Institutional Review Board, Tata Memorial Centre (IRB, TMC)

Title: Review of Serious Adverse Events (SAE) Reports

SOP Code: SOP 09/V1 Date : 05/09/2012 Pages: 1 to 20

9.1 Purpose

The purpose of this SOP is to describe the process on the submission, reporting, review of serious adverse events **(**SAEs) and unexpected events for any active study approved by the IRB

Unanticipated risks are sometimes discovered during the course of studies. Information that may impact on the risk/benefit ratio should be promptly reported to and reviewed by the IRB 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 subjects in the study.

9.2 Scope

This SOP applies to the DSMSC/ IRB review of SAEs and unexpected events reports, both onsite and off site, including follow up reports submitted by investigators. The detailed instructions regarding on site and off site SAE review are described in the following section 9.4

Investigators, IRB members and DSMSC members must now follow the procedure notified in the Gazette of India notification GSR 53(E) dated January 30, 2013, amending the Drugs and Cosmetics Rules, 1945, including Appendix XII of the amended Rules. This amendment prescribes procedures for reporting of SAEs and the provision of compensation in case of injury or death during clinical trial.

9.3 Responsibility

The primary responsibility of the DSMSC/IRB is to review and address SAE and unexpected events involving risks to research participants. In addition, the committee is authorized to offer mediation under appropriate circumstances.

IRB should also make sure that researchers are made aware of the policies and procedures concerning reporting and continuing review requirements.

The IRB Secretariat is responsible for receiving the complete SAE / unexpected events reports and directing them to DSMSC for detailed review. Following the DSMSC meeting, the Secretary, DSMSC will then forward the minutes of the DSMSC meeting to the IRB. DSMSC minutes are discussed in the subsequent IRB meeting.

Notifying the IRB/DSMSC does not relieve the PI from his/her responsibility to notify the sponsor and regulatory authorities.

9.4. Detailed instructions

A. On site SAEs

9.4.1 Instructions for PI

- **All SAEs including Deaths** should be reported *within 24 hours of their occurrence* to

1. IRB
2. Sponsor or its representative
3. CDSCO (in case of studies that have required approval of the CDSCO)

- The report of the **serious adverse event of Death**, *after due analysis* shall be forwarded by the Investigator to
    1. The Sponsor
    2. Chairman of the IRB
    3. In case of studies that have required approval of the CDSCO, also report to the Chairman of the Expert Committee constituted by the CDSCO, with a copy of the report to the CDSCO and the Head of the Institution where the trial has been conducted *within ten calendar days of the occurrence of the serious adverse event of death*.
- The report of the **serious adverse event other than death** *after due analysis* shall be forwarded to the
    1. Sponsor and
    2. Chairman of the IRB and
    3. In case of studies that require approval of the CDSCO, a report should be sent to the CDSCO and the Head of the Institution where the trial has been conducted *within ten calendar days of the occurrence of the serious adverse event.*
- In case the event is Death due to progressive disease the event should be notified in the SAE reporting format unless specified in the protocol.
- If the patient is out of trial and on survival follow up the event should be notified unless specified in the protocol
- SAE reports are received at IRB as one original + 2 photo copies+ soft copy
- Serious Adverse Event should be graded as per CTCAE Version 3.0/CTCAE Ver. 4.02
- Follow-up reports on the SAEs should be submitted within 15 days of the initial report or when any additional information regarding the event is

available, whichever is earlier.

- **In case of research involving human subjects conducted, supported or otherwise subject to regulation by any United States government federal department or agency which takes appropriate administrative action (e.g. NIH, HHS),** the PI must promptly communicate to the appropriate US Federal Department Agency head and the Office for Human Research Protection (OHRP) within 10 working days from the occurrence or knowledge of any of

    1. Any unanticipated problems involving risks to subjects or others
    2. Any serious or continuing noncompliance with the United States HHS policy
    3. Any serious or continuing noncompliance with the requirements or determinations of the IRB;
    4. Any suspension or termination of IRB approval

Contact details for the OHRP are:
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Telephone: (240) 453-6900
Fax: (240) 453-6909
E-mail: OHRP@hhs.gov

9.4.2 SAE related activities before IRB meeting

- SAEs are received at the DSMSC office as original and two photo copies and a soft copy of the SAE.
- The IRB Secretariat will verify that the reports are complete, signed and dated by the PI/CoPI/CoI and are checked for dates and typo errors in the SAE event description, SAE event term and CTCAE grading
- In case the IRB Secretariat notes that the report is incomplete, the report will be reverted back to PI by the consent of Member Secretary, DSMSC
- The IRB secretariat should receive the reports of all SAEs including deaths for IRB approved studies within 24 hours of the occurrence of the SAE.
- In case of Death reporting, the hard copy is reviewed by DSMSC & IRB Secretary else the soft copy is sent to DSMSC secretary and IRB Secretary

for comments within 24 hrs of SAE reporting.

- The SAE reported for death will be stamped “Death” on the right corner of the 1st page of SAE form for easy / immediate identification.

9.4.3 Actions to be taken by Member Secretary, IRB

- The Member Secretary will review the SAE Report, write comments and forward it to the Secretary, DSMSC, immediately.
- If the outcome of any SAE reported is ‘death’, the Member Secretary, IRB, will review the SAE report and forward it to Member Secretary, DSMSC within 1 working day for immediate action either the hard copy or via email. If deemed necessary, Member Secretaries of IRB I and II and Member Secretary, DSMSC will review the SAE, death, either in person, by e-mail or telephone and inform the Chairperson, IRB.
- Any queries raised are emailed to the PI for action
- In case of urgency or if a particular significant trend in serious unexpected and related or unrelated events is observed on any trial a meeting may be held based on comments and action suggested by the DSMSC/IRB Secretary
- SAE received from 1st – 31st of every month, scheduled to be discussed in the subsequent DSMSC meeting are listed in the next month agenda.
- Two lead discussants are assigned by Secretary DSMSC for SAE review. It is ensured that the lead discussant is not a part of the study team and has no conflict of interest.
- Agenda is sent to Secretary, DSMSC for finalization and signature
- The original signed hard copy of agenda is filed. The meeting agenda and SAEs are sent to DSMSC members.

9.4.4 After the DSMSC review of SAE

- After meeting, the Minutes are finalized by the Secretary, DSMSC.
- The IRB secretariat will send a formal letter signed by DSMSC Secretary to the investigator/s with instructions for specific actions as per the DSMSC decision.
- In case a PI fails to respond to the DSMSC letter, the matter will be discussed at the next full board IRB meeting and a decision will be taken for specific action by simple majority.
- The IRB secretariat will send the letter and file a copy of the letter in the master file of the research protocol.
- The original signed hard copy of Minutes of meeting is filed in the ‘DSMSC AGENDA and MINUTES file’

- Minutes are ratified in the next DSMSC meeting.
- The reply to DSMSC queries from PI are reviewed by Secretary DSMSC,

These replies get discussed in the meeting next scheduled DSMSC meeting and may be forwarded to IRB in case further opinion is required. (Decision Pending)

SAE rel

- The Member Secretary will table the SAEs and the DSMSC minutes in the next earliest full board meeting of IRB-I or II irrespective of the IRB that had approved the project.

9.4.4a Responsibilities of the IRB in case of studies that have required approval of the CDSCO:

In case of Death occurring to the clinical trial subject, the IRB shall forward it's report on the serious adverse event of death, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the sponsor or his representative to the Chairman of the Expert Committee constituted by the CDSCO, with a copy of the report to the CDSCO within 21 calendar days of the occurrence of the serious adverse event of death.

In case of serious adverse event other than death occurring to the clinical trial subject, the IRB shall forward its report on the serious adverse event after due analysis along with its opinion on the financial compensation, if any to be paid by the Sponsor or his representative, to the CDSCO, within twenty one calendar days of the occurrence of the serious adverse event.

9.4.4b Responsibilities of the IRB in case of Research involving human subjects conducted, supported or otherwise subject to regulation by any United States government federal department or agency which takes appropriate administrative action (e.g. NIH, HHS)

Any serious or continuing noncompliance with the requirements or determinations of the IRB; or any suspension or termination of IRB approval must be communicated to the concerned US Federal Department Agency head as well as to the Office for Human Research Protection (OHRP), within 10 working days of the occurrence of the event.

Contact details for the OHRP are:
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Telephone: (240) 453-6900

Fax: (240) 453-6909
E-mail: OHRP@hhs.gov

9.4.5 During the IRB meeting

On site SAEs

- The Secretary, DSMSC will inform all the IRB members about the SAEs and actions taken. The minutes of DSMSC meeting will be discussed.
- If appropriate, specific action or combination of actions will be taken, based on the consensus decision of the IRB discussion. Some of which are listed below:

    - Note the SAE report in the IRB records if information submitted is found to be adequate
    - Direct the PI to inform participants already enrolled in the study about the SAE and request them to undertake additional visits, additional procedures, additional investigations, etc. as per recommendation
    - Direct the PI to inform participants already enrolled in the study about the SAE and obtain their consent regarding continuation in the research study, if necessary.
    - Request further follow up information
    - Request additional details
    - Recommend an amendment to the protocol, the ICD, Participant information sheet, investigator brochure and/ or any other document.
    - Recommend whether or not compensation should be paid to the patient /his nominee for trial related injury / death as per institutional policy.
    - Suspend certain activities under the protocol (while going on with activities intended to protect the safety, well-being of participants who have already been enrolled);
    - Suspend enrolment of new research participants;
    - Suspend the study till amendments requested for by the IRB are accepted
    - Suspend the study for a fixed duration of time;
    - Suspend the study till additional information is obtained;
    - Suspend the study till review is completed;
    - Terminate the study;
    - Any other action

9.4.6 Actions to be taken by Chairperson

The Chairperson, IRB on basis of the information and comments received from the Member Secretary IRB and DSMSC, and applying his/ her judgment will direct the IRB Secretariat to any one or more actions listed below, but are not limited to.

- soliciting opinion of one or more expert in writing. The information can be provided to expert after he/ she/ they agree(s) to the confidentiality clause and abide by the rules and regulations of IRB. The expert would be requested to provide an opinion in writing within 2-14 working days, depending upon the gravity and seriousness of the matter.
- calling for an emergency review by full board.
    - This review should be initiated within 48 working hours (2 working days) of receipt of information.
    - This review could be done through a meeting, teleconference, email or telephonic conversation.
    - The IRB Secretariat will take appropriate steps to ensure that IRB members are informed about this full board meeting.
    - Depending upon the complexity of the issue(s) involved, the chairperson could direct the member Secretary, IRB, to invite one or more experts whose opinion would be valuable. These experts could participate after they agree to the confidentiality clause and abide by the rules and regulations of IRB.
- suspend trial-related procedures as listed by the secretariat
- suspending all trial related procedures (except those intended for safety and well-being of the participant) till further review by the IRB
- suspending enrolment of new research participants till further review by the IRB

B. Off Site SAEs

- Off Site SAEs where adverse event reports that are serious, unexpected and related (definitely, probably and possibly) to the drug need prompt reporting to the IRB.
- The SAEs that are expected (if listed in the informed consent) or unexpected but unrelated to the drug (classified as per the Off site SAE Classification form – AX2-V1SOP09/V2) have to be logged by the PI and to be submitted timely The following log has to be maintained continuously until the end of the study.
- Those off site SAEs which qualify for prompt reporting, (classified as per the Off site SAE Classification form – AX2-V1SOP09/V) will be reported to IRB Secretariat, and forwarded to Member Secretary, IRB and Secretary, DSMSC.

- If the IRB and DSMSC need to review the offsite SAE reports, the committee will request copies of SAE reports at any time, as and when necessary.
- If a trend is observed in SAEs by PI, such a trend will be reported to IRB Secretariat, action on such reports will be taken by the Member Secretary, IRB and Secretary DSMSC, as per 9.3-9.4
- The IRB Secretariat will not accept the complete set of "Off site SAE reports" and/ or the log. However, the IRB will accept the log of the SAEs every 3 months and/or at the time of continuing review/ annual status report.

9.5 Off site SAEs

- The PSUR/Line listings submitted by PI on a monthly/quarterly/biannual basis are filed by DSMSC as a detailed review of the same is out of the scope of IRB/DSMSC.
- It is the PI's responsibility to review the listings in detail and report if a trend is observed and communicate the same to DSMSC.
- **T**he offsite SAEs are received in the format as per SOP and one copy is acknowledged and returned back to PI
- The soft copy is saved
- The same is entered in the Offsite SAE entry book by IRB secretariat
- The SAEs are checked and stamped 'For DSMSC/Noted & File' and then forwarded to IRB for signature/review
- If any queries are raised by the IRB Secretary they are sent to PI by email or letters as applicable; else the Offsite SAEs are filed in the respective project files.
- Depending on the trend observed b the PI, if appropriate, specific action or combination of actions will be taken. Some of which are listed below:
    - Note the SAE report in the IRB records if information submitted is found to be adequate
    - Direct the PI to inform participants already enrolled in the study about the SAE and request them to undertake additional visits, additional procedures, additional investigations, etc. as prescribed in the amendment.
    - Direct the PI to inform participants already enrolled in the study about the SAE and obtain their consent regarding continuation in the research trial, if necessary.
    - Request further follow up information
    - Request additional details
    - Recommend an amendment to the protocol, the ICD, Participant information sheet, investigator brochure and/ or any other document.
    - Suspend certain activities under the protocol (while going on with

activities intended to protect the safety, well-being of participants who have already been enrolled);
- o Suspend enrolment of new research participants;
- o Suspend the study till amendments requested for by the IRB are accepted
- o Suspend the study for a fixed duration of time;
- o Suspend the study till additional information is obtained;
- o Suspend the study till review is completed;
- o Terminate the study;
- o Any other action

9.6 DCGI Query on Serious Adverse Events

1) Principal Investigator informs the DSMSC about SAE query raised by Drugs Controller General India (DCGI) requesting IRB opinion for a SAE

2) DCGI queries on SAEs which are already discussed in DSMSC and ratified in a previous IRB meeting will be answered based on the opinion and findings of the DSMSC and IRB at that time. IRB discussion or opinion at that time will be conveyed to DCGI and Principal Investigator. This will be notified in the full board meeting.

3) In potentially contentious issues, Member Secretary, IRB will inform Chairperson and Chairperson may use his/her discretion to bring it to the full board IRB meeting. The reply to DCGI is sent with a copy of same to Principal Investigator.

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)
4. Schedule Y (Drugs and Cosmetic Act 1940; amendment 20th January 2005) Retrieved from - *http://www.cdsco.nic.in/html/Schedule-Y 20 (Amended 20Version- 2005)* accessed 24 March 2008

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 can not 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.

Onsite- Event occurring at TMH

Offsite- Event occurring at other centres/sites

AX1-V1/SOP09/V2

Annexe 1
Effective Date:
Effective date: 22 April 2013

AX-V2/SOP9/V2 SERIOUS ADVERSE EVENT REPORT Tata Memorial Centre	TMH PROJECT NO:
	Reg with DCGI: Yes/ No CTRI Reg. No:

As per ICH-GCP:
Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is Any untoward medical occurrence (due to the participation in the concerned trial) that at any dose that:
• 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
Investigator(s) shall report all SAE's including Death to the IRB, Sponsor and CDSCO within 24 hours of their occurrence of the knowledge of the PI. If a delay is expected kindly notify the same by email.

For DSMSC Office use:
(Strike out what is not applicable)
Item No: - -/N/A

Recd on:

Date of occurrence of event:

Notification/ Follow-up

1. Title of project:		
2. Principal Investigator:		
3. Report date:		
Report type □ Initial □ Follow up_____ If Follow-up report, state Date of Initial report _____ □ Final		
4. Date of Occurrence of SAE:		
5. Patient Case No:	6. a. Age:	5 b Gender:
6. Mention the total number of SAE (prior) occurred at this site:_____ Other site(s):_____		
7. Mention number of similar SAEs (prior) occurred for same study at this site:_____ Other site(s):_____		

8. A] State SAE Event term: B] CTCAE Grade: (Kindly refer to CTCAE V3.0 and/or V4.2 where applicable) (where applicable)
9. Does the Principal Investigator feel this SAE is related to participation in the trial □ Yes □ No □ Cannot say
10. Tick whichever is applicable for serious adverse event: (Kindly note that this refers to IP/intervention being evaluated and NOT disease process) A] □expected event □ unexpected event
B] □ hospitalization □ increased hospital stay □ death □ others In case of Death , state probable cause of death _____ (If others, please specify):
C] □ No permanent significant functional/ cosmetic impairment □ Permanent significant functional/ cosmetic impairment □ Not applicable
11. If there was a research related injury/hospitalization, the cost of treatment/hospitalization was borne by, □Patient □ Institute □ Sponsor/CRO

Suspect drug information (refers to drug/ device/ procedure under investigation)	
12. Suspect drug (include generic name)/device/intervention:	
13. Dose Dosage Form:	14. Route(s) of administration:
15. Therapy dates (from/to) :	16. Therapy duration:
17. Did the reaction decline after stopping the drug/procedure (Dechallenge & Rechallenge information) □ YES □ NO □ NA	

Concomitant drugs and history (drugs that the patient maybe on and /or used for management of the SAE)
18. Concomitant drug(s) and date of administration:

19. Patient relevant history (e.g. diagnosis, allergies):

SAE Details

20. Description of adverse event (indicate if this is follow-up report and if so, include follow-up information only)

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21. Describe the medical treatment provided (ifany) to the research subject: This is an update on treatment given during hospitalization.

Medication	Dose	Start date	End date

22. Outcome was

□ resolved □ ongoing □ death

23. Was the research subject continued on the research protocol

□ yes □ no □ NA (Mark 'NA' in case of death)

24. What phase of the research protocol is the patient in?

□ On active treatment □ Short term follow-up □ Long term follow-up □ Surveillance/ Monitoring

25. In your opinion, does this report require any alteration in trial protocol?

□ yes □ no

If yes then please specify.

Name of Principal investigator :

Profession (Specialty) :

Signature of Principal investigator _____ Date: _____

Contact No. of PI: _____

Upon receipt of this report, the IRB/DSMSC will decide whether additional information is needed or whether further investigation of the incident is required. A follow-up report with further details should be submitted by PI within 10 days or earlier (of occurrence of the SAE) to the IRB

For IRB use only

I ____ agree _____ disagree with the assessment of the principal investigator.

DSMSC Reviewer _____ date: _____

Explanation:

AX2-V1/SOP09/V2

Off site Safety Reports Classification Form

NOTE to PI:

The following questions will act as a guide for submission of the “Safety Reports”. This form is merely providing guidance for reporting / logging of Off site Safety Reports’.

If the answer to all three questions is "**Yes", prompt reporting is required** and such off site safety reports need to be reported to IRB along with the log.
If any one answer is "**No", it needs to be logged as prescribed format**. (AX3-V1/SOP 09/V2).
This log should be submitted to the IRB Secretariat every 3 months and/or along with Continuing Review report.

Project No.

Project Title

Questions	Yes	No
Is adverse event serious?		
Is adverse event related?		
Is adverse event unexpected?		

Date of reporting
Signature of PI
Name of PI

AX3-V1/SOP09/V2

Off Site Safety Reports Log

NOTE to PI:

1. Please log in details of Off Site Safety Reports.
2. The following log has to be maintained continuously until the end of the study.
3. This log should be submitted to the IRB Secretariat every 3 months and/or along with Continuing Review report.
4. The log must be submitted to the IRB Secretariat immediately, if prompt reporting is required and/or if a trend related to the occurrence of SAE is observed.
5. Please note the complete set of Off site Safety Reports need not be sent to IRB Secretariat as and when received. If the IRB needs to review the reports, they can request copies at any time.

Project No.:
Project Title:
Total Sample Size-
Total No of patients to be enrolled -
No. of Participants already enrolled -
No. of patients active on Treatment-
No.of patients on FU-
No of Patients lost to follow up-
No of Consent Withdrawn-
No of patients withdrawn by Principal Investigator-
No of patients completed treatment-

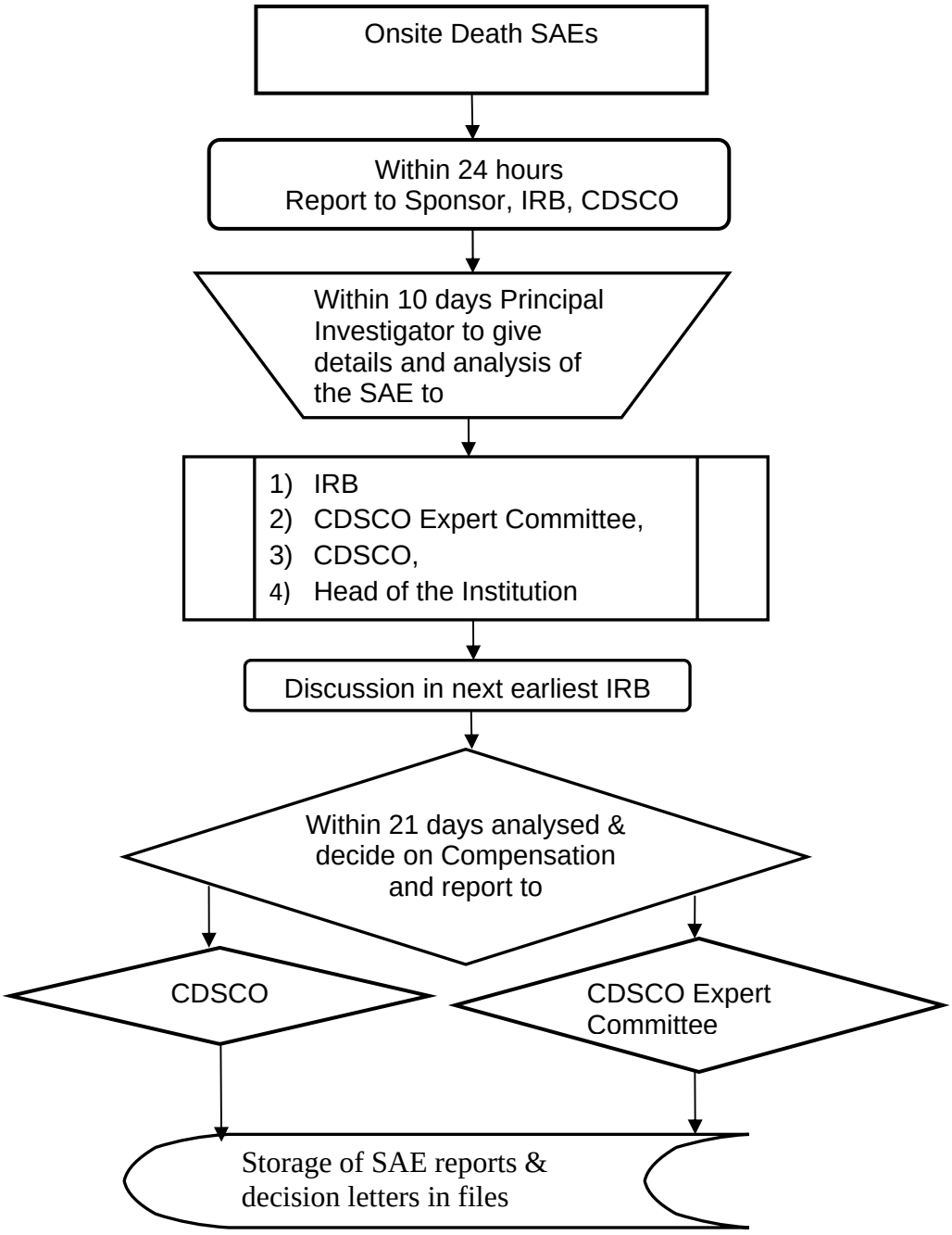
S. No.	Country	Date of Onset	Adverse event	Out Come	Remarks

PI Assessment:

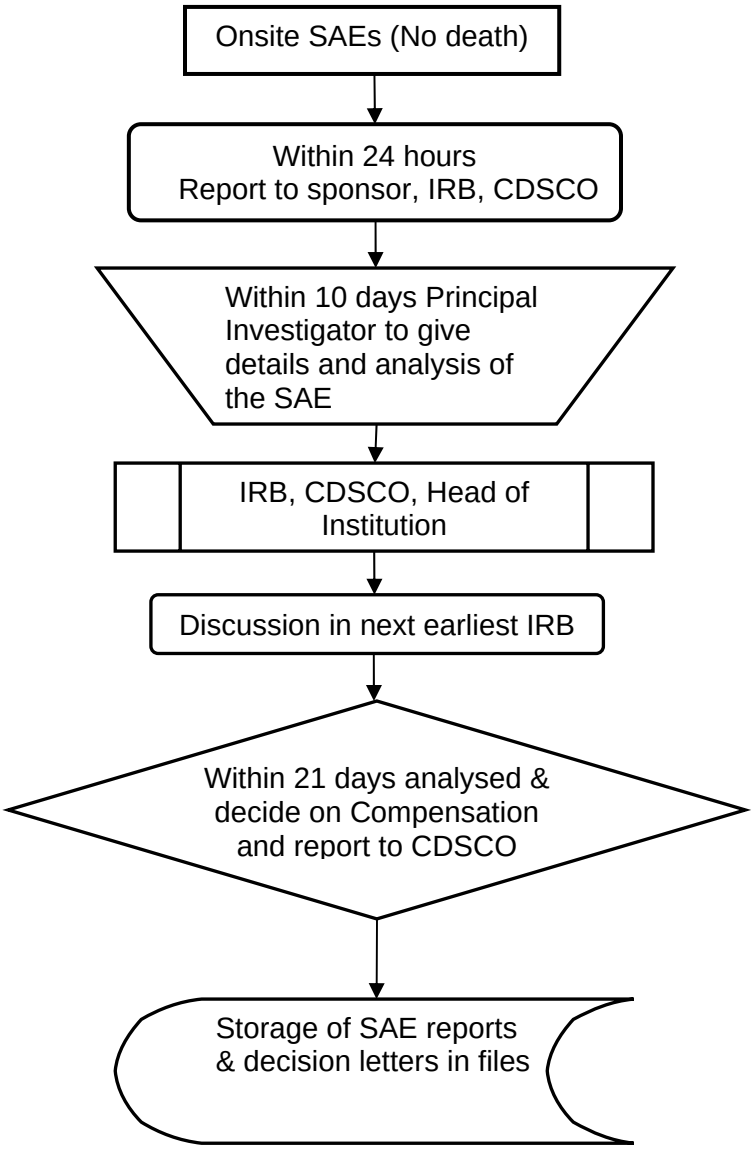
Do you observe a trend?
☐Yes ☐No

Name and Signature of Principal Investigator: Date:

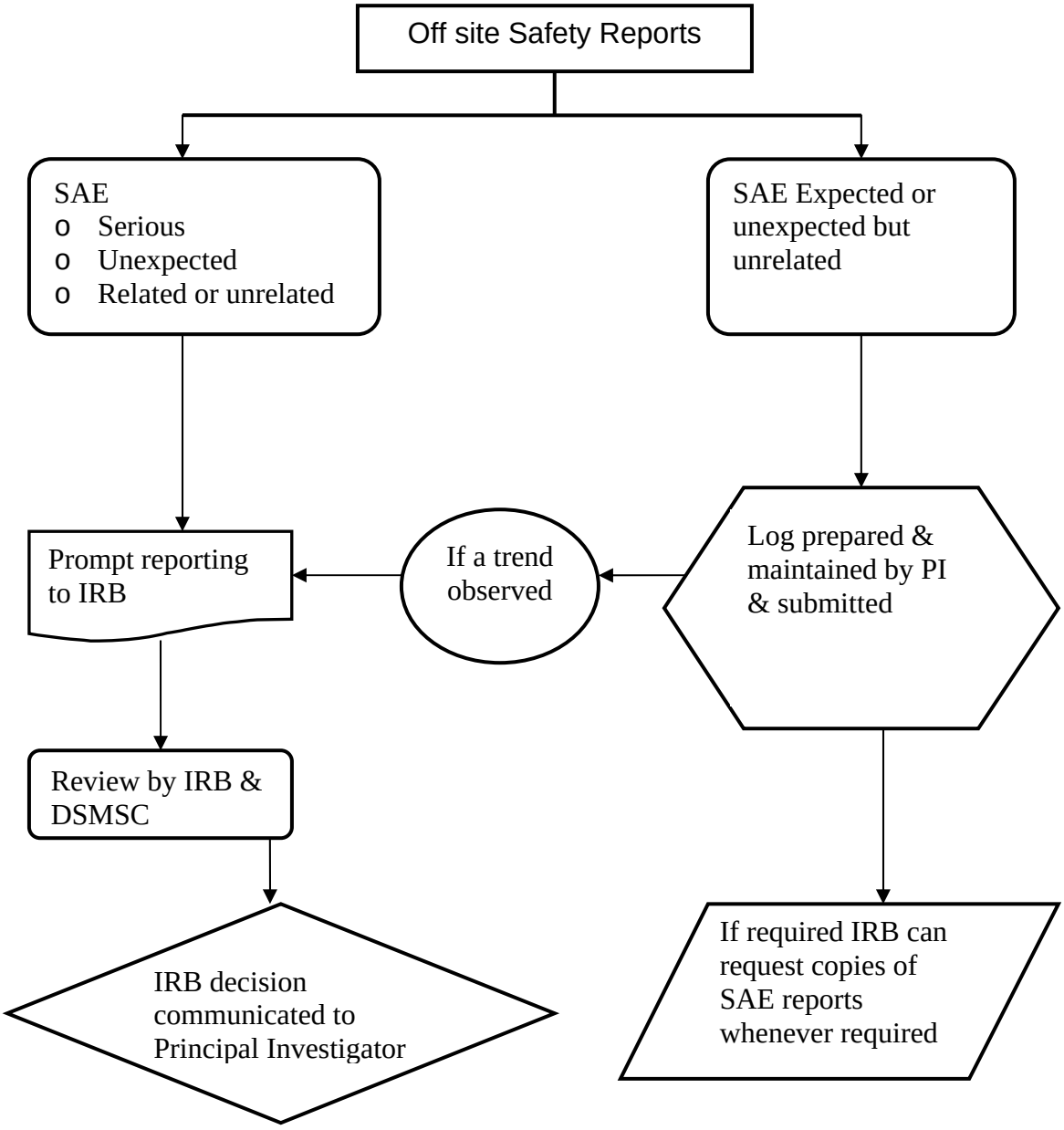
Flow Chart


Onsite Death SAEs
Within 24 hours
Report to Sponsor, IRB, CDSCO
Within 10 days Principal Investigator to give details and analysis of the SAE to
1) IRB
2) CDSCO Expert Committee,
3) CDSCO,
4) Head of the Institution
Discussion in next earliest IRB
Within 21 days analysed & decide on Compensation and report to
CDSCO
CDSCO Expert Committee
Storage of SAE reports & decision letters in files

Flow Chart


Onsite SAEs (No death)
Within 24 hours
Report to sponsor, IRB, CDSCO
Within 10 days Principal Investigator to give details and analysis of the SAE
IRB, CDSCO, Head of Institution
Discussion in next earliest IRB
Within 21 days analysed & decide on Compensation and report to CDSCO
Storage of SAE reports & decision letters in files

Flow Chart


Off site Safety Reports
SAE
o Serious
o Unexpected
o Related or unrelated
SAE Expected or unexpected but unrelated
Prompt reporting to IRB
If a trend observed
Log prepared & maintained by PI & submitted
Review by IRB & DSMSC
IRB decision communicated to Principal Investigator
If required IRB can request copies of SAE reports whenever required