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Sponsor Standard Operating Procedure

Title: **SERIOUS ADVERSE EVENT REPORTING**

SOP ref: **TA014**	**Effective from date :**
Version and date: v4.0 4th January 2023	**18th January 2023**
Superseded version and date: v**3.0 4th August 2017**	**Review cycle: 2 yrs after effective date**

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Document history: 1. V1.0, November 2008, superseded. 2. V2.0 Aug 2010 superseded. 3. V2.1 25th June 2013 superseded 4. V2.5 17TH Dec 2014 superseded 5. v3.0 4th August 2017	1. Update of references to eSUSAR to the ICSR Submissions portal. 2. Reference to the Research Governance Framework updated.

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1. PURPOSE and SCOPE

PURPOSE:
To describe the procedures for the reporting of Serious Adverse Events (SAEs) that may occur in clinical trials, in compliance with all applicable government directives, UK legislation and European guidance and directive documents.

SCOPE:
This SOP is applicable to all researchers conducting clinical trials that are governed by the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031 and/or the UK Policy Framework for Health and Social Care Research 2017.

2. NOTES

2.1 The definition of an SAE as given in the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031, shall be adopted within all clinical study protocols:

''A Serious adverse event, serious adverse reaction or unexpected serious adverse reaction means any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect.''

2.2 Subject to 2.1, the protocol shall make clear distinction between those events that may be expected because of known effects of the treatment given and the level at which they may be expected, and those events that are outside of these criteria and therefore require reporting as an SAE.
In the event of uncertainty or lack of clear distinction all SAEs must be reported.
Similarly, in the event of uncertainty of causality the SAE shall be assumed to be related to the treatment given and assessed accordingly.

2.3 SAEs must be reported **immediately** of knowledge of the event (but see section 4.2)

Clinical Trials of IMPs:

2.3.1 All Suspected Unexpected Serious Adverse Reactions (**SUSARs**) occurring in the trial at any of the participating sites, including outside the UK must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) within **seven days** of knowledge of the event and any follow-up information and reports within a **further eight days**.

2.3.1.1 Reporting is electronic via the Individual Case Safety Reports (ICSR) Submissions portal. In order to be able to access this portal and report for the University of Nottingham you must be allocated an account. Contact the Research Governance Team for this to be set up.

2.3.2 SUSARs occurring in the UK must be reported to the Research Ethics Committee (REC) for the trial within the same time-frames.
Non-UK SUSARs do not need to be reported to the UK REC but must be reported within the member state concerned according to local legislation.

2.3.3 SUSARs must be reported immediately to the Sponsor. Although the Sponsor delegates the responsibility of reporting to the MHRA, REC and other investigators as required to the Chief Investigator or nominated deputy, the Sponsor shall be kept informed and be sent copies of all documentation relating to the SUSAR.

2.3.4 All SAEs and SARs (both non-SUSAR) should be reported to the Chief Investigator and any further reporting to the trial specific Data Monitoring Committees or any other group according to the protocol.

Non-IMP Clinical Trials:

2.3.5 SAEs for non-IMP trials deemed to be directly related to, or an unexpected result of, the trial procedure or treatment, require expedited reporting to the REC that gave a favourable opinion for the trial. Reporting should be within 7 days of knowledge of the event, with any follow-up information within a further 8 days.

2.3.6 All SAEs including those not deemed directly related to the trial treatment or procedures should be reported to the Chief Investigator and any further reporting to the trial specific Data Monitoring Committees or any other group according to the protocol.

2.4 Assessment of seriousness and any requirement for expedited reporting is the overall responsibility of the Chief Investigator. This duty may not be delegated other than to a Deputy. A Deputy must be nominated.

2.4.1 The Chief Investigator and/or any investigator and the treating doctor must take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

2.4.2 If such measures are taken these should be reported immediately to the Chief Investigator who shall **inform the Sponsor** and any Principal Investigators no later than 3 days from the date the measures are taken. Where appropriate (the event is related to an Investigational Medicinal Product or directly to the trial procedures), the Chief Investigator shall give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.
See Work Instruction 2 TA014

2.4.3 Events that lead to the suspension of the trial are classed as a substantial amendment and must therefore be notified to the MHRA and REC within fifteen days of the trial being suspended. See SOP TA013, Protocol Amendments.

2.5 For international trials the UK Chief Investigator (CI) has overall responsibility for safety assessment for the trial and will report to the appropriate international study committee and national competent authorities and ethics committees as required.

2.6 It is the responsibility of the local investigator in any UK NHS Trust to comply with the reporting guidelines for that NHS Trust.

3. CROSS REFERENCES

3.1 Statutory Instrument 2004 No.1031, The Medicines for Human Use (Clinical Trials) Regulations 2004, part 5.
3.2 The EU Directive, 2001/20/EC, April 2004, articles 16, 17 and 18.
3.3 Protocol Amendments SOP TA013
3.4 SAE reporting form RF1 TA014
3.5 Annual and Safety Reporting WI1 TA014
3.6 Urgent Safety Measures WI2 TA014

4. PROCEDURE

4.1 All clinical and trials staff at the locations where the trial is conducted are responsible for identifying Serious Adverse Events (SAEs). The Principal Investigator must ensure that appropriate procedures are in place locally to provide assurance that SAEs are recognised and that staff are appropriately trained to fulfil the reporting requirements.

4.2 Trial staff are obliged, immediately upon knowledge of a serious event, to notify the Chief Investigator. In practice this should be within 24 hours of event onset or of the event being assessed as serious.

4.3 Notification shall be according to the procedure stipulated in the trial protocol or by using the standard SAE Reporting Form, RF1 TA014.

4.3.1 In the first instance a verbal report may be given e.g. telephone, in order to discuss the event and make provision for patient safety and any emergency measures necessary. The Principal Investigator in consultation with the Chief Investigator and other clinical colleagues as needed, must determine seriousness and causality of the event as soon as possible and define as such on form RF1 TA014.

Note: The grading of an SAE by the local investigator should not be down-graded by the CI, unless a specific mistake has been made such as pressing the wrong key on an eCRF.
Where more than one IMP is used in a trial all identified SARs must be assessed for relatedness to *all* IMPs used at the time and if not a known side effect of one or more IMPs and if the event is also unexpected for any of those IMPs then the event must be reported as a SUSAR

4.3.2 RF1 TA014 must be signed by the local Principal Investigator or deputy and sent to the Chief Investigator immediately (fax or email – use a scanned signature if using this route) for corroboration and authorisation. Retain a copy locally in the Trial Site File (TSF).

4.3.3 For eCRFs the correspondence and authorisation may be by electronic routes. In these instances a print out of all SAEs should be retained in the TMF

The **Chief Investigator** shall:

4.4 Assess the event for seriousness, severity, causality and relatedness to any IMP or trial treatment and record this assessment on RF1 TA014 with an authorising signature.

4.4.1 If the event is deemed unrelated to the Investigational Medicinal Product or the trial procedures no further expedited safety reporting is required regardless of outcome. Return* a completed copy of the RF1 TA014 form to the Principal Investigator for inclusion in the Trial Site File. Retain the original form in the Trial Master File (TMF).
*fax a photocopy or email an electronic copy using a scanned signature for authorisation

4.4.2 Ensure that the appropriate Case Report Form for the trial is completed and ensure the event is recorded according to the protocol.

Note: In the event of the CI or a deputy not being available for initial consultation regarding the severity and causality of the event then the PI shall take responsibility for the assessment, record as such on RF1 TA014, and take appropriate action depending on the assessment. In this instance the CI must be informed as soon as possible.

The CI may then amend accordingly. Records of all amendments must be retained in both the TSF and TMFs.

Clinical Trials of IMPs:

4.5 In the event of an SAE being deemed a **SUSAR** the Chief Investigator must:

4.5.1 Report the SUSAR to the MHRA using the ICSR Submissions portal:

https://icsrsubmissions.mhra.gov.uk/login

Note: For this you will need an account allocated by the University's ICSR Submission portal Administrators - the Research Governance Team. Ensure that this is set up before the trial commences.

4.5.2 Login and click on 'report'. Select your trial then follow the on-screen instructions to add the SUSAR report and subsequently any additional information as it becomes available.

4.5.2.1 Reporting to other EEA Member State Competent Authorities must be carried out in accordance with each individual Member State's requirements.

4.5.3 Inform the Sponsor: Download a PDF of the ICSR Submission portal report and send via email to sponsor@nottingham.ac.uk. Add your contact details and any relevant supporting information to the email.

4.5.4 Inform the REC that approved the study. Use the REC reporting form and a covering letter:

http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form/

A PDF of the ICSR Submission portal report may also be submitted to the REC in addition to the REC form.

4.5.5 Inform any other trial committee or organisation that needs to be informed according to the trial protocol.

4.6 Devise and implement urgent safety measures as required and disseminate to all trial sites and staff as per Work Instruction WI2 TA014.

Non-IMP Clinical Trials:

4.7 In the event of an SAE being deemed directly related to *and* an unexpected result of any trial treatment or procedure the Chief Investigator must:

4.7.1 Within 7 days inform the REC that approved the study. Use the REC reporting form and a covering letter:

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

Any follow-up information should be submitted within a further 8 days.

4.7.2 Inform any other trial committee or organisation that needs to be informed according to the trial protocol.

4.7.3 Inform the Sponsor.

All clinical trials:

4.8 The Chief Investigator / Principal Investigator shall send a copy of *all* subsequent correspondence to the Sponsor.

4.9 Copies of all correspondence and forms must be retained in the TSF and TMF and all SAE events reported in the annual safety and progress reports required by the MHRA and REC. See Work Instruction, WI1 TA014, Annual and Safety Reporting.

5. FLOW CHART

Not applicable.