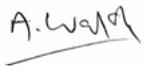
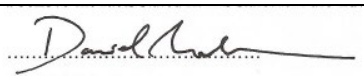
UNIVERSITY OF SUSSEX

This is a controlled document
Any printed versions of this document will be classed as uncontrolled

Standard Operating Procedures for Adverse Events in Clinical Trials of Investigational Medicinal Products (CTIMPs)

SOP Reference:	**SOP/RG/21**
Version Number	**1.0**
Date:	**15 June 2021**
Effective Date:	**1 July 2021**

Author: Antony Walsh **Designation:** Research Governance Officer	**Signature** 	**Date** 26 May 2021
Authorised By: Dr Daniel Michelson **Designation:** SSC Chair		11 June 2021

Version	Date	Reason for Change
1.0	1 June 2021	-

Disclaimer

- When using this document ensure that the version you are using is the most up to date either by checking on the Research Governance webpages[1] for any new versions or by contacting the author to confirm the current version
- Staff and students may print off this document for training and reference purposes but are responsible for regularly checking for the current version. Any print-off of this document will be classed as uncontrolled
- Out of date documents must not be relied upon

Acknowledgements – University of Aberdeen

[1] http://www.sussex.ac.uk/staff/research/governance

UNIVERSITY OF SUSSEX

1. Purpose & Scope

1.1 The EU Good Clinical Practice (GCP) Directive 2001/20/EC was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union. It was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments will be referred to as the Regulations in the rest of this document[2].

1.2 This Standard Operating Procedure (SOP) informs any individual delegated the task of identifying, recording and reporting an Adverse Event (AE), Adverse Reaction (AR), Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR) occurring in a Clinical Trial of Investigational Medicinal Products (CTIMP), sponsored by University of Sussex (US).

1.3 The scope of the document is for all schools at the University of Sussex, all members of staff with substantive employment and students registered at the University (including Brighton and Sussex Medical School) undertaking CTIMPs. The scope of the document includes anyone undertaking activities for a Clinical Trial on behalf of the University.

2. Introduction

2.1 To comply with the Regulations which set out the responsibilities of the sponsor, this SOP will focus on the trial site team procedures for the adequate recording, evaluation and reporting of AEs, ARs, SAEs, SARs and SUSARs in trials involving IMPs. It will further outline the Investigator's responsibilities to ensure oversight and management of pharmacovigilance systems in University of Sussex sponsored trials.

Definitions

2.2 The following definitions have been adapted from the UK regulations:

Adverse Event (AE)

2.3 Any untoward medical occurrence in a clinical trial participant to whom an Investigational Medicinal Product (IMP) has been administered, but which is not necessarily caused by or related to that product.

2.4 Only AEs that are identified in the protocol as critical to evaluations of safety in the trial should be recorded. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease.

Adverse Reaction (AR)

2.5 All untoward and unintended responses to the IMP, related to any dose administered to that participant. ARs are all adverse events judged by the reporting PI, CI, or Delegated Investigator, as having a reasonable causal relationship to the IMP.

2.6 ARs may be classed as either:

(i) Expected: the AR is consistent with the AR profile of the trial drug listed in the trial protocol, Investigator Brochure (IB) Reference Safety information (RSI) or Summary of Product Characteristics (SmPC/SPC).

(ii) Unexpected: the AR is not consistent with the AR profile in the trial protocol, IB, RSI or SmPC/SPC. Or the documented AR has occurred at a greater frequency or severity than expected.

Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

2.7 The classification of serious is:

Any untoward medical occurrence, event or reaction that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalisation, or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life threatening resulting in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above.

2.8 Life threatening, by definition, refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

2.9 Medical judgement by the CI/PI or delegate shall be exercised in deciding seriousness of an AE or AR.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

2.10 Any AR classed as serious and possibly, probably or definitely caused by the IMP (see 2.14) (but not consistent with the known information on that product, as documented in either the trial protocol, SmPC/SPC, RSI or IB), is termed unexpected and is a Suspected Unexpected Serious Adverse Reaction (SUSAR).

2.11 The trial protocol should include a list of known side effects for each drug in the study or provide a clear reference to where the Reference Safety Information (RSI) can be accessed. This should be consulted when a SAR occurs, to determine expectedness. If the event is not listed, or has occurred in a more serious form, or more frequently than expected, it should be considered to be a SUSAR. All deaths related to the IMP should be considered to be SUSARs.

Relatedness (Causality)

2.12 Depending on the type of study, the attribution of causality or relatedness may differ.

2.13 Phase I and Phase II studies will usually be based on a five-point scale:

i. **Unrelated**: There is no evidence of any causal relationship.
ii. **Unlikely to be related**: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial IMP). There is another reasonable explanation for the event (e.g. the patient's clinical condition, or other concomitant treatment).
iii. **Possibly related**: There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial IMP). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, or other concomitant treatment).
iv. **Probably related**: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
v. **Definitely related**: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

2.14 Phase II and III studies may use may use 'Definitely related' (v), 'Probably related' (iv), 'Possibly related' (iii), 'Unlikely to be related' (ii) or Not related, following discussion with the CI and as per the pharmacovigilance section of the Protocol.

2.15 Phase IV studies will usually require the answering of 'yes' or 'no' in response to considering causal relationship.

3. Responsibilities

Chief Investigator (CI)

3.1 The CI has responsibility for reporting, assessing and signing off SAE/SUSARs.

Clinical Reviewer/ delegate(s)

3.2 Clinician performing a clinical review on behalf of the Sponsor.
The role is delegated by the Sponsor and can be the study Chief Investigator (CI), or clinical member of the Trial Management Group (TMG), or an independent clinician.

Principal Investigator (PI)

3.3 The PI has responsibility for reporting, assessing and signing off SAE/SUSARs

Sponsor

3.2 The Sponsor has responsibility for ensuring that SUSARs are reported by the CI or assigned clinical reviewer to the MHRA.

4. Procedure

Protocol safety section

4.1 The decision on what AEs to record and report should be determined during the trial protocol development and informed by the CI and Sponsor risk assessment. This should also be noted for SAEs (which are a subset of AEs) particularly in relation to whether any will be recorded as outcomes rather than as SAEs.

4.2 The trial protocol or SAE reporting guidelines shall clearly define:

- How AEs shall be identified and the follow up period when they will be identified.
- Which AEs will be recorded.
- Whether any AEs will be recorded as outcomes, rather than AEs.
- Which AEs are expected as a result of the participant's condition.
- Which AEs are expected following administration of the IMP (reference should be made to the Reference Safety Information (RSI)).
- That AEs where the frequency and/or severity (see sections 4.8 and 4.9) are not in keeping with the RSI shall be recorded as unexpected events.
- The procedure for dealing with incidental findings (i.e. recorded as AEs or not).
- The procedure for dealing with abnormal measurements (e.g. laboratory results).
- Whether any auxiliary investigational medicinal products (AMPs) are to be supplied to participants in the trial (e.g. support/rescue medication or preventative, diagnostic or therapeutic treatments to ensure good medical care to participants).

- Whether the CI will review PI assessment of SAEs before or after reporting to Sponsor.
- The procedure for un-blinding in blinded trials.
- If it is necessary to record pregnancy and whether it should be an exclusion.

4.3 On review of data, the Data Monitoring Committee (DMC) may note events which could be relevant for the safety of trial subjects and may also require assessment as potential AE/ARs.

Identifying the Adverse Event

4.4 AEs shall be identified by, or notified to, the research team.

4.5 Unless stated in the protocol a member of the research team shall ask participants at each trial visit (or telephone contact) about hospitalisations, consultations with other medical practitioners, disabilities, incapacities, or if any AEs have occurred since the previous trial contact. In addition, participants may self-report AEs via direct contact to the trial team or by completion of research project questionnaires.

4.6 Potential AEs may also be identified during the assessment of trial outcomes by support departments, for example, clinical laboratories, and radiology. Where notification of abnormal values or measurements is not standard clinical practice, the procedure for notifying such out of range events to the CI or PI must be clearly documented in the trial protocol or study specific SOPs. Such out of range events may or may not constitute AEs.

Assessment of Adverse Event

4.7 AEs must be assessed for seriousness by the study team. If deemed serious then the PI or CI must be informed and a decision then made as to whether the event is related to the MP or not (see section 4 for definitions). If related to the IMP the CI or PI shall determine if the event is expected or unexpected. The assessment must be recorded on a RGSAE form (Appendix 1) or study SAE form developed by the study team or CTU if applicable, For blinded studies, AEs shall be assessed as though the trial subject was taking the IMP.

4.8 For all SAEs the CI or Delegated Investigator shall make an assessment of severity. The assessment shall be recorded on the SAE form according to the following categories where reference is ***not*** made to existing precise criteria related to the disease or condition that shall be specified in the Protocol[2] :

[2] E.g. the AIDS (DAIDS) Table for Grading the Severity of Adverse Events or the Common Terminology Criteria for Adverse Events (CTCAE)

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

ii. **Moderate:** an event that is sufficiently discomforting to interfere with normal everyday activities.

iii. **Severe**: an event that prevents normal everyday activities.

4.9 The term 'severe' used to describe the intensity of an event or reaction should not be confused with the term 'serious' which is a regulatory term used for trial participant/event outcome. For example, a headache may be severe but not serious, while a minor stroke may be serious but not severe.

4.10 The SAE form shall be completed by a member of the research team and signed by the PI/or Delegated Investigator.

Reporting SAEs by the Delegated Clinical Reviewer on behalf of Sponsor[3]

4.11 All SAEs must be reported to the Sponsor within 24 hours of the CI/PI or delegate's awareness of the event. This is delegated to the CI by the Sponsor and is formally documented in the CI responsibilities letter issued by Sponsor. All reports must be on a study specific SAE Reporting Form (RGSAE-Form), emailed to researchsponsorship@sussex.ac.uk. [4]The SAE form should be as complete as possible within the time frame and signed and dated by the CI/PI, or medically qualified delegate. Documents shall be assessed by a medically qualified individual or CI of the study, on behalf of the Sponsor, checked for completeness, and a follow up requested if appropriate.

4.12 All SAEs must also be recorded on the on-going Trial Log of SAEs. This shall be forwarded to the Sponsor at the same time as the SAE Reporting Form.

4.13 The Sponsor shall review all reported SAEs. For blinded CTIMPs, SAEs shall be assessed as though the trial subject was taking the IMP. The Sponsor shall email the outcome of the Sponsor assessment to the study team. The Sponsor may disagree with the CI or PI assessment and this shall be recorded by the study team in the Trial Log of SAEs.

[3] Please see the Safety Reporting Flowchart made available by the NIHR - http://www.ct-toolkit.ac.uk/routemap/safety-reporting/downloads/safety-reporting-flowchart.pdf

[4] Studies being managed by the Brighton and Sussex CTU should refer to CTU SOPs.

4.14 If the event has been considered by either the CI, PI or Sponsor as a SUSAR, the participant shall be un-blinded, if a randomised trial, and the event reported to the MHRA if the participant was taking IMP.

4.15 If the CI is delegated to be the clinical reviewer on behalf of the Sponsor two assessments are required:

- From the site - PI or Delegated Investigator (or CI if not Delegated Clinical Reviewer)
- From the Sponsor - usually the CI as clinical reviewer if delegated

4.16 Due to the necessity to report SAEs within 24 hours it is anticipated that there may be additional information which will be submitted as a follow-up report. All follow-up reports shall be submitted to researchsponsorship@sussex.ac.uk[5] along with an updated log and shall be reviewed by Sponsor as detailed in 4.11

4.17 Any follow-up to an SAE must be reviewed using the RSI that was approved and relevant at the time of the initial report. Any changes to this shall be documented and reported to Sponsor.

4.18 Should the CI become aware of a systematic issue or identify a factor in the SAEs being recorded (e.g. events occur at a higher than expected frequency, identify a risk factors in patient population or potential drug-drug interactions) they shall notify the Sponsor immediately (researchsponsorship@sussex.ac.uk).

4.19 All recorded AEs and SAEs shall be reported as part of an Annual Progress Report to the REC which provided the favourable opinion for the trial, and to the MHRA as part of the Development Safety Update Report (DSUR). The DSUR shall also be forwarded to the REC.

Reporting SUSARs to the Sponsor

4.20 SUSARs shall be reported to the Sponsor using the same procedure as outlined above for SAEs.

4.21 It may be necessary to un-blind the participant in order to make a definitive assessment of an SAR that is unexpected, and hence to confirm whether it is a SUSAR or not. If in doubt contact the Sponsor.

4.22 The trial protocol shall set out the procedure for un-blinding in such circumstances. Efforts should be made to ensure that any study team member involved in further study

[5] For Brighton & Sussex CTU supported studies, the SAE should also be sent to bsctusafety@bsms.ac.uk

assessments of the un-blinded participant remains blinded. In such cases, the Sponsor can be contacted for advice.

4.23 If all the required information is not available at the time of reporting a SUSAR to the Sponsor, the site PI or Investigator must ensure that any missing information is provided to the Sponsor as soon as this becomes available in a follow-up report (see 4.13). It shall be supplied using the **SAE reporting form** (See Appendix 1)) or study SAE form developed by the study team or CTU if applicable with a clear indication that the new information is a follow-up report to a previously reported event. [6]

Filing

4.23 All SAE forms and any follow-up communication with any information to/from the Sponsor or MHRA shall be retained in the Trial Master File (TMF) or Investigator Site File (ISF). The updated SAE log, and the SAE report for a SUSAR received by the Sponsor, together with any follow-up information, shall be kept in the Sponsor File. If stored electronically, the file path shall be clearly indicated.

Expedited reporting of SUSARS to REC, MHRA and additional trial sites

4.24 The CI is responsible for reporting SUSARs in writing to the MHRA and REC, which gave the favourable opinion about the trial, as soon as possible (see Appendix 1). For fatal or life threatening SUSARs this should be done no later than 7 calendar days of the study team's awareness. All other SUSARs must be reported within 15 calendar days of the CI first becoming aware. This also applies to SUSARs occurring after the end of the trial.

4.25 The assessment of causality made by the investigator cannot be downgraded by the CI or Sponsor. Where the assessment of causality made by Sponsor and investigator differ, both assessments shall be recorded.

4.26 If an event has been considered by either the CI, PI or Sponsor as a SUSAR, the participant shall be un-blinded, if a randomised trial, and the event reported to the MHRA if the participant was taking IMP.

4.27 All SUSARs should be reported to the MHRA via the MHRA eSUSAR website: https://esusar.mhra.gov.uk/.

[6] For Brighton & Sussex CTU supported studies, the clinical reviewer (which may be the CI) will review on behalf of sponsor but the complete SAE form with all reviews will be forwarded on to the Sponsor.

4.28 Fatal or life-threatening SUSARs should be reported to the MHRA as soon as possible, but no later than 7 days after first being aware of the reaction. Any additional relevant information must be sent within 8 days of the report.

4.29 Non-fatal or non-life threatening SUSAR should be reported as soon as possible to the MHRA but no later than 15 days after first being aware of the reaction.

4.30 The CI shall report SUSARs to the REC which provided the favourable opinion for the trial using a completed REC safety form available from https://www.hra.nhs.uk/approvalsamendments/managing-your-approval/safety-reporting/.

4.31 For multicentre studies, the CI must forward details of all SUSARs reported in the trial to the PIs at all trial sites. Details must be forwarded to PIs within 14 days of the SUSAR being followed to resolution.

4.32 In addition to filing requirements (see 4.23) all relevant correspondence with MHRA/REC should be maintained in TMF/ISF.

Reporting of Urgent Safety Measures to Sponsor, REC and MHRA

4.33 An **Urgent Safety Measure** (USM) is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the REC (and MHRA where applicable), in order to protect clinical trial participants from any immediate hazard to their health and safety. Such safety measures may include a temporary halt to the study.

4.34 Any USM relating to a CTIMP should be communicated to the MHRA and REC immediately by telephone, ideally within 24 hours of measures being taken and no later than three days from the date of the measures taken. The Sponsor must also be informed via researchsponsorship@sussex.ac.uk.[7]

4.35 The telephone call should be followed up with an email for traceability to include the time and date of the telephone call, the content of the conversation and the name of the MHRA safety scientist and UK REC contact. Should further clarification be required the sponsor may be contacted by a medical assessor at the MHRA.

[7] https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#urgent-safety-measures

4.36 The CI must also provide written notification to the PIs of additional sites (if a multi-centre study) and relevant NHS Research and Development (R&D) offices (marked 'Urgent Safety Measure') within 3 days of the measures being taken and the reason(s) for the measures. A copy of the notification must be filed in the TMF and the ISF (as appropriate).

4.37 The CI must discuss the implications of the USM on the conduct of the trial with the Sponsor as a matter of urgency.

Substantial Amendment

4.38 Following initial written notification a substantial amendment is required to be submitted.[8]

4.39 The substantial amendment covering the changes made as part of the Urgent Safety Measure is anticipated within approximately 2 weeks of notification of the USM to the MHRA.

4.40 The substantial amendment shall be submitted to the Sponsorship Sub-Committee in the usual manner. Review and approval can be expedited for Chair's Action as required.

Archiving

4.41 Following the closure of a study the essential documents should be archived in accordance with SOPRG033 Archiving of Paper Trial Documents (for University of Sussex as Sponsor) and SOPRG034 for Archiving CTIMP Paper Trial Documents (Sites).

5. Training

5.1 This is a 'read and understand' SOP. Please note that the Research Ethics, Integrity and Governance Team discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the University website.

6. Abbreviations

AE	Adverse Event

[8] https://www.myresearchproject.org.uk/help/hlpamendmentsresearch.aspx

CA	Competent Authority
CI	Chief Investigator
COA	Compliance Oversight Advisor
CR	Clinical Reviewer
CRF	Case report form
CRN	Clinical Research Network
CRO	Clinical Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DCF	Data Clarification Form
eCRF	Electronic Case report form
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
HSC	Health and Social Care
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
IVD	In Vitro Diagnostic
JCRO	Joint Clinical Research Office
LIP	Local Information Pack
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PAF	Portfolio Application Form
PPI	Patient and Public Involvement
PVG	Pharmacovigilance Manager
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RM(ATIMPS)	Regulatory Manager for ATIMPS
RM(P)	Regulatory Manager (Pharmaceuticals)
RSI	Reference Safety Information

SI	Statutory Instrument
SIV	Site Initiation Visit
SmPC/SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Trial Manager
TMF	Trial Master File
US	University of Sussex
USM	Urgent Safety Measure

7. Cross Referenced SOPs

SOPRG04	Risk Assessment
SOPRG07	Essential Document Management
SOPRG033	Archiving of Paper Trial Documents (for University of Sussex as Sponsor)
SOPRG034	Archiving CTIMP Paper Trial Documents (Sites)

8. References

Good Clinical Practice Guide MHRA/ Stationery Office (Great Britain), London: 2012

Appendix 1

SERIOUS ADVERSE EVENT REPORT[9]

Study Title:	
Patient Study Number and Initials	

This form is to be completed within 24 hours of awareness of the Serious Adverse Event

1.Type of Report **Initial** ☐ **Follow Up** ☐ **Final** ☐
(Tick relevant box)

Date of Report ____/____/_____

Serious Adverse Event: _____

Date of Onset ____/____/____

Date Study Team Aware ___/____/_____

2.Serious Criteria:

☐ **Resulted in death**

☐ **Life threatening**

☐ **In-patient hospitalisation or prolongation of existing hospitalisation**

☐ **Persistent or significant disability/incapacity**

[9] For trials not supported by BSCTU

☐ **Congenital anomaly/birth defect**

☐ **Other**

3.Narrative -Briefly describe the event (attach supporting documentation if applicable)

	4)
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	

Was the event related to a study device/procedure or intervention

☐ Yes ☐ No

5) Was the event related to a protocol violation?

☐ Yes ☐ No

6) Was the patient withdrawn from the study as a result of this event?

☐ Yes ☐ No

7) Outcome of the Event

☐ Resolved

☐ Resolved with Sequalae

☐ Ongoing

☐ Unknown at present

☐ Fatal Date of Death:

Cause of Death .....

Cause of death obtained from (tick one)

Working Diagnosis ☐ Coroners Inquest ☐ Death Certificate ☐

Supporting documentation to be supplied with SAE

Reporting Person:	Principal Investigator/Delegated medically qualified individual as agreed by the sponsor
Name:	Name :
Role:	Role:
Signature:	Signature:
Date:	Date:
Contact No:	Contact No:

This form must be sent to the Chief Investigator within 24 hours of the event

CHIEF INVESTIGATOR:
Please send to Sponsor within 24 hours of receipt

Research Governance Office
Falmer House
University of Sussex
Brighton BN1 9QF

researchsponsorship@sussex.ac.uk

Unexpected SAEs related to the study procedure must be reported to NHS REC within 15 days

Safety reporting flowchart

Adverse Event Reporting: UK Open Label Trial

SYMONS ASSOCIATES LTD
Clinical Research Consultancy

PI assesses causality[1]

- **Related** → **Adverse Reaction (AR)**
- **Not related** → **Adverse Event (AE)**

PI assesses seriousness

- **Not serious[2]** → **Adverse Event/Reaction (AE/R)**
  PI records and notifies sponsor as per protocol
- **Serious SAE/R**

PI checks protocol to confirm whether SAE/R requires expedited reporting

- **NO** → **'Non-Expeditable' (SAE/R)**
  PI records and notifies sponsor as per protocol
- **YES**

PI notifies sponsor of SAE/R within 24 hours

Sponsor's assessment of causality[3]

- **Unrelated to IMP** → **Serious Adverse Event (SAE)**
  Sponsor keeps records and follows up until resolution
- **Related to IMP**

Serious Adverse Reaction (SAR)

Sponsor's assessment of expectedness using the RSI[4]

- **Unexpected** → **Suspected Unexpected Serious Adverse Reaction (SUSAR)**
  Sponsor to report to MHRA and Ethics Committee:
  - Fatal or life threatening SUSARs within 7 days
  - All other SUSARs within 15 days

  SUSARs reported to PIs as per protocol
- **Expected**

Expected Serious Adverse Reaction (SAR)
Sponsor keeps records and follows up until resolution

Adverse Event (AE):
Any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR):
Any untoward and unintended response to an IMP which is related (a reasonable causal relationship) to any dose administered.

Serious Adverse Event/Reaction (SAE/R):

- Results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- any other safety issues considered medically important.

PI should **actively seek** follow-up information on reported SAE/Rs.

Footnotes

[1] PI or delegate.
[2] Notable or safety critical events must be reported as per protocol.
[3] Sponsor cannot downgrade the PI's causality assessment, but can upgrade it.
[4] Reference Safety Information (RSI) in IB or SmPC.

S
S
Date:
Version: