Document Title: Adverse Event Reporting Process

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Summary of Amendments

Version No:	Modification:
8.0	Minor changes throughout
9.0	Minor changes and updated for new MHRA SUSAR reporting

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 setting up and running research studies managed by Royal Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth NHS Foundation Trust.
- For non-Royal Papworth sponsored studies the adverse event reporting process in the study protocol must be followed.

1 Purpose and Content

- 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 Papworth sponsored and hosted CTIMPs. For externally sponsored CTIMPs safety reporting processes must be detailed within the protocol and sponsor SOPs.

a.

b. 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. This document details the responsibilities delegated to the Chief Investigator by the Sponsor regarding adverse event reporting.

d. 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 (DN70) 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 (DN70), where applicable.

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

c. Staff involved in the conduct of CTIMPs must comply with the requirements set out in this SOP.

Event Definitions:

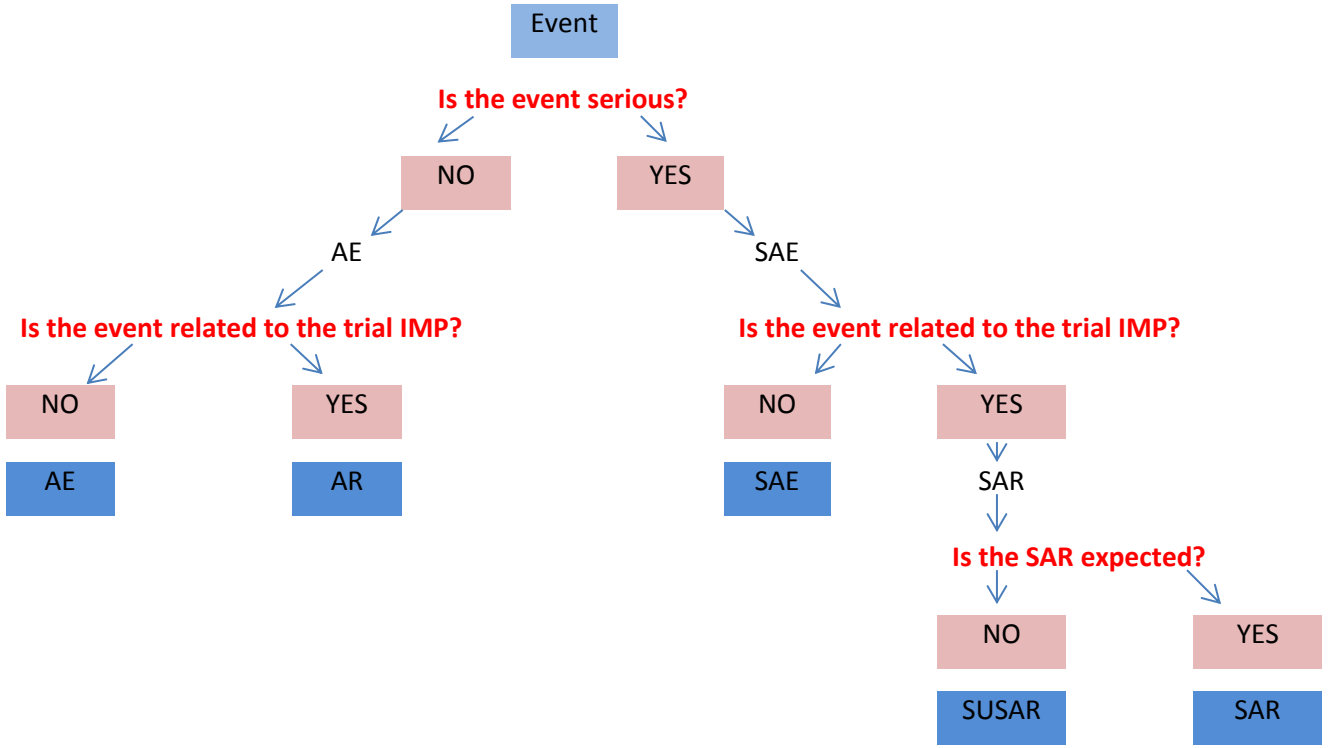
Acronym:	Full term:	Definition:
AE	Adverse event	SI 2004/1031: Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.
AR	Adverse reaction	SI 2004/1031: Any untoward and unintended 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. However, this can be further defined to in included/excluded in the trial protocol. It is the responsibility of the investigator to clarify this during trial development and document any decisions 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 NB: admissions to A&E departments do not usually constitute hospital admission as defined for the purpose of SAEs. However, this can be further defined to in included/excluded in the trial protocol.
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 summary of product characteristics for that product in the case of a product with an authorisation, or within the investigator's brochure relating to the trial in question in the case of any other investigational medicinal 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
Causality	PI or other delegated medically qualified member of staff	Assessment of whether or not the event is in any way related to the trial IMP and 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 the categorisation of the SAE becomes an SAR
Expectedness	PI and sponsor	Assessment of whether of the not the SAR is expected. • All CTIMPs must have clearly documented Reference Safety Information for all investigational medicinal products (IMPs) being used within the trial. • For IMPs that have a marketing authorisation the RSI will 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 either the SPC or the IB – the event is deemed to be expected and, as such, no further expedited reporting is required

		For SARs that that are not cited in either the SPC or the IB – the event is deemed to be unexpected and expedited reporting is required (see section 3.3). The Sponsor cannot downgrade an Investigator's causality assessment, if the sponsor disagrees that the event is related to the drug, clarification will be sought from the Investigator. If the sponsor still disagrees, both opinions must be provided with the report. However, the sponsor may upgrade the report.

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 within 24 hours of knowledge of the event
SAR	3.2	Investigator must immediately report to the sponsor followed up by a written report within 24 hours of knowledge of the event
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 the sponsor via this mailbox: Papworth.safety-reporting@nhs.net.

b. The safety reporting mailbox will be monitored daily for incoming notification of events by the Clinical Trials Monitoring and Audit Co-ordinator. 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 Project Manager responsible for the trial
3. The 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)

Method and timeframes for reporting

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

b. All AEs must also be recorded within the patient's health record i.e. for Royal Papworth Hospital NHS Foundation Trust this will be in Lorenzo. Please access the following link for full detail on how this must be completed: S:\R&D\Lorenzo\QRG

c. For non-CTIMPs AE reporting must be done either via completion of FRM005: Adverse Event Reporting for AEs/ARs or on OpenClinica. This will be agreed prior to the study starting.

d. For CTIMPs, all AEs will be recorded within OpenClinica – see section 3.5

e. The investigator 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. It is the responsibility of the investigator to identify any such events and these must be documented in the trial protocol.

f. The sponsor is required to keep a detailed record of all AEs reported by the investigator

g. The investigator must assess all AEs for seriousness and causality

h. It will be the responsibility of the sponsor in assessing if an increase of ARs merits an urgent safety measure or SUSAR reporting.

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

Method and timeframes for reporting:

Method of reporting:

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

b. For non-CTIMPs the recording of SAEs will either be via OpenClinica (OC), or can be recorded on the R&D FRM007: Adverse Event Reporting Form for SAEs. This is to be agreed prior to the study starting

c. For CTIMPs, all SAEs and SARs will be recorded within OpenClinica - see section 3.6

All SAEs must also be recorded within the patient's health record i.e. for Royal Papworth Hospital NHS Foundation Trust this will be in Lorenzo. Please access the following link for full detail on how this must be completed: S:\R&D\Lorenzo\QRG

Process for reporting:

d. ***Immediate***: the investigator or their delegated representative must report the SAE to the sponsor. This may be completed either verbally or in writing. However, in all events a detailed written report must follow any immediate method of reporting within 24 hours of knowledge of the event.

e. Where knowledge of an SAE necessitates further information being obtained either from the patient's GP or the admitting hospital, then it is permissible for detail to be entered as soon as this becomes available.

f. For those events that are reported initially as "continuing" follow-up of the event must be completed. This must be documented within the follow-up CRF within OC (please see section 3.6h for detail)

3.3 SUSARs

Identification of a SUSAR and Unblinding:

a. All procedures for reporting of SARs must be followed

b. Assessment of expectedness of the SAR will identify whether or not the event is a SUSAR. If the trial includes an IMP and comparator drug, initial expectedness needs to be completed against both sets of reference safety information.

c. If the reaction is unexpected for either, the blind should be broken in accordance with SOP069: Code breaking/un-blinding of Clinical Trials. The unblinding for regulatory purposes should be carried out by a sponsors representative. A procedure must be put into place to protect the blind for the study team.

d. If the reaction is unexpected for the product the unblinding reveals, then this is a SUSAR and must be reported as detailed below.

Method of reporting:

e. All SUSARs occurring in Great Britain or Northern Ireland must be reported to the MHRA using the following platform: www.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.

f. 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).

g. If the SUSAR resulted in death or was life threatening then eSUSAR reporting must be completed within 7 days of knowledge of the original SAR

h. For all other SUSARs completion of the eSUSAR reporting must be completed within 15 days of knowledge of the original SAR

i. All SUSARs must also be reported to the research ethics committee (REC) who granted original approval for the trial. For details on how to report to the REC please see: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

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

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 to a trial specific consent form. Consent should be sought for follow-up 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:

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 outlined 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 data entry rights:

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 or 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
4. Severity: severity of the event to be selected from the drop down options available (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 (to be completed by a medically qualified member of the research team)
6. SAE: 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 or managed 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.

d. **SAE Initial Reporting** – This eCRF describes the event, it can be completed by any 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.

e. **SAE Medical Assessment** – This eCRF can only be completed by medically qualified study personnel. The medically qualified personnel should review the SAE and determine the causality, severity and expectedness and record this in the SAE Medical Assessment eCRF. Once all of the details have been entered this eCRF can be marked complete.

f. **SAE PI Assessment** – This eCRF can only be completed by the PI. The PI should review the SAE Medical Assessment eCRF and determine whether they agree with the causality, severity and expectedness documented in the medical assessment. Confirmation of agreement is then recorded by the PI within the PI assessment CRF. In the event that the PI does not agree with the medical assessment, they are able to amend the detail within the medical assessment CRF, and must then document the reason for any changes made within the PI assessment CRF.

g. **SAE Sponsor Assessment** – This eCRF can only be completed by a sponsor representative who should be medically qualified. The sponsor representative should review the SAE and assess whether the event is expected per study Reference Safety Information (ref: SOP079: Reference Safety Information). The sponsor may not downgrade any assessment made by the PI. However, they are able to record an assessment more severe than that recorded by the PI i.e. increased causality or expectedness. If the sponsor assessment differs from that of the PI,

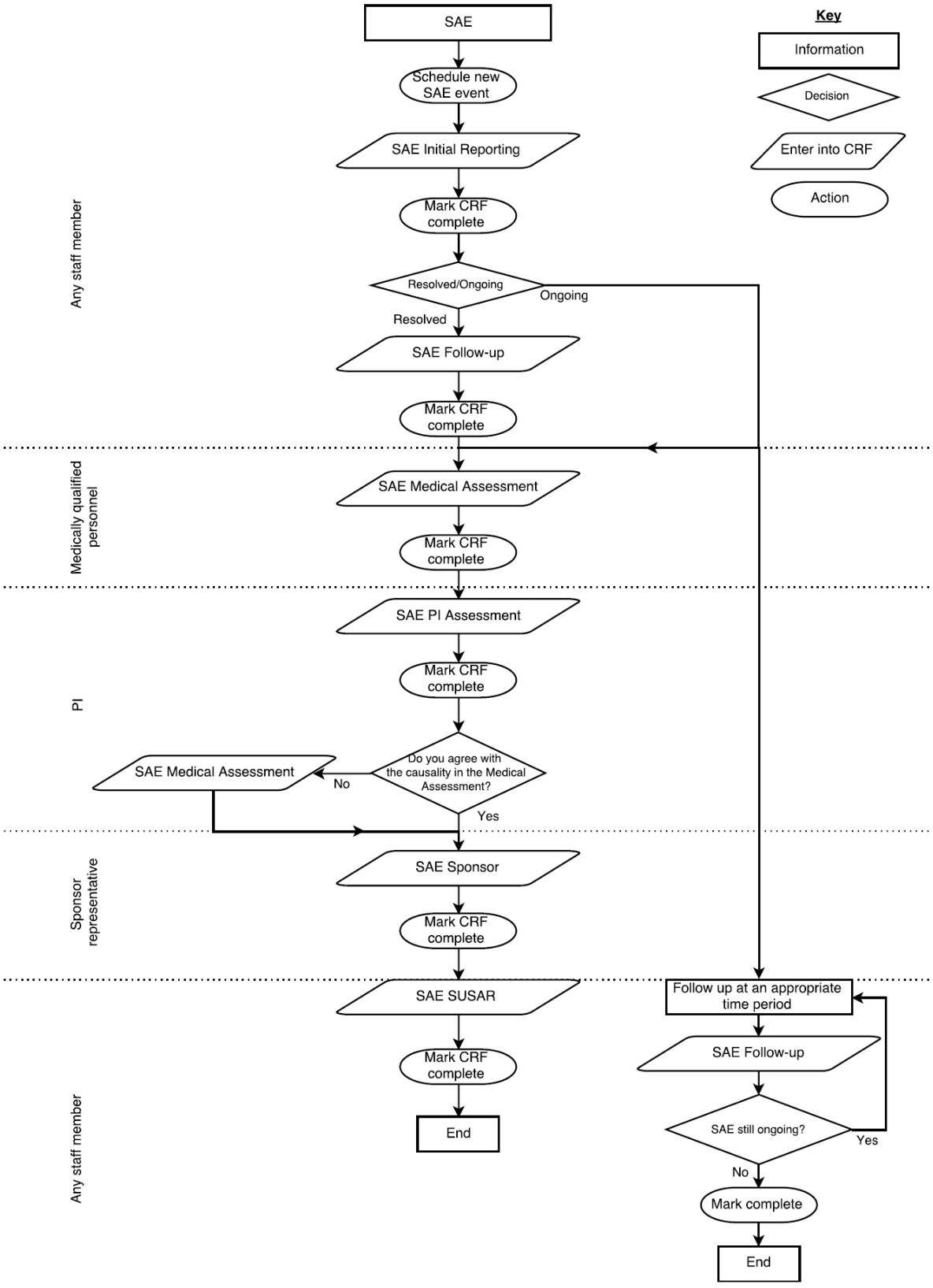
the comment box within the sponsor assessment CRF must be completed by the sponsor. Once all of the details have been entered this eCRF can be marked complete.

h. **SAE Follow Up** –If the SAE is marked as ongoing within the initial reporting CRF, a section will appear that is used to record the follow up of all SAEs. 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.

i. **SAE SUSAR** – This eCRF can be completed by any staff member. It is an administrative eCRF used to record any event where an SAE is assessed as being a SUSAR. This CRF will only appear if a combination of potential causality and unexpectedness are such that a SUSAR is possible. For further reporting of SUSARs please refer to section 3.3 above in this SOP.

j. **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 onto Lorenzo.

SAE Flowchart



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 Investigator and Sponsor Master 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 (2018).
Key related documents:	Trust Research Policy FRM035 CTIMP under quarantine FRM036 Quarantine File Log

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:	August 2026

I certify the contents of this SOP has been reviewed and ratified

Patrick Calvert 10-02-2024

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Signed by Dr Patrick Calvert, Clinical Director of R&D Date

SOP release date: .....