# Standard Operating Procedure (SOP)

## Recording, Assessing & Reporting Adverse Events in Clinical Research

| For Completion by SOP Author | |
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Portsmouth Hospitals University NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

# Contents

## 1. INTRODUCTION

Portsmouth Hospitals University NHS Trust (PHU) is a research and innovation-based organisation, acting as both host and sponsor to high quality research activity. This document has been produced to ensure the Trust meets UK clinical trial regulatory requirements; as well as the Heath Research Authority's (HRA) reporting procedures, and standards of good practice for the management and reporting of Adverse Events during clinical research studies.

Adverse Events and clinical incidents which occur during any research study should be recorded and monitored because they can indicate when things are going wrong; for example, when the safety profile of an investigational product has changed, or when a study protocol or procedure may be causing harm. It is therefore important that we know when an event or incident is serious, unexpected, occurring at an unexpected frequency or an escalation of events; and when an event may be caused by a research intervention, investigation, procedure, or due to the study design. This information will help us to make decisions and act where necessary to ensure the safety of our research participants and our patients.

The Medicines for Human Use (Clinical Trials) Regulations 2004 in conjunction with the Amendment Regulations (collectively referred to hereafter as "the Regulations") stipulates the reporting requirements for Clinical Trials of Investigational Medicinal Products (CTIMPS) and these are incorporated into this procedure. A serious breach of these regulations may constitute a breach in criminal law.

## 2. PURPOSE

The purpose of the document is to provide the Standard Operating Procedure (SOP) for investigators, when recording, assessing, and reporting adverse events during clinical research at PHU, or for which PHU is responsible.

This SOP should be read in conjunction with the Trust's clinical research safety monitoring policy, (PHU/RDPOLICY/002) and the Trust's Policy for the Management of Safety Learning Events, Including Serious Incidents Requiring Investigation.

## 3. SCOPE

**This Standard Operating Procedure applies to:**

- All clinical research activity conducted at PHU.
- All clinical research activity for which PHU is responsible as Sponsor (including external sites).
- All clinical research for which the Trust has been delegated pharmacovigilance monitoring responsibilities.

**Terminology within this SOP**

Throughout this SOP the term Serious Adverse Event (SAE) is used. For simplicity, where this term is used it refers to any adverse event, reaction or effect that has been assessed as serious. An SAE can be further defined as a Serious Adverse Reaction (SAR), Suspected Unexpected Serious Adverse Reaction (SUSAR), Serious Adverse Device Effect (SADE), Anticipated Serious Adverse Device Effect (ASADE) or Unanticipated Serious Adverse Device Effect (USADE).

**Who should follow this SOP**

All investigators and staff involved in delivering research at PHU and for which PHU is responsible (as sponsor or a host site), and those responsible persons outlined in Section 5.

*The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals University* NHS *Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP does not conflict the SOP outlined below. If the PHU user suspects there may be conflict between such SOPs, they should discuss this with the PHU Research Office and document any decisions taken in the study file.*

*In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety.*

## 4. DEFINITIONS & ACRONYMS

| Abbreviation | Meaning |
|---|---|
| ADE | Adverse Device Event |
| AE | Adverse Event |
| AR | Adverse Reaction |
| ASADE | Anticipated Serious Adverse Device Effect |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTA | Clinical Trial Assistant |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| DSMC | Data Safety Monitoring Committee |
| DSUR | Development Safety Update Report |
| e-SUSAR | MHRA Electronic SUSAR |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| IB | Investigator's Brochure |
| IMP | Investigational Medicinal Product |
| ISF | Investigator Site File |
| MHRA | Medicines and Health products Regulatory Agency |
| PAS | Patient Administration System |
| PHU | Portsmouth Hospitals University NHS Trust |
| PI | Principal Investigator |
| PV | Pharmacovigilance |
| REC | Research Ethics Committee |
| RF | Research Facilitator |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SmPC | Summary of Product Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| USADE | Unanticipated Serious Adverse Device Effect |

For Definitions please refer to Appendix 10.1

### 4.1. DEFINING STUDIES OF ADDITIONAL SAFETY RISK

The Trust considers the following studies to be of a safety risk that is additional to normal patient care or routine practice, and therefore require detailed safety reporting procedures to be set out in the protocol or supporting documents:

(a) All Clinical Trials of IMP (CTIMPs)*.

(b) All interventional studies of a novel procedure or device without UKCA marking or used outside of its UKCA mark, (including regulated Device trials*).

(c) All studies, where the protocol procedures are considered to be of an additional safety risk to participants, compared with routine clinical practice, as evidenced by a completed risk assessment (refer to Risk Assessment SOP: PHU/RDSOP/018). Studies in which routine drugs or devices are being used outside of their licensed range of use.

**In addition,** the Trust will ensure safety reporting procedures are in place and followed for any study with specified safety objectives as part of the study design and purpose (this includes observational studies).

**Means there is also a regulatory requirement to report SAEs.*

## 5. DUTIES AND RESPONSIBILITIES

**All Health Care Professionals** are responsible for:

1. Reporting any Serious Adverse Event to the PI and/or local research study team, as soon as they become aware of an SAE.

**Investigators (and delegated persons)** are responsible for:

<u>All studies</u>

1. Reporting all safety concerns, hazards and clinical incidents to the Trust in accordance with the procedures outlined in this SOP.

<u>CTIMPS & Studies of Additional Safety Risk Only</u>

Regulation 32 of the Clinical Trials Regulations (2004 No.1031) sets out the following responsibilities (1-4) for the notification of adverse events to sponsors during CTIMP studies, and the Trust has agreed that the duties also apply to studies of additional safety risk, as defined above:

1. *An investigator shall report any serious adverse event which occurs in a subject at a trial site which he is responsible for the conduct of a clinical trial immediately to the sponsor. As per 'the Regulations', "in practice, this means within 24 hours of the investigator's knowledge of the event".*
2. *An immediate report may be made either orally or in writing.*
3. *Following the immediate report of a serious adverse event, the investigator shall make a detailed written report on the event.*

4. *Paragraphs 1 to 3 do not apply to serious adverse events specified in the protocol or investigator's brochure as not requiring immediate reporting.*

Other AEs identified in the protocol as critical to evaluation of the safety of the trial (i.e. notable events) should be notified to the sponsor in accordance with the requirements, including the time periods for notification, specified in the protocol.

In addition, investigators shall:

2. Report all SUSARs/ Non-CTIMP SUSARs or safety observations to the PHU Research Office (and the study sponsor if this is not PHU), in accordance with the procedures outlined in this SOP.

3. Where SAEs/SUSARs/Non-CTIMP SUSARs are required to be reported, ensure the inclusion of an SAE Alert Notice in all versions of the Health Record for the SAE reporting period.

4. Follow up of any adverse event until its conclusion.

5. Check for any adverse events at each contact with the research participants by specific questioning and examination.

6. Regularly review PAS to check whether additional/multiple hospital notes have been created for their research participants during the study, which may contain evidence of adverse event occurrence and follow SAE capture/recording procedures.

7. Regularly review electronic health records for any reportable safety events, in line with the study protocol.

**Chief Investigators (CI's) of PHU Sponsored studies** are additionally responsible for the following:

CTIMPS & Studies of Additional Safety Risk Only

1. Ensuring that study personnel are suitably trained for the purposes of AE recording, assessment and reporting and that this is adequately documented (via training logs, delegation logs etc.).

2. Supporting the Research Office in the assessment of all SAEs, SARs, SUSARs and Non-CTIMP SUSARs.

3. Notifying participating sites of any SUSARs or Non-CTIMP SUSARs, which occur during the study; as well as any information which might adversely affect the safety of their patients.

4. Ensuring that all Adverse Events and Reactions, which were recorded during the research study are subject to a statistical analysis; and that any subsequent conclusions are included in the study's final report, copied to the Reaserch Office.

5. Ensuring the timely submission of annual progress reports to the Research Office, REC/HRA as appropriate.

6. Ensuring the timely submission of annual Developmental Safety Update Reports (DSUR) for all Trust Sponsored CTIMPS to the MHRA,

7. Notifying the Research Office, (and the MHRA and REC as applicable), of any significant findings and recommendations made by an Independent Data Safety Monitoring Committee (DSMC), if not directly notified by the DSMC.

**The Research Office** is responsible for:

1. Ensuring that departmental mailboxes designated to receive SAE reports are checked daily. Where an SAE report is submitted over the weekend or a bank holiday, this will be picked up immediately once the next working day commences and actioned as a priority.

2. The timely recording and assessment of SAE forms reported to the Research Office.

3. Activating the appropriate tracking procedure for the assessment and management of SAEs, SSARs, SUSARs and Non-CTIMP SUSARs, including ensuring the timely expedited reporting of events to the MHRA and the REC as appropriate.

4. Maintaining a database of all reported SAEs/SSARs, SUSARs and Non-CTIMP SUSARs for central monitoring, providing safety reports to the appropriate study oversight and governance group based within the Research Department. Such groups would be either the Research Governance & Risk Group, Sponsored Oversight Group or Research Delivery Meeting, depending on the nature of the reportable event and the urgency of review (the Research & Development Manager can advise on which group should review such events), Additionally, the PHU Sponsored study safety tracker is regularly reviewed by senior members of the Research Team at the Sponsored Oversight Group meetings.

5. Forming a study specific DSMC where appropriate; coordinating transfer of safety data to the DSMC and convening meetings, for studies where PHU is the Sponsor.

6. The review of all protocols at study set up to ensure appropriate safety reporting processes are in place prior to Research Department confirmation of capacity and capability.

7. Suspending recruitment and other study activity or withdrawing approval for a study if appropriate. This may happen (but is not limited to), where public health and safety is considered to be at risk or where the safety and wellbeing of research subjects or staff are considered to be at risk.

8. Providing SAE Alert templates to research staff who are involved in studies with SAE reporting requirements.

9. Providing safety reports to the appropriate study oversight and governance group based within the Research Department.

# 6. PROCESS

## 6.1. PHU SPONSORED STUDIES

### 6.1.1. Flowchart 1 – PHU sponsored studies process

# PHU Sponsored Studies

Portsmouth Hospitals University NHS Trust

Responsibilities

Investigator/delegated

Research Office

Adverse Event identified

Document in the patient's medical notes and CRF (if applicable)

Investigator to assess for Seriousness

Serious Adverse Event (SAE)

Adverse Event (AE)

Record as SAE and consult protocol for specified method of recording

Record on Study Line listing

Record on **AE Form 1**

Assess for Causality, Expectedness and Intensity

If AE is related to a CTIMP or MHRA Notifiable device study Notify Research Office in a timely manner.

If required by the protocol report to the Research Office using **SAE Form 2** within **24 hours** of identification. Mark email 'Urgent - SAE Report' Record SAE onto EDGE.

Incomplete SAE form. Additional information requested

Research Office will acknowledge receipt within one working day

Follow up participants and submit follow up report every 7 days until SAE resolved. Use **SAE Form 3.**

Research Office will add to safety database and save form in study folder on G-Drive

If SUSAR – escalation to MHRA & REC within:
**7 days** - fatal/life threatening
**15 days** - other SUSARs

Pregnancy
Report to Research office, within 7 days, if linked to a CTIMP participant or required by the

Clinical Incidents
Consider if appropriate to report via Trust's incident reporting procedures (Datix)

### 6.1.2. SAE Alert Notice

Studies requiring safety reporting must use the SAE alert sticker in the participant's notes to advise non-research staff what action to take. Comparable information must also be recorded in the participant's digital notes to alert other healthcare professionals for the need of immediate reporting where required.

### 6.1.3. Safety reporting period

Adverse events should be captured from the time of a participant's enrolment into a study until the end of their participation (unless otherwise specified in the protocol).

Enrolment should be defined in the protocol, however if no definition is provided the following can be used: "*Enrolment is the point in time from which participant-related study procedures commence after informed participant consent has been given, including screening tests etc.*".

End of trial participation should also be defined in the protocol. Where end of trial is not defined by the Sponsor, investigators should use the REC definition as follows: *"The end of the research should be defined in relation to the collection of all data required to answer the research questions in the protocol. Where a clinical trial protocol requires follow-up monitoring and data collection to meet secondary or tertiary endpoints, the end of trial should be the final data capture rather than the last treatment visit"*.

### 6.1.4. Recording adverse events

All adverse events should be recorded in the participant's medical notes. The following information should be provided as a record: description, start time, end time, duration, severity, treatment and outcome.

### 6.1.5. Reporting adverse events

Adverse Events should be recorded as per the research protocol. **AE Form 1, AE Assessment Form** may be used if no provision is made elsewhere, for example in the CRF.

The CI should maintain a line listing or database of AEs. Periodic reports and statistical analysis can be carried out as required.

For Non-CTIMP and non-MHRA notifiable studies; AEs are only required to be recorded as mentioned above and in the participant's medical records as per section 6.1.4.

For CTIMPS & MHRA notifiable device studies sponsored by PHU; all AE's are required to be reported by notifying the Research with details of each AE. This can be done by completing a copy of the AE form or via email and must contain the following information:

- Study name
- Patient ID
- Date of onset and end date
- Brief description of AE
- Intensity, Relatedness, Expectedness and Seriousness
- Brief description of action taken

- Outcome (resolved/ongoing)

There are no specified timelines for AE reporting however this should be done in a timely manner.

All adverse events should be assessed by the investigator or delegated individual. For CTIMP studies this assessment must be made by a medically qualified individual. Appendix 10.2 flowchart illustrates adverse event assessment.

Investigators should observe levels of intensity, expectedness and causality of events, in case the frequency of these events changes. A change deemed to be of clinical significance by the local investigator must be reported to the Sponsor immediately.

The current, approved versions of the following documents should be used for reference when assessing any AE in a trial:

- Protocol.
- Safety reference documents (e.g. SmPC or IB).
- Unblinding procedures if applicable.

All AEs must be assessed for **Intensity**, **Causality**, **Expectedness** and **Seriousness** – refer to Appendix 10.3 for more detail on these assessments**.**

The PI's assessment cannot be downgraded however the CI can upgrade an event.

### 6.1.6. Reporting Serious Adverse Events- PHU SPONSORED STUDIES

If an AE has been assessed as serious, notify the Research Office (Sponsor) immediately; that is within **24 hours** of identification. If the investigator suspects the event to be a SUSAR this should be clearly identified on the report form.

Telephone notification may be made in the first instance but must always be followed up in writing.

The SAE should be reported using **AE Form 2 – SAE/SSAR/SUSAR Initial Report Form**. Include as much information as is available at the time, and it should make clear the investigator's assessment of intensity, causality, expectedness and seriousness.

The Research Office will confirm receipt by the next working day however, if not received this should be followed up by the investigator team.

Additionally, consider if the SAE is a reportable incident to be captured on any Trust wide reporting system, e.g. DATIX. An SAE would qualify for this if it could reasonably be related to something systemic or the reporter feels it is a beneficial learning point for the wider department. If in doubt as to whether an SAE should be reported in this way, seek advice from a member of the Senior Research Nurse or Research Office teams.

### 6.1.7. Reporting to the PHU Research Office

All written notifications to the Trust Research Office should be marked "**Urgent - SAE Report**" and made via:

- Email: research.office@porthosp.nhs.uk

- Hand: Research Office, First Floor, Lancaster House, Queen Alexandra Hospital, Cosham, Hants. PO6 3LY

The Research Office will acknowledge receipt of the report and allocate a reference number designated via the Research Safety database. An Independent Medical Assessment will be sought by the office team and the outcome informed to the Chief Investigator.

#### 6.1.8. SAE Follow Up reports

If the SAE remains unresolved, regular follow up reports should be sent to the Research office using **AE Form 3 – SAE/SSAR/SUSAR Follow-up Form**

Follow Up reports must be made by the research delivery team (nurses/PI/CI etc.) every 7 days until the SAE is concluded. When the SAE is resolved a final follow up form should be sent, marking the SAE as resolved and detailing the date of resolution.

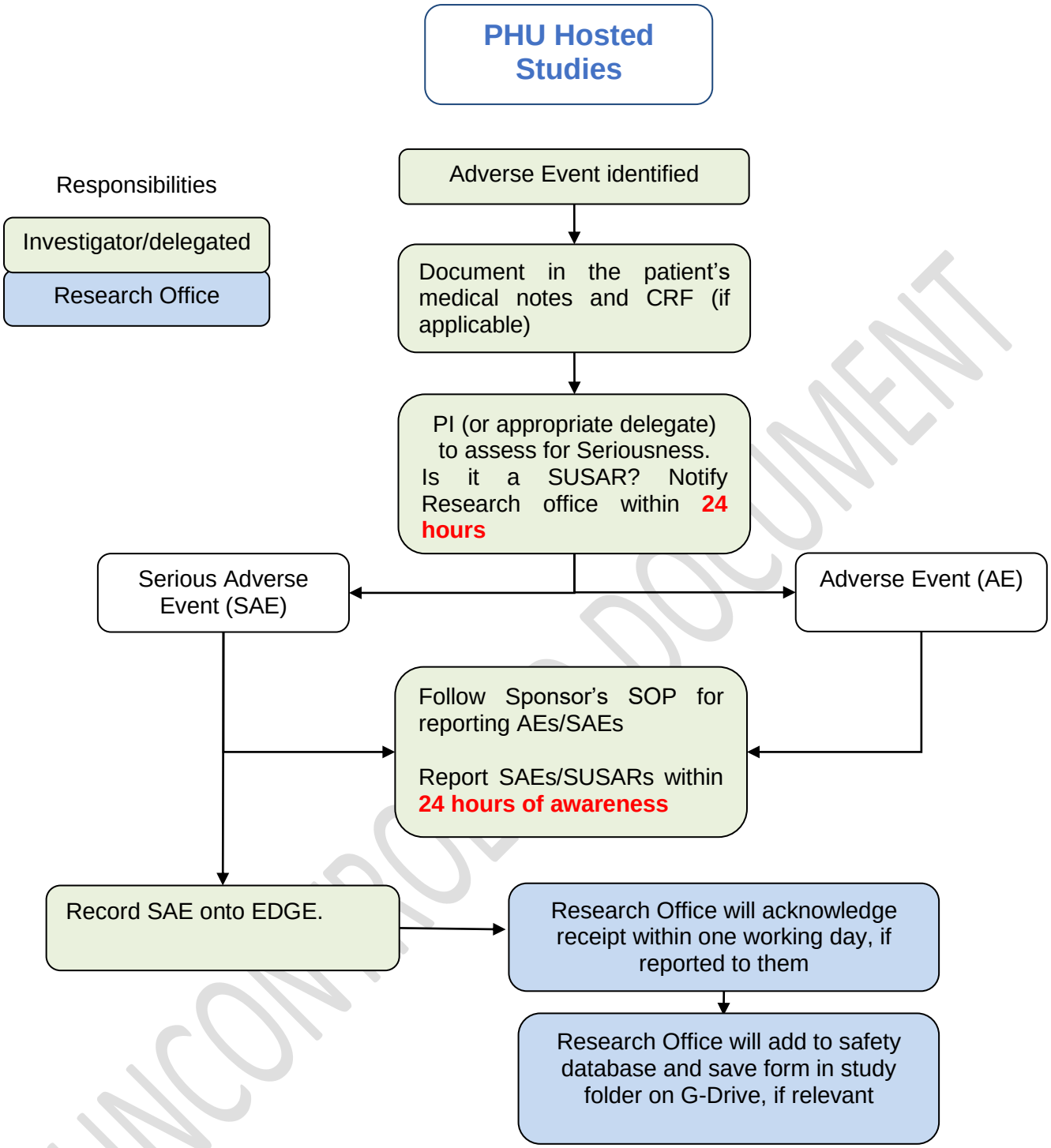
#### 6.1.9. Expedited Reporting - SUSARs

SUSARs require expedited reporting to the MHRA within **7 days** if it is fatal or life threatening or within **15 days** for all other SUSARs (including from clinical investigations of medical devices).

A copy of the report is also sent to the REC. Where PHU is the sponsor, the Research Office is responsible for expedited reporting to the MHRA and HRA/REC.

### 6.2. HOSTED STUDIES

#### 6.2.1. Flowchart 2 – PHU hosted studies process






SAEs and SUSARs occurring in studies hosted by PHU must be reported to the Sponsor within 24 hours of awareness in accordance with the Sponsor's SOP and in line with the study protocol.

Any necessary expedited reporting to the MHRA and HRA/REC is the responsibility of the Sponsor.

It is the responsibility of the PI at PHU to ensure the Research Office is notified if there are unacceptable or concerning patterns of SAEs emerging from a protocol which have the potential to affect the care or safety of patients.

### 6.2.2. SUSARs

SUSARs identified in a PHU hosted study must be notified to the Research Office within 24 hours of the investigator's knowledge of the event. Notification can be made by copying the Research Office in on the notification to the Sponsor. Alternatively, **SAE form 2** can be used as per the process for Sponsored studies above.

## 6.3. Other Reportable Safety Issues

Safety issues other than those that directly affect a study participant can occur. In such cases the Research Office should be informed as soon as reasonably possible and appropriate action will be taken.

Examples of other observable safety issues might include:

- An increase in the rate of occurrence of an expected serious adverse event or reaction.
- A qualitative change of an expected serious adverse event or reaction that is judged to be clinically important.
- Post-study unexpected, serious and related events/reactions that occur after the patient has completed a study and are reported by the investigator to the sponsor.
- Significant hazards to the subject population such as lack of efficacy of an investigational product used for the treatment of a life-threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).
- Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same investigational products in another country by the same sponsor.
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety.

## 6.4. Admission of research participants

When patients are admitted into PHU, the admitting member of staff is prompted to confirm whether the patient is taking part in a research study. This is done via several methods.

Firstly, when the patient is added onto the BedView system (the Trust clinical system for managing inpatients) one of the admission questions is whether the patient is taking part in research. The admitting staff member should check with the patient, or personal representative, if this is the case. If yes, this gets recorded onto BedView and the patient is 'flagged' as a research participant. The admitting staff are then prompted to inform the Research Team of the participant's admission via email or phone. This system will be further developed to enable automated reporting to the research team when the flag is put onto the BedView system.

### 6.5. Reporting A Pregnancy

A pregnancy itself may not be considered an SAE, however any congenital anomaly or birth defect is. Any pregnancy occurring in a female CTIMP subject, or partner of a male CTIMP subject during the course of a study, must be reported to the Sponsor and the PHU Research Office.

Follow up of the pregnancy outcome should be conducted and where necessary the development of the newborn may be monitored for an appropriate period post delivery.

For **PHU Sponsored studies** the pregnancy should be reported within 7 days of becoming aware of the pregnancy. With consent, the pregnancy should be tracked until the end of the pregnancy and the outcome known.

### 6.6. Reporting an overdose

The PI and Sponsor must be immediately informed (within 24 hours) of an overdose in a trial participant (accidental or intentional).

A protocol deviation log must be completed and the medical notes, CRF and AE log updated to reflect this information. If the overdose is related to an SAE/AE then the two events should be linked.

In the event of an SAE/AE associated with the overdose, appropriate reporting should be carried out in accordance with this SOP.

### 6.7. Blinded Studies

Please refer to the SOP for Randomisation and Blinding for Randomised Controlled Trials

### 6.8. Arrangements for PHU sponsored multisite studies

External sites hosting a PHU sponsored study should follow this SOP. If this SOP conflicts with their local procedures this must be discussed as soon as this is identified, ideally during study set up.

The CI is required to notify host sites of any SUSARs that occur in the study, ensuring investigators are fully informed of all safety information. SUSARs relating to the IMP occurring in other studies should also be notified to sites.

There is no specific timeline for this information to be disseminated, however it is recommended this is carried as soon as is practicable.

### 6.9. Annual safety reporting requirements for PHU sponsored studies

#### *6.9.1.* Annual Developmental Safety Update Reports (DSURS): *CTIMP Studies Only*

In addition to the expedited reporting required for SUSARs, the Trust is required to submit annual safety reports to the MHRA and the Ethics Committee for any Sponsored CTIMP.

For PHU Sponsored studies, this reporting responsibility is delegated to the Chief Investigator, with support from Research Office staff.

The aim of the annual safety report is to concisely describe all new safety information relevant for one or several clinical trial(s) and to assess the safety of subjects included in these studies.

The annual safety report should take into account all new available safety information received during the reporting period.

### Reporting Period

DSURs should be provided at yearly intervals, by the Chief Investigator, throughout the study or on request.

The annual reporting period is from the Development International Birth Date (DIBD) until the data lock point for that year. The report is due 60 days from the data lock point.

- The Development International Birth Date (DIBD) is the date of the first MHRA CTA approval or, for trials with marketed products, the date of the first marketing authorisation granted in the EU,
- The data lock point for the year is the last day of the twelfth month from the DIBD,
- All DSURS must be submitted to the MHRA and REC **no later than** 60 days after the annual data lock point (12 months from DIBD).

A calendar template can be provided to aid the research team in remembering the DIBD and report due dates

### The DSUR should include the following information:

**Part 1:** Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit.

**Part 2:** A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries.

**Part 3:** An aggregate summary tabulation of SUSARs that occurred in the concerned trial(s).

The Research Office holds a template for DSURS and Chief Investigators shall be reminded in advance of their submission due date. Chief Investigators should consult with the Research Office at an early stage for support in the development of their return and must submit their completed reports to the Research Office two weeks before the submission date for review and approval. For further details please see;

https://database.ich.org/sites/default/files/E2F_Guideline.pdf or the MHRA website (see refs)

The DSUR should be signed by the person submitting the report and should be submitted in PDF to the MHRA and REC. All enclosures should be listed and referenced on the report.

Refer to the MHRA website for the current submission process. This will also be supported by the Research Office.

Evidence of sending the DSUR should always be kept in the TMF in order to evidence submission. The MHRA no longer acknowledge receipt.

#### Final DSUR

When the study has completed, a final DSUR is required. The cover letter to the MHRA should explain that the DSUR submitted serves as the final one for the IMP.

### 6.9.2. Annual Progress Report: All PHU Sponsored Studies

Annual progress reports are required to be submitted to the HRA/REC and the Research Office for all PHU sponsored studies. This is in addition to the annual safety report for CTIMP studies

Responsibility for submission of annual progress reports is delegated to the Chief Investigator.

**For studies with HRA & REC approval:** A progress report should be submitted to the REC which gave the favourable opinion (the 'main REC') 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter until the end of the study. A calendar template can be provided to aid the research team in remembering the DIBD and report due dates

**For studies with HRA approval only** (no REC approval)**: Reports are not required to be submitted.**

Reports should be submitted in accordance with guidance at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

Evidence of receipt and/or acknowledgement should be filed in the TMF in order to evidence submission.

## 7. TRAINING REQUIREMENTS

All research staff should be trained in this SOP. Evidence of training shall be required for PHU sponsored CTIMP studies and other high risk PHU Sponsored studies. Research staff involved in studies with SAE reporting requirements will be provided with SAE Alert templates by the Research Office at approval, or on request.

The Research Department, will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the Research & Innovation website. Updates on SOPs will feature in Research newsletters and communications and disseminated at local research meetings. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.

When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high risk PHU Sponsored studies.

Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

All staff are responsible for maintaining their own SOP Training Records and copies must be made available to line managers, the SOP Controller or study monitors on request.

## 8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated documents

- SAE Alert Notice Sticker
- AE Form 1 – AE Assessment Form
- AE Form 2 – SAE/SSAR/SUSAR Initial Report Form
- AE Form 3 – SAE/SSAR/SUSAR Follow-up Form
- PHU/RDPOLICY/002: Clinical Research Safety Monitoring Policy
- Policy for the Management of Safety Learning Events, Including Serious Incidents Requiring Investigation. *Portsmouth Hospitals University NHS Trust.*

References


- The Medicines for Human Use (Clinical Trial) Regulations 2004 and the Medicines for Human Use (Clinical Trial) Amendment Regulations 2006, the Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008, and the Medicines for Human Use (Miscellaneous Amendments) Regulations 2009.
- Health Research Authority *(Last accessed April 2023)*
- UK policy framework for health and social care research, Nov 2017
- ICH Guideline for Good Clinical Practice E6 (R2) Dec 2016
- https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/ *(Last accessed April 2023)*
- https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/ *(Last accessed April 2023)*
- MRC/DH Joint Project Work stream 6: Pharmacovigilence, July 2012
- MHRA website: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm *(Last accessed April 223)*
- EudraLex – Volume 10 – clinical trial guidelines - 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use CT-3 2011
- Medical devices: EU regulations for MDR and IVDR (Northern Ireland) - GOV.UK (www.gov.uk), *(Last accessed April 223)*


## 9. VERSION HISTORY LOG

| Version | Date Implemented | Details of Significant Changes |
|---|---|---|
| 1.0 | 31/01/13 | New document |
| 2.0 | 07/04/16 | Removal of references, addition of 'other' category for SAE, additional information regarding SOP training added and minor typographic changes |
| 3.0 | 25/04/23 | PHU logo updated<br>Routine review of SOP<br>Reformatting throughout<br>Revision of SUSAR definition |

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| | | Redesign of process flow chart for sponsored and hosted studies<br>Follow up form submission timeline changed from 5 days to 7 days<br>Addition of managing multisite studies<br>Addition of reporting an overdose<br>Addition of Blinded Studies<br>Addition of HRA decision tree for adverse event reporting in appendix<br>Update to links/references<br>Addition of EDGE upload instructions<br>Colour coding for Sponsored/Hosted specific sections |
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# 10. APPENDICES

## 10.1 Definitions

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| **Adverse Device Effect** | Adverse event related to the use of an investigational medical device.<br><br>**Comment:** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.<br>**Comment:** This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device. |
| **Adverse Events (AE)** | Any unfavourable and unintended sign (including abnormal lab results), symptom or disease temporally associated with a clinical research protocol.<br>**In CTIMPS**, The Regulations define 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<br><br>**Comment:** An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical trial (including those in an untreated control group), whether or not considered related to the intervention investigational medicinal product |
| **Adverse Incident (AI)** | An event or omission, which caused physical or psychological injury to a patient, visitor or staff member or any event of circumstances arising during NHS care that could have or did lead to unintended or unexpected harm, loss or damage.<br><br>**Comment:** An AI might be for example, a lack of essential or life saving equipment available in a research setting during an interventional clinical study |
| **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.<br><br>**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 as there is evidence or argument to suggest a causal relationship.<br><br>All adverse reactions are adverse events**.** |
| **Anticipated Serious Adverse Device Effect (ASADE)** | An effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report |
| **Clinical Trial of an IMP (CTIMP)** | Any investigation in human subjects, other than a non-interventional trial, intended:<br><br>• To discover or verify the clinical, pharmacological or other pharmaco-dynamic effects of one or more medicinal products,<br>• To identify any adverse reactions to one or more such products, or<br>• To study absorption, distribution, metabolism and excretion of one or more such products, with the objective of ascertaining the safety or efficacy of those products, |

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| **Device Deficiency** | Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. |
| **Investigational Medicinal Product (IMP) (CTIMPS Only)** | A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including a medicinal product which has a marketing authorisation but is, for the purposes of the trial, being used or assembled (formulated or packaged) in a way different from the approved form or being used for an unapproved indication or when used to gain further information about an approved use. |
| **Non-Investigational Medicinal Products (NIMP)** applies to **CTIMPs ONLY.** | Medicinal products that are not the object of an investigation (i.e. other than the tested product, placebo or active comparator), which may be supplied to subjects participating in a clinical research study and used in accordance with the protocol. This might be, for example, medicinal products such as support/rescue medication given 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) and are called non-investigational medicinal products (NIMPs) |
| **Non-CTIMP SUSAR***<br><br>**(USADE in medical device trials)** | Any Serious Adverse Event judged to be:<br><br>• Related to the administration of any intervention or any study procedure of interest to the study i.e. having a reasonable causal relationship to that procedure or intervention,<br>• Unexpected, i.e. not listed in the protocol (or product information) as an expected occurrence for those specified procedures/intervention, and,<br>• Unrelated to the administration of an IMP i.e., having no reasonable causal relationship to an IMP.<br><br>**For Medical Device Trials this may be classified as an Unanticipated Serious Adverse Device Effect (USADE).* |
| **Pharmacovigilance (drug safety)** | The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. |
| **Serious Adverse Device Effect (SADE)** | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| **Serious Adverse Event (SAE):** | An adverse event, adverse reaction or unexpected adverse reaction that:<br><br>• results in death,<br>• is life-threatening***,**<br>• requires hospitalisation or prolongation of existing hospitalisation,<br>• results in persistent or significant disability or incapacity<br>• consists of a congenital anomaly or birth defect,<br>• Other - any other safety concern<br><br>**Comment:** Medical judgment should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening |

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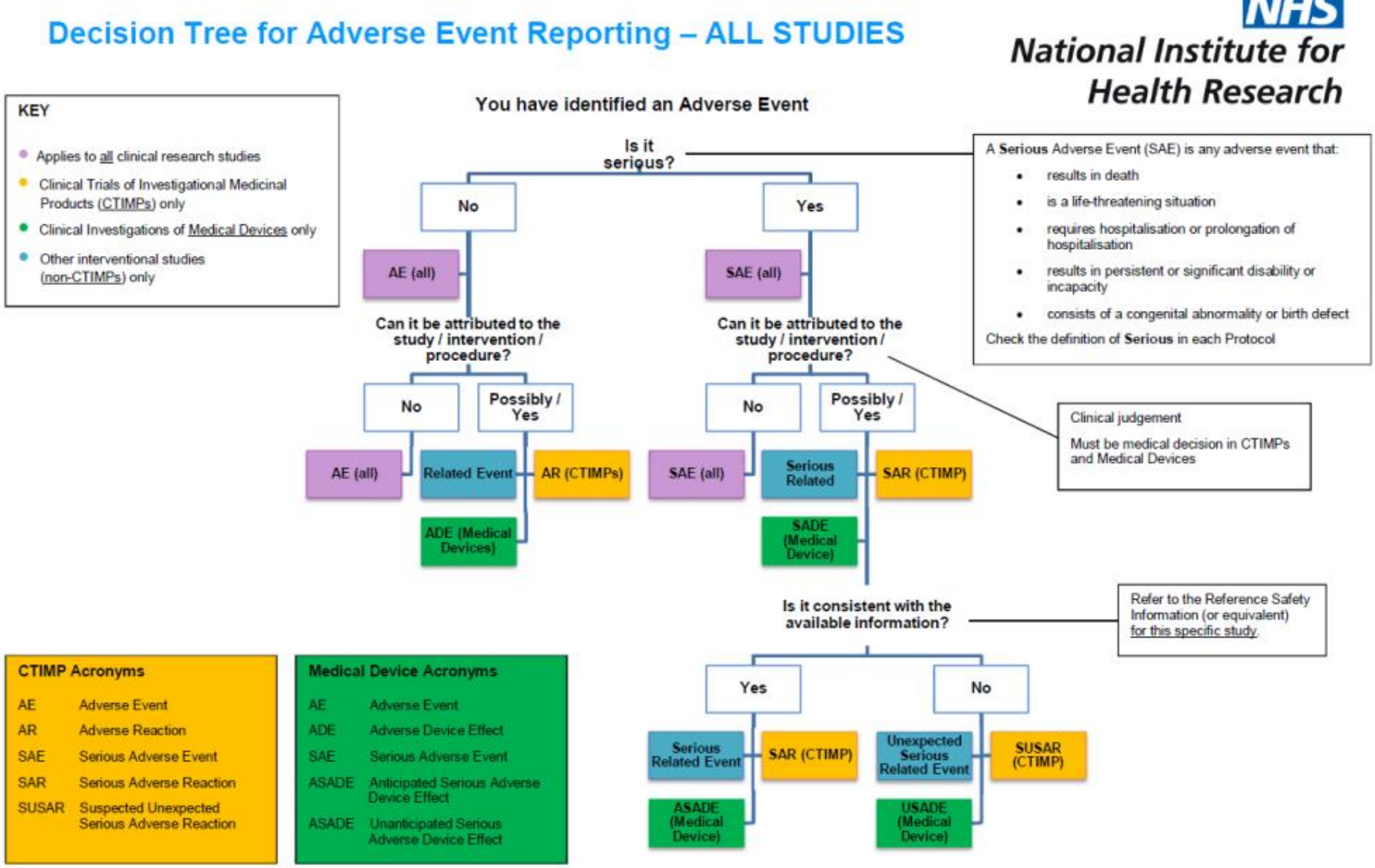
| | or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.<br><br>*****Life-threatening in the definition of a serious adverse event or serious adverse reaction 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 which hypothetically might have caused death if it were more severe. |
| **SAE ALERT Notice** | A template sticker to be inserted in the health record where SAE reporting is required by the Sponsor. The sticker is provided by the Research Office. |
| **Suspected Serious Adverse Reaction (SSAR)** | Any serious adverse reaction that is suspected (*possibly* or *probably*) to be related to an Investigational Medicinal Product. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics or the investigator's brochure<br><br>**Comment:** All adverse events that are suspected to be related to an investigational medicinal product and are both unexpected and serious are considered to be SUSARs. |
| **Source Documents** | Original documents, data and records e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subjects files, and records kept at the pharmacy, at the laboratory and at medico-technical departments involved in the clinical research. |
| **Unexpected Adverse Reaction** | An adverse reaction the nature and severity of which is not consistent with the information about the IMP/product or procedure in question as set out:<br><br>• In the case of an IMP with a marketing authorisation, in the Summary of Product Characteristics (SPC) for that product,<br>• In the case of other IMPs, in the investigator's brochure (IB) relating to the trial in question,<br>• In the case of non-CTIMP interventions or procedures, in the protocol or other reference documents.<br><br>**Comment:** Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented adverse reactions constitute unexpected events |
| **Unanticipated Serious Adverse Device Effect (USADE)** | Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. |

## 10.2 Flow chart 3 – AE assessment decision tree



## 10.3 Assessing adverse events

- **Intensity**

The assessment of an event's intensity will be based upon 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 causes discomfort sufficient to cause interference with normal activities.
- Severe: An event that prevents normal everyday activities.

Note: 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.

- **Causality**

The relationship between an adverse event and the study interventions, IMP or procedures, must be assessed and categorised as below. The assessment will be based upon the investigators clinical judgement to determine the relationship, considering alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc.

The Investigator should consult the protocol, IB, SmPC and any other product information which has been approved by the MHRA before making a final judgement that the event is one of the following:

- Not related: Temporal relationship of the onset of the event, relative to administration of the product or procedure, is not reasonable or another cause can by itself explain the occurrence of the event.
- Unlikely to be related: Temporal relationship of the onset of the event, relative to administration of the product or procedure, 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 or procedure, 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 or procedure, is reasonable and the event is more likely explained by the product/procedure than any other cause.
- Definitely related: Temporal relationship of the onset of the event, relative to administration of the product or procedure, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

Note: Where an event is assessed as possibly, probably, or definitely related, the event is an adverse reaction.

- **Expectedness**

The expectedness of an adverse event shall be determined according to the reference documents as defined in the study protocol (e.g. investigator brochure or marketing information).

Adverse events should be considered unexpected if they add significant information on the specificity or severity of an event.

- Expected: Event is previously identified and described in the protocol and/or reference documents e.g. Investigator Brochure, summary of product characteristics (SmPC) for CTIMP studies.

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

- **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.
- Other - any other safety concern.

**Comment:** Medical judgment should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions 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 of the other outcomes listed in the definition above, should also be considered serious.

****** Life-threatening in the definition of a serious adverse event or serious adverse reaction 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 which hypothetically might have caused death if it were more severe.

### 10.4 Adding SAEs/AEs onto EDGE

To log safety events onto EDGE:

- Go to the patient tab on the red level and open the patient.
- Click on “Events” on the left hand side.
- Click Add.
- Complete event details (there are three sections to complete, please give as much details as possible) and Save.

# CONFIRMATION OF SOP TRAINING RECORD

**A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).**

| **SOP Details:** To be completed by the SOP Controller | |
|---|---|
| Title of SOP | Recording, Assessing & Reporting Adverse Events in Clinical Research |
| Reference Number | PHU/RDSOP/007 |
| Version | V3.0 24 April 2023 |
| Issue Date | 25 April 2023 |
| Implementation Date | 23 May 2023 |

| **Personnel Details** | |
|---|---|
| Name | |
| Job Title & Research Role | |
| Date of Training | |
| Nature of Training | Self Directed/Delivered by etc |
| Records of any meetings to clarify details in SOP | |
| | |
| | |
| | |

| **Signatures** |
|---|
| I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities<br><br>Signature of Trainee …… Date …… |
| I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities<br><br>Signature of Trainer …… Date …….. |
| **Additional Notes & Signatures** |

Signature of Trainer (where appropriate)

I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities

Signature of Trainer …… Date ……..