Title: Review of Serious Adverse Event (SAE) Reports

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SOP Constitution and Approval:

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1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe procedures for the review of initial and follow-up reports of serious adverse events (SAE) reported to the IHEC for any study under the oversight of the Institutional Human Ethics Committee.

2. Scope

This SOP applies to the review of SAE reports (Adverse events/ SAE onsite as well as SAEs of the multicenter studies occurring at other offsite) submitted to the IHEC.

3. Responsibility

It is the responsibility of the IHEC to review all SAEs reported to the IHEC in a timely manner.

4. Definitions

1] Serious Adverse Event (SAE) / Serious Adverse drug Reaction (SADR)

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect

2] Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

5. Detailed instructions

5.1 SAE Subcommittee

- An SAE Subcommittee is constituted within the IHEC for reviewing SAE reports..
- The Serious Adverse Event (SAE) Subcommittee of the Institutional Human Ethics Committee (IHEC) will review all serious adverse events (SAE) at the site / other sites involving human participants approved by IHEC.
- The committee will consist of members who collectively have the qualifications and experience to review and evaluate the scientific, medical and ethical aspects of adverse event reports involving human participants.

Composition of the SAE Subcommittee

- The SAE Subcommittee will be appointed by the **Dean of IHEC**.
- The SAE Subcommittee will be multidisciplinary and multi - sectoral in composition.
- The SAE Subcommittee will be composed of at least 5 and a maximum of 10 individuals who are members of the IHEC.
- The composition shall be as follows:
    - Chairperson of the SAE Subcommittee
    - One Executive Secretary
    - At least one member with post graduate qualification in the discipline of
        - Medicine
        - Medical Pharmacology
        - Any other relevant clinical specialties in the institution
- IHEC Secretary will be Ex-Officer member of the SAE Subcommittee.
- The SAE Subcommittee may invite legal expert of the IHEC to provide opinion on the legal implication of adverse event.
- The Chairman of the SAE Subcommittee will be responsible for conducting SAE subcommittee meetings, and will lead all discussions and deliberations pertinent to the review of adverse event reports.
- The Chairman of the SAE Subcommittee/ Executive Secretary will sign minutes of the

SAE Subcommittee meeting.

- In case of anticipated absence, the Head of SAE subcommittee will nominate a SAE subcommittee member as acting head. The acting Head will have all the powers of the Chairman of SAE subcommittee for that meeting.
- For the SAE subcommittee meeting, a quorum will consist of at least 4 members as follows- one member (preferably pharmacologist), one member (preferably clinician), Member secretary and Head/ Acting head of the SAE subcommittee.
- The SAE subcommittee will meet at least once in a month (or as often as required)

Membership requirements

- An IHEC Member will be appointed for the SAE Subcommittee if they show willingness and commitment in terms of time to perform the role and responsibility as SAE Subcommittee member.

- Dean is responsible for appointing the SAE Subcommittee members. The appointed person may be suggested by the IHEC members and the Chairperson to the Dean. The final decision regarding appointment of members will be taken by the Dean.

- The tenure will be for 4 years and member will be eligible to be appointed for the new tenure consecutively four times.

- The SAE Subcommittee member may resign from membership by submitting a letter of resignation to the Executive Secretary of the SAE Subcommittee. The member may or may not assign reasons for resignation.

- A SAE Subcommittee member may be disqualified from SAE Subcommittee membership if the member fails to attend more than 5 regular consecutive SAE Subcommittee meetings without prior intimation. The Head of SAE Subcommittee will inform Chairperson, in writing, if a member has not attend more than five consecutive regular meetings of the SAE Subcommittee. The Chairperson will take up the issue of disqualification for discussion at the full board meeting and allow the concerned SAE Subcommittee member to state his reasons for unauthorized absence.

Functions of the Executive Secretary of the SAE Subcommittee

1. To schedule and organize the SAE Subcommittee meetings.
2. To prepare and maintain meeting agenda and minutes.
3. To conduct SAE subcommittee meetings
4. To prepare the communication letters related to the adverse event reports.
5. To communicate with IHEC members, regulatory authorities and investigators in timely manner.
6. To provide necessary administrative support for SAE Subcommittee related activities.
7. To ensure adherence of the SAE Subcommittee functioning as per SOPs

5.2 Onsite SAE

5.2.a. Receipt of SAE report

- The IHEC Secretariat will receive the following documents within the specified time frame if an SAE is experienced by any research participant:

  i. Initial SAE report to be submitted by the Principal Investigator (PI) within 24 hours of occurrence as per the format specified in AX 01/SOP 12/V2.

  ii. Due analysis should be submitted by the PI within 14 days from the occurrence of the SAE along with the format specified in AX 02/SOP 12/V2.

  iii. Due analysis will also be submitted by the sponsor within 14 days in the format specified in AX 02/ SOP 12/V2.

  iv. The follow up reports of all on-site SAE till the event is resolved.
- The IHEC Secretariat will verify that the report is complete in all respects and that it has been received at the IHEC office within the specified timelines.

- If the report has been received beyond the specified time, it will be considered as a protocol violation and action should be taken.

- The IHEC Secretariat will sign and write the date on which the report is received.

- The Secretariat will forward these reports to the IHEC Member Secretary or executive Secretary of the SAE Subcommittee (if constituted) within two working days.

5.2 b. Review and Decision on SAE Reports and Communication to PI and Regulatory Authority by IHEC

- Member Secretary or Executive Secretary of the SAE will review the SAE report and present to the full board / SAE subcommittee (as applicable) for review and opinion.
- At the meeting of IHEC, the SAE reports will be reviewed with a special focus on relatedness to the clinical trial, medical management and financial compensation to be given to the research participants. The applicable formulae and guidelines from the regulatory authority will be used during this discussion.
- If deemed necessary, a decision to hold emergency IHEC meeting may be taken to discuss about financial compensation. An emergency IHEC meeting will be scheduled within 7 days for the same.
- The Executive Secretary of the SAE subcommittee may refer the SAE report to full board for review if deemed necessary.
- The minutes of the SAE Subcommittee/ IHEC meeting will include the information on SAE at the site along with the opinion on the above points on the onsite SAE.

Participant ID	Letter no./and date of reporting	Type of Report (I/FU)	Date of onset	whether study drug withheld	SAE Outcome	Causality in the Opinion of PI	Recommendation (s) by SAE Subcommittee

I-Initial, FU- Follow-Up

The minutes will be circulated to the IHEC members *via* email and approval/ objection will be sought from the members in a period of 5 working days.

- The IHEC secretariat will draft a formal letter to the concerned PI and inform him/ her about the IHEC decision. This letter will be signed and dated by the Member-Secretary or Chairperson (IHEC) and will be sent to the PI within a period of 7 days from the SAE subcommittee meeting.
- The PI will be requested to reply to the query letter on the SAE report within 7 working days.
- The opinion regarding relatedness, medical management and compensation for research

related injury will be communicated to the Licensing authority (DCGI) within 30 calendar days of the occurrence of the SAE in case of regulatory clinical trials.

- The IHEC Secretary will file a copy of these letters in the study file.

5.3 Reports of SAE Occurring at other Sites

The investigator will need to submit the SAEs occurring at other sites (CIOMS and SUSARS) in the form of soft copies only (CD) along with the appropriate covering letter (hard copy) mentioning the total number of reports and its details in the following format:

SNo.	Country	Type of Report (I/FU)	SAE event	Date of onset	Date of report	Outcome	Causality	
							Investigator	Sponsor

I-initial, FU- Follow-Up

- For every SAE term, a separate row of the above table is to be used (the SAE terms should not be combined).
- Causality to be stated as related (R) or not related (NR)
- The SAEs occurring at other sites will be reviewed by the Secretary of the IHEC / SAE Subcommittee (as applicable) and informed to other members and discussed in the forthcoming scheduled meeting. The agenda and minutes of the meeting will include the information on SAEs at other sites.

5.4. Onsite AE

The IHEC Secretariat will receive the following documents pertaining to AE experienced by the research participants for research proposals approved by the IHEC:

1. On site AE reports to be submitted by the PI annually in the continuing review report.
2. In view of the risk assessment of a given research proposal the IHEC can request adverse events to be reported earlier, if deemed necessary at specified timelines in the project approval letter.

- The IHEC Secretariat will verify that the report is complete in all respects and signed and dated by the PI and that it has been received at the IHEC office within the specified timelines. If the report has been received beyond the specified time, it will be considered as deviation.
- For all the onsite AE reports received at the IHEC office, the Administrative Officer will forward these reports to the Member Secretary of IHEC for review.
- Member Secretary of IHEC may put the AE reports for discussion at full board if deemed necessary
- Queries, if any on the report will be communicated to the PI by the Member Secretary of IHEC following full board meeting
- The IHEC Secretary will file a copy of these letters in the study file.

5.5. Review During the Full board IHEC meeting

- The IHEC Member Secretary will read out the minutes of all the monthly SAE Sub-committee meetings including the recommendations/ decisions of the SAE sub-committee (if constituted).

- In case of the SAE occurring at the site to be discussed at the full board meeting, the member secretary will also provide the relevant information including updates on SAE that have occurred earlier at the site. The Chairperson will invite members to voice their opinions and ensure free and frank discussion.

- The decision can be arrived at by consensus. If not agreed by consensus, the issue would be put for voting. (a majority vote for a decision is 2/3rd majority of the members present and voting)

5.6 Decision of IHEC on SAE review

The SAE Subcommittee/IHEC may take one or more of the following decisions on review of the SAE reports.

5.6a. Type of Actions Taken by IHEC/ SAE Subcommittee on Review of SAE Report

Following detailed review of the SAE reports and related documents, the IHEC/ SAE Subcommittee (if constituted) can suggest one of the following actions:

- Note the information about the SAE in records for future reference.
- Request further follow up information and/ or additional details.
- Ask for periodic follow-up of the research participant till SAE is resolved
- Depending on complexities of issue, **IHEC/ SAE Subcommittee** may decide to seek opinion of outside expert consultant who is requested to respond within 10 working days.
- Provide recommendations regarding/ raise queries related to compensation for study related injury and death

5.6b. Type of Actions Taken by IHEC following full board review

- Suggest changes/ amendments in protocol, Patient Information Sheet/ Informed Consent Document/ Investigators' Brochure/ any other study-related documents.
- Suspend the study till additional information is available.
- Suspend the study till review is completed (safety monitoring of ongoing patients to be continued).
- Suspend the study till amendments requested for by the IHEC are carried out.
- Suspend enrollment of new participants.
- Suspend certain activities under the protocol.
- Direct the PI to inform participants already enrolled in the study about the AEs and if required obtain their consent again (re-consent) regarding continuation in the research trial.
- Direct the PI to inform participants already enrolled in the study about the AE and request them to undertake additional visits, additional procedures, additional investigations, etc. as prescribed in the amendment.

- Terminate the study.
- Any other appropriate action.
- The decision shall be recorded in the minutes of the full board IHEC meeting.
- If the recommendation from the IHEC includes suspension of the study or suspension of any one or more of the study-related procedures or activities, amendments in the protocol or other study-related documents (excluding Investigators' brochure), re-consenting of research participants, the decision will be conveyed to the PI through telephone, fax or email within 24 hours. Such a communication will be documented by the IHEC Member-Secretary in the study file. A formal letter to the PI informing about the IHEC recommendations in such situations will be sent within 5 working days of the IHEC meeting having taken place.

6. References to other applicable SOPs

- **SOP 07A/V2 -** *Full-Board Review of research Study Protocols*
- **SOP 08/V2 –** *Agenda Preparation, Meeting Procedures and Recording of Minutes*
- **SOP 10/V2 –** *Continuing Review of Study Protocols*

7. 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 unfavorable or unintended sign or experience associated with the use of the investigational product, whether or not related to the product.
Serious Adverse Drug Reaction	A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function
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; pseudo membranous 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.
SUSAR (Suspected Unexpected Serious Adverse Report)	An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out. • In the case of a licensed product, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the IB relating to the trial in question.

8. Annexures

Annexure 1 AX 01/ SOP 12/V2– As per Schedule Y Appendix XI: Data Elements for Reporting Serious Adverse Events occurring in a clinical trial (Schedule Y http://dbtbiosafety.nic.in/act/schedule_y.pdf)

Annexure 2A AX 02A/ SOP 12/V2 - Checklist for Onsite Serious Adverse Event submission

Annexure 2B AX02B/ SOP 12/V2– Onsite Serious Adverse Event Analysis Report

Annexure 1: AX 01/ SOP 12/V2

Data Elements for reporting serious adverse events occurring in a clinical trial

1. Patient Details

- Initials & other relevant identifier (hospital/OPD record number etc.)
- Gender
- Age and/ or date of birth
- Weight
- Height

2. Suspected Drug(s)

- Generic name of the drug
- Indication(s) for which suspect drug was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)
- Route of administration
- Starting date and time of day
- Stopping date and time, or duration of treatment

3. Other treatments

- Provide the same information for concomitant drugs (including non-prescription / OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Suspected Adverse Drug Reaction(s)

- Full description of reaction(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.
- Start date (and time) of onset of reaction.
- Stop date (and time) or duration of reaction.
- Dechallenge and rechallenge information.
- Setting (e.g. hospital, out-patient clinic, home, nursing home).

5. Outcome

- Information on recovery and any sequelae; results of specific tests and / or treatment that may have been conducted.
- For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; Any post mortem findings.
- Other Information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history, findings from special investigations etc.

6. Details about the Investigator

- Name
- Address & Telephone number
- Profession (speciality)
- Date of reporting the event to Licensing Authority:
- Date of reporting the event to Ethics Committee overseeing the site:
  Signature of the Investigator

Annexure 2A AX 02A/ SOP 12/V2
Checklist for Onsite Serious Adverse Event (SAE) submission

SNo.	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 participant (Please specify Yes/No) in the box		
4.	Protocol Title		
5.	Protocol Study No./ ID /Code		
6.	Copy of Clinical Trial permission obtained from CDSCO		
7.	CTRI Registration No.		
8.	Sponsor(Address with contact no and Email)		
9.	CRO (Address with contact no and Email)		
10.	Initial / Follow-up (FU)		
11.	In case of follow-up: Date & Diary no of initial or recently submitted report information		
12.	**Patient Details**		
a)	Initials & other relevant identifier (hospital/OPD record number etc.)		
b)	Gender		
c)	Age and/or date of birth		
d)	Weight		
e)	Height		
13.	**Suspected drugs**		
a)	Generic name of the drug		
b)	Indication(s) for which suspect drug was prescribed or tested		
c)	Dosage form and strength		
d)	Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)		
e)	Route of administration		
f)	Starting date and time of day		
g)	Stopping date and time, or duration of treatment		
14.	**Other Treatment(s)**		
	Provide the same information for concomitant drugs (including non prescription/OTC Drugs) and non- drug therapies, as for suspected drug(s)		
15	**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.		
b)	In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.		

c)	Start date (and time) of onset of reaction.		
d)	Stop date (and time) or duration of reaction.		
e)	Dechallenge and rechallenge information.		
f)	Setting (e.g., hospital, out-patient clinic, home, nursing home).		
16.	**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 including allergy, drug or alcohol abuse; family history; findings from special investigations etc.		
17	**Details about the Investigator**		
a)	CT Site Number, if any		
b)	Name		
c)	Address		
d)	Telephone/Mobile Number & Email		
e)	Profession (specialty)		
f)	Date of reporting the event to Licensing Authority:		
g)	Date of reporting the event to Ethics Committee overseeing the site:		
h)	Signature of the Investigator		
18.	**Details about the Ethics Committee**		
a)	Name & Address		
b)	Name of Chairman & Address		
c)	Telephone/Mobile Number		
d)	Email		
19.	Adverse Event Term/ Details of SAE		
20.	Causality Assessment (Related/Unrelated) by Investigator		
21.	Causality Assessment (Related/Unrelated) by Sponsor/ CRO		
22.	Details of compensation provided for injury or death. In case no compensation has been paid, reason for the same		
23.	Duly filled SAE Form as per Appendix XI of Schedule Y		
24.	Laboratory investigations report /Discharge summary (if available and applicable)		
25.	Post-mortem report (if applicable)/ Any additional documents)		

Note: Information not relevant to a particular SAE should be marked with NA

Annexure 2B AX 02B/ SOP 12/V2
Onsite Serious Adverse Event Analysis Report

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 participant (Please specify Yes/No) in the box		
4.	Protocol Title		
5.	Protocol Study No./ ID /Code		
6.	Copy of Clinical Trial permission obtained from CDSCO		
7.	CTRI Registration No.		
8.	Sponsor(Address with contact no and Email)		
9.	CRO (Address with contact no and Email)		
10.	Initial / Follow-up (FU)		
11.	In case of follow-up: Date & Diary no of initial or recently submitted report information		
12.	**Patient Details**		
a)	Initials & other relevant identifier (hospital/OPD record number etc.)		
b)	Gender		
c)	Age and/or date of birth		
d)	Weight		
e)	Height		
13.	**Suspected drugs**		
a)	Generic name of the drug		
b)	Indication(s) for which suspect drug was prescribed or tested		
c)	Dosage form and strength		
d)	Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)		
e)	Route of administration		
f)	Starting date and time of day		
g)	Stopping date and time, or duration of treatment		
14.	**Other Treatment(s)**		
	Provide the same information for concomitant drugs (including non prescription/OTC Drugs) and non- drug therapies, as for suspected drug(s)		
15	**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.		

b)	In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.		
c)	Start date (and time) of onset of reaction.		
d)	Stop date (and time) or duration of reaction.		
e)	Dechallenge and rechallenge information.		
f)	Setting (e.g., hospital, out-patient clinic, home, nursing home).		
16.	**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 including allergy, drug or alcohol abuse; family history; findings from special investigations etc.		
d)	**Details about the Investigator**		
e)	CT Site Number, if any		
f)	Name		
g)	Address		
h)	Telephone/Mobile Number & Email		
i)	Profession (specialty)		
j)	Date of reporting the event to Licensing Authority:		
k)	Date of reporting the event to Ethics Committee overseeing the site:		
l)	Signature of the Investigator		
18.	**Details about the Ethics Committee**		
a)	Name & Address		
b)	Name of Chairman & Address		
c)	Telephone/Mobile Number		
d)	Email		
19.	**Adverse Event Term/ Details of SAE**		
20.	Causality Assessment (Related/Unrelated) by Investigator		
21.	Causality Assessment (Related/Unrelated) by Sponsor/ CRO		
22.	Details of compensation provided for injury or death. In case no compensation has been paid, reason for the same		
23.	Duly filled SAE Form as per Appendix XI of Schedule Y		
24.	Laboratory investigations report /Discharge summary (if		

	available and applicable)		
25.	Post-mortem report (if applicable)/ Any additional documents)		

Details of payment for medical management of SAE? (please give information whopaid how much was paid, to whom, with evidence of the same)

What is the investigator's assessment for the amount of compensation to be paid?

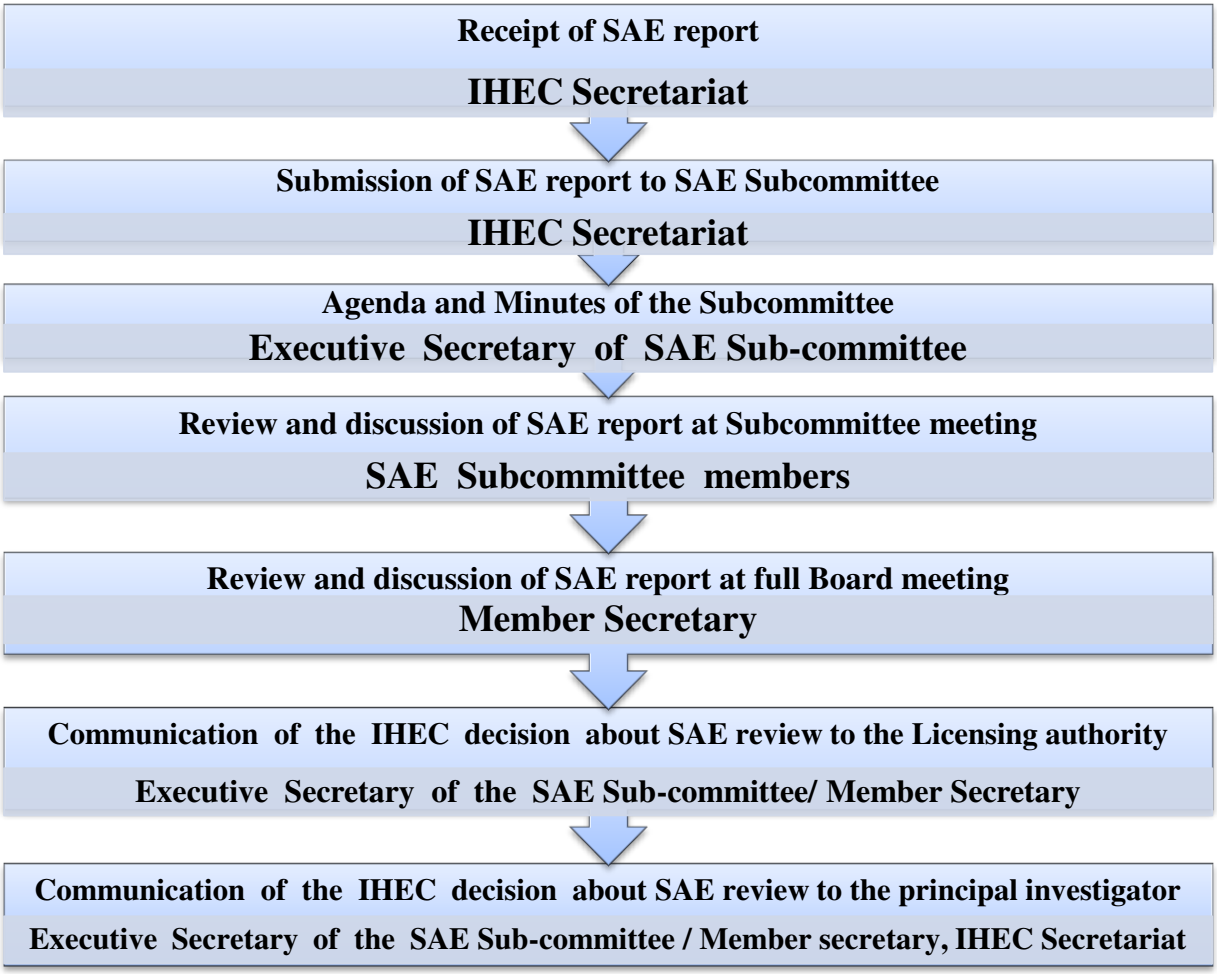
What is the sponsor's assessment for the amount of compensation to be paid?

Has the participant made a claim? Yes No
If yes, for how much amount _____

If no, please ensure that the participant / nominee have been made aware of his/her' rights regarding compensation. Please submit documentation regarding the same_____

Signature of the Principal Investigator : Date:

7. Flowchart



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