Title: Review of Protocol Deviations / Violations

1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe action(s) to be taken by the EC 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 (EC) for the conduct of human research,
- respond to the EC requests regarding statutory, ethical, scientific or administrative matters.

2. Scope

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

3. Responsibility

The EC Secretariat is responsible for receiving deviation/ violation reports as per (*AX 01/SOP 11/V4*) submitted by the Principal Investigator (PI) /others and placing it on the agenda of the meeting. Reporting of deviation/ violation in any other reporting format will not be accepted. The EC members should review and take action on such reports.

4. Detailed instructions

4.1 Detection of Protocol deviation/ violation

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

a. Protocol deviation/ violation may be reported by Investigator/ study site/ sponsor/ Contract-Research Organization to the EC.

b. The EC members performing monitoring of the project at trial site may detect protocol deviation/violation if the project is not been conducted as per protocol/ national/ international regulations.

c. The Secretariat may detect protocol deviation/ violation from failure to comply with statutory requirements/ failure to respond to requests from EC within reasonable time limit/ failure to respond to communication made by EC.

d. The EC members may detect protocol deviation/ violation when scrutinizing annual/ periodic reports/ SAE reports/ any other communication received from the Investigator/ trial site/ sponsor/ study monitor/ contract research organization.

e. The EC Secretariat and/ or EC members may become aware of a protocol deviation/ violation while reviewing study-related documents including reports filed in by the Principal Investigator (PI).

f. Communication/ complaint/ information received from a research participant who has been enrolled or any individual who has been approached for enrolment.

g. Any report/ communication brought to the notice of Member, Secretary/ Jt. Secretary/ Chairman of EC by an independent person.

h. Communication received from the Head of the Institution informing EC about an alleged protocol violation/ protocol deviation.

4.2 Receipt of protocol deviation / violation report by the Secretariat

1. The PI will report the protocol deviation/violation as per Annexure 1 *AX 01/SOP 11/V4*.
2. In case protocol deviation/violation is detected by any other person (See Section 5.1) and reported to the EC (there is no format for this), the Member Secretary will write to the PI to submit a protocol deviation/violation as per Annexure 1 *AX 01/SOP 11/V4*
3. The Secretariat will notify the Member Secretary of any protocol deviation/violation report received from the PI/ from any source within 2 working days of receipt of the notification.

4.3 Actions to be taken

1. The action of the EC will be based on:
    - The nature and seriousness of the deviation / violation.
    - Frequency of deviation/ violation in the study in the past.
    - Frequency of deviation/ violation in previous studies conducted by the same PI/ Co-PI or in the same department.
2. Member Secretary will decide on the impact of the protocol deviation / violation and act accordingly. Depending upon the seriousness, the EC shall do the following (not limited to these actions):
    - Ask PI for written clarification as soon as the deviation is received
    - If the impact is serious, this report will be shared with the Chairman and two or more EC members designated by the Chairman.
    - If the impact of the protocol deviation is serious enough, the Member Secretary will instruct the Secretariat to call for and schedule a full-board meeting specifically to discuss the issue within 7 working days of the initial scrutiny
    - The Secretariat will put up the information and communication at the next full board meeting for discussion.
3. The Member Secretary in consultation with EC members will review the information available and deliberate on it.
4. The Chairman will take a final decision depending on the seriousness of the 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 voting. A majority vote for approval, disapproval or request for modifications of a study suspension or termination of an ongoing study is defined as $2/3^{rd}$ of the voting members present at the meeting.
5. The decision taken by EC could include one or more of the following:

- Determine that no further action is required, or take other actions as appropriate.
- Inform the PI that the EC has noted the violation / deviation, and instruct the PI to ensure that deviations/ violations do not occur in future and to follow EC recommendations.
- Enlist measures that the PI would undertake to ensure that such deviations / violations do not occur in future.
- Observe the research or consent process (depending on the nature and frequency of the deviation).
- Suggest modifications to the protocol.
- Alter the interval for submission of the continuing review/ annual project status.
- Ask for additional training of the investigator and study team
- Reprimand the PI.
- Seek additional information from the PI.
- Conduct audit of trial by the EC.
- Suspend the study till additional information is made available and scrutinized.
- Suspend the study till recommendations made by the EC are implemented by the PI and found to be satisfactory by the EC.
- Suspend the study for a fixed duration of time.
- Suspension or termination of the study.
- 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.

6. This final decision will be recorded on *AX 01/SOP 11/V4* by the Member Secretary.

4.4 Procedure for notifying the PI and other concerned authorities

- The Member Secretary will draft a notification letter.
- The signed letter by Member Secretary will be sent to the PI and Department Head(s) (if required on case to case basis) and Institutional Officials (if required on case to case basis).
- The EC secretariat will send a copy of the notification to the relevant national authorities (if required on case to case basis) and institutes (if required on case to case basis in case of multi-centric trials).

4.5 Definitions

Protocol Deviation and Protocol Violation:

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 IRB. Upon discovery, the Principal Investigator is responsible for reporting protocol deviations to the IRB using the standard reporting form.

Protocol Violation- A protocol violation is a deviation from the IRB 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 IRB 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.

4.6 Records and follow up to be kept by EC secretariat

- The Secretariat will keep a copy of the notification letter in the respective project file.

5. References to other applicable SOP/s - nil

6. Annexures

Annexure 1 *AX 01/SOP 11/V4* - Protocol Violation / Deviation Reporting Form (Reporting by case)

Annexure 01/SOP/11/V4

Protocol Violation / Deviation Reporting Form (Reporting by case)

SMVMCH-EC Ref. No. (for office use) :

Title of study:

Principal Investigator (Name, Designation and Affiliation):

1. Date of EC Approval: Date of Start of study:
2. Participant ID: Date of occurrence:
3. Total number of deviations /violations reported till date in the study:

4. Deviation/Violation identified by:
   - Principal Investigator/study team ☐
   - Sponsor/Monitor ☐
   - SAE Sub Committee/EC ☐
5. Is the deviation related to (Tick the appropriate box) :
   - Consenting ☐
   - Enrollment ☐
   - Laboratory assessment ☐
   - Investigational product ☐
   - Safety reporting ☐
   - Source documentation ☐
   - Staff ☐
   - Participant non-compliance ☐
   - Others (specify) ☐
6. Provide details of Deviation/Violation:

7. Corrective action taken by PI/Co-PI:

8. Impact on (if any): Study participant ☐ Quality of data ☐
9. Are any changes to the study/protocol required? Yes ☐ No ☐

If yes, give details

Signature of PI with date

7. Flow Chart

No.	Activity	Responsibility
1	Detection and reporting of Protocol deviation/ violation	EC members/ Secretariat/ principal investigator
2	Receipt of protocol deviation / violation report	Secretariat
3	Review, board discussion, decision and action	EC Members, Member Secretary and Chairman
4	Notify the Principal Investigator/ concerned authorities of EC action	Secretariat
5	Maintain records	Secretariat

8. References

1. Forum for Ethics review Committees in India (FERCI). Standard Operating Procedures of Institutional Ethics Committee (cited 22nd October 2018). Available from: http:// www.ferci.org/sops/
2. [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_examples 8-07.pdf Accessed on 3rd June 2015]

3. Ethical guidelines for biomedical research on human participants. (2017). Indian Council of Medical Research. Available from: http://www.icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf

4. Ministry of Health and Family Welfare. New Drugs and Clinical Trials Rules, 2019. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

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