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Category: Study conduct

Title: Dealing with protocol deviations and violations in any clinical study

SOP No.: D 20/07 **Total pages:** 09

Date first effective: 01 Jan 2025 **Next Review date:** 31 Dec 2025

Version: 07

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1. Table of Contents

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1. Purpose:

This standard operating procedure (SOP) describes the responsibilities of the research team towards procedures to be followed in the event of protocol deviations and violations in investigator initiated or sponsored studies.

2. Scope

This SOP is limited to describing procedures while dealing with protocol deviations and violations in any clinical study.

3. Responsibilities:

Principal Investigator (PI), Co-investigator (Co-I), Study Co-Ordinator or any other appropriately qualified staff in the team, as delegated by the PI, will be responsible for proper documentation and reporting of all study related protocol deviations and violations.

4. Applicable rules, regulations and guidelines

- New Drugs and Clinical Trials Rules, 2019
  https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

- National Ethical Guidelines for Biomedical and Health Research involving Human Participants ICMR, 2017
  https://www.indiascienceandtechnology.gov.in/sites/default/files/file-uploads/guidelineregulations/1527507675_ICMR_Ethical_Guidelines_2017.pdf

- International Conference on Harmonization, Guidance on Good Clinical Practice ICH GCP E6 (R3)
  https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf (Adopted on 06 January 2025)

- Standard-Operating-Procedures of Institutional Ethics Committee, Seth GS Medical College and KEM Hospital, Mumbai https://www.kem.edu/wp-content/uploads/2024/12/institutional-ethics-committee/Standard-Operating-Procedures(SOPs)V7-effective-from-9th-Dec-2024_.pdf (last accessed 20th Dec, 2024)

5. Reference to other applicable SOPs

SOP No: D 03/07: Responsibilities of the study team

SOP No: D 05/07: Administering and documenting informed consent.

SOP No: D 17/07: Continued communication with Ethics Committee

SOP No: D 21/07: Contact and communication with sponsor

6. Detailed instructions

6.1. During the conduct of the research, there may be either planned or unplanned changes made to the approved research protocol. Amendments are changes to the approved research protocol. As a rule, any planned change(s) in the protocol must be reviewed and approved by the Institutional Ethics Committee (IEC) prior to implementation (Refer SOP No: D 17/07: Continued communication with Ethics Committee), except when necessary to eliminate apparent immediate hazards to the participant.

6.2. If a planned change is made to eliminate apparent immediate harm to the participant, then this type of change can be initiated without prior IEC approval. However, the IEC must be notified in writing within 24 hours giving specific justification for such an occurrence (SOP No: D 17/07: Continued communication with Ethics Committee).

6.3. A protocol deviation is any change or alteration from the procedures stated in the study protocol, consent document, recruitment process, or study materials (such as questionnaires) originally approved by the IEC. Deviation is a general term and includes protocol exceptions, changes made to avoid immediate harm to subjects, and protocol violations.

6.4. A protocol exception is any temporary protocol change that is approved by the IECs prior to its initiation (See Appendix I for example). A protocol exception is made for a single subject or a small group of subjects but is not a permanent revision to the research protocol.

6.5. Similar to an amendment, a protocol exception must be approved by the IEC prior to its implementation.

6.6. If the study is a sponsored study, prior approval of the sponsor is also required for a protocol exception except in an emergency situation to eliminate immediate harm (SOP No: D 21/07: Contact and communication with sponsor)

6.7. Protocol violations are changes in the conduct of the research that are implemented without prospective IEC review and approval prior to implementing the change. These could have resulted through human error or from willful or voluntary misconduct on the part of the PI or a member of the research team.

6.8. The study team should attempt to minimize these occurrences. Protocol violations may be:

- **Major violations**: An act that may impact the participant's safety or posed a significant risk/harm to a research participant and/or compromised the scientific integrity of the data collected or confounded the scientific analysis of the study results which can affect the participant's willingness to participate in the study.

6.9. The PI/Co-I/Study coordinator should accurately document the protocol violation as well as actions taken as a result of the violation in the source documents and case record forms (CRFs), or any other documents stipulated in the protocol.

6.10. Details of the violation along with explanation as well as the corrective actions should be informed to the

- Sponsor (within 24 hours)
- IEC within 7 working days.

6.11. The PI should take note of the IEC's view on the adequacy of the corrective measures including their decision to accept or reject the action taken.

6.12. If the protocol violation introduces new information that may affect a participant`s willingness to continue in the study, the IEC must be informed. If the IEC so desires, a revised consent form may be drafted, and approval obtained. If applicable, participants may be asked to renew their consent in writing.

6.13. If eligibility criteria are regularly overridden (protocol violation), the protocol will have to be reviewed and if necessary amended. Amendments should take into account the statistical consequences of protocol violation as well as blinding methodology (if appropriate).

6.14. In case of minor protocol violations, the Principal Investigator should document all minor protocol violations occurring since the previous IEC review and submit the information to IEC in a summary document at the time of continuing review.

6.15. While writing the protocol, the Statistical Analysis Section should indicate how protocol deviations will be analyzed.

6.16. The final study report should state the frequency and type of protocol deviations and explain their impact on the results.

6.17. All documentation related to non-compliance with the protocol should be available for inspection by the IEC, regulatory authorities, and the sponsor.

6.18. Repeated violations or a single major violation seriously impacting patient's safety can lead to termination of investigator and/or the study coordinator without any notice.

7. <u>Appendix</u>:

Illustrative examples:

<u>a. Protocol exception and amendment:</u>

In a clinical study if the inclusion criteria state that individuals aged between 18 and 40 years will be recruited, and PI wishes to recruit two individuals aged 41 and fulfilling all other eligibility criteria, then this would be a protocol exception if the PI took permission

from the sponsor and IEC to recruit these participants and recruited them. If on the other hand the PI wishes to change eligibility criteria for the rest of the protocol to 18 to 45 years, then this would qualify as a protocol amendment.

Other examples of protocol amendment

1. Increase in number of participants,
2. Changes in investigators or key personnel,
3. Change to the funding source,
4. Changes in procedures, or
5. Revised consent documents/investigators brochures.

b. Protocol violation

Major:

Examples of major protocol violations (this list is not exhaustive and will include any deviation from IEC approved protocol/related documents and procedures that may impact the participant's safety or posed a significant risk/harm to a research participant and/or compromised the scientific integrity of the data collected or confounded the scientific analysis of the study results which can affect the participant's willingness to participate in the study.)

Examples

1. Failure to obtain informed consent from the subject.
2. Patient being consented after the screening procedures are completed.
3. Patient being consented after the first dose of the drug has been given.
4. Wrong version of the informed consent form being used.
5. Enrolling a subject who does not meet the inclusion and exclusion criteria.
6. Performing study procedures that have not been approved by the IEC.
7. Failure to perform a required laboratory test or procedure that could impact upon the safety of the subject.

8. Continuing research activities after IEC approval has expired.
9. Use of recruitment procedures that have not been approved by the IEC.
10. Enrolling significantly more subjects than was proposed to and approved by the IEC.
11. Enrollment of a subject from a vulnerable population (i.e. children, pregnant women, prisoners) without prior IEC approval for that vulnerable population

Minor:

Minor protocol violations usually occur as an error on the part of the participant, investigator, or study staff and not due to conscious non-compliance with regulations or policies and procedures. Often deviations or violations result from a lack of attention to detail, inadequate staffing, or lack of supervision and training.

Examples

1. Sample collections at different time points than specified in the protocol.
2. Use of unapproved slightly altered recruitment procedures or materials.
3. Inappropriate consent process documentation (dated by someone other than the participant, missing signature of person obtaining consent, incorrect date on consent)
4. Study visits outside the protocol-prescribed visit window (for example. if the participant was on vacation or was ill and was one week late for a visit)
5. Failure of the participant to return study medication or diary card.
6. Enrollment numbers that exceed specifications

8. Abbreviations:

i. Co-I : Co-Investigator
ii. CRF : Case Record Form
iii. GCP : Good Clinical Practice
iv. ICH : International Council for Harmonization of Technical

Requirements for Pharmaceuticals for Human Use

v.	ICMR	: Indian Council of Medical Research
vi.	IEC	: Institutional Ethics Committee
vii.	PI	: Principal investigator
viii.	SOP	: Standard Operating Procedure

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