromised their clinical care".

The study protocol may have been written to exclude reporting of certain conditions of the disease under investigation. These events would not be classed as Serious Adverse Events.

1.1 Definitions

1.1.1 Adverse Events (AE)

A research-related adverse event is any untoward medical occurrence in a patient during clinical research involving a pharmaceutical product, or clinical intervention. Where the research involves a medical device, any event which gives rise to, or has the potential to produce, unexpected or unwanted effects involving the safety of patients, users or other persons is described as an adverse incident. In either case, the event or incident does not necessarily have a causal relationship with the treatment under investigation.

1.1.2 Adverse Reaction (AR)

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

1.1.3 Serious Adverse Event (SAE)

An adverse event, adverse reaction or unexpected adverse reaction respectively that

- (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 consists of a congenital anomaly or birth defect

CLPG19 SOP16 Safety Reporting in Externally Sponsored Clinical Trials

An adverse reaction is considered to be 'unexpected' if its nature and severity are not consistent with the information about the medicinal product set out in the investigator brochure or, if the product has a marketing authorisation, in the summary of product characteristics

1.1.4 Suspected Serious Adverse Reaction (SSAR)

An adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the case of

- a) a licensed product, in the summary of product characteristics (SmPC) for that product
- b) any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question

1.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out

- a) in the protocol
- b) in the case of a licensed product, in the summary of product characteristics (SmPC) for that product
- c) in the case of any other investigational medicinal product, in the IB relating to the trial in question

2. REPORTING PROCEDURES

It is essential that Serious Adverse Events are reported immediately upon knowledge of the event. Several different organisations need to be informed of the event including the main research ethics committee, the Medicines and Healthcare products Regulatory Agency and the sponsor. The person discovering the event is not responsible for notifying all of these organisations but they are responsible for initiating the process by following the procedures set out below.

2.1 Responsibilities of the person discovering a Serious Adverse Event Incident

- All Adverse Events and Serious Adverse Events/ Incidents must be recorded in the patient's medical records.
- Inform the Principal Investigator. If the Principal Investigator is not available, inform the designated person responsible for the study, who must then inform the Principal Investigator at the earliest opportunity.
- Complete a trial Serious Adverse Event Form as provided by trials centre.
- Where the incident represents a risk that threatens either staff, patients or the environment outside the scope of the study and/or may impact upon the organisation, the incident should be reported on the DATIX system and the R&D manager should be notified. Please contact the R&D Office and Risk Management Department for assistance with this or advice.
- See **Appendix A** for flow diagram

CLPG19 SOP16 Safety Reporting in Externally Sponsored Clinical Trials

2.2 Risk Management's Responsibilities

- The Risk Department will record any incident in the usual way.
- The Risk Manager will bring to the immediate attention of the R&D Manager any particular concerns.

2.3 Reporting Requirements for SUSARS

Suspected Unexpected Serious Adverse Reactions [SUSARS] associated with the use of any investigational medicinal product [IMP] must be notified to the Medicines and Healthcare products Regulatory Agency [MHRA] and to the Main REC. This is the responsibility of the Principal Investigator.

- A SUSAR which is *fatal or life-threatening* must be reported to the REC as soon as possible and in any event within 7 days after the sponsor became aware of the event.
- Any additional relevant information must be reported within 8 days of sending the first report.
- A SUSAR which is *not fatal or life-threatening* must be reported to the REC as soon as possible and in any event within 15 days after the sponsor first became aware of the event.
- Where a SUSAR is associated with an active comparator drug used in the trial, this should also be reported to the MHRA and the main REC.

Events associated with placebo will not normally satisfy the criteria for a SUSAR. If this occurred exceptionally it should be reported. In addition, the sponsor should ensure that all investigators in its trials are informed of any SUSAR occurring in relation to an IMP used in the trial or in another trial for which the sponsor is responsible.

2.4 Principal Investigator's Responsibilities

The Principal Investigator is responsible for the following:

- Reporting all research-related Serious Adverse Events to the organisation sponsoring the study
- Ensuring that a log of all research-related Serious Adverse Events/ Incidents is maintained in the study file
- Ensuring that adverse events have been recorded in the patient's notes
- Assessing the overall safety of the study
- Liaising with the R & D Office to ensure correct reporting of events to the main Research Ethics Committee or Medicines and Healthcare products Regulatory Agency, as appropriate
- Reviewing and disseminating any SUSARS/SSRs sent to the site from the Sponsor or CRO

The PIs team (should be a medically qualified person to assess causality and expectedness) is responsible for evaluating each AE for seriousness, causality, expectedness and severity. If the SAE form does not ask if the event was expected, then this should be added to the form by the person completing and processing the form. The responsibility for the evaluation of causality and expectedness can be shared between the PIs and any of their delegated medical team as listed on the site

CLPG19 SOP16 Safety Reporting in Externally Sponsored Clinical Trials

delegation log. Ideally this evaluation should be done by the PI, however if they are unavailable then a designated medical member of staff can carry out the assessment. The PI must sign and date this assessment.

2.5 Evaluation of AEs for Causality:

Every effort must be made by the CI/PI to obtain all the required information to determine whether the AE is related to the trial intervention. A suggested 4-point scale maybe used as described below.

Not Related	The temporal relationship of the onset of the event, relative to the administration of the product, is not reasonable or another cause can itself explain the occurrence of the event
Possibly Related	The temporal relationship of the onset of the event, relative to the administration of the product, is reasonable but the event could have been due to another, equally likely cause
Probably Related	The temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the drug than by any other cause
Definitely Related	The temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and there is no other cause to explain the event or a re- challenge (if feasible) is positive

Please note the PI is not expected to break the code of blinded studies in order to assess causality. If it is necessary to break the code to ensure patient safety, this may be done, preferably by an appointed Data Safety Monitoring Committee or Independent person. An AE becomes an AR if the PI assesses the event as “having a reasonable causal relationship to the IMP”. Of the four categories above, possibly”, “probably” and “definitely” related to an IMP qualifies as an AR. “Not related” would not qualify as a reasonable causal relationship and therefore not qualify as an AR.

Pregnancy itself is not regarded as an adverse event unless there is suspicion that the study medication may have interfered with the effectiveness of the contraceptive or that it might be harmful to the foetus. Should a pregnancy occur, it must be recorded and reported in accordance with the procedures described in protocol.

2.6 Evaluation of AEs for Severity:

It is common practice for events to be assessed for clinical severity (intensity) of the specific event. This must not be confused with “serious” which is a regulatory definition based on subject/event outcome or action criteria. The PI &/or research nurse should describe the event as “mild”, “moderate” or “severe” or assign the appropriate toxicity grading score as stated in the protocol. This should be included in the written report.

CLPG19 SOP16 Safety Reporting in Externally Sponsored Clinical Trials

2.7 Recording of AEs:

The PI or research nurse must record all AEs (with assessments of seriousness, causality and severity) onto the trial AE recording form provided by the Sponsor. The appropriate person identified in the delegation log must record all AEs on the trial AE record form and file in the subject's CRF and send copies to the Sponsor or the Sponsor will collect them as stipulated in the protocol. The PI may also be asked to provide their evaluation of "expectedness" for such events. This opinion must be recorded on the SAE form before submission to the Sponsor. Copies of the SAE forms must be filed in the Investigator Site File (ISF) for source verification purposes or inspection.

2.8 Reporting Of Medical Device Incidents To The Medical Devices Agency (MDA)

If the incident involves medical equipment or devices, the equipment must be removed from use and clearly marked "DO NOT USE". The incident must be reported to the Trust's Medical Engineering Department so that an inspection of the equipment can be made. They will advise on appropriate action. The Trust's MDA liaison officer, who is based in the Medical Engineering Department, will report the incident to the Medical Devices Agency.

3. CONTACTS

R&D Office <https://eput.nhs.uk/about-us/research/>

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Appendix A: Responsibilities Following a Serious Adverse Event/SUSAR

5. REFERENCES

MHRA reporting process: <https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues>

CLPG19 SOP16 Safety Reporting in Externally Sponsored Clinical Trials

APPENDIX A: Responsibilities Following a Serious Adverse Event/SUSAR

Responsibility of PI or Person Discovering Event

