York and Scarborough Teaching Hospitals NHS Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S13

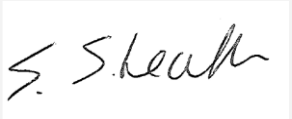
R&D SAE/ SAR/ SUSAR Handling and Assessment Procedure

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.research.yorkhospitals.nhs.uk/sops-and-guidance-/ and/or Q-Pulse

SOP Reference:	R&D/S13
Version Number:	6.0
Author:	Deborah Phillips
Implementation date of current version:	6th December 2022

Approved by:	Name/Position:	Lydia Harris, Head of R&D
	Signature:	
	Date:	8th November 2022
	Name/Position:	Sarah Sheath, SOP Controller
	Signature:	
	Date:	8th November 2022

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	10th September 2009	
2.0	1st July 2010	eSUSAR reporting incorporated
3.0	1st April 2011	Inclusion of statement to clarify that the Sponsor may not downgrade an investigator assessment of an SAE.
4.0	22nd April 2013	Change of SOP Controller. Removal of references to the North and East Yorkshire R&D Alliance.
5.0	17th August 2017	
6.0	6th December 2022	Change of link to R&D website. Change of Trust name. Removal of reference to notification via fax. General changes made to fit in with current R&D structure. Removal of reference to 'holding files' and replacing with TMFs.

Contents

1 Introduction, Background and Purpose

This SOP describes the actions to be taken by the R&D Unit upon receiving notification of a Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) for a Sponsored research studies, hosted study, or for a study for which York and Scarborough Teaching Hospitals NHS Foundation Trust is contracted to provide pharmacovigilance services.

R&D/S05 & S19 describe the procedures for reporting research related events for CTIMP and non-CTIMP studies.

2 Who Should Use This SOP

This SOP should be used by all members of the R&D Unit when SAE/ SAR or suspected SUSAR notification is received.

3 When this SOP Should be Used

This SOP should be followed by members of the R&D Unit upon receiving notification of an SAE/SAR or suspected SUSAR. The purpose is to ensure that all SAE/ SAR/ SUSARs reported to the R&D Unit are acted upon within the specified timescales.

Collectively the above reports that notify the Sponsor of safety issues with studies are referred to as 'safety notifications' for the purpose of R&D Unit SOPs

4 Procedure(s)

Research related Adverse Events and Adverse Reactions must be reported following the procedure in R&D/S05 for CTIMP studies, or R&D/S19 for non-CTIMP studies.

Adverse Incidents should be reported by the Investigator following the Trust's Adverse Incident Reporting System (Datix) .

It is the responsibility of the Research Quality Assurance Manager (QAM) and Research Quality Assurance Co-ordinator (RQAC) to handle safety notifications reported to the R&D Unit. In the absence of the QAM or RQAC then the R&D Senior Manager on duty will be responsible for carrying out this SOP.

4.1 Serious Adverse Events Reported to the R&D Unit

Any safety notifications must be made in an expedited fashion to research.governance@york.nhs.uk

For clarity, the date of initial email notification to the R&D Unit will be designated as day 0 of the reporting period. This is regardless of when R&D Unit personnel act upon the notification.

Roles and responsibilities for the R&D Unit staff when receiving & acknowledging safety notifications is covered in R&D/S12.

4.1.1 Notification via Email

Upon receipt of an SAE/SAR or SUSAR report by the R&D Unit via email, the QAM or RQAC will review the event and allocate a unique SAE/SAR/SUSAR reference number to it.

The original notification report will be filed in the Quality Assurance: '*SARs and SUSARs*' Folder on X drive. The QAM or RQAC or a designated individual will then be responsible for ensuring that:

1. acknowledgement of receipt of the SAE/ SAR/ SUSAR was sent to the Investigator reporting it as soon as possible and before noon of the following working day.

2. the received SAE/ SAR/ SUSAR is logged in the Research QA SARs and SUSARs spreadsheet

3. the notification form is checked for completeness and signatures (in the event of missing information then a request will be made for an updated report)

4. a checklist (R&D/F49) can be completed and filed alongside the SAE/ SAR/ SUSAR documentation and key correspondence

5. check with the relevant research team if the SAE/ SAR/ SUSAR is logged in the relevant section of the TMF for Trust sponsored studies, or in the ISF for hosted studies.

6. for Trust sponsored or co-sponsored studies - the Medical Expert (ME) named in the TMF is contacted to undertake an independent assessment of the SAE/ SAR/ SUSAR (where applicable). For hosted studies - the study sponsor is contacted to confirm their assessment.

4.1.2 Follow up Reports

Follow up information should be provided by the Investigator each time new information is available using the appropriate Follow up Report Forms. All follow up reports must be acknowledged, logged, checked and actioned as per 4.1.1.

4.2 Assessment of SAE/SAR/SUSAR

For Trust sponsored studies, if the assigned ME is unavailable, then advice will be sought from the Research Adviser or Lead Research Nurse as to who to approach as an alternative expert.

The ME will make an independent assessment of intensity, causality, expectedness and seriousness using the criteria described in R&D/S05 or R&D/S19 in consultation with the R&D Unit staff who can co-ordinate the provision of any additional information required by the ME.

For hosted studies, the study sponsor will coordinate assessment of intensity, causality, expectedness, and seriousness as per their procedures.

If the study Sponsor considers the reported event to be unexpected (as specified in the study approved RSI), then for blinded studies the sponsor will issue a request to unblind the subject following the procedure for unblinding as described in the study protocol. No member of the investigator team may unblind a subject or be notified of the result of unblinding for the purpose of assessing an SAE/ SAR/ SUSAR (refer to Appendix A).

For CTIMPs the request to unblind should be made by RQM or RQAC (or a designated individual) via email to the Pharmacy Clinical Trials Team at YorkPharmacy.ClinicalTrialsTeamMailbox@york.nhs.uk

and copied to the Pharmacy Clinical Trials Manager.

The request should have the subject heading SPONSOR REQUEST TO UNBLIND and must contain the following information:

1. Trial Name
2. EudraCT number
3. IRAS number
4. CI/PI name
5. Sponsor
6. Participant study ID
7. Participant initials

QAM or RQAC or designated individual will complete the Sponsor Report Form (R&D/F09) detailing the Sponsor assessment and whether and how the subject was unblinded.

4.3 Retention of documentation

All forms, documentation, file notes, correspondence pertaining to the SAE/ SAR/ SUSAR will be filed in the Research Quality Assurance Folder on X drive, as well as in the study TMF for trust sponsored studies, and in the study ISF for hosted studies.

4.4 Reporting Timescales for SAEs and SUSARs

If an SAE is assessed by either the Investigator or the sponsor to be ***related*** it becomes a SAR, if a SAR is then confirmed as ***unexpected*** (as listed in the study approved RSI), it becomes a SUSAR.

All SUSARs must be reported to the MHRA and/or the Research Ethics Committee that granted approval within the specified timescales as detailed below. Note: All reports must be submitted unblinded.

For CTIMP studies all SUSARs assessed as fatal or life-threatening must be reported within seven days of becoming aware of the event. SUSAR assessed as NOT fatal or life threatening must be reported within 15 days of becoming aware of the event.

For non-CTIMP studies should be submitted to the REC. These should be sent within 15 days of becoming aware of the event.

Study sponsors have the right to suspend or withdraw approval for a study. This may happen, but is not limited to, where public health and safety is considered to be at risk, where the safety and well being of research subjects or staff are considered to be at risk. For more information on urgent safety measures refer to relevant SOP.

4.5 SUSAR Reports to the MHRA

The Sponsor of a trial or any other person to whom the Sponsor has delegated this responsibility to must report all suspected unexpected serious adverse reactions (SUSARs) which happen during the course of the trial to the MHRA.

For hosted studies this will be undertaken by the external sponsors.

For all trials for which the Trust is providing Pharmacovigilance services, including all Trust sponsored studies, this will be undertaken by QAM or RQAC (or a designated individual).

They shall report a SUSAR to the MHRA in one of the following ways:

- using ICSR Submissions, which replaces the EudraVigilance website (EVWEB). The ICSR Submissions route is used to submit single reports.
- using the MHRA Gateway, which replaces the Eudravigilance Gateway. The Gateway route is used to submit bulk reports. To gain access to the MHRA Gateway you need to register to another portal called MHRA Submissions.

The QAM or RQAC or designated individual will complete the online form using the information provided by the investigator, following the user instructions. On submission a full report should be downloaded for submission to the main REC and for consideration at the next R&D Group meeting.

4.6 SUSAR Reports to the Ethics Committee

Reports of SUSARs will also be submitted to the main ethics committee that granted approval for the study. The report generated by and downloaded from the MHRA Submissions website as described in section 4.5 can be used. All safety reports to the main REC should be accompanied by a covering form. This document can be downloaded from the HRA website.

4.7 SUSAR Reports to Concerned Investigators

It is the responsibility of the Sponsor to ensure that SUSARs are reported to all concerned investigators. A concerned investigator is any investigator in trials sponsored by the same Sponsor who is using the same IMP. The frequency with which this will be performed may be determined as part of the risk assessment (R&D/S18) and will be documented in the TMF for Trust sponsored studies, but will be no less frequently than quarterly under any circumstances.

Note: Any immediate safety concerns must be communicated to all concerned investigators in an expedited fashion.

For all multi-site studies, the Chief Investigator must inform all Principal Investigators of SUSARs occurring on the study. It is the responsibility of the CI to communicate all information to the PIs, in particular any information that could adversely affect the safety of subjects. This notification must be documented in the TMF.

4.8 SAE/SUSAR Reports to the Data Monitoring Committee (DMC)

For CTIMPS the DMC may require notifying of SAEs/ SARs/ SUSARs during the trial. It is important to check the study specific information regarding this.

4.9 Non-Investigational Medicinal Products (NIMPs)

Products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to subjects participating in the trial and used in accordance with the protocol. This might be, for example, medicinal products such as support or rescue/escape medication 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) in Directive 2001/20/EC and are called non-investigational medicinal products (NIMPs).

If, following unblinding, it is revealed that the subject received the comparator drug, but the event still meets the criteria of a SUSAR, in that it is unexpected according to the comparator reference document (which should be defined in the protocol), then it should be reported in an expedited fashion to the Regulatory Authorities and to the drug company holding the Marketing Authorisation (MA) for the comparator. The MA holder should be named in the Summary of Product Characteristics (SmPC).

If unblinding reveals the IMP to be placebo this will not require expedited reporting unless, in the opinion of the ME, Investigator or the RA (or designated individual), the event was related to a reaction to the placebo.

Other non-investigational medicinal products (NIMPs) used in the trial may also be subject to reporting requirements and details should be provided in the study protocol.

The following scenarios when an adverse reaction to a NIMP would require reporting:

- If the adverse reaction is suspected to be linked to an interaction between a NIMP and an IMP and is serious and unexpected
- If a SUSAR is reported and it might be linked to either a NIMP or an IMP but cannot be attributed to only one of these
- If an adverse reaction associated with the NIMP is likely to affect the safety of the trial subjects

Serious Adverse Reactions (SARs) associated with a NIMP should be reported to the Marketing Authorisation Holder (MAH) in order that this information may be used in the MAH's ongoing safety monitoring procedures. The MA holder should be named in the SmPC.

A SAR associated with a NIMP which does not have a Marketing Authorisation in the UK must be notified to the MHRA.

4.10 Reporting to R&D Group

All SUSARs for sponsored and hosted studies will be reported to the R&D Group via the Quarterly QA report. In the event of a requirement to notify the R&D Group urgently (for example, in the event that the study may need to be suspended or

terminated) then this will be communicated by email and discussed with the Chair of the R&D Group and the Clinical Lead for Research by telephone/in person.

5 Related SOPs and Documents

R&D/S05 Research Related Adverse Event Reporting Procedure for CTIMP Studies

R&D/S19 Research Related Adverse Event Reporting Procedure for non-CTIMPs

R&D/F07 Research Related SAE/SUSAR Initial Report Form

R&D/F08 Research Related SAE/SUSAR Follow up Report Form

R&D/F09 Research Related SAE/SUSAR Sponsor Report Form

R&D/S68 Urgent Safety Measures

R&D/F46 AE/SAE Log

R&D/F47 SUSAR Data Collection Form

R&D/F49 SAE/SUSAR R&D Unit Checklist

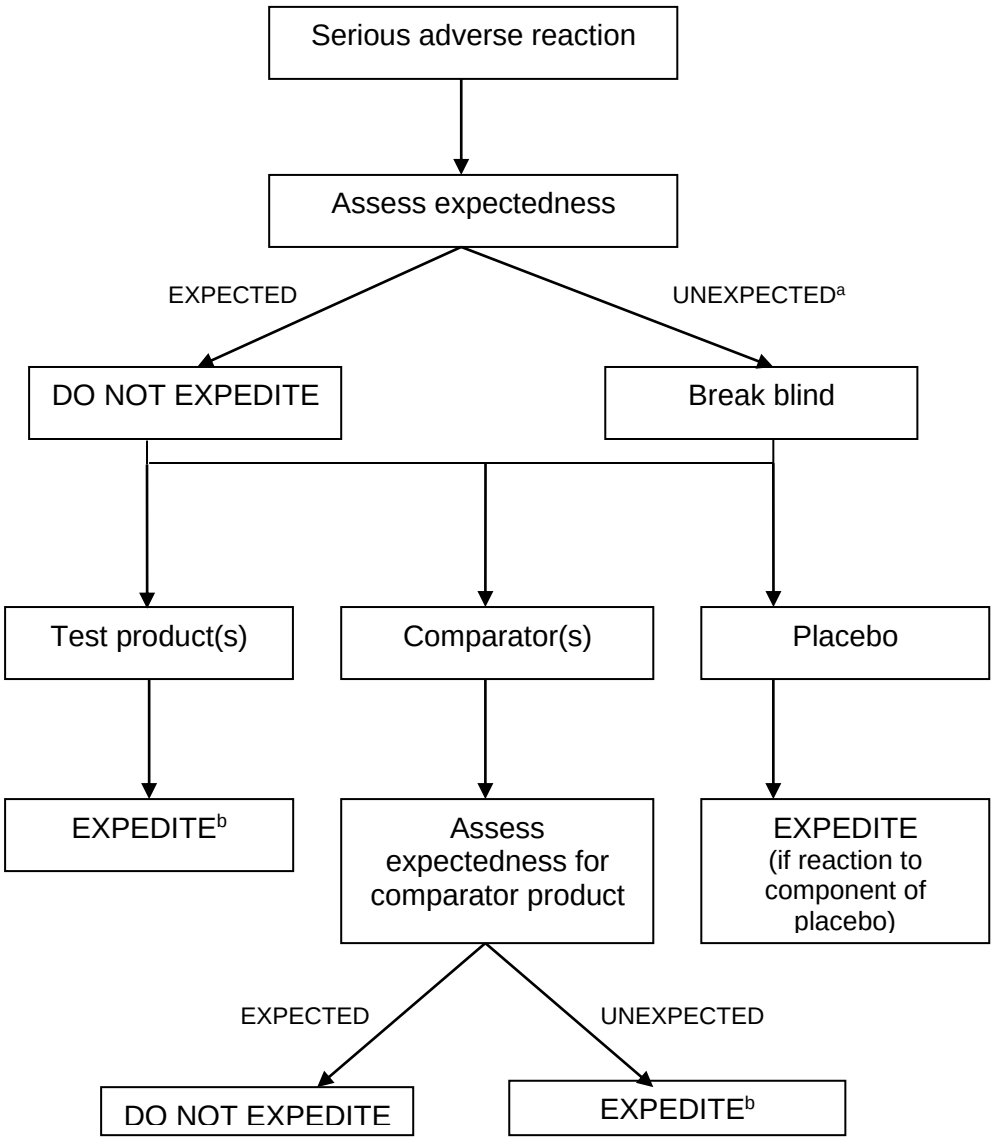
R&D/F09 SAE/SUSAR Unblinding Record

R&D/S12 Receiving and Acknowledging Safety Notifications to the R&D Unit

Good Pharmacovigilance Practice Guide – MHRA Publication Published 2009

6 Appendix A

Considerations for Blinded Trials (from the Good Pharmacovigilance Practice Guide)



[a] for any of the test products administered to that subject

[b] If the reaction is unexpected for the actual test or comparator product administered to that trial subject