STANDARD OPERATING PROCEDURE

S22 – Safety Reporting

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Author & Position	Alison Kerridge, Assistant R&D Manager
Signature	
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Approver & Position	Helen Quinn, R&D Director
Signature	
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Controlled document

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DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

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Full History			
Version	**Date**	**Author**	**Reason**
1.0 Final	March 2011	Assistant R&D Manager	First document
2.0 Final	August 2011	Assistant R&D Manager	Changes to layout Delegation of duties is more specific as are requirements for following up patients until the AE has resolved. Inclusion of e-SUSAR reporting. Appendix 3 was updated to include the comments from the MHRA Inspector.
3.0	September 2013	Assistant R&D Manager	Change to annual reporting requirements updated from Annual Safety Report to Development Safety Update Report. Inclusion of reporting requirements for Comparators, Placebos and NIMPs. REC reporting requirements for SUSARs updated to include link to new form. Appendix 3 links to documents
4.0	November 2017	Assistant R&D Manager	Improved scope. Updated into Trust template
5.0	December 2017	Assistant R&D Manager	Minor errors corrected and inclusion of reporting on unexpected pregnancies
6	October 2021	Assistant R&D Manager	Expanded scope to include all research studies. Added pregnancy information re safety reporting. Amended procedure for hosted study safety reporting. Minor clarifications Updated into Trust template

Associated Trust Policies/ Procedural documents:	R&D Policy R&D/Reporting Required for Sponsored CTIMPs/S31 R&D/Urgent Safety Measures/S52 R&D/How to Enter a Safety Report on Q-Pulse/WI01 FRM24 SAE/SAR Report Form FRM58 AE/AR Report Form
Key Words:	R&D SOP AE/AR/SAE/SAR/SUSAR Pharmacovigilance Safety Reporting Datix
In consultation with: Quality Assurance Group	

Contents

1. INTRODUCTION

For Clinical Trials of Investigational Medicinal Products (CTIMPs) there is a legal requirement for the management and reporting of adverse events (AEs) in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004. The regulations set out the requirements for notification and reporting of AEs and adverse reactions (ARs) during a CTIMP.

This Standard Operating Procedure (SOP) aims to ensure that arrangements are in place to protect patient safety in all research involving human subjects, that investigators are aware of the safety implications of their research, and that the appropriate bodies are notified of safety information relating to medicines and interventions. Research-related adverse events are not uncommon and range from mild expected drug reactions i.e. Adverse Reactions (ARs) to fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs). All adverse events need to be reported correctly and within strict timeframes, in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004. These state that a Sponsor shall ensure that all relevant information about a SUSAR is recorded and reported to the Medicine and Healthcare Regulatory Agency (MHRA) and the Health Research Authority (HRA).

2. PURPOSE

The objectives of this SOP are:

- To define and classify Adverse Events (AEs) and Adverse Reactions (ARs).
- To describe the Royal Devon University Healthcare NHS Foundation Trust (hereafter referred to as 'the Trust') research procedure for identifying safety events when developing/setting up research; discovering, recording, reporting during the research; and following up of all AEs, ARs, Serious Adverse Events (SAEs), Suspected Serious Adverse Reactions (SSARs) and SUSARs
- To describe the procedure for reporting pregnancies occurring during research studies.

3. SCOPE

This SOP applies to:

- All researchers conducting research at the Trust. This includes CTIMPs, interventional research and other research where safety events are required to be reported.
- R&D personnel administering the Safety Reporting process on behalf of the Sponsor. In circumstances where the Trust has delegated the responsibilities to a third party such as an external Clinical Trials Unit (CTU), the safety reporting procedures will be outlined in a trial specific agreement between the Sponsor, the third party and the Chief Investigator.

4. DEFINITIONS & ABBREVIATIONS

AE	Adverse Event - any unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment.
AR	Adverse Reaction - adverse events but causally related to investigational medicinal products.
DSUR	Development Safety Update Report
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
Expedited Reporting	a term used by REC and MHRA to mean immediate/quick/efficient reporting
EPR	Electronic Patient Record
GCP	Good Clinical Practice
GOG	Governance Oversight Group
HRA	Health Research Authority
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research & Development
Royal Devon	Royal Devon University Healthcare NHS Foundation Trust
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event - any untoward medical occurrence(s) that at any dose results in death, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity or a congenital anomaly or birth defect.
SAR	Serious Adverse Reaction - an adverse reaction that at any dose results in death, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity or a congenital anomaly or birth defect
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction - when a SAR (see above) is unexpected
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

5. DUTIES AND RESPONSIBILITIES OF STAFF

5.1 All Researchers

It is the responsibility of all researchers in contact with research participants to discover, record and notify the Principal Investigator (PI) and/or Chief Investigator

(CI) of all AEs/ARs not stated in the Protocol or Reference Safety Information (RSI) as being exempt from the recording process.

5.2 Royal Devon Sponsored Trials

5.2.1 Staff and Sponsor Responsibilities

In respect of Trust sponsored trials, the safety reporting functions of the Sponsor will be delegated to the CI or Nominated Designee. All delegation from the Sponsor to the CI will be clearly documented and acknowledged by all parties concerned.

Only the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the MHRA will be retained by the Sponsor.

5.2.2 Chief Investigator (CI)

As Sponsor, the Trust delegates the following duties to the CI:

- On-going safety evaluation of the Investigational Medicinal Product (IMP) or intervention, to include annual reviews and where necessary, updating the RSI (typically either an Investigator Brochure (IB) and/or Summary of Product Characteristics (SmPC)).
- Keeping records of all AEs/ARs occurring at the Trust and, if multi-centre, at participating sites. These records should be stored in the Trial Master File/Investigator Site File (TMF/ISF).
- Reporting Serious Adverse Reactions (SARs) and Serious Adverse Events (SAEs) which are listed in the Protocol as requiring expedited reporting to the Competent Authority(ies), and the Sponsor, within the required timeframes.
- Reporting all incidents whereby a trial participant unexpectedly becomes pregnant to the Sponsor, see Section 6.1.12 (sponsored) or 6.2.4 (hosted) below for further guidance.
- Ensuring the recording and prompt reporting of SUSARs to the Sponsor.
- Providing an annual list of SUSARs and a Development Safety Update Report (DSUR) to the MHRA (CTIMPs only), see S31 for details of DSUR reporting requirements.
- Providing an Annual Report to REC (CTIMPS and non-CTIMPs).
- For multi-centre studies, promptly notifying all participating investigators of findings that could adversely affect the safety of the Trial participants, impact adversely on the conduct of the Trial or alter the REC's favourable opinion to continue the Trial.

N.B. The R&D Office (as Sponsor's representative) must be copied into all correspondence concerning safety reporting with Regulatory Authority(ies) and REC.

Where the CI further delegates any of these tasks to a member of the research team, this must be clearly documented on the Delegation Log and signed/dated by all parties concerned.

5.3 Principal Investigator (PI)

For all Trust sponsored and hosted studies, it is a legal requirement for the PI to:

a) Report all SAEs/SARs immediately to the CI/Trial Sponsor unless specified in the Protocol or IB as not requiring expedited reporting.
b) Report all AEs/ARs identified in the Protocol as being critical to the evaluation of trial safety to the CI/Trial Sponsor.
c) Report all incidents whereby a trial participant unexpectedly becomes pregnant, to the CI and Sponsor see Section 6.1.12 (sponsored studies) or 6.2.4 (hosted studies) below for further guidance.
d) Supply the CI, Sponsor and the REC with any additional requested information.

Where the PI further delegates any of these tasks to a member of the research team, this must be clearly documented on the Delegation Log and signed/dated by all parties concerned.

N.B. If a Nominated Designee undertakes the Safety Reporting functions (which may be necessary for blinded trials), this must be stated in the trial Protocol and clearly documented on the Delegation Log for the trial. The person(s) to whom the reporting functions have been delegated must be suitably qualified to assess the relatedness and expectedness of the adverse event and to understand the reporting requirements.

6. PROCEDURES

6.1 Safety Reporting in Royal Devon Sponsored Studies

6.1.1 Study Set-up and Safety Considerations

Before initiating a clinical trial and finalising the protocol, a study assessment should be conducted by the CI and the Sponsor. Careful consideration should be given to the following points:

1) Whether a Data Monitoring Committee (DMC) and/or a Trial Steering Committee (TSC) is required;
2) Which AEs/ARs need to be recorded and reported;
3) How often SAEs need to be reviewed.

Depending on what is known about the safety profile of the IMP or the intervention (particularly in the population to be studied), it may be decided not to record or report any non-serious AEs and/or disease-related SAEs. In addition, it may be decided to exclude 'expected' SARs from expedited reporting to the trial Sponsor. Importantly, all AEs (serious and non-serious) to be excluded from the recording and/or expedited reporting process must be clearly defined in the Study Protocol (and/or the RSI in the case of a CTIMP).

Specific requirements/procedures for assessing, recording, notifying and reporting AEs must be clearly defined in the Study Protocol, including the specific timelines to be followed. This includes details of delegated responsibilities where appropriate.

6.1.2 Reference Safety Information (CTIMPs)

The RSI is the list of known adverse reactions for the IMP/IMPs under study and must be approved by the Medicines and Healthcare products Regulatory Agency (MHRA) as part of the original Clinical Trial Authorisation or through a substantial

amendment in the event of an update to the RSI. Only the approved RSI can be used to assess the expectedness of any SAR that occurs during the trial. It is the Sponsor's responsibility to determine the RSI for the trial however this task may be delegated to the CI.

In general, the RSI may be a section within the Investigator Brochure (for IMP without a Marketing Authorisation) or the Summary of Product Characteristics (SmPC) (for IMP with a Marketing Authorisation and being used within the licensed indication). There can only be one RSI for each IMP under study.

6.1.3 Highlighting Reporting Adverse Events (AEs) at Enrolment

Upon enrolment into a study, the Research Team must flag the patient's participation onto the electronic patient record (EPR, also known as EPIC), along with entering the lead contact, PI and brief summary of the study. The team can then run daily reports to identify hospitalisations or illnesses occurring whilst in the trial.

Upon enrolment, the participant should also be given a trial participant card/leaflet. This will instruct the participant to inform a member of the trial team of any hospitalisation or illness occurring whilst in the trial. It is important that each participant be given a completed card (i.e. with participant's name, trial name and contact details for the Research Team) when enrolling in a trial.

6.1.4 Discovering AEs/ARs

Trial staff with responsibility for AE/AR reporting i.e. the CI/PI or delegated individual (as identified on the Delegation Log) must be able to identify AEs/ARs and be able to distinguish different types of AEs/ARs from one another. Timely identification and defining of AEs/ARs is very important since each type of AE/AR is governed by its own particular reporting timescales.

Training around safety reporting is available through the NIHR Good Clinical Practice courses.

In the event of perceived immediate harm to a participant, the SOP on Urgent Safety Measures (S52) should be consulted.

Information regarding the occurrence of Serious and Non-Serious AEs/ARs must be sought from medical notes and followed up with the clinical teams, as well as asking all study participants at each trial visit. Participants must be asked about hospitalisations, disabilities or whether any other AEs have occurred.

6.1.5 Evaluating different types of AEs/ARs

It is expected that the CI/PI is responsible for making an informed judgement with regards to classifying AEs/ARs as they occur. When analysing AEs/ARs the CI/PI will assess for:

a) Seriousness

An AE/AR is classified as Serious if it:

- 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

b) Expectedness

Whether the nature and severity of the AE/AR are consistent (expected) or not consistent (unexpected) with information about the IMP set out in the IB or SmPC. In the case of non-CTIMPs, judgement must be made by the CI or PI about the expectedness of an event/reaction in relation to the intervention.

c) Causality

A causal association is suspected between the Investigational IMP and the AE if the relationship is classified as 'possibly', 'probably' or 'definitely' using the definitions below:

1) Not related

Temporal relationship of the onset of the AE, relative to the administration of the IMP, is not reasonable or another cause can itself explain the occurrence of the event.

2) Unlikely

Temporal relationship of the onset of the AE, relative to the administration of the IMP is unlikely but cannot be ruled out.

3) Possibly

Temporal relationship of the onset of the AE, relative to the administration of the IMP, is reasonable and the event could have been due to another, equally likely cause.

4) Probably

Temporal relationship of the onset of the AE, relative to the administration of the IMP, is reasonable and the event is more likely explained by the drug than by any other cause.

5) Definitely

Temporal relationship of the onset of the AE, relative to the administration of the IMP, is reasonable and there is no other cause to explain the event or a re-challenge is positive.

Note these causal associations can be extended to relationship to an intervention in the case of non-CTIMP studies.

d) Severity (intensity)

The clinical severity of an AE/AR is classified as mild, moderate or severe. It should be noted that the clinical severity and seriousness of an AE/AR are not the same thing. For example, a patient may have a severe headache, which is not classified as serious unless it meets any of the outcome criteria in Section 6.1.5a).

6.1.6 Recording and Reporting AEs/ARs

Unless the Protocol/RSI states otherwise, all AEs/ARs (serious and non-serious) must be recorded. The person responsible for recording AEs/ARs must record the AE/AR in the:

a) Source document (i.e. in the patient notes if applicable)
b) Relevant participant's Case Report Form (CRF)
c) Trial Master File/Investigator Site File (TMF/ISF)

An initial assessment of the AE/AR must be made on an Adverse Event Form (displayed on the RDEResearch Website under Templates and Forms). The record should include a description of the AE, its start date, duration/end date; outcome and assessment of its seriousness, relatedness, expectedness and severity.

For SAEs a Serious Adverse Event Form (same location as above) must be completed unless it is disease-related and has been specified in the Protocol as not requiring recording.

For SUSARs see section 6.1.10.

6.1.7 Reporting Requirements - Research Team

6.1.7.1 Single-Centre (Royal Devon only)

All safety events which occur within Trust single centre sponsored studies, should be reported to R&D (or delegated third party if applicable e.g. CTU supported study) within 24 hours of knowledge of the event.

- AEs, SAEs and SUSARs for both CTIMPs and non-CTIMPs must be sent by the CI or Nominated Designee(s) to the R&D Department (rde-tr.RandDSafetyReporting@nhs.net) in the timeframe specified above.
- For some studies it will be appropriate instead to send a record of all AEs/ARs occurring during the life of the trial to be sent to the Sponsor (via the R&D office) on a periodic basis and this will be agreed and documented prior to the trial commencing. Any changes to reporting during the trial must be agreed by the Sponsor.
- The CI or Nominated Designee must in turn forward a copy of the SAE to the REC and MHRA if required.
- Non-CTIMPs: the Trust AE or SAE report form must be scanned and emailed to the R&D generic email inbox as shown below; a CI/PI (or delegated individual) must assess causality/severity/expectedness and countersign the Trust form
- CTIMPs: the Trust AE or SAE report form must be scanned and emailed to the R&D generic email inbox as shown below; a CI/PI (or delegated individual) must assess causality/severity/expectedness and countersign the Trust form.
- The above AE and SAE Trust reporting forms must be used unless prior agreement is made with the Sponsor that study specific or third party (in the case of CTU supported studies) safety reporting forms containing all the required information can be used.

In order to meet the prescribed 24-hour timeline for reporting SAEs to the Sponsor (or delegated party), it may not always be possible for the CI/PI (or delegated individual's) signature to be included on the SAE form. Where this is the case the form should be re-sent in due course with the CI/PI's signature included.

The generic email inbox address for ALL types of safety reporting is as follows: rde-tr.RandDSafetyReporting@nhs.net. The correct versions of the report forms are available on the RDEResearch Website under Templates and Forms.

Copies of all safety reports and logs must be kept in the site ISF and the TMF.

All safety events should be routinely reviewed by the CI & study team both individually and for trends.

6.1.7.2

Multi-Centre Sponsored Studies

All safety events which occur within Trust multi centre sponsored studies should be reported to the delegated central coordinating site e.g. CTU or Trial Manager and the CI within 24 hours of knowledge of the event as laid out either in the protocol or a study specific SOP. These will be reported periodically (as agreed with Sponsor at the outset) to the Sponsor (typically via the Trial Management Group/TMG) for Sponsor oversight. In small multicentre studies with no trial manager, all safety events should be reported to the CI and also the Sponsor directly by sites emailing the generic safety inbox, rde-tr.RandDSafetyReporting@nhs.net.

In the case of any SUSAR, the Sponsor must be informed within the 24-hr period in addition to the central coordinating site. For further details see section 6.1.9 and 6.1.10.

It is expected that the Royal Devon safety reporting forms will be used unless prior agreement has been made for an alternative form containing all the relevant information to be employed.

Copies of all safety reports and logs must be kept in the site ISF and the TMF.

All safety events should be routinely reviewed by the CI & study team both individually and for trends.

6.1.8 **Reporting Requirements - R&D Department**

Upon receipt of the safety report form by the R&D designee (QA Coordinator or R&D Facilitator), the completeness of the form will be checked and any queries relayed back to the study team for corrections to be made as necessary before being entered onto the Q-Pulse Quality Management system as per R&D Work Instruction WI01.

A DTX reference number will be generated by Q-Pulse and this should be marked on the form, which is then forwarded to the Assistant R&D Manager for assessment and follow-up.

A copy of the safety report form (with DTX reference number displayed) should also be saved in the R&D study folder within section 2 'Safety Reporting' P:\RESEARCH DEVELOP\Studies\Folders. This applies for initial reports, follow ups and final reports.

If the CI/PI has confirmed their causality assessment over email a copy of the email trail should also be saved in the R&D study folder with a reference to the relevant DTX number.

If an event is marked as 'Continuing' the R&D designee will liaise with the Research Team and Assistant R&D Manager or Research Governance and Quality Manager until the Outcome is 'Recovered/Resolved'/'Resolved with Sequelae'/'Fatal' and the Assistant R&D Manager or Research Governance and Quality Manager has signed off the DTX report on Q-Pulse.

When the safety reporting function has been delegated to a third party e.g. CTU or Trial Manager, the safety reports will not come direct to the Sponsor and will not be added to Q pulse as outlined above. The Assistant R&D Manager (or Research Governance and Quality Manager in their absence) will receive periodic safety event listings from the delegated party for sponsor oversight. These listings will be reviewed to ensure they are correctly assessed, timely and followed up. The listings will be saved in the R&D study folder and a summary plus any highlighted events reported to GOG every month. In studies where a Sponsor Oversight Group is established (in CTIMPs), full safety event listings will also be supplied.

6.1.9 Expedited Reporting

"Expedited Reporting" is a term used by REC and MHRA to mean immediate/quick/efficient reporting. The Regulations set time limits for expedited reporting:

Fatal or life-threatening SUSARs – not later than 7 calendar days after the Sponsor has information that the case reported fulfils the criteria for a fatal or life threatening SUSAR, with any follow up information to be reported within a further 8 calendar days.

All other SUSARs – Not later than 15 calendar days after the Sponsor has information that the case fulfilled the criteria for a SUSAR.

6.1.10 SUSAR Reporting in Royal Devon Sponsored Studies

All Expedited Reports of SUSARs for Trust sponsored studies must be completed by the CI or Nominated Designee and must be reported to the Sponsor within 24hrs via the generic safety reporting inbox: rde-tr.RandDSafetyReporting@nhs.net

This will enable the Sponsor, in the case of a CTIMP, to report to the MHRA electronically via their eSUSAR website at https://esusar.mhra.gov.uk/, within the appropriate timescales (as per above). Once the eSUSAR form is submitted, a PDF copy of the form must be saved for the Trial Master File/Site File (TMF/ISF) and for the R&D File as evidence of submission. A copy must also be sent to REC.

N.B. All SUSARs must be reported to the MHRA in an unblinded state. Upon discovery of the SUSAR and initial report to the Sponsor, the CI must provide the unblinded information to the Sponsor within 3 days in order to enable the Sponsor to meet the reporting requirements of the MHRA.

All SUSARs, both in CTIMP and non-CTIMP research, must be reported to the REC by the Sponsor in collaboration with the CI using the CTIMP safety form and non-CTIMP safety form respectively. There is no need for the form to be signed prior to submission. It must be sent by email to the REC. The REC co-ordinator will acknowledge receipt of the safety report within 30 days. The email address for the REC can be found on their initial approval letter for the trial. Refer also to SOP S31 on CTIMP Reporting.

In addition to following the expedited reporting process and entering the event onto Q-Pulse, details of the SUSAR will be entered onto the Trust Incident Reporting System (Datix) by the Assistant R&D Manager (or Research Governance and Quality Manager in their absence). SUSARs will be escalated by the Assistant R&D Manager to the Sponsor Oversight Group (in CTIMPs) for their immediate review and highlighted to the Governance Oversight Group (GOG) at their routine meetings. For non-CTIMPS, GOG will be informed at the next scheduled meeting.

6.1.11 Managing Safety Events to Conclusion

All safety events must be followed through until they are resolved or resolved with sequalae, unless determined otherwise by the Assistant R&D Manager, even if the participant(s) affected has/have been withdrawn from the trial.

In the case of SUSARs, the CI/PI is required to inform R&D in writing that they are happy to continue with that trial and the study drug/intervention in question. This information will be relayed at the next R&D GOG, where the Assistant R&D Manager routinely reports on all safety events and SUSARs occurring in each study.

The risk of an AE or AR re-occurring will be reduced if the reasons why the AE or AR occurred in the first place are recognised and the lessons shared with all staff involved in the trial and, if possible, more widely.

6.1.12 Pregnancy Reporting in Trust Sponsored Studies

Pregnancy is not considered an AE or SAE; however, an abnormal outcome would be. For this reason, the Investigator must collect pregnancy information for female trial participants or female partners of male trial participants who become pregnant while participating in a CTIMP or trial where pregnancy is relevant to the intervention. This should be outlined in the protocol.

For female partners of male trial participants who become pregnant while participating in a study, consent should be obtained to follow up the pregnancy.

The Investigator should record the information on a Pregnancy Notification Form. (FRM46) and to Sponsor within 14 days of being made aware of the pregnancy.

Any pregnancy that occurs in a trial participant or a trial participant's partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the new-born for an appropriate period post-delivery. Follow up information should be recorded on the Pregnancy Follow Up Form (FRM47) and sent to the Sponsor.

6.2 Safety Reporting in Hosted Studies

6.2.1 Highlighting Reporting Adverse Events (AEs) at Enrolment

Upon enrolment into a study, the research team must flag the patient's participation onto the electronic patient record (EPR, also known as EPIC), along with entering the lead contact, PI and brief summary of the study. The team then can run daily reports to identify hospitalisations or illnesses occurring whilst in the trial.

6.2.2 Recording and Reporting AEs/ARs

Safety reporting requirements for Hosted studies are defined by the Sponsor in the study Protocol. The Sponsor's instructions/guidance should be followed. It is not necessary to report hosted safety events to R&D with the exception of SUSARs, see section 6.2.3.

6.2.3 SUSAR Reporting in Hosted Studies

SUSAR reporting requirements for Hosted studies are defined by the Sponsor in the study Protocol. The Sponsor's instructions/guidance should be followed.

All Expedited Reports of SUSARs which occur at the Trust must be completed by the PI or Nominated Designee and must be reported as follows:

1) To the Sponsor as outlined in the protocol within 24hrs to enable the Sponsor to report to the MHRA & REC
2) To the Trust R&D department via the generic safety reporting inbox: rde-tr.RandDSafetyReporting@nhs.net, again within 24hrs of the Investigator being aware.

In addition to following the expedited reporting process and entering the event onto Q-Pulse, details of any SUSARs which occur at the Trust will be entered onto the Trust Incident Reporting System (Datix) by the Assistant R&D Manager (or Research Governance and Quality Manager in their absence). The Assistant R&D Manager will escalate these to the R&D Governance Manager in the first instance who will bring to the attention of GOG.

6.2.4 Pregnancy Reporting in Hosted Studies

Pregnancy is not considered an AE or SAE; however, an abnormal outcome would be. For this reason, the Investigator must collect pregnancy information for female trial participants or female partners of male trial participants who become pregnant while participating in a CTIMP or trial where pregnancy is relevant to the intervention. This should be outlined in the protocol.

For female partners of male trial participants who become pregnant while participating in a hosted study, follow the study Protocol.

Pregnancy reporting requirements for Hosted studies should be defined by the Sponsor in the study Protocol. The Sponsor's instructions/guidance should be followed.

If the Sponsor does not provide any study pregnancy report forms, the Trust R&D department's pregnancy notification form (FRM46) and pregnancy follow up form (FRM47) can be used to record the required information.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the RDE Research website shortly after having been released.

7.2 All staff whose activities are subject to this SOP should ensure that they take time to read and understand the content of this SOP.

7.3 *If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.*

8. MONITORING COMPLIANCE AND EFFECTIVENESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	Ensure reportable safety events are recorded by the research team	EPR, logs and forms in TMF/ISF
2.	Ensure SAEs are reported to the sponsor (or delegated party) within 24hrs of awareness	SAE reporting form in TMF/ISF, Q-pulse
3.	Ensure SUSARS are expediated to the regulatory bodies in a timely fashion	TMF/ISF, R&D study file
4.	All safety events are followed up to completion	SAE reporting form in TMF/ISF, Q-pulse
5.	Sponsor oversight of all reportable safety events	R&D file, Q-pulse, minutes of oversight committees (e.g. Trial Management Group/TMG, Trial Steering Committee/TSC)

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the RDE Research website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

Commission Directive (2005/28/EC) on Good Clinical Practice
EU Clinical Trials Directive 2001 (2001/20/EC)
Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I.2004/1031)
Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (S.I.2006/1928)

Appendix 1 - An AE occurs during a RESEARCH project, what do I do next?

Untoward incident is reported by participant or is evident in medical notes

Is it a serious adverse event (SAE)?

An SAE is defined as any untoward medical occurrence or effect that results in either death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect.

Yes / No

1. Record AE on the AE Log in the site file, the Case Report Form and in the participant's medical notes (source documentation) if applicable to the study.
2. Follow up AE until resolved (if applicable).

Is the SAE likely to be a REACTION to the investigational Medicinal Product (IMP)?

All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship (SOP section 5.2) to a medicinal product qualify as ADVERSE REACTION (AR).

Yes / No

1. RECORD SAE on the SAE Log in the site file, the Case Report Form and, in the participant's medical notes (source documentation).
2. Inform the trial Sponsor within the time line stated in the protocol (unless agreed in the protocol that EXPECTED events do not need REPORTING).
3. For all studies sponsored by the Trust, the SAE form must be scanned and emailed to the R&D office at the generic inbox: rde-tr.RandDSafetyReporting@nhs.net
4. Follow up SAE until resolved (if applicable).
5. SAEs in non CTIMPs that are related to the project and unexpected should be reported to REC by submitting the following form to the REC that gave the favourable opinion for the study. The SAE must be reported to the Research Ethics Committee.

Is the Serious Adverse Reaction (SAR) expected?

Reactions are considered EXPECTED if they are listed in the Investigators Brochure (IB), Summary of Product Characteristics (SmPC) or in the Protocol.

1. Record SAR on the SAE/SAR Log in the Site File, Case Report Form and, in the participant's medical notes (source documentation).
2. Inform the trial Sponsor within the time line stated in the Protocol (unless agreed in the Protocol that Expected events do not need Reporting).
3. For all studies sponsored by the Trust complete and sign an R&D SAE/SAR form which must then be emailed to the R&D office at the generic inbox: rde-tr.RandDSafetyReporting@nhs.net.
4. Follow up the SAR until resolved (if applicable).
5. The SAR must be reported to MHRA when submitting the Development Safety Update Report and sent to the REC for information.

This event is a SUSAR (Suspected Unexpected Serious Adverse Reaction) – ACTIONS TO BE TAKEN:

1 The Investigator who identified the SUSAR to record the event on the SAE/SAR Log in the Site File, the Case Report Form and, in the participant's medical notes (or other source documentation if notes not used in the study).
N.B. If the above Investigator is not the CI, then they must inform the CI within 24 hours of becoming aware of the event. They are then required to follow their Trust's procedure on reporting adverse events.

2 Once the CI is aware of the SUSAR, they must complete the Trust's SAE reporting form which can be found on the RDE Research website.

3 The CI to scan and email the **signed** form to the Sponsor, **as soon as possible and within one working day**. The CI to contact the Sponsor and ensure that the report form has been received (if multi-site the PI might send the form to the CI).

4 R&D to record SUSAR on both Q-Pulse Management System and also the Trust Incident Reporting System (Datix)

5 R&D to escalate to the Sponsor Oversight Group for review and GOG

6 If the trial is multi-site, the CI to inform the PIs at each site of the SUSAR

7 The Sponsor reports the SUSAR to MHRA via the eSUSAR website within 7 days for death and life-threatening SUSARs and within 15 days for all other SUSARs.

8 The CI to inform REC, submitting a copy of the eSUSAR submission (pdf). Reports must be accompanied by a completed CTIMP 'Safety Report to Research Ethics Committee' form & copy the Sponsor into any correspondence.

9 CI follows up the SUSAR until the event is resolved and records the information in source documentation.

10 PI to confirm in writing to R&D that they are happy to continue with the study drug.