Sponsor processes for reporting Suspected Unexpected Serious Adverse Reactions

NJRO-REG-SOP-011

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1. Background/Introduction

The Sponsor is responsible for ensuring that all Suspected Unexpected Serious Adverse Reactions (SUSARs) are managed and notified according to The Medicines for Human Use (Clinical Trials) Regulations 2004. SUSARs must be reported within the required timeframes to the Medicines and Healthcare Products Regulatory Agency (MHRA) via their electronic SUSAR (eSUSAR) online reporting site. The purpose of expedited reporting to the competent authority is to provide an early warning of any potential issues with IMPs or with the conduct of the trial in the time between the annual reviews of the risk-benefit profile of the IMP in the development safety update reports (DSURs).

2. Purpose

The purpose of this SOP is to describe the procedure within the Newcastle Joint Research Office (NJRO) for reporting SUSARs to the appropriate NHS Research Ethics Committee (NHS REC) and the MHRA. This SOP is specific to Clinical Trials of Investigational Medicinal Products (CTIMPs) and trials of Advanced Therapy Medicinal Products (ATMPs) which are sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH FT).

3. Scope of Document

This SOP is applicable to all Chief Investigators (CIs) of CTIMPs and ATMP trials sponsored by NUTH FT, all staff within the NJRO delegated the responsibilities and all other staff delegated trial management duties described within this SOP.

4. Definitions

Adverse Reaction (AR) - as any untoward and unintended response in the recipient of an Investigational Medicinal Product (IMP) which is related to any dose administered to that subject.
Suspected Unexpected Serious Adverse Reaction (SUSAR) - any AR that is classified as serious and is suspected to be caused by the IMP that is not consistent with the known safety information listed in the current approved Reference Safety Information for the trial, usually contained with the Investigator's Brochure (IB) or the SmPC (Summary of Product Characteristics).

5. Roles & Responsibilities

The Regulatory Compliance Team (RCT) is responsible for ensuring SUSARs are reported to the MHRA and REC in accordance with applicable legislation.

The CI and members of the trial management team are responsible for ensuring potential SUSARs are reported to the RCT as described in this SOP.

6. Procedures

6.1. Reporting Timelines

The CI (or authorised delegate) must contact the NJRO within 24 hours of becoming aware of a potential SUSAR to allow the report to be prepared and sent by the RCT within the required timelines (See also NJRO-REG-SOP-007). All potential SUSARs must be submitted to sponsor via the safety reporting inbox: tnu-tr.safetyreporting@nhs.net.

All SUSARs are subject to expedited reporting under strict timelines to the MHRA, NHS REC, and other relevant bodies as required (e.g. other Competent Authorities if the trial is multi-national). It is the Sponsor's responsibility to ensure that all SUSARs are reported accordingly. For CTIMPs/ATMP trials sponsored by NuTH FT, it is the responsibility of the RCT to perform this task.

Fatal/life threatening SUSARs*:*
Must be reported as soon as possible but no later than **7 calendar days** after the Sponsor becomes aware of the event. Any relevant follow-up information must be sought and reported within a **further 8 calendar days of submitting the initial report**. This reporting is required to both the MHRA and the REC.

Non- fatal and non-life threatening SUSARs:
Must be reported as soon as possible, but no later than **15 calendar days** after the Sponsor has first knowledge of the event. Further relevant follow-up information should be provided as soon as possible. This reporting is required to both the MHRA and the REC.

Where significant new information on an already reported case is received by the sponsor, the clock starts again at 'day 0', that is, the date when new information is received. The new information is then reported as a follow up report within the 15 day timeframe (or 7 calendar days for fatal/life threatening events).

6.2. Notification Process to the NJRO

SUSARs can be reported to the NJRO in any format (e.g. email or telephone) although an email submission via the safety reporting inbox is preferred (tnu-tr.safetyreporting@nhs.net).

The notified person or appropriate delegate should begin using the NJRO SUSAR Reporting Checklist (NJRO-REG-T-013) to collect relevant information regarding the event. They should contact the trial management team as a matter of urgency to confirm that a SUSAR has occurred i.e. that the event is serious, unexpected and that the IMP is either possibly, probably or definitely the cause of the AR.

If the AR is definitely or strongly identified as a SUSAR by the CI then a copy of the NJRO SUSAR Reporting Form (NJRO-REG-T-012) must be completed by the RCT and the trial management team in order for the SUSAR to be reported. In line with The Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the reporting timeframe starts when the sponsor is in receipt of a minimum set of information, which includes:

1. R&D reference and trial name (sponsor reference)
2. EudraCT number
3. Patient trial number
4. Name of IMP(s)
5. Date of notification of the event
6. Medical description of the event
7. Date and time of the onset of the event (including end date if applicable)
8. Causality assessment
9. Seriousness of the event, particularly if life threatening or if the participant died as a result. This will affect the reporting timeline (see 6.1)
10. One identifiable reporter (e.g., Principal Investigator (PI))

6.3. Completion of the NJRO SUSAR Reporting Form

This form should be sent to the study team to collect relevant information regarding the event. A deadline should be set for completion of 48 hours for fatal/life threatening SUSARs and 4 days for non-fatal/non-life threatening SUSARs.

Once the form is received back by the RCT it should be reviewed by the notified person for clarity and to ensure all questions have been answered; the CI should be contacted if any queries arise.

The form should then be passed to the Regulatory Compliance Manager (RCM) or an appropriately qualified delegate for review. This review should be completed within 24 hours for fatal/life threatening SUSARs and 4 days for non-fatal/non-life threatening SUSARs. If the RCM or appropriately qualified delegate is unavailable the form should be reviewed by the Clinical Director of R&D or the Head of the NJRO.

Any resulting queries must be followed up accordingly. Each task on the NJRO SUSAR Reporting Checklist (NJRO-REG-T-013) must be completed and the form signed and dated.
The completed checklist should be saved within the Sponsor Oversight File (SOF).

6.4. Blinded Studies

For blinded CTIMPs and ATMP trials the blind must be broken in order to report the SUSAR. The blind should be broken by a representative of the sponsor and only for the specific participant. Unblinded information should only be accessible to those who need to be involved in the safety reporting or those who perform ongoing safety evaluations during the trial (See also NJRO-REG-SOP-001)

The break blind process detailed in the trial specific protocol should be followed.

6.5. Comparators, Placebos and Non-Investigational Medicinal Products (NIMP)

Comparators and placebos are classified as IMPs and as such follow the same reporting requirements as for the test IMP. SUSARs related to a comparator must also be notified to the pharmaceutical company that holds the Marketing Authorisation for the comparator. The company should be named in the SmPC.

NIMPs are products that are not being tested as part of the trial but may be supplied to trial participants as part of the protocol (e.g., rescue or prophylactic substances given to ensure medical care of the participants). NIMPs fall outside of the regulations and so do not usually fall within the reporting requirements. However there are a few scenarios that would cause a reaction with a NIMP to be reported:

- A serious, unexpected adverse reaction suspected to be due to an interaction between the NIMP and the IMP
- A SUSAR that may have been caused by the NIMP or the IMP and it cannot be determined which caused the reaction
- If the reaction due to the NIMP is likely to affect the safety of the trial subjects

A SUSAR associated with a NIMP should be reported to the relevant holder of the Marketing Authorisation for the NIMP so that this information can be used in the ongoing safety monitoring procedures. The holder of the Marketing Authorisation should be listed on the SmPC.

If the NIMP does not have a Marketing Authorisation in the UK then the SUSAR must be notified to the MHRA.

6.6. Notification Process to the MHRA

The notified person (or appropriate delegate) must notify the MHRA of suspected SUSARs via the eSUSAR website (https://esusar.mhra.gov.uk/). The electronic SUSAR (eSUSAR) reporting form is available for use by all sponsors to electronically submit SUSAR reports to the MHRA. Registered users must log in to the site in order generate a form and make a submission.

The eSUSAR form requests that both the Sponsor and CI assess the causality individually: either reasonable possibility, or no reasonable possibility, that the event was caused by IMP. When the information has been entered onto the eSUSAR form, a draft should be saved and sent to the RCM, sponsor representative coordinating the SUSAR reporting process, CI and any other relevant members of the trial management team (e.g. Trial Manager) to confirm accuracy; comments should be returned via email within 24 hours.

When confirmed as accurate the eSUSAR form should be submitted via the eSUSAR website. Once submitted there is an option to print a copy of the report; the printed form should be saved to the R&D SOF as evidence of reporting. A copy should also be sent to the REC (see 6.7).

For fatal or life-threatening SUSARs follow up information must be provided via eSUSAR within 15 days of the SUSAR occurring.

6.7. Notification Process to the NHS REC

SUSARs must be notified to the REC that gave the favourable ethical opinion by the notified person within the RCT. Notification must be within 15 days of the CI becoming aware of the event. Notification should be via email (if the documents are quite large they should be submitted on CD). All SUSAR reports must be accompanied by a completed CTIMP Safety Report to REC form or the REC will not acknowledge receipt of the safety report (this form does not need to be signed prior to submission). A copy of the completed CTIMP Safety Report to REC form should be saved in the SOF. The REC will acknowledge receipt of the report within 30 days by signing and returning a copy of the submitted CTIMP Safety Report to REC form. Once received, a copy of the REC confirmation of receipt should be saved in the SOF.

6.8. Notification to Local Investigators

The Sponsor is required to ensure that the investigators responsible for the conduct of a trial are informed of any SUSARs that occur in relation to an IMP used in the trials it is involved with. This is the case whether that SUSAR occurs in the trial that the investigator is involved in, or another trial using the same IMP for which the sponsor is responsible. The notified person should compile a list of all relevant NUTH FT sponsored studies using the IMP(s), to include: CI name, study title, R&D number, REC reference, EudraCT reference; for each study the corresponding site name(s) and PI name(s) should also be listed.

A letter will be sent by the Trial Management team to each PI to inform them of the SUSAR and relevant clinical details; this should be done in a timely manner to ensure that investigators are kept fully informed of the safety information. This may be checked during site monitoring to verify that investigators have received and read this information. If a significant safety issue is identified, the sponsor (or authorised delegate) should issue a communication to all investigators as soon as possible. If necessary, the Sponsor or CI may take appropriate urgent safety measures to protect subjects. In such cases the Sponsor (or authorised delegate) must notify the REC and MHRA immediately (which may be by telephone); written information must follow within 3 days describing the measures taken and the reasons why implemented.

6.9. Further Notification within NuTH FT

A copy of the SUSAR form should be sent to NuTH FT Associate Director of Pharmacy and the relevant NuTH FT Pharmacy contact(s) for the trial.
The incident must be reported via the Trust's DATIX system by the notified person within the NJRO. The Incident Type should be entered as: "Research Incident/Accident"; Directorate: 'Medical Director's Directorate'; Speciality: 'Research Development and Governance'; Site: 'Regent Point'; Location: 'Research Buildings' (entries selected from the drop down menus). (See also NuTH FT "Managing and Reporting of Accidents and Incidents Policy".)

The RCM, Quality Assurance Manager (QAM) or an appropriately qualified delegate should also assess the SUSAR to confirm whether or not the event constitutes a serious incident (SI). This is defined as an event or incident that resulted in unexpected or avoidable death, or serious harm, to one or more patients, staff, visitors or members of the public. If the event has been classed as (or is suspected to be) a SI, the RCM, QAM or appropriately qualified delegate will inform the Director of Quality and Effectiveness, via the Clinical Governance and Risk Department, (CGARD) as soon as possible by telephone. (Please refer to NUTH FT "Serious Incidents Reporting and Management Policy" for further information including categories of SIs.)

7. References

- The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments - http://www.legislation.gov.uk/
- eSUSAR Website - https://esusar.mhra.gov.uk/
- MHRA Website - Clinical trials for medicines: manage your authorisation, report safety issues - https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues
- European Commission - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), (2011/C 172/01)
- Health Research Authority – Safety Information - https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/
- NJRO-REG-SOP-007 - Adverse Event Reporting for CTIMPs and ATMPs
- NJRO-REG-SOP-001 - Randomisation and Code Breaking
- NUTH FT – Serious Incidents Reporting and Management Policy
- NUTH FT – Management and Reporting of Accidents and Incidents Policy

8. Appendices

- NJRO SUSAR Reporting Checklist
- NJRO SUSAR Reporting Form
- CTIMP Safety Report to REC