Review of Serious Adverse Events (SAE) Reports and Unexpected Adverse Events (UAE)

For Institutional Ethics Committee

Tagore Medical College and Hospital

Melakkottaiyur, Rathinamangalam, Chennai-127

Ph: 044-30101111

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Copy Holder Name and Designation : **Dr. R. Geetha, Member Secretary, IEC**

Prepared By	Reviewed By	Approved By
R. Geetha		
Dr. R. Geetha Member secretary of IEC	Dr. I. Kannan Member of IEC	Dr. S. Seethalakshmi Chairperson of IEC

1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe procedures for the review of initial and follow-up reports of adverse events (AE), serious adverse events (SAE) and unexpected adverse events (UAE) reported to the IEC by our sites and other site reports at Tagore Medical College and Hospital for any study under the oversight of the Institutional Ethics Committee (IEC).

2. Scope

This SOP applies to the review of AE, SAE and UAE reports submitted to the IEC.

3. Responsibility

It is the responsibility of the IEC to review AEs, SAEs and UAEs reported to the IEC. These could be AEs, SAEs and UAE occurring at Tagore Medical College and Hospital or other sites for the given project/related project.

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4. Flow chart

No.	Activity	Responsibility
1	Receipt of AE, SAE and UAE report.	Secretariat.
2.	Submission of AE, SAE and UAE report to the Subcommittee.	Secretariat.
3	Agenda and Minutes of the Subcommittee.	Secretary of the SAE Sub-committee.
4.	Review and discussion of SAE report at the Subcommittee meeting.	SAE Subcommittee members.
5.	Discussion/ Decision at the IEC meeting.	Members of the IEC.
6.	Communication of the IEC decision about SAE review to the principal investigator.	Secretariat.
7.	Communication of the IEC decision about SAE review to DCGI.	Member Secretary / Chairperson of the IEC.
8	Discussion/Information at the full board IEC meeting	Member Secretary of the IEC.

5. Detailed Instructions

5.1 Onsite SAE and UAE:

5.1.1 Receipt of SAE/UAE report:

• The IEC Secretariat will receive the following documents within the specified time frame pertaining to SAE /UAE experienced by the research participants ON SITE for research proposals approved by the IEC:

i. On site SAE or UAE report to be submitted by the Principal Investigator within 24 hours of their occurrence as per the format.
ii. In the case of SAE, the report with due analysis will be submitted by the Principal investigator within 14 days along with the format.
iii. In the case of SAE, the report with due analysis will be submitted also by the sponsor within 14 days along with the format.
iv. The follow up reports of all on site SAE / unexpected AE reports till the event is resolved with the format.

• The IEC Secretariat will verify that the report is complete in all respects and is signed and dated by the Principal Investigator (PI) or Sponsor as the case may be and that it has been received at the IEC office within the specified timelines above. If the report has been received beyond the specified time, this will be considered as a violation.
• The IEC Secretariat will sign and write the date and type of report on which the report is received.
• For all the onsite SAE/ UAE reports received at the IEC office, the Administrative Officer will forward these reports to the executive secretary of the SAE Subcommittee within two working days.

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5.1.2 Review of SAE, UAE Reports:

• Secretary of the SAE Subcommittee will review the SAE /UAE report and arrange a meeting depending on the timelines.
• SAE and UAE reports submitted to the IEC will be reviewed by the SAE subcommittee at least weekly or more often (as needed).
• At the meeting, the members of the SAE subcommittee will review all the SAE/UAE reports received in the earlier week and submit a report stating the recommendations on the SAE/UAE report discussed in the meeting to IEC.

5.1.3 Communication to the IEC:

i. The IEC Secretariat will receive the minutes within 5 working days of the meeting of the SAE subcommittee and recommendation taken on the onsite SAE /UAE report.
ii. This report will be circulated to the IEC members *via* email and approval/ objection will be sought from the members in a period of 2 days.
iii. If approval is obtained from all the IEC members the decision will be communicated to the Licensing authority (DCGI) within 30 days of the occurrence of the SAE.
iv. If the SAE is death then the decision will be communicated to DCGI within 30 days of the occurrence of the SAE- Death.
v. If decision is that research participant is entitled for financial compensation an emergency IEC meeting will be scheduled within 7 days for the same.
vi. If objection is received from more than 2 IEC members an emergency IEC meeting will be scheduled within 7 days for the same.

The decision taken at the emergency IEC meeting regarding the onsite SAE/UAE report will be communicated to the Licensing authority (DCGI) within 30 days of the occurrence of the SAE. If the SAE is death then the decision will be communicated to DCGI within 30 days of the occurrence of the SAE- DEATH.

5.1. 4 Inform Investigator:

• The IEC secretariat will draft a formal letter to the concerned Principal Investigator and inform him/ her about the IEC decision. This letter will be signed and dated by the Member-Secretary / Chairperson (IEC) and will be sent to the Principal Investigator within a period of 7 days from the date of the SAE subcommittee meeting.
• The Principal Investigator will be requested to reply to the query letter on the SAE report within 7 working days. If no response is received (within 7 days of dispatch of EC query letter) from the investigator regarding the query raised on the given SAE/UAE, a reminder letter will be sent to the investigator stating that the response to the query letter must be sent within 5 working days of the dispatch of reminder letter. If no response is received to the reminder letter, this should be informed by the member secretary of the IEC in the full board meeting and decision will be taken on case-to-case basis.
• The principal investigator will be requested to forward follow-up reports after due analysis of the SAE/unexpected AE report to the IEC within 14 days of the occurrence of the SAE/unexpected AE report.
• The Administrative Officer will file a copy of the query letter in the study file.

5.1.5 Inform Licensing authority (DCGI):

• The Member-Secretary / Chairperson (IEC) of the IEC will forward the letter describing the opinion on the SAE report death, along with the opinion on financial compensation, to the Chairperson of the Expert Committee constituted by the Licensing authority (DCGI) and also a copy to DCGI within 30 days of the occurrence of the SAE-death.
• The Member-Secretary / Chairperson (IEC) of the IEC will forward the letter the decision taken on the given SAE report (other than death)/unexpected adverse event report along with the opinion on financial compensation to the Licensing authority (DCGI) within 30 days of the occurrence of the SAE/ unexpected adverse event.
• The Administrative Officer will file a copy of these letters in the study file.

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5.2 Onsite AE:

5.2.1 Receipt of AE report:

• The IEC Secretariat will receive the following documents pertaining to AE experienced by the research participants for research proposals approved by the IEC:
1. On site AE reports to be submitted by the Principal Investigator annually.
2. In view of the risk assessment of a given research proposal the IEC can request adverse events to be reported earlier, if deemed necessary at specified timelines in the project approval letter.
• The SAE/IEC Secretariat will verify that the report is complete in all respects and is signed and dated by the Principal Investigator (PI) and that it has been received at the IEC office within the specified timelines above. If the report has been received beyond the specified time, this will be considered as violation.
• The IEC Secretariat will sign and write the date on which the report is received.
• For all the onsite AE reports received at the IEC office, the Administrative Officer will forward these reports to the executive secretary of the SAE Subcommittee within two working days.

5.2.2 Review of AE Reports:

• AE reports submitted to the IEC will be reviewed by the SAE subcommittee at the scheduled meetings as per procedures described in SOP 11A and minutes communicated to IEC Secretariat.

5.2.3 Inform Investigator:

• The SAE/IEC secretariat will draft a formal letter to the concerned Principal Investigator and inform him/ her about the IEC decision on the concerned AE report. This letter will be signed and dated by the Member-Secretary/ Chairperson (IEC) and will be sent to the

Principal Investigator within a period of 7 days from the date of the SAE subcommittee meeting.

• The principal investigator will be requested to reply to the query letter on the AE report within 7 working days. If no response is received (within 7 days of dispatch of EC query letter) from the investigator regarding the query raised on the given AE report, a reminder letter will be sent to the investigator stating that the response to the query letter must be sent within 5 working days of the dispatch of reminder letter. If no response is received to the reminder letter, this should be informed by the member secretary of the IEC in the full board meeting and decision will be taken on case-to-case basis.

5.2.4 Further action:

• The Administrative Officer will file a copy of these letters in the study file.
• If deemed necessary Licensing Authority will be informed.

Custodian:

5.3 SAEs occurring at other sites:

The investigator will need to submit the SAEs occurring at other sites 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:

Sr. No.	Country	MFR Control No.	Type of Report	SAE event	Date of onset of ADR	Date of ADR report	Outcome	Causality	
								Investigator	Sponsor

• For every SAE term use separate row. Do not club SAE terms.

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• Please mentioned causality as related (R) or not related (NR)[do not use word possibly, unlikely, probable]
• The SAEs occurring at other sites will be reviewed by the Secretary of the SAE Subcommittee and informed to other members of the Subcommittee and discussed in the forthcoming scheduled Subcommittee meeting. The agenda and minutes of the SAE Subcommittee will include the information on SAEs at other sites.
• The discussion will be communicated by the SAE Subcommittee Executive Secretary to the Secretariat who will include it in the appropriate IEC agenda.

5.4 During the Full board IEC meeting:
• The IEC Member Secretary will read out the minutes of all the weekly SAE Subcommittee meetings including the recommendations/ decisions of the SAE subcommittee.
• In case of the AE/ SAE/UAE occurring at the site to be discussed at the full board meeting, the member secretary will also provide the relevant information including updates on AE/ SAE/ UAE that have occurred earlier at the site. The Chairperson will invite members to voice their opinions and ensure free and frank discussion.
• If appropriate to the discussions and any issues put forth by SAE subcommittee, the issue can be re-discussed and decision can be arrived at by voting (a majority vote for a decision is 2/3rd majority of the members present and voting) or by consensus.

Actions are listed below:

- *Terminate the study.*
- *Suspend the study till review is completed (safety monitoring of ongoing*
- *patients to be continued).*
- *Suspend the study till additional information is available.*
- *Suspend the study for a specified duration of time.*
- *Suggest changes/ amendments in protocol, Patient Information Sheet/*
- *Informed Consent Document/ Investigators' Brochure/ any other study related documents.*
- *Suspend the study till amendments requested for by the IEC are carried out.*

- *Suspend enrollment of new participants.*
- *Suspend certain activities under the protocol.*
- *Direct the Investigator 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 Investigator 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.*
- *Note the information about the SAE in records for future reference.*
- *Request further follow up information and/ or additional details.*
- *Provide periodic follow-up of the research participant till SAE is resolved or till death occurs (whichever is earlier).*
- *Any other appropriate action.*

The decision shall be recorded in the minutes of the full board IEC meeting.

• If the recommendation from the IEC 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 Principal Investigator through telephone, fax or email within 24 hours. Such a communication will be documented by the IEC Member-Secretary in the study file. A formal letter to the Principal Investigator informing about the IEC recommendations in such situations will be sent within 5 working days of the IEC meeting having taken place.

6. References

1. World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, (Geneva 2000)- *https://www.who.int/tdr/publications/documents/ethics.pdf* (last accessed 22nd October 2020).

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2. International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996-*http://www.ich.org/LOB/media/MEDIA482.pdf* (last accessed 22nd October 2020).
3. National Ethical Guidelines for Biomedical and Health Research involving Human Participants, ICMR 2017

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