York Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S13

R&D SAE/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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.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.northyorksresearch.nhs.uk/sops.html and/or Q-Pulse

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	Signature:	Signed copy held by R&D Unit
	Date:	17th July 2017
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	Signature:	Signed copy held by R&D Unit
	Date:	17th July 2017

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	

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) or Suspected Unexpected Serious Adverse Reaction (SUSAR) for a Sponsored research studies or for a study for which York Teaching Hospital NHS Foundation Trust is contracted to provide pharmacovigilance services. R&D/S05 describes the procedure for reporting suspected Serious Adverse Events (SAEs) to the R&D Unit.

2 Who Should Use This SOP

This SOP should be used by all members of the R&D Unit.

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 for a study for which the R&D Unit is providing pharmacovigilance or safety oversight. The purpose is to ensure that all SAE/SUSARs reported to the R&D Unit are acted upon within the specified timescales.

4 Procedure(s)

For definitions of Adverse Events and Adverse Reactions arising from clinical trials of investigational medicinal products (CTIMPS), refer to the Research Related Adverse Event Reporting SOP (R&D/S05). Research related Adverse Events and Adverse Reactions must be reported following the procedure in R&D/S05 or R&D/S19 for non-CTIMP studies. Adverse Incidents should be reported by the Investigator following the Trusts own Adverse Incident Reporting System or Process.

It is the responsibility of the Research Quality Assurance Manager (QAM) or Research Adviser (RA) to handle SAEs reported to the R&D Unit. In the absence of the QAM or RA then the Head of R&D will be responsible for carrying out this SOP. In the absence of the above personnel then the R&D Unit representative who receives notification must act upon it until such a time that one of the above personnel is available.

In this document, when reference is made to the R&D Unit taking responsibility then the responsibility is as outlined above.

4.1 Serious Adverse Events Reported to the R&D Unit

A Serious Adverse Event should be reported to the R&D Unit via Fax (Fax: 01904 725700) following the Research Related AE Reporting Procedure.

If the R&D Unit fax is unresponsive or if it has been agreed with the R&D unit in advance then an Investigator may email the notification to research.governance@york.nhs.uk. This email box is checked every working day and it is the responsibility of the individual signing the fax log to ensure this is done.

For clarity, the date of initial faxed/emailed 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 safety notifications is covered in R&D/S12.

4.1.1 Notification via Fax

Upon receipt of an SAE/SUSAR report by the R&D Unit via fax (or email), the QAM (or RA) will review the event and allocate a unique SAE reference number to it. Reference numbers will include a trial identifier (using characters) followed by a three digit integer which will increase sequentially throughout the trial for reported SAE/SUSARs. An example of such a reference number might be TROP001, which will be followed by TROP002 etc. The notification report will be photocopied and the original placed in the Holding File located in the R&D Unit. The QAM (or a designated individual) will then be responsible for ensuring that:

1. the SAE is logged in the relevant section of the Study Sponsor File;
2. the form is checked for completeness and signatures (in the event of missing information then a request will be made for an updated report);
3. a checklist (R&D/F49) is completed and attached to the SAE documentation retained in the holding file;
4. acknowledgement of receipt of the SAE is sent to the Investigator reporting the SAE as soon as possible and before noon of the following working day. The acknowledgement should be sent to the fax machine or email address from which the notification was made;
5. the Medical Expert (ME) named in the Sponsor file is contacted to undertake an independent assessment of the SAE (where applicable).

4.1.2 Follow up Reports

Follow up information will be provided by the Investigator each time new information is available using the Follow up Report Form (refer to Section 5). All follow up reports will be photocopied, and the original placed in the Holding File until the SAE resolves or until a decision is made not to continue follow up. SAE follow-up reports will be acknowledged as per 4.1.1 and logged on the SAE checklist.

4.2 Assessment of SAE

If the ME is unavailable then advice will be sought from the Head of R&D 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.

If *either* the investigator or the Sponsor (in consultation with the ME) consider the SAE to be possibly, probably or definitely related AND unexpected then for blinded studies the QAM or RA (or designated individual) 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 (refer to Appendix A).

For CTIMPs the request to unblind should be made by email to the Pharmacy Clinical Trials Team at pharmacyclinicaltrialsteam@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

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

For CTIMPs the QAM (or designated individual) will request that the reporting investigator immediately completes a SUSAR Form (refer to Section 5). This information should be returned to the R&D unit within 48 hours detailing the information available at the time.

For all studies, the QAM (or designated individual), together with the RA and ME, will consider whether any actions, in addition to those already taken by the investigator, are required and will discuss these with the Investigator and Head of R&D.

4.3 Retention of documentation

All forms, documentation, filenotes and/or correspondence pertaining to the SAE/SUSAR will be retained within the Holding File until such a time that the SAE has resolved or a decision not to continue follow up has been made. This decision will be made by the QAM or RA (taking advice from the ME if required) and the CI or PI. This decision will be documented.

Upon the conclusion of the SAE/SUSAR the documentation retained in the holding file will be transferred to the Study Sponsor File along with the completed checklist.

4.4 Reporting Timescales for SAEs and SUSARs

If the SAE is assessed to be ***related and unexpected*** by *either* the investigator or the Sponsor (in consultation with the ME) then the QAM or RA (or designated individual) will be responsible for reporting the SAE/ SUSAR 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 CTIMPS

The QAM (or designated individual) will report all SUSARs that are assessed by the R&D Unit or the investigator as fatal or life-threatening to:

- the Medicines and Healthcare products Regulatory Agency (MHRA)
- the competent authorities (equivalent of MHRA) of any EEA State, other than the United Kingdom, in which the trial is being conducted
- The research ethics committee that granted approval

within seven days of becoming aware of the event.

The QAM (or designated individual) will report any additional relevant information to the bodies within eight days of the report described being made.

The RA (or designated individual) will report all SUSARs that are not assessed as life threatening or fatal by either the sponsor or the investigator to:

- the Medicines and Healthcare products Regulatory Agency (MHRA)
- The competent authorities (equivalent of MHRA) of any EEA State, other than the United Kingdom, in which the trial is being conducted
- The research ethics committee that granted approval

within 15 days of becoming aware of the event.

The R&D Unit reserves 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.

FOR NON-CTIMPS OR DEVICE STUDIES

For all other studies, including clinical investigations of medical devices, only reports of related and unexpected Serious Adverse Events (SAEs) should be submitted to the REC. These should be sent within 15 days of the chief investigator becoming aware of the event. Reports of related and unexpected SAEs in double-blind trials should be unblinded.

4.5 SUSAR Reports to the MHRA

All trials for which the Trust is providing Pharmacovigilance services will be registered on the MHRA's eSUSAR database and activated when permission to begin recruiting to the trial is granted.

The QAM (or designated individual) is responsible for submitting the SUSAR report. SUSAR reports must be made electronically via the MHRA's eSUSAR website: http://esusar.mhra.gov.uk/. The RA is the R&D Unit's eSUSAR Administrator and all individuals to whom the task of reporting eSUSARS may

be delegated will have been granted individual access in order to undertake this task.

The QAM (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 grated approval for the study. The report generated by and downloaded from the eSUSAR 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 Sponsor File 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

For CTIMPS the DMC may require notifying of SAEs or 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 SAE/SUSARs will be reported to the R&D Group via the Quarterly Progress Reports submitted for all sponsored studies. 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

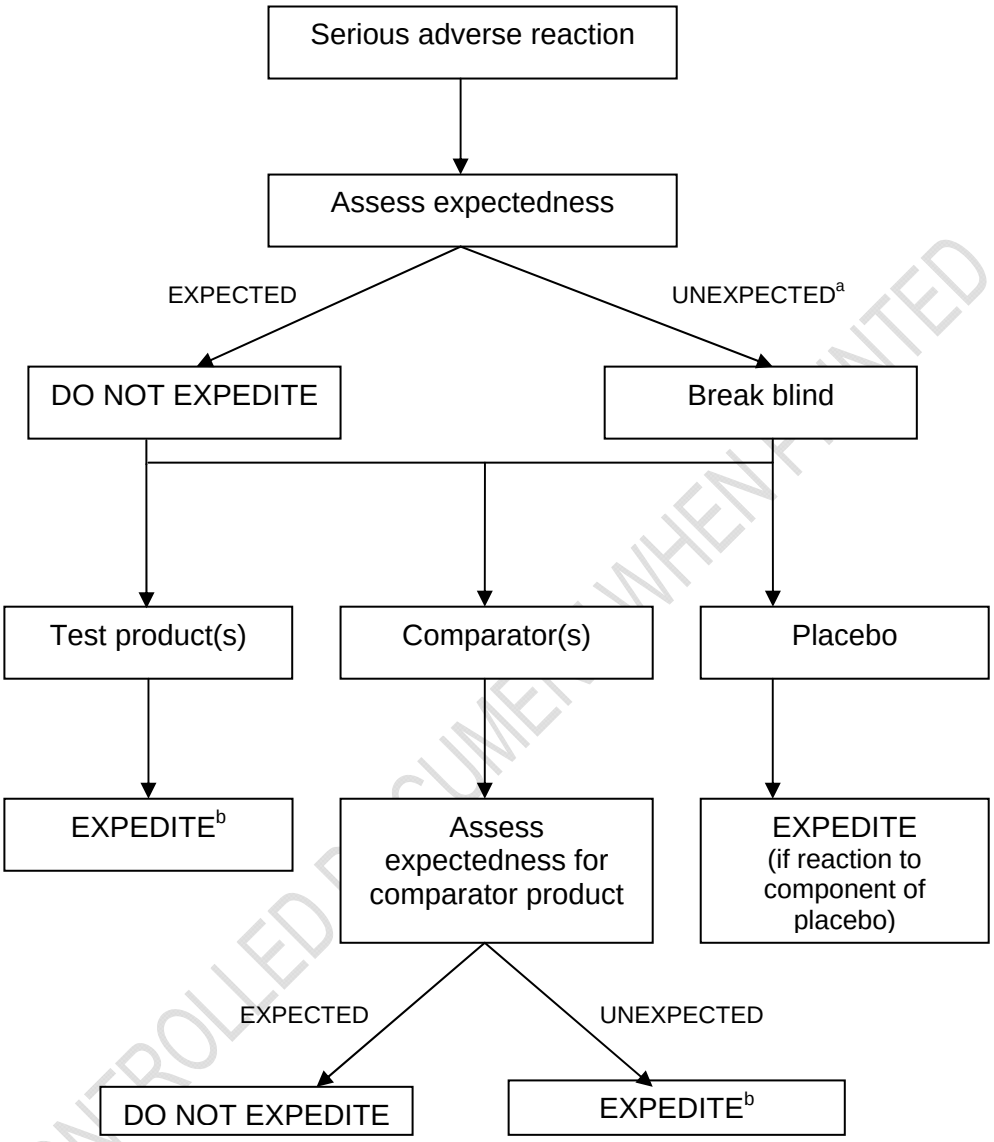
R&D/F09 SAE/SUSAR Unblinding Record

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