Royal Papworth Hospital
NHS Foundation Trust

Document Title: Adverse Event Reporting Process

Document Number: PTUC SOP012

Staff involved in development: *Job titles only*	Senior R&D Manager, R&D Operational Manager, Clinical Project Managers, QA Manager
Document author/owner:	Senior R&D Manager
Directorate:	Research and Development
Department:	Research and Development
For use by:	NHS Staff Trust-Wide
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Summary of Amendments

Version No:	Modification:
8.0	Updated throughout the document including changes to section 3.3 SUSARs.
7.0	No change to procedure but substantial administrative changes to clarify the procedure, including for Adverse Event reporting.

Key Related Documents	DN070 Trust policy for reporting accidents, adverse events, incidents and defects FRM005 Adverse Event Reporting FRM007 Serious Adverse Event Reporting Form – Non CTIMP only FRM079 Notification of Pregnancy in a CTIMP FRM080 Pregnancy on a Clinical Trial – Follow up Form SOP069: Code breaking/un-blinding of Clinical Trials. SOP071 Urgent Safety Measures SOP079 Reference Safety Information SOP087 Adverse Event Reporting for Device Trials SOP088 Clinical Trial Participants and Pregnancy TPL038 Patient Information & Consent Form – Pregnancy

Key Points of this Document

- This document sets out the adverse event reporting procedures to be followed by all Royal Papworth Staff who are involved in setting up and running research studies managed by Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth NHS Foundation Trust.
- In this SOP where the term 'sponsor/ed' is used it refers to those studies that are directly sponsored by Royal Papworth NHS Foundation Trust AND those studies that are run and managed by Papworth Trials Unit Collaboration (PTUC) where an external sponsor has delegated responsibility for safety reporting to PTUC.
- For non-Royal Papworth sponsored studies the adverse event reporting process in the study protocol must be followed.

1 Purpose and Content

a. All clinical trials of investigational medicinal products (CTIMPs) must be conducted in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments (2004/1031, 2006/1928, 2006/2984, 2008/941, 2009/1164). As such, this SOP serves to clarify the process for Royal Papworth sponsored and hosted CTIMPs. For externally sponsored CTIMPs safety reporting processes must be detailed within the protocol and sponsor SOPs.

b. For CTIMP trials the sponsor is required under the Clinical Trials Regulations to ensure that adverse events are appropriately recorded, reviewed and reported to the Research Ethics Committee (REC) and the Medicines and Healthcare Products Regulatory Agency (MHRA).

c. For non-CTIMP studies it is the Sponsor's responsibility to decide what level of safety event recording is required before the study starts.

d. This document details the responsibilities delegated to the Chief Investigator by the sponsor regarding adverse event reporting.

e. The reporting requirements in this SOP are mandatory in addition to the Trust's policy for the reporting of accidents / adverse events / incidents and defects (DN070) and non-compliance (where applicable).

2 Roles and Responsibilities

a. All staff are responsible for ensuring that all adverse events, whether or not related to research, are reported in accordance with the Royal Papworth Hospital NHS Trust's policy for the reporting of accidents / adverse events / incidents and defects (DN070), where applicable.

b. This SOP applies to all personnel that are conducting research at the Trust.

c. Staff involved in the conduct of trust hosted or sponsored research studies must comply with the requirements set out in this SOP.

Event Definitions:

Acronym:	Full term:	Definition:
AE	Adverse event	Any untoward medical occurrence in a research participant.
AR	Adverse reaction	SI 2004/1031: Any untoward and unintended response in a subject to an investigational medicinal product (that is related to any dose administered to that subject).
SAE	Serious adverse event	SI 2004/1031: Any adverse event which results in death, is life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect. NB: admissions to A&E departments do not usually constitute hospital admission as defined for the purpose of SAEs. This can be further defined in the trial protocol.
SAR	Serious adverse reaction	Any adverse reaction which results in death, is life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.
SUSAR	Suspected unexpected serious adverse reaction	SI 2004/1031: A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question, as defined in the Reference Safety Information (RSI) for that product.

Assessment Definitions:

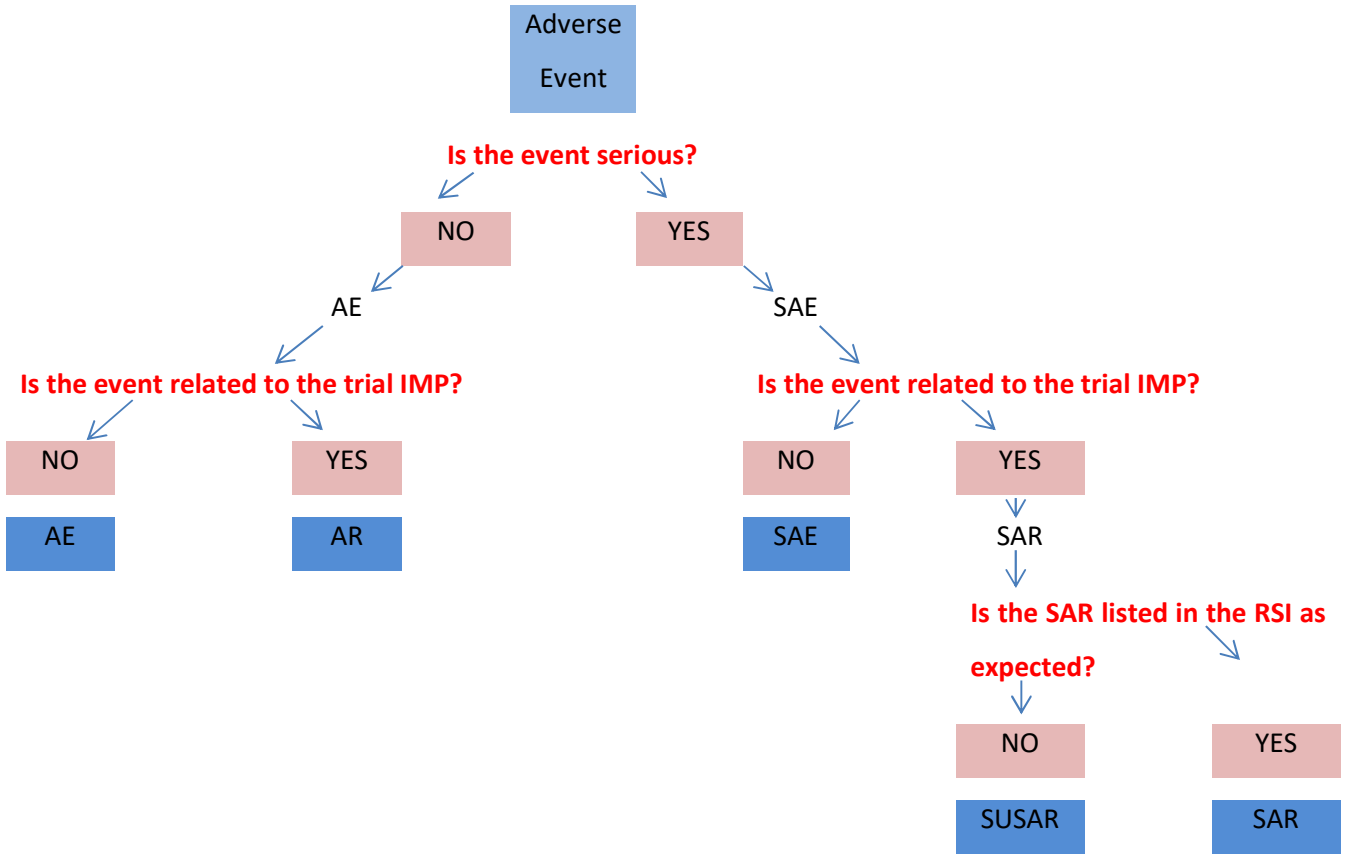
Assessment type:	**Person responsible for undertaking assessment:**	**Explanation of assessment:**
Seriousness	Member of the research team	An event is defined as being serious if it results in any of the following: • Death • Is life threatening • Results in hospitalisation • Hospitalisation is prolonged • Results in disability or incapacity • Consist of a congenital anomaly or birth defect • Is an important medical event
Severity	PI/Medically qualified research team member	Assessment based on clinical judgement: • Mild • Moderate • Severe
Causality	PI/Medically qualified research team member	Assessment of whether or not the event is in any way related to the trial IMP/comparator or placebo are categorised as: • Definitely related (would become a serious adverse reaction) • Probably related (would become a serious adverse reaction) • Possibly related (would become a serious adverse reaction) • Unlikely to be related (would remain a serious adverse event) • Unrelated (would remain a serious adverse event) If the event is deemed to be ***in any way related, i.e. by a selection of definitely, probably or possibly related,*** to the trial IMP/comparator the categorisation of the SAE becomes an SAR.
Expectedness	PI and/or sponsor	If an event becomes a SAR, it must undergo expectedness assessment to determine whether or not the SAR is expected in line with its RSI. • All CTIMPs must have clearly documented Reference Safety Information for all investigational medicinal products (IMPs) being used within the trial. • Comparator drugs and placebos used as a reference in a clinical trial should also have Reference Safety Information /Safety Data Sheet or equivalent available should it be required.

		• For IMPs that have a marketing authorisation, the RSI will usually be listed within the Summary of Product Characteristics (SPC). • For those IMPs without a marketing authorisation, the RSI will be listed in the Investigator Brochure (IB) for that trial. • Please refer to SOP079: Reference Safety Information. For SARs that are cited in the RSI – the event is deemed to be expected and, as such, no further expedited reporting is required. For SARs that that are not cited in the RSI – the event is deemed to be unexpected and expedited reporting is required (see section 3.3).

Other Terms

Term	Description
Investigational Medicinal Product	SI 2004/1031 an Investigational Medicinal Product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used in a reference product in a clinical trial.
Comparator	A comparator is a reference standard used to compare the effectiveness of a new drug or treatment against an existing one. This comparator can be either an investigational or marketed product (active control) or a placebo (inactive control). All drugs used in clinical trials as comparators, even those with market authorisation, are considered IMPs. Comparators are therefore subject to the same reporting requirements as the trial drug, and it is the responsibility of the Sponsor to report adverse events in relation to comparators.
Placebo	'Placebo' is defined as an inactive substance or preparation used as a control in an experiment or test to determine the efficacy of a medicine or treatment.

Decision making flow chart



	SOP section:	Requirements:
AE	3.1	No requirement for expedited reporting
AR	3.1	No requirement for expedited reporting
SAE	3.2	Investigator must immediately report to the sponsor followed up by a written report the following business day
SAR	3.2	Investigator must immediately report to the sponsor followed up by a written report the following business day
SUSAR	3.3	Investigator must immediately report to the sponsor and complete all required expedited reporting detailed as section 3.3

3 Safety Reporting Mailbox.

a. All SAEs/SARs/SUSARs must be reported to QA Safety Team via this mailbox: papworth.safety-reporting@nhs.net.

b. The safety reporting mailbox will be monitored daily for incoming notification of events by the QA Manager and Trial Monitor. Where periods of extended leave occur, this will be delegated to a rota of Clinical Project Managers and Senior R&D management.

c. **For the purpose of reporting timelines, the point at which the email is received into the mailbox is counted as day zero.**

d. The following sequence of events must then take place:

1. The notification email must be responded to by way of acknowledgement of receipt.
2. The notification email and acknowledgement of receipt must be forwarded to the Clinical Project Manager responsible for the trial.
3. The Clinical Project Manager is responsible for filing all emails as appropriate record keeping. These will not be saved or filed within the safety-reporting mailbox.

3.1 Adverse Events (AEs) and Adverse Reactions (ARs)

a. Recording and reporting of AEs must be defined in the trial protocol and timelines dictated within this must be adhered to.

b. Anyone can report a suspected adverse event. This must be reported to the Principal Investigator (or other delegated member of the Research team).

c. It is the responsibility of the Principal Investigator (or suitable delegate) to review the reported suspected adverse events and follow the procedures for recording and onward reporting outlined in the protocol. The Principal Investigator (or suitable delegate) is required to report to the sponsor any AEs that are identified in the protocol as critical to evaluations of the safety of the trial.

d. All AEs must also be recorded within the patient's electronic health record, for full details on how to access this for Royal Papworth Hospital patients refer to the Trust intranet. Please access the following link for full detail on how this must be completed: S:\R&D\Lorenzo\QRG

e. All AEs must be assessed for seriousness, severity and causality. Severity and causality must be completed by a medically qualified individual who has been delegated this task.

f. For CTIMPs the assessment of causality must be performed against the IMP which includes the comparator (if applicable). For Interventional studies (excluding CTIMPs) the causality assessment must be performed against the intervention or as directed in the protocol.

g. The sponsor cannot downgrade the PIs causality assessment but if a disagreement exists, both opinions should be provided.

h. For non-CTIMPs where AE reporting is required this must be done either via completion of FRM005: Adverse Event Reporting Form, or on the study database. This will be agreed prior to the study starting.

i. For Papworth sponsored or PTUC managed CTIMP trials all AEs will be recorded within OpenClinica – see section 3.5.

j. The QA Safety Team is required to have oversight of all AEs reported for all Interventional studies (including CTIMPs).

k. For CTIMPS it is the responsibility of the sponsor to assess if an increase of ARs merits an urgent safety measure or SUSAR/expediated reporting.

3.2 Serious adverse events (SAEs) or serious adverse reactions (SARs)

a. The process for recording and reporting of SAE/SARs must be documented in the trial protocol.

Method of recording:

b. For non-CTIMPs the recording of SAEs will either be via the study database or by using the FRM007: SAE Reporting Form. This is to be agreed prior to the study starting.

c. For Royal Papworth sponsored and PTUC managed CTIMPs, all SAEs and SARs will be recorded within OpenClinica - see section 3.6.

d. All SAEs must also be recorded within the patient's electronic health record, for full details on how to access this for Royal Papworth Hospital patients refer to the Trust intranet. Please access the following link for full details on how this must be completed :S\R&D\Lorenzo\ORG

Process for reporting:

e. ***Immediate***: the Principal Investigator or their delegated representative must report the SAE to the QA Safety Team. This may be completed verbally, via OpenClinica or in writing via an email to papworth.safety-reporting@nhs.net, this inbox is monitored daily. For all events a written report, containing all currently available information, must be submitted following notification of the SAE. Where knowledge of an SAE necessitates further information being

obtained e.g. from the patient's GP or the admitting hospital, then it is permissible for detail to be entered as soon as this becomes available. However, waiting for specific details should not delay the initial notification of the event to the sponsor.

f. For those events that are reported initially as "ongoing," follow-up of the event should be completed until resolution or as stipulated in the study protocol. For CTIMPs this must be documented within the follow-up eCRF within OC (please see section 3.6.c.5 for detail) and for non-CTIMPS this could be in the study database or by submitting a follow up FRM007, as agreed for the study.

g. In any CTIMP that is controlled by the use of either a comparator or a placebo, and where a serious adverse *reaction* is deemed to have occurred – the participant must be unblinded so that the expectedness assessment can be made against the correct reference safety information i.e. that of the IMP or the comparator/placebo. The unblinding must be carried out by the Sponsor representative in order for the study team to remain blinded.

3.3 SUSARs

Identification of a SUSAR and Unblinding:

a. All procedures for recording of SARs must be followed as detailed in Section 3.2 above.

b. The assessment of expectedness of the SAR will be completed by the PI and sponsor with reference to the approved Reference Safety Information or Safety Data Sheet (for placebo). If the event is deemed unexpected following inspection of the RSI the event is a SUSAR.

c. The unblinding for reporting to the competent authority (e.g. MHRA in UK) and REC must be carried out by a sponsor's representative or delegated individual. The MHRA will not accept SUSAR reports containing blinded information. A procedure must be put into place to protect the blind for the study team as far as is practical.

d. If unblinding is required for patient care the blind should be broken in accordance with SOP069: Code breaking/un-blinding of Clinical Trials.

e. If the unblinding reveals that the reaction is expected for the product, then this is not a SUSAR and does not require onward reporting.

Method of reporting:

a. All SUSARs must be reported to the MHRA using the following platform: https://icsrsubmissions.mhra.gov.uk/

Access to this platform is managed by R&D so please contact a member of the R&D QA team (papworth.randdqa@nhs.net) for advice as necessary.

b. For CTIMP trials submitted via the combined review process, only one single submission via the ICSR submission platform is required, with no need for a separate notification to ethics. For CTIMP studies *not* submitted using the combined review process and non-CTIMPs a separate notification must be made to the REC who approved the original trial submission. Follow the HRA website guidance for safety reporting: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/.

c. For trials ongoing in both the UK and the European member states dual reporting is required. You will need to report each SUSAR to both the MHRA and to the European Medicines Agency (EMA's) EudraVigilance Clinical Module (EVCTM).

d. If the SUSAR resulted in death or was life threatening, then SUSAR reporting must be completed to the MHRA (and REC as necessary) within 7 days of knowledge of the original SAR. Any additional relevant information must be sent within 8 days of the initial report.

e. For all other non-fatal or non-life threatening SUSARs completion of the SUSAR reporting to the MHRA (and REC as necessary) must be completed as soon as possible but no later than 15 days from knowledge of the original SAR.

f. The Sponsor of a 'trial performed in the UK' (UK trial) must report the following UK relevant SUSARS to the MHRA:

    - All SUSARs occurring in that trial in UK sites.
    - All SUSARs occurring in that trial in sites outside the UK.
    - All SUSARs originating in a non-UK trial of the same medicinal product if the trial is run by the same sponsor of the trial running in the UK.
    - All SUSARs originating in a non-UK trial of the same medicinal product if the Sponsor of the trial outside the UK is either part of the same mother company or develops the medicinal product jointly, on the basis of a formal agreement, with the Sponsor of the UK trial.

g. The ICSR Submission website should be tested every 6 months by the organisational lead to check that Royal Papworth Hospital has a continuous active account.

h. Studies involving a device must complete safety reporting to the MHRA via the MORE portal: https://www.gov.uk/guidance/mhra-portal-register-to-submit-forms (see SOP087 Adverse Event Reporting for Device Trials).

i. SUSARs must be reported to the trial oversight committees as documented in the trial protocol.

3.4 Special considerations:

Pregnancy:

a. The process for reporting a pregnancy is documented in SOP088 Clinical Trial Participants and Pregnancy.

b. Pregnancy does not meet the definition of an SAE, but a congenital abnormality or birth defect is classed as an SAE.

c. For all CTIMPs, if a pregnancy occurs either in a female participant or the female partner of a male participant, the pregnancy should be followed up until at least the end of the pregnancy (FRM080).

d. The investigator is responsible for notifying the sponsor as soon as they become aware of a pregnancy (FRM079).

   The Investigator must obtain consent using TPL038 for follow-up of the pregnancy from the trial participant (or their partner in the case of male participant subjects). The following method of follow-up is appropriate:

   1. The pregnancy would be that of the trial participant already consented to the trial with a standard trial consent form and follow-up would be part of that trial and documented in the clinical notes.

   2. The pregnancy would be that of the partner of the trial participant in which case we would not consent her with a trial specific consent form. Consent should be sought for follow-up of the pregnancy only and this should be documented with the GP. Under these circumstances follow-up should also be documented on the participant's clinical notes and study related documentation if consent for this has been provided by the partner.

e. Following the end of the pregnancy an SAE form must be completed and reported appropriately if there is a congenital abnormality or birth defect.

Urgent safety measures:

a. Urgent safety measures may be identified as being necessary through safety reporting within a clinical trial. An urgent safety measure should be taken by the sponsor or investigator in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

Should this be necessary please refer to SOP071: Urgent Safety Measures.

3.5 Process for AE reporting within OpenClinica

a. Reporting of AEs within OC is completed following the steps below. Each separate AE requires the following information to be completed within predefined grids and, where required, must be completed by a medically qualified member of the research team. All other information may be recorded by any member of the trial team with appropriated delegated responsibility:

1. **Adverse event/reaction**: initial description regarding the event.

2. **Start date/end date**: dates of the event to be entered if known (end date may not be known at the time of reporting but this may be completed at a later date).

3. **Outcome**: the outcome of the specific event to be selected from the drop-down options available (for example: resolved/resolved with sequelae/ongoing /death).

4. **Severity**: severity of the event to be selected from the drop-down options available; for example, mild, moderate and severe (must be completed by a medically qualified member of the research team).

5. **Causality assessment**: assessment to be made from drop down options on the degree of relatedness of the event (must be completed by a medically qualified member of the research team). See page 4 definitions for further information on causality assessment options.

6. **Seriousness assessment**: simple yes/no selection as to whether or not the event constitutes an SAE.

7. **SAE form completed**: simple yes/no selection based on whether or not the event continues to SAE reporting within OC.

3.6 Process for SAE reporting within OpenClinica

See flow chart below for summary of process

a. For all Royal Papworth Sponsored CTIMPs, Serious Adverse Events (SAEs) are reported electronically using OpenClinica.

b. To report an SAE electronically the user should begin by creating a new SAE event on OpenClinica. The SAE event is a repeating event; therefore, if the participant already has an SAE recorded, the user should select "Add Another Occurrence."

c. Each SAE event contains ***seven electronic case report forms*** (eCRFs), which must be completed in the order they are listed below. The eCRFs contain hidden sections that will appear if certain criteria are met, these sections will appear once the user has saved the current section.

1. **SAE Initial Reporting** – This eCRF describes the event, it can be completed by any delegated staff member. This eCRF should always remain as a snapshot of the current status of the SAE at initial reporting. Therefore, if the SAE is ongoing at initial reporting the 'stop date' field should always remain blank. When the SAE is no longer ongoing the stop date will be recorded in the SAE Follow Up eCRF. Once all of the details have been entered this eCRF can be marked complete.

2. **SAE Medical Assessment** – This eCRF can only be completed by a study team member who is medically qualified. In most cases this will be the PI, but where the PI is not medically qualified this assessment must be delegated to a medically qualified member of the study team. They should review the SAE and record the severity, causality and expectedness in the SAE Medical Assessment eCRF. Once all of the details have been entered this eCRF can be marked complete.

3. **SAE PI Assessment** – This eCRF can only be completed by the PI.

   - If they are medically qualified, they should review the SAE Medical Assessment eCRF and determine whether they agree with the documented medical assessment. Confirmation of agreement is then recorded within the PI assessment eCRF. In the event that they do not agree with the medical assessment, they are able to amend the detail within the medical assessment eCRF and must then document the reason for any changes in the comment section of the PI assessment eCRF.

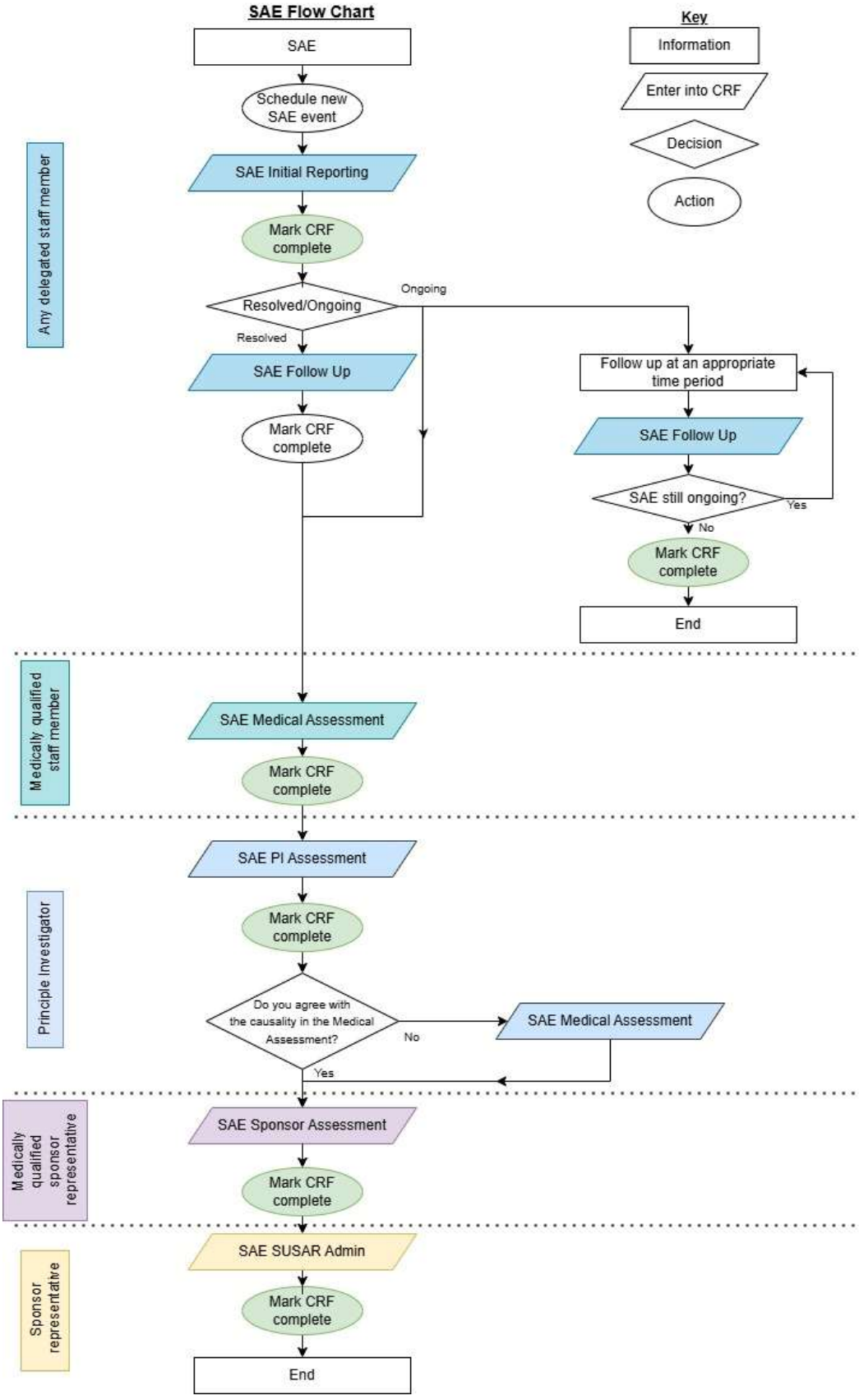
   - If they are not medically qualified, they will not be able to make any changes to the SAE Medical Assessment eCRF.

4. **SAE Sponsor Assessment** – This eCRF must be completed by a medically qualified sponsor representative (see Section 3.3 for the process). The sponsor will review the SAE Medical Assessment eCRF and enter an independent sponsor level expectedness assessment to determine if the event is a SUSAR. If the sponsor assessment differs from that in the SAE Medical Assessment eCRF, the comment box within the sponsor assessment eCRF must be completed. Once all of the details have been entered this eCRF can be marked complete.

5. **SAE Follow Up** – If the SAE is marked as ongoing within the initial reporting eCRF, a section will appear that is used to record the follow up of the SAE. Any member of the study team can enter the event follow up details. Each time the SAE is followed up a new row should be added. Each row should contain details from the follow up, the date, and if the SAE is now resolved. Once the SAE is marked as resolved a section will appear asking for the SAE end date. Only once the eCRF has been marked as resolved with an end date can this eCRF be marked complete.

6. **SAE SUSAR Admin Form** – This eCRF must be completed by a delegated sponsor representative. If the SAE Sponsor Assessment eCRF identifies the SAE as a SUSAR this admin form will automatically be visible. This form is used to record administrative actions regarding the onward reporting of the SUSAR to regulatory bodies, as necessary. For further details on the reporting of SUSARs please refer to section 3.3 above.

7. **SAE Print** – This is a read-only eCRF that is auto-populated from responses in the other eCRFs. The purpose of this eCRF is to bring all the key information together for ease of printing and uploading on the electronic patient record.


SAE Flow Chart
Key
Information
Enter into CRF
Decision
Action
SAE
Schedule new SAE event
SAE Initial Reporting
Mark CRF complete
Resolved/Ongoing
Ongoing
Resolved
SAE Follow Up
Mark CRF complete
Follow up at an appropriate time period
SAE Follow Up
SAE still ongoing?
Yes
No
Mark CRF complete
End
Any delegated staff member
Medically qualified staff member
SAE Medical Assessment
Mark CRF complete
SAE PI Assessment
Mark CRF complete
Principle Investigator
Do you agree with the causality in the Medical Assessment?
No
SAE Medical Assessment
Yes
Medically qualified sponsor representative
SAE Sponsor Assessment
Mark CRF complete
Sponsor representative
SAE SUSAR Admin
Mark CRF complete
End

4 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Site and Sponsor File.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Management/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	Current active version approved date
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2023)

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	No	No	No	No	No	No	No
Positive/Negative							

Review date:	July 2028