BU Bournemouth University

BU RDS SOP 011 V1

Title: Safety Reporting	
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1. Scope

This Standard Operating Procedure (SOP) outlines the requirement for safety reporting in research studies. Depending on the nature of the project, safety reporting requirements will vary.

2. Responsibilities

The *Chief Investigator (CI)/Researcher* via the *Sponsor* is responsible for reporting, assessing and signing off safety reports (defined in section 4 of this SOP).

3. Purpose

3.2 The research study protocol should outline what safety reporting is required for the study, and should be REC approved.

With regard to Adverse Events (AEs), the protocol should clearly set out:

- How AEs will be identified and the follow-up period in which they will be identified;
- How AEs will be recorded;
- Whether the AE will be recorded as an outcome rather than an event;
- Which AEs are expected, depending on the participant's condition;
- Which AEs are expected with the medicinal product/intervention in question, referencing the safety information provided with the intervention;
- The procedure for addressing incidental findings;
- The procedure for addressing abnormal values or measurements (e.g. blood test results, ECG results etc.);
- If a study involves a medicinal product, the protocol should clarify whether any supplementary medicines or interventions will be supplied to participants, in order to ensure their medical care is not compromised;
- Whether the CI will review sites' PI assessment of SAEs prior or after reporting to the Sponsor;
- The procedure for un-blinding in blinded trials;
- Whether it is necessary to record pregnancy and whether it should form part of the exclusion criteria.

3.3 For non-CTIMP studies, including clinical investigations of medical devices, only Serious Adverse Events (SAEs) that are:

- related to the study (i.e. they resulted from administration of any of the research procedures) and
- unexpected (i.e. not listed in the protocol as an expected occurrence)

- should be submitted to the REC using the Non-CTIMP safety report to REC form.

These should be sent within 15 days of CI becoming aware of the event. Reports of SAEs in double-blind trials should be un-blinded. There is no requirement for annual safety reports in addition to the information provided through the annual progress report.

Identifying Adverse Events (AEs)

3.4 AEs will be identified by, or notified to the research team. A full record of what AEs have been identified and reported must be kept in study files.

3.5 It is good practice and a requirement of GCP for a member of the research team to ask trial participants at each visit and during each phone-call correspondence, as to whether the participant has had any hospitalisations or visits with other healthcare providers. In addition they should enquire about disabilities, incapacities or whether the participant has experienced other AEs since previous study contact.

Sometimes, AEs may be reported by the participant themselves by directly contacting the study team, or by completion of study questionnaires (if applicable).

3.6 AEs may be identified by support departments as required by the study; for example, the hospital laboratory reporting an abnormal liver function test, identified on the participant's post-randomisation bloods.
If abnormal result reporting is not standard practice at a site, the protocol should outline the procedure by which the CI or PI should be notified of such events. The event may or may not constitute an AE.

Assessing Adverse Events

3.7 Appendix 1 outlines the decision tree for assessing AEs, in conjunction with the definition in section 4.

AEs must be assessed by the study team, for *seriousness* (see section 4). If they deem the AE serious then PI or CI must be informed and a discussion should take place as to whether the event is related to the medicinal product or not (see section 4). If related then the CI or PI must determine whether the event was expected or unexpected and the assessment must be recorded on the study SAE reporting form.

3.8 The CI or PI should assess SAEs for severity, and record this assessment on the SAE form. Severity is categorised as either:

Mild – an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate – an event that is sufficiently discomforting which interferes with normal everyday activities.

Severe – an event that prevents normal everyday activities.

Please note, severe and serious are not interchangeable terms. Serious is a regulatory term used for identifying events, e.g. a migraine may be severe but not serious, whilst a minor stroke may be serious but not severe.

3.9 The SAE form should be completed by a member of the research team but signed off by the PI/CI on the study delegation log.

Reporting SAEs to the Sponsor

3.10 SAEs must be reported to the Sponsor using the SAE form within 24 hours, but **as soon as the site becomes aware** of the event, even if the information they can provide is minimal. The form can be added to by supplying a follow-up report, but the initial report must be sent straightway, signed by the CI/PI, or medically qualified delegate as assigned on the study delegation log. The SAE/SUSAR should be sent to researchgovernance@bournemouth.ac.uk.

3.11 SAE reports and follow-up reports must be filed in the Trial Master File (TMF).The Sponsor will review all reported SAEs and follow-up reports and feedback via email, the outcome of their assessment. The Sponsor's assessment may disagree with that of the CI/PI's assessment. This will be recorded in the TMF alongside the SAE report.

3.12 If the event has been identified by the CI, PI or Sponsor as a SUSAR (Suspected Unexpected Serious Adverse Reaction), then the participant shall be un-blinded (in the case of randomised studies), and the event reported to the MHRA if the participant was taking the Medicinal Product (MP).

3.13 If the CI/PI becomes aware of a systematic issue or identifies a factor in the SAEs being reported (e.g. multiple reports of the same event, potential drug-drug interactions), then they should notify the Sponsor immediately.

3.14 All reported AEs and SAEs will be fed back as part of the Annual Progress Report (APR) to the REC that granted the favourable opinion for the study, and to the MHRA as part of the Development Safety Update Report (DSUR). The DSUR must also be forwarded to the REC.

Reporting SUSARs to the Sponsor

3.15 SUSARs should be reported to the Sponsor in the same way that SAEs are (above).

3.16 It may be deemed necessary to un-blind the participant in order to make a definitive assessment of whether an SAR (Serious Adverse Reaction) was unexpected, therefore confirming whether it is a SUSAR. The Sponsor should advise sites as to the appropriate procedure. Please note than un-blinding one participant may mean un-blinding the whole study, and so the guidance of the Sponsor must always be sought before any action taken.

3.17 The study protocol should set out the procedure for un-blinding in the circumstances set out above. If un-blinding occurs then the member of staff who undertook this procedure, should remain blinded to the participant's medication. The Sponsor should likewise advise on this.

3.18 As with SAE reporting, the SUSAR must be reported **as soon as the site is aware**. Any addition information can be provided to the Sponsor once it becomes available in a follow-up report. All reports and correspondence, inclusive of correspondence with the regulatory bodies, must be filed in the TMF.

Reporting of SUSARs to REC, MHRA and study sites

3.19 The CI is responsible for reporting SUSARs to the MHRA and REC (which gave the favourable opinion for the study) as soon as possible. For fatal or life-threatening SUSARs, they must do so no later than **7 calendar days** of the study team's awareness. If any additional relevant information becomes available it may be sent with **8 days** of the report.

All other SUSARs must be reported within **15 calendar days** of the CI becoming aware. This metric also applies to SUSARs occurring after the trial has ended.

3.20 The causality assessment made by the investigator cannot be downgraded by the CI or the Sponsor. If the assessment made by the Sponsor differs to that of the investigator, both assessments should be recorded.

3.21 If an event has been identified as a SUSAR by the CI, PI or Sponsor then the participant should be un-blinded if a randomised trial. The event should then be reported to the MHRA if the participant was taking the IMP.

3.22 SUSARs must be reported to the MHRA using the eSUSAR website (https://esusar.mhra.gov.uk), by the trial team. Appropriate members of the team should be granted access to the portal.

3.23 If the study is multicentre, then the CI must forward details of all SUSARs reported to the PIs at each site participating in the study. Details must be forward within **14 calendar days** of the SUSAR being resolved. All reports and correspondence must be filed within the TMF/ISF.

Urgent Safety Measures and Reporting

3.24 In the interests of patient safety, a CI, PI, or the Sponsor, can deviate from the study protocol, or implement a change to the protocol without approval from the REC or MHRA. This is called an *Urgent Safety Measure*. If this is instigated by the CI or PI, then the Sponsor should be informed immediately by email – researchgovernance@bournemouth.ac.uk.

The CI/Sponsor must also contact and discuss the issue with a medical advisor at the MHRA, details on their website.

3.25 The CI must notify the MHRA (in the case of CTIMPs) and REC immediately. They should then submit a substantial amendment to the MHRA (if applicable) and REC *within 3 days*. In this correspondence they should detail the reason(s) for the measures and the measures that were taken, with a description of the event.

Relevant NHS Research & Developments (R&D) and site PIs should be notified of the measures being taken immediately. The notification must be filed in TMF and ISF.

- Email the Sponsor at researchgovernance@bournemouth.ac.uk;
- Email the MHRA clintrialhelpline@mhra.gov.uk, mark the correspondence as 'Urgent Safety Measure', a substantial amendment will then need to be made covering the changes made as part of the Urgent Safety Measure;
- Email the REC who gave the favourable opinion, marking the email as 'Urgent Safety Measure';
- Email the relevant NHS R&D offices, marked as 'Urgent Safety Measure'.

3.26 The CI must discuss the implications of the Urgent Safety Measure on the conduct of the study, with the Sponsor, urgently.

Pregnancy Reporting

3.27 Pregnancy is not considered an AE or SAE. If required by the study protocol, the CI should collect pregnancy information for participants who become pregnant, or for partners of participants who become pregnant.

3.28 The CI or delegate must inform the Sponsor of this development.

3.29 Any trial participant who becomes pregnant, or partner of a participant who becomes pregnant during the trial, will be followed-up to outcome. Depending on the study, it may be necessary to monitor the development of the new-born for an appropriate period, post-delivery. The protocol will set out any requirements.

3.30 If the pregnant participant or pregnant partner of a participant does not wish for this information to be collected, then this should be recorded in the medical records and on the Case Report Form (CRF).

4. Abbreviations and definitions

4.1 There are five categories of safety reporting, defined in Good Clinical Practice (GCP) as follows:

- **Adverse Event (AE)** – Any untoward medical occurrence in a clinical trial participant to whom a medicinal product has been administered which is not necessarily caused by or related to that product.

  Only AEs identified as critical to evaluations of safety in the study, as set out in the protocol, should be recorded.

- **Adverse Reaction (AR)** – All untoward and unintended responses to the medicinal product at any dose administered to the participant. The PI, CI or delegated consultant will judge as to whether the reaction has a causal relationship with the medicinal product.

ARs are identified by referring to the expected adverse reactions of the drug, as listed in the protocol, Investigator Brochure (IB) if the drug does **not** have marketing authorisation, or the Summary of Product Characteristics (SmPC/SPC) if the drug has marketing authorisation.

They will either be consistent with the aforementioned documents, or unexpected.

- **Adverse Events of Special Interest (AESI)** – although not defined within UK Clinical Trial Regulations, these types of events are now being commonly requested, especially within trials investigating unlicensed medicinal products.

  An AESI is identified as '(a) noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (e.g. hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in protocols or protocol amendments, and instructions provided for investigators as to how and when they should be reported to the sponsor.[1]

- ***Serious* Adverse Event (SAE), *Serious* Adverse Reaction (SAR)**

An event or reaction becomes *serious* when it meets one or more of the following criteria:

  - Results in death;
  - Is life-threatening;
  - Requires hospitalisation or a prolongation of hospitalisation;
  - Results in persistent or significant disability or incapacity;
  - Consists of a congenital abnormality or birth defect.

- **Suspected Unexpected *Serious* Adverse Reaction (SUSAR)** – If the AR is classed as serious according to the categories above, and it is possibly, probably or definitely caused by the medicinal product, but not consistent with the known information on the product as documented in the protocol, IB or SmPC/SPC, then it is 'unexpected', and therefore a SUSAR.

4.2 The causality of an event will need to be categorised with one of the following terms:

Unrelated: where the AE is not considered to be related to the medicinal product;

Possibly: a relationship to the MP cannot be ruled out entirely, the nature of the event, underlying disease, concomitant medication or temporal relationship may make other explanations possible;

Probably: the temporal relationship and absence of a more likely explanation signifies that the event could be related to the medicinal product;

[1] Globalpharmacovigilance.tghn.org. (2018). Glossary of Drug Safety Terms - Global Pharmacovigilance. [online] Available at: https://globalpharmacovigilance.tghn.org/resources/glossary/ [Accessed 3 May 2018].

Definitely: the known effects of the medicinal product, or its therapeutic class, or based on challenge testing, signifies that the medicinal product is the most likely cause.

Device Trials

- **Adverse Device Effect (ADE)** – An AE that relates to the use of an investigational medical device, including any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation or any malfunction of the investigational medical device. It also includes any event as a result of a user error or intentional misuse.

- **Device Deficiency (DD)** - The inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error, and inadequate labelling. This includes devices already marketed, but that are being evaluated for a new indication, in new populations, new materials or changes in design.

- ***Serious* Adverse Device Effect (SADE)** – An ADE that has resulted in any of the consequences that are characteristic of an SAE, including those that:

    - Led to a death;
    - Led to a serious deterioration in health that either:
        - Resulted in a life-threatening illness or injury;
        - Resulted in a permanent impairment of a body structure or a body function;
        - Required in-patient hospitalisation or prolongation of an existing hospitalisation;
        - Resulted in medical or surgical intervention to prevent a life-threatening illness or injury, or permanent impairment to a body structure or a body function.
    - Led to foetal distress foetal death or a congenital abnormality or birth defect

- **Unanticipated Serious Adverse Device Effect (USADE)** – A SADE which by nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

5. Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
APR	Annual Progress Report
AR	Adverse Reaction
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DD	Device Deficiency
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
MP	Medicinal Product

ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
PI	Principal Investigator
R&D	Research & Development (NHS Research Governance)
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

6. Related documentation and references

e-SUSAR reporting - https://esusar.mhra.gov.uk

Globalpharmacovigilance.tghn.org. (2018). Glossary of Drug Safety Terms - Global Pharmacovigilance. [online] Available at: https://globalpharmacovigilance.tghn.org/resources/glossary/ [Accessed 3 May 2018].

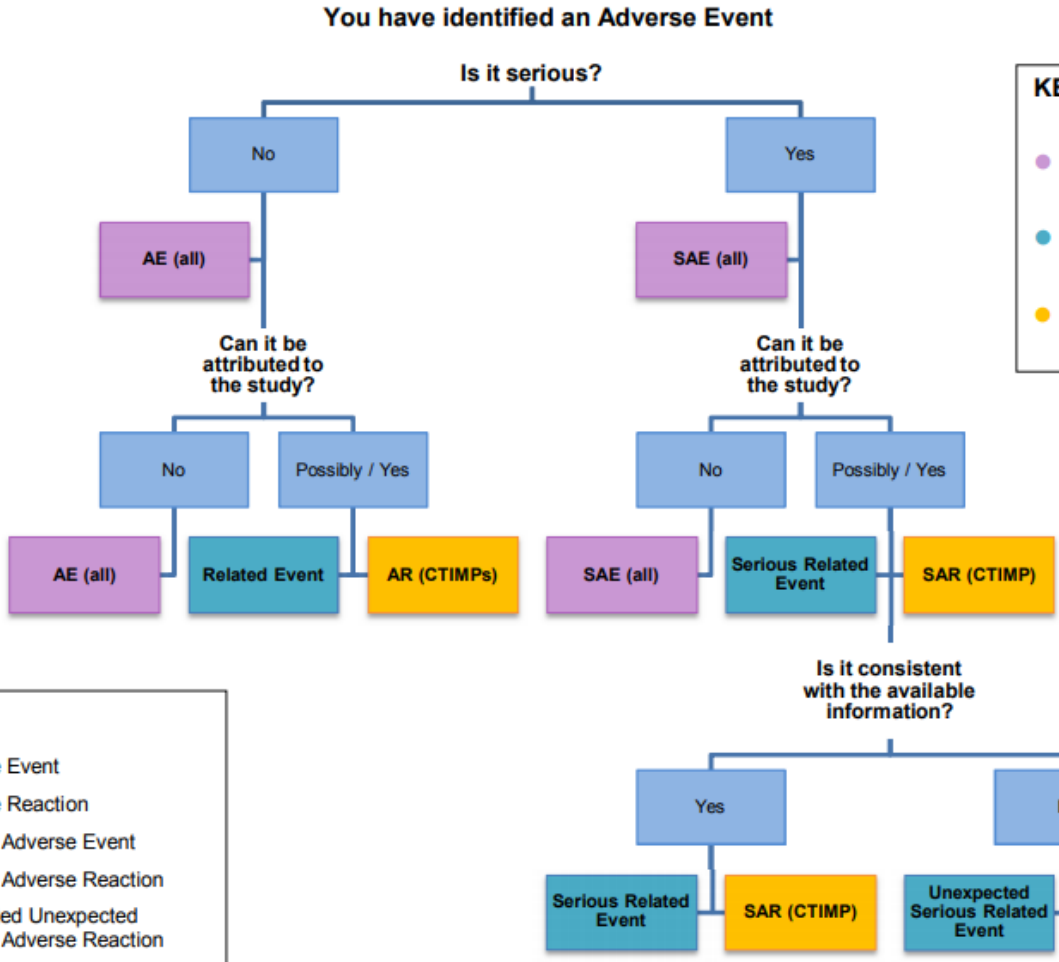
GOV.UK. (2014). Clinical trials for medicines: manage your authorisation, report safety issues. [online] Available at: https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues [Accessed 10 Jul. 2018].

nihr.ac.uk. (2018). [online] Available at: https://www.nihr.ac.uk/our-faculty/documents/Decision%20Tree%20for%20Adverse%20Event%20Reporting.pdf [Accessed 9 Jul. 2018]

Non-CTIMP safety report to REC form

Decision Tree for Adverse Event Reporting

NHS National Institute for Health Research



KEY

- Definition for CTIMPs and non-CTIMPs
- Definition for non-CTIMPs only
- Definition for CTIMPs only

CTIMP Acronyms

AE	Adverse Event
AR	Adverse Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction