Institutional Review Board (IRB)
Seth G.S. Medical College and K.E.M. Hospital, Parel, Mumbai 400 012.

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

SOP Code: **SOP 14/V3.2 dated 15th February 2013**

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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 adverse events(AE), serious adverse events (SAE) and unexpected adverse events (UAE) reported to the IRB by sites at Seth GS Medical College and KEM Hospital for any study under the oversight of the Institutional Review Board (IRB).

2. Scope

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

3. Responsibility

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

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 emergency IRB meeting	Members of the IRB
6.	Communication of the IRB decision about SAE review to the principal investigator	Secretariat
7.	Communication of the IRB decision about SAE review to the Chairperson of the Expert Committee constituted by the Licensing authority /DCGI	IRB chairperson

8	Discussion/ Information at the full board IRB meeting	Member Secretary of the IRB

5. Detailed Instructions

5.1 Onsite SAE and UAE

5.1.1 Receipt of SAE/UAE report

- The IRB 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 IRB:
  - i. On site SAE or UAE report to be submitted by the Principal Investigator within 24 hours of their occurrence as per the format specified in *AX 01/SOP 14/V3.2* (as per Appendix XI of Schedule Y)
  - ii. In the case of SAE, the report with due analysis will be submitted by the Principal investigator within 10 calendar days along with the format specified in *AX 02/SOP 14/V3.2*
  - iii. In the case of SAE, the report with due analysis will be submitted also by the sponsor within 10 calendar days along with the format specified in *AX 02/SOP 14/V3.2*
  - iv. The follow up reports of all on site SAE / unexpected AE reports till the event is resolved
- The IRB 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 IRB office within the specified timelines above. If the report has been received beyond the specified time, this will be considered as a violation.
- The IRB Secretariat will sign and write the date on which the report is received.
- For all the onsite SAE/ UAE reports received at the IRB office, the Administrative Officer will forward these reports to the executive secretary of the SAE Subcommittee within two working days.

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 IRB will be reviewed by the SAE subcommittee at least weekly or more often (as needed).
- The constitution and functioning of the SAE subcommittee is described in SOP 14A.
- 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 IRB

5.1.3 Communication to the IRB

i. The IRB 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 IRB 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 IRB members the decision will be communicated to the Licensing authority (DCGI) within 21 calendar days of the occurrence of the SAE.
iv. If the SAE is death then the decision in addition to DCGI will also be communicated to the Chairperson of the Expert Committee within 21 calendar days of the occurrence of the SAE.
v. If decision is that research participant is entitled for financial compensation an emergency IRB meeting will be scheduled within 7 days for the same (refer SOP 017/ v3.2)
vi. If objection is received from more than 2 IRB members an emergency IRB meeting will be scheduled within 7 days for the same.

    - The decision taken at the emergency IRB meeting regarding the onsite SAE/UAE report will be communicated to the Licensing authority (DCGI) within 21 calendar days of the occurrence of the SAE. If the SAE is death then the decision in addition to DCGI will also be communicated to the Chairperson of the Expert Committee within 21 calendar days of the occurrence of the SAE

5.1. 4 Inform Investigator

- The IRB secretariat will draft a formal letter to the concerned Principal Investigator and inform him/ her about the IRB decision. This letter will be signed and dated by the Member-Secretary or Chairperson (IRB) 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 IRB 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 IRB within 10 calendar 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 Chairperson of the IRB 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 21 calendar days of the occurrence of the SAE-death.
- The Chairperson of the IRB 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 21 calendar days of the occurrence of the SAE/ unexpected adverse event.
- The Administrative Officer will file a copy of these letters in the study file.

5.2 Onsite AE

5.2.1 Receipt of AE report

- The IRB Secretariat will receive the following documents pertaining to AE experienced by the research participants for research proposals approved by the IRB:
  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 IRB can request adverse events to be reported earlier, if deemed necessary at specified timelines in the project approval letter.
- The IRB 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 IRB office within the specified timelines above. If the report has been received beyond the specified time, this will be considered as violation.
- The IRB Secretariat will sign and write the date on which the report is received.
- For all the onsite AE reports received at the IRB 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 IRB will be reviewed by the SAE subcommittee at the scheduled meetings as per procedures described in SOP 14A and minutes communicated to IRB Secretariat

5.2.3 Inform Investigator

- The IRB secretariat will draft a formal letter to the concerned Principal Investigator and inform him/ her about the IRB decision on the concerned AE report. This letter will be signed and dated by the Member-Secretary or Chairperson (IRB) 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 7days 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 IRB 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

5.3 SAEs occurring at other sites:

The investigator will need to submit the SAEs occurring at other sites (CIOMS, SUSARS and Appendix XI) 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

- 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 IRB agenda

5.4 During the Full board IRB meeting

- The IRB Member Secretary will read out the minutes of all the weekly SAE Sub-committee meetings including the recommendations/ decisions of the SAE sub-committee.
- 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 IRB 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 IRB meeting

- If the recommendation from the IRB 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 IRB Member-Secretary in the study file. A formal letter to the Principal Investigator informing about the IRB recommendations in such situations will be sent within 5 working days of the IRB meeting having taken place.

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 unfavorable 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.
Unexpected adverse event	An adverse event, the nature or severity of which is not consistent with the applicable product information (eg: Investigator's brochure for an unapproved investigational product or package insert /summary of product characteristics for an approved product)
SAE (Serious Adverse Event)	The adverse event is SERIOUS and should be reported when the patient outcome is: **<u>Death:</u>** Report if the patient's death is suspected as being a direct outcome of the adverse event. **<u>Life-Threatening:</u>** 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.

7. References

[1] World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, (Geneva 2000) - *www.who.int/tdr/publications/publications/* (last accessed 24 September 2008).

[2] International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996 - *http://www.ich.org/LOB/media/MEDIA482.pdf* (last accessed 24 September 2008)

[3] Nationwide Children's Hospital, Standard Operating Procedure: SAE Reporting and Review – http://etrac.ccri.net/CRI/Doc/0/2137HUSRMVKKFBHAT542EHDME8/011%20Adverse%20Event.pdf (last accessed 24 September 2008)

8. Annexure

Annexure 1	*AX 01/SOP 14/V3.2*	Checklist for Serious Adverse Event & Unexpected Serious Adverse Event Submission
Annexure 2	*AX 02/SOP 14/V3.2*	Serious Adverse Event Analysis Report (**For SAE at the site)**

Annexure 1

AX 01/SOP 14/V3.2

Checklist for Serious Adverse Event & Unexpected Serious Adverse Event submission

Sr. 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. (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.	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 Drug(s)**		
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 the 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. 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).		
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 (speciality)		
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. a)	Duly filled SAE Form as per Appendix XI of Schedule Y		
b)	Laboratory investigations report /Discharge summary (if available and applicable)		
c)	Post-mortem report (if applicable)/ Any additional documents)		

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

Annexure 2

AX 02/SOP 14/V3.2

Serious Adverse Event analysis Report

(For SAE at the site)

Sr. No.	**Details**		
14.	**Country (Name of the country should be specified)**		
15.	**SAE report of death or other than death, Please tick (✓)**	**Death** ☐	**Other than Death** ☐
		Yes / No	**Page No.**
16.	**In case of Serious Adverse Event(SAE), please specify if there is any injury to the participant (Please specify Yes/No) in the box**		
17.	Protocol Title		
18.	Protocol Study No./ ID /Code		
19.	Copy of Clinical Trial permission obtained from CDSCO		
20.	CTRI Registration No. (Mandatory for Clinical Trial Permitted after 15/06/09)		
21.	Sponsor(Address with contact no and Email)		

22.	CRO (Address with contact no and Email)		
23.	Initial / Follow-up (FU)		
24.	In case of follow-up: Date & Diary no of initial or recently submitted report information		
25.	**Patient Details**		
f)	Initials & other relevant identifier (hospital/OPD record number etc.)		
g)	Gender		
h)	Age and/or date of birth		
i)	Weight		
j)	Height		
26.	**Suspected Drug(s)**		
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 the 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. 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).		
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 (speciality)		
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. a)	Duly filled SAE Form as per Appendix XI of Schedule Y		
b)	Laboratory investigations report /Discharge summary (if available and applicable)		
c)	Post-mortem report (if applicable)/ Any additional documents)		

Details of payment for medical management of SAE? (please give information who paid 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:_____
For IRB office use only **Verified by:** Name: _____ (Signature with date of IRB administrative staff) _____

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