Title: Review of Serious Adverse Event (SAE) Reports

SOP Code: SOP/15/V1.3

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1. Purpose

The purpose of this SOP is to provide instructions on the review and follow-up reports of serious adverse experience and unexpected events for any active study approved by the NIRRH Ethics Committee for Clinical studies. The Serious Adverse Events must be reported by the investigators to the IEC within 24 hours after the incident. The unexpected events should be included in the continuing review report submitted to IEC.

Unanticipated risks are sometimes discovered during the course of studies. Information that may impact the risk/benefit ratio should be promptly reported to and reviewed by the IEC to ensure adequate protection of the welfare of the study participants.

The unanticipated risks may as well include any event that in the investigator's opinion, may adversely affect the rights, welfare or safety of the participants in the study.

2. Scope

This SOP applies to the review of SAE reports submitted by Investigators to IEC members or other concerned parties.

3. Responsibility

The primary responsibility of the IEC is to review and address SAE and unexpected events involving risks to participants.
IEC should also make sure that researchers are made aware of the policies and procedures concerning reporting and continuing review requirements of SAE and unexpected events.

- The Principal Investigator should submit within 24 hours on site SAE report or the unexpected adverse event report to the IEC or by email.
- The report of SAE of death after due analysis shall be forwarded by the Investigator to chairman of the IEC and Chairman of the Expert Committee constituted by the Licensing Authority under Appendix XII with a copy of the report to the head of the institution where the trial is been conducted within 14 calendar days of SAE of death.
- The report of the SAE other than death after due analysis shall be forwarded by the Investigator to chairman of the IEC and the head of the institution where the trial is been conducted within 14 calendar days of occurrence of SAE.
- The report should be accompanied by detailed narrative of the SAE and appendix XI form of the CDSCO.
- It should be submitted as per checklist detailed by Licensing Authority.

The sponsor or his representative shall pay the compensation in case of clinical trial related injury or death within 30 days of the receipt of such an order from Licensing Authority.

The IEC Secretariat is responsible for initial screening of the reports and assessing / seeing whether they need a review of full Board, Chairperson, other qualified IEC members or experts.

4. Flow chart

S.No	Activity	Responsibility
1	SAE related activities before an IEC meeting ↓	IEC Secretariat, members
2	Review and determine the review channel ↓	IEC Secretariat, members
3	Decide the criteria for the review ↓	IEC Secretariat, members
4	Review and discuss during the IEC meeting ↓	IEC members and Chairperson
5	Decide what action should be taken ↓	IEC members and Chairperson
6	Inform investigator**,** regulatory authorities and head of institution within 30 days of receipt of the SAE	Secretariat and Chairperson

5. Detailed instructions

5.1 Before each IEC meeting

5.1.1 Review and determine the review channel

- IEC Secretariat or members review the reporter's assessment to determine whether the report requires review by full Board or by the Chairperson or other qualified IEC member(s).

5.1.2 Criteria for the review

The **review criteria** are as follows:

- Assessment of adverse experience is unknown or unlikely
- Report is forwarded to the Chairperson for review and determination if report should be reviewed at the convened meeting by full Board.
- Assessment of relatedness of the SE as per the criteria of GSR 52 with amendments of 12th June 2015 .
- The report is added to the agenda for review at a convened meeting by full Board.
- An adverse experience/Investigational New Drug safety Report has been previously seen by full Board but being resubmitted by another investigator participating in the multi-study site (as part of a multi-center/site study).
  - This notification does not require full Board review.
  - Reviewed by the Chairperson or other qualified IEC members and secretariat

5.2 During the IEC meeting

5.2.1 Review and discuss

- After reading and reviewing the report, the Chairperson or designee entertains discussion on the study and similar adverse experiences or advisories.

- If appropriate to the discussions, the Chairperson or another EC member may call for a consensus on whether to:

- *Request an amendment to the protocol or the consent form.*
- *Request further information.*
- *Suspend or terminate the study.*

5.2.2 Decide what action should be taken

- If any of the above *actions are taken*, the IEC Secretariat or designee notifies the investigator of the action taken.
- If the IEC *takes no action*, a notation is made in the minutes and the study is allowed to continue.

5.2.3 Inform investigator or clinical trial office

- The IEC secretariat member drafts a formal letter to the investigators or the clinical trial office to notify them of the action they should take according to the IEC decision.
- Get the Chairperson to approve, sign and date the letter.
- Send the letter and record the delivery date.

6. Glossary

Adverse Event
Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. The adverse event can therefore be any unfavourable or unintended sign or experience associated with the use of the investigational product, whether or not related to the product.

Adverse Drug Reaction
In the pre-clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not established all noxious or unintended responses to the product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between the product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed products, a response to a product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

IND
Investigational New Drugs means substances with potential therapeutic actions during the process of scientific studies in human in order to verify their potential effects and safety for human use and to get approval for marketing.

SAE
(Serious Adverse Event)
The adverse event is SERIOUS and should be reported when the patient outcome is:

Death - Report if the patient's death is suspected as being a direct outcome of the adverse event.

Life-Threatening - Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death.
Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing.

Hospitalization (initial or prolonged) - Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event.
Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization.

Disability - Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy.

Congenital Anomaly - Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child.
Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.

Requires Intervention to Prevent Permanent Impairment or Damage –

Report if suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.
Examples: Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

Unexpected ADR Unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the informed consent /information sheets or the applicable product information (e.g., investigator's brochure for the unapproved investigational product or package insert / summary of product characteristics for an approved product.

7. References

7.1 World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000.

7.2 International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996.

7.3 Forum for Ethical Review Committees in Asia and the Western Pacific SOPs 2006

7.4 National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, ICMR, 2017

8. ANNEX

ANNEX 1	AF/EC/01/15/V1.3	Serious Adverse Event Report
ANNEX 2	AF/EC/02/15/V1.3	Unexpected Adverse Event Summary Report
ANNEX 3	AF/EC/03/15/V1.3	Document History
ANNEX 4	AF/EC/04/15/V1.3	Checklist for Submission of SAE

ANNEX 1 **AF/EC/ 01/15/V1.3**

Serious Event Report

Project No.: **Principal Investigator:**

Study Title:

Name of the study medicine/device:

Report Date:

☐ **initial** ☐ **follow-up** ☐ **close out**

Onset date:

Subject's initial/number: : Age: ….. Yrs. ☐ Male ☐ Female

Subject's history: Laboratory findings: ----------

SAE: Treatment: ----------

Outcome: ☐ resolved ☐ on-going

Seriousness:

☐ Death
☐ Life Threatening
☐ Hospitalization –○ initial ○ prolong
☐ Disability / Incapacity
☐ Congenital Anomaly
☐ Other……

Relation to ○ Drug ○ Device ○ study

☐ Not related ☐ Possibly ☐ Probably ☐ Definitely related ☐ Unknown

Changes to the protocol recommended? ☐ No ☐ Yes , attach proposal

Changes to the informed consent form recommended?

☐ No ☐ Yes , attach proposal

Reviewed by:……

Comment:…….

Date:……

Action:……

ANNEX 2 **AF/EC/02/15/V1.3**

Unexpected Adverse Event Summary Report

Principal Investigator:……

Study Title:……...

Name of the studied medicine/device……..

Sponsor:……...

#	Description of Unexpected Adverse Events	Date of Event (D/M/Y)	Date start and end of Tx (D/M/Y)	F or M	Initial	Age (Y)	Serious Yes No	Related to Study Yes No	Concomitant medication	Inter-vention

Comment:

Reviewed by**:……**

Date:

ANNEX 3 **AF/EC/03/15/V1.3**

Document History

Author	Version	Date	Description of the Change
Dr. Ragini Kulkarni	Version 1.1	24th September 2014	Timelines for reporting SAEs included on page no.3
Dr. Ragini Kulkarni	Version 1.2	1st September 2016	Pg.4, added under flow chart point 6- regulatory authorities and head of institution within 30 days of receipt of the SAE
Dr. Ragini Kulkarni	Version 1.3	7th November 2017	Pg.10 Annxure 4 for Checklist for submission of SAE added

ANNEX 4 **AF/EC/04/15/V1.3**

CHECKLIST FOR SUBMISSION OF SERIOUS ADVERSE EVENT REPORT (SAE) OCCURRING IN CLINICAL TRIAL/BIO-EQUIVALENCE STUDY

S.No.	Details		
1.	**Country (Name of the country should be specified)**		
2.	**SAE report of death or other than death, Please tick (✓)**	Death ☐	Other Than Death ☐
		Yes/No	**Page No.**
3.	**In case of Serious Adverse Event(SAE), please specify if there is any injury to the subject (Please specify Yes/No) in the box**		
4.	Protocol Title		
5.	Protocol Study No./ ID /Code		
6.	Copy of Clinical Trial permission/ BE-NOC obtained from CDSCO		
7.	CTRI Registration No. (Mandatory for Clinical Trial Permitted after 15/06/09)		
8.	Sponsor(Address with contact no and Email)		
9.	CRO (Address with contact no and Email)		
10.	Clinical Trial Site address and site number.		
11.	Initial / Follow-up (FU)		
12.	In case of follow-up: Date & Diary no of initial or recently submitted report information		
13.	**Patient/Subject Details**		
a.	Initials & other relevant identifier (Hospital/OPD record number etc.)		
b.	Gender		
c.	Age, Date of birth, Weight & Height		
14.	**Suspected Drug(s)/Medical Device**		
a.	Generic name of the Drug(s)/Device.		
b.	Indication(s) for which suspect/study drug was prescribed or tested.		
c.	Dosage form and strength / Dosage regimen		
d.	Route of administration.		
e.	Starting date and time of day.		
f.	Stopping date and time & duration of treatment		
g.	Baseline values of investigations prior to administration of Suspected Drug(s)/ Medical Device.		
15.	**Other Treatment(s) / Concomitant Drug History**		
	Provide the same information for concomitant drugs (including non-Prescription /OTC Drugs) and non-drug therapies, as for the suspected drug(s).		
a.	Generic name of the Drug(s)/Device.		
b.	Indication(s) for which suspect/study drug was prescribed or tested.		
c.	Dosage form and strength / Dosage regimen		
d.	Route of administration.		
e.	Starting date and time of day.		
f.	Stopping date and time & duration of treatment		

16.	**Details of the events**		
a.	Full description of event (s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.		
b.	Start date (and time) of onset of reaction.		
c.	Stop date (and time) or duration of reaction.		
d.	Dechallenge and rechallenge information.		
e.	Setting (e.g., hospital, out-patient clinic, home, nursing home).		
f.	Expectedness of SAE (Expected / Unexpected) as per IB		
17.	Outcome		
a.	Information on recovery and any sequelae; results of specific tests and/or treatment that may have been conducted.		
b.	For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; any post-mortem findings.		
c.	Other information: anything relevant to facilitate assessment of the case, such as medical history with date including allergy, drug or alcohol abuse; family history; findings from special investigations etc.		
18.	Details about the Investigator		
a.	Name		
b.	Address		
c.	Telephone/Mobile Number & Email		
d.	Profession (speciality)		
e.	Date of reporting the event to Licensing Authority:		
f.	Date of reporting the event to Ethics Committee overseeing the site:		
g.	Date of reporting the event to Sponsor/CRO		
h.	Signature of the Investigator		
19.	Details about the Ethics Committee		
a.	Name & Address		
b.	Name of Chairman & Address		
c.	Telephone/Mobile Number		
d.	Email		
20.	Adverse Event Term / Details of SAE		
21.	Causality Assessment by Investigator with reasoning for Relatedness/Un-relatedness along with supporting investigational documents.For SAE-Death the name(s) of the suspected drug(s) must be provided after Unblinding.		
22.	Causality Assessment by Sponsor/ CRO with reasoning for Relatedness /Un-relatedness. For SAE-Death the name(s) of the suspected drug(s) must be provided after Unblinding.		
23.	Causality Assessment by Ethics Committee with reasoning for Relatedness /Un-relatedness.For SAE-Death the name(s) of the suspected drug(s) must be provided after Unblinding.		
24.	Details of compensation provided for injury or death. In case no compensation has been paid, reason for the same.		
25.	Duly filled SAE Form as per Appendix XI of Schedule Y		
26.	Laboratory investigations report /Discharge summary during the time of SAE.		
27.	Post-mortem report & Medical death certificate (if applicable)		
27.	Copy of Signed Informed Consent Form of the Subject/Patient along with English version.		

28.	Filled copy of CRF		
29.	Socioeconomic background of subject/patient viz. Qualification, Occupation, Monthly income.		
30.	Copy of latest amended version of Protocol approved by CDSCO.		
31.	Copy of Investigator's Brochure (In case of SAE-death)		