Title: **Protocol Deviation/Violation**

SOP Code: **SOP 10/V5 dated 26th July 2017**

Authors:

Dr. Sharmila Jalgaonkar (Member Secretary, IEC - I)	Sjalgaonkar
Dr. Snehalata Gajbhiye (Member Secretary, IEC-II)	

Reviewed by:

Dr. Urmila Thatte(Member IEC - I)	
Dr. Padmaja Marathe (Member, IEC-II)	Padmaja Marathe

Approved by:

Dr. Padmavathy Menon, **Chairperson, IEC - I** (Signature with Date)	**Dr. Alan Almeida,** **Chairperson, IEC - II** (Signature with Date)

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1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to provide instructions for taking action(s) when investigator(s)/trial site(s) fail(s) to:

- follow the procedures written in the approved protocol
- comply with national and/ or international guidelines, statutory provisions, institutional guidelines or rules or procedures mandated by the Institutional Ethics Committee (IEC) for the conduct of human research
- respond to the IEC requests regarding statutory, ethical, scientific or administrative matters

2. Scope

This SOP applies to all IEC approved research protocols involving human research participants.

3. Responsibility

1. It is responsibility of IEC secretariat to receiving deviation /violation reports as per (AX 01/SOP10/V5) submitted by the Principal Investigator and forward it to the member secretary / chairperson with required documents if needed.
2. It is responsibility of the member secretary / chairperson to categorized the submitted protocol deviations as minor and major and assign one/ two primary reviewers accordingly.
3. It is responsibility of the designated reviewers to review the protocol deviations and take the decision regarding the same.
4. It is responsibility of the IEC secretariat to record and communicate the decision to the PI.

4. Flow chart

No.	Activity	Responsibility
1	Receiving deviation /violation reports and forward it to the member secretary /chairperson	Secretariat
2	categorized the protocol deviations and assign one/ two primary reviewers	Member Secretary /Chairperson
3	To review the protocol deviations	IEC members
4	Record and communicate the decision to the PI.	IEC Secretariat

5. Detailed instructions

- ***Detection of Protocol deviation/ non-compliance/ violation***

Protocol deviation/non-compliance/violation may be detected in one the following ways (but not limited to those listed below):

1. Protocol deviation/ non-compliance/ violation may be reported by Investigator/ study site/ sponsor/ Contract-Research Organization to the IEC

2. The IEC members performing monitoring of the project at trial site may detect protocol deviation/non-compliance/violation if the project is not been conducted as per protocol/ national/international regulations.
3. The Secretariat may detect protocol deviation/non-compliance/violation from failure to comply with statutory requirements/failure to respond to requests from IEC within reasonable time limit/failure to respond to communication made by IEC.
4. The IEC members may detect protocol deviation/non-compliance/violation when scrutinizing annual/ periodic reports/ SAE reports/ any other communication received from the Investigator/ trial site/ sponsor/ study monitor/ contract research organization.
5. The IEC secretariat and/ or IEC members may become aware of a protocol deviation/ non-compliance/ violation while reviewing study-related documents including reports filed in by the Principal Investigator.
6. Communication/ complaint/ information received from research participant who has been enrolled or any individual who has been approached for enrollment
7. Any report/ communication brought to the notice of Member, Secretary/ Jt. Secretary/ Chairperson of IEC by an independent person
8. Communication received from the Head of the Institution informing IEC about an alleged protocol violation/ non-compliance/ protocol deviation

5.1 Receiving deviation /violation reports and forward it to the member secretary / chairperson

The Secretariat will receive 1 copy (soft and hard) of protocol deviation Report filled as per the format – *AX 01/SOP 10/V5* from the Principal Investigator.

- It is the responsibility of the IEC Secretariat to review the report for completeness. If necessary, the IEC secretariat will retrieve the master file from the archiving with permission of the Member Secretary.
- The Secretariat shall forward the protocol deviation Report along with protocol deviation Form- *AX 01/SOP 10/V5* and sends it to the Member secretary.

5.2 categorized the protocol deviations and assign one/ two primary reviewers

- The member secretary or chairperson will categorized the protocol deviations as minor or major.

For Minor protocol deviations

The **Minor** protocol deviations and related documents will be reviewed by either member secretary or chairperson.

For Major protocol deviations

Major protocol deviations and related documents will be reviewed by either one / two designated primary reviewers or after review by the designated primary reviewers will be discussed in the upcoming full board meeting. In case the decision is to discuss the **Major** protocol deviations at the full board meeting, the Primary reviewer / Secretary will present a brief oral summary of the major protocol deviations and the comments of the IEC members/Chairperson in the IEC Full Board meeting.

- **Definitions**

Protocol Deviation (Minor) and Protocol Violation (Major):

Protocol Deviation - A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IEC. Upon discovery, the Principal Investigator is responsible for reporting protocol deviations to the IEC using the standard reporting form.

Protocol Violation (Major protocol deviations):): - A protocol violation is a deviation from the IEC approved protocol that may affect the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data. If the deviation meets any of the following criteria, it is considered a protocol violation. Example list is not exhaustive.

I. The deviation has harmed or posed a significant or substantive risk of harm to the research subject. For example

• A research subject received the wrong treatment or incorrect dose.
• A research subject met withdrawal criteria during the study but was not withdrawn.
• A research subject received an excluded concomitant medication.

II. The deviation compromises the scientific integrity of the data collected for the study.
For example

• A research subject was enrolled but does not meet the protocol's eligibility criteria.
• Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes. (if it involves patient safety it meets the first category above)
• Changing the protocol without prior IEC approval.
• Inadvertent loss of samples or data.

III. The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s). For example

• Failure to obtain informed consent prior to initiation of study-related procedures
• Falsifying research or medical records.
• Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing)

IV. The deviation involves a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures. For example

• Working under an expired professional license or certification
• Failure to follow federal and/or local regulations, and intramural research or CC policies
• Repeated minor deviations

V. The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles. For example

- A breach of confidentiality.
- Inadequate or improper informed consent procedure.

Minor Protocol Deviation- A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

5.3 To review the protocol deviations

- The Chairperson / member secretary / primary reviewers will review the submitted protocol deviations and assess the impact of the deviation on the safety wellbeing of the participants and data integrity of the study along with risk benefit analysis.
- Primary reviewers will send the comments to the member secretary with the decision.
- The Chairperson/member secretary / IEC members will review the information available and take a decision depending on the seriousness of the deviation / violation. The decision will be taken to ensure that the safety and rights of the research participants are safeguarded. The decision will be taken by consensus / voting. The actions taken by IEC could include one or more of the following:
  - ✓ Inform the Principal Investigator that IEC has noted the deviation / violation
  - ✓ Direct the PI to ensure that deviations/violations do not occur in future and follow IEC recommendations.
  - ✓ Enlist measures that the PI would undertake to ensure that deviations/violations do not occur in future
  - ✓ Reprimand the PI.
  - ✓ Call for additional information.
  - ✓ Suspend the study till additional information is made available and is scrutinized.
  - ✓ Suspend the study till recommendations made by the IEC are implemented by the PI and found to be satisfactory by the IEC.
  - ✓ Suspend the study for a fixed duration of time.
  - ✓ Inform the Institutional Head/ Director/Dean.
  - ✓ Revoke approval of the current study.
  - ✓ Inform DCGI/ Other relevant regulatory authorities.
  - ✓ Keep other research proposals from the PI/ Co-PI under abeyance.
  - ✓ Review and/ or inspect other studies undertaken by PI/Co-PI.
  - ✓ Refuse to review subsequent applications from an investigator cited for non-compliance for a specified duration of time.

- ✓ Any other action considered appropriate by the IEC for safeguarding the interests of the research participants participating in the current trial or in future trials.

- The action that the IEC will be based on:
  - [1] The nature and seriousness of the deviation / violation
  - [2] Frequency of deviation / violation in the study in the past
  - [3] Frequency of deviation / violation in previous studies conducted by the same PI/ Co-PI or in the same department.
- This action will be recorded by the Member Secretary.

5.4 Record and communicate the decision to the PI.

- ✓ The decision will be communicated to the PI within 14 days except if the decision is project suspension/termination, which will be communicated to the Principal Investigator **within 1 working day of the meeting.**
- ✓ The Secretariat will record the decision reached on the protocol deviation / violation in the minutes of the meeting.

6. References

[1] National Institute of Health IRB Professional Administrators Committee Regulatory Process Workgroup Version 5.1, 11/18/2005 Available from https://www.genome.gov/Pages/Research/Intramural/IRB/Deviation_Violation_examples8-07.pdf Accessed on 31st July 2017]

[2] World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, (Geneva 2000) - *www.who.int/tdr/publications/publications/* (last accessed 31st July 2017)

[3] International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996- *http://www.ich.org/LOB/media/MEDIA482.pdf* (last accessed 31st July 2017)

7. Annexure

Annexure 1 *AX 01/SOP 10/V5* Déviation/Violation Record

Annexure1

AX 01/SOP 10/V5

Deviation / Non-Compliance / Violation Record

IEC Protocol no.:	
Study Title:	
Principal Investigator:	
Department:	
☐ Deviation from protocol	☐ Violation
Description of deviation (s)/violation(s) [If protocol deviations / violoations are more than one please give the information in following tabular form:	
Reported by (Name of Principal Investigator): Signature with date:_____	

Sr. No	Patient initials & Patient ID.	Protocol deviation	impact of the deviation		Corrective measures by PI
			Safety wellbeing of the participants	Data integrity	
1.					
2.					