

Category : Study conduct-All studies (Government funded/NGO funded/Regulatory)

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

SOP No / Version No. : DCP 20/08

Date first effective: 01 Jan 2026

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Department of Clinical Pharmacology, 1st Floor, New MS Building,
Seth GS Medical College & KEM Hospital, Parel, Mumbai 400012.

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Author: 1) Dr. Shiva Krishna Rao.T
1st Year DM Resident

Shiva
01 Jan/2026

2) Dr. Shital Bendkhale
Project Scientist- II

Bendkhale
1 JAN 2026

Signature with date

Reviewer: Dr. Roopa Parida
Assistant Professor

Signature with date

Parida
01/Jan/2026

Approved by: Dr. Nithya Gogtay
Professor and Head

Signature with date

Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

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1.1.26

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W/ 1-1-26
Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

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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 pharma sponsored studies.

2. Scope

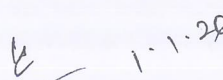
This SOP is limited to describing procedures while dealing with protocol deviations and violations in any clinical study.

3. Responsibilities:

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

4. Applicable rules, regulations and guidelines

- National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017), https://ethics.ncdirindia.org/ICMR_Ethical_Guidelines.aspx, last accessed on 1st Jan2026.
- New Drugs and Clinical Trials Rules (2019), <https://cdsco.gov.in/opencms/opencms/en/Acts-and-rules/New-Drugs/>, last accessed on 1st Jan2026.
- ICH HARMONISED GUIDELINE GOOD CLINICAL PRACTICE (GCP) E6(R3), https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf, last accessed on 1st Jan2026.
- India GCP guidelines (Draft, September 2024), https://ethics.ncdirindia.org/asset/pdf/Indian_GCP_guideline.pdf, last accessed on 1st Jan2026.


Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
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- National Ethical Guidelines for Biomedical Research Involving Children. https://ethics.ncdirindia.org//asset/pdf/National_Ethical_Guidelines_for_BioMedical_Research_Involving_Children.pdf last accessed on 1st Jan2026.
- Standard-Operating-Procedures of Institutional Ethics Committee, Seth GS Medical College and KEM Hospital, Mumbai
https://www.kem.edu/wp-content/uploads/2025/03/SOPs_V7_effective_from_9th_Dec_2024_Seth_GSMC_&_KEMH_Mumbai.pdf V7-effective-from-9th-Dec-2024_.pdf (last accessed 10th Dec, 2025)

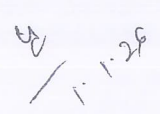
5. Reference to other applicable SOPs

SOP No / Version No: 03/08: Responsibilities of the study team

SOP No / Version No: 05/08: Administering and documenting informed consent

SOP No / Version No. 17/08: Continued communication with Ethics Committee

SOP No / Version No 21/08: Contact and communication with sponsor


Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

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6. Detailed instructions

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 usually any planned change(s) in the planned protocol must be reviewed and approved by the Institutional Ethics Committee prior to implementation (Refer SOP No / Version No. 17/08: Continued communication with Ethics Committee), except when necessary to eliminate apparent immediate hazards to the participant.
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 Institutional Ethics Committee approval. However, the Institutional Ethics Committee must be notified in writing within 24 hours giving specific justification for such an occurrence (SOP No / Version No. 17/08 Continued communication with Ethics Committee).

3. Case Definitions:-

A **protocol deviation** is defined as any unplanned or unintentional departure from the protocol, Investigator's Brochure, approved informed consent process, or applicable regulatory requirements, occurring after Institutional Ethics Committee (IEC)/Independent Ethics Committee (IEC/IRB) approval. Such deviations are generally not implemented prospectively and typically do not have a significant impact on participant rights, safety, or well-being, nor on the reliability of study data. In accordance with ICH GCP E6(R3), all protocol deviations must be documented, evaluated for their impact on participant safety and data integrity, and managed through appropriate corrective and preventive actions (CAPA), as applicable.


Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

1.1.26

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A **protocol violation** is defined as a significant or serious non-compliance with the approved protocol, Good Clinical Practice (GCP), or applicable regulatory requirements that may affect the rights, safety, or well-being of trial participants, or compromise the integrity and reliability of study data. Protocol violations may arise from failure to adhere to protocol-specified procedures, inadequate oversight, or systemic non-compliance. In line with ICH GCP E6(R3), such violations require prompt identification, documentation, root cause analysis, and implementation of corrective and preventive actions (CAPA). Reporting to the sponsor and IEC/IRB must be performed within defined timelines, especially for violations that meet criteria for serious non-compliance.

A **protocol exception** is defined as a prospectively planned and approved departure from the protocol for an individual participant or a specific situation, granted prior approval by the IEC/IRB (and sponsor, where applicable), in accordance with ICH GCP E6(R3). Protocol exceptions are implemented when strict adherence to the protocol is not feasible but where participant safety, rights, and data integrity are not compromised. These exceptions are not considered protocol amendments and do not constitute permanent changes to the protocol. All protocol exceptions must be justified, documented, and approved prior to implementation, except where necessary to eliminate immediate hazards to participants, in which case the deviation must be reported promptly to the IEC/IRB.

4. 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 / Version No 21/08: Contact and communication with sponsor)
 - a. Protocol violations represent instances of non-compliance implemented without prior IEC/IRB approval, contrary to the requirement for prospective review and approval of protocol changes, except where necessary to

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eliminate immediate hazards to trial participants. Such violations may arise due to unintentional human error, inadequate oversight, or systemic process deficiencies, or may reflect willful or deliberate non-compliance by the Principal Investigator or study team. In alignment with ICH GCP E6(R3), all such occurrences must be promptly identified, documented, and evaluated to determine their impact on participant safety, rights, and data integrity. A root cause analysis should be undertaken, and appropriate corrective and preventive actions (CAPA) must be implemented to prevent recurrence. Serious or persistent non-compliance should be reported to the IEC/IRB and sponsor in accordance with applicable regulatory timelines and may warrant further actions, including increased oversight, suspension, or termination of study activities

5. 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.

- **Minor violations:**

An act that represents a less significant non-compliance with the approved protocol, which does not have a meaningful impact on the participant's safety, rights, or well-being, and does not compromise the scientific integrity or reliability of the study data. These do not affect the overall risk-benefit assessment of the study or the participant's willingness to continue participation but should be documented, monitored, and reviewed periodically to ensure they do not recur or indicate systemic issues.

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6. The Principal Investigator/Co-investigator Study coordinator/medical officer should accurately document the protocol violation as well as actions taken as a result of the violation in the source documents and case report forms (CRFs) or any other documents stipulated in the protocol.
7. Details of the violation along with explanation as well as the corrective actions should be informed to the
 - Sponsor immediately (within 24 hours)
 - Institutional Ethics Committee within 7 working days.
8. The Principal Investigator should take note of the Institutional Ethics Committee's view on the adequacy of the corrective measures including their decision to accept or reject the action taken.
9. If the protocol violation introduces new information that may affect a participant's willingness to continue in the study, the Institutional Ethics Committee (IEC) must be informed. If the Institutional Ethics Committee so desires, a revised consent form may be drafted and approval obtained. If applicable, participants may be asked to renew their consent in writing.
10. 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).
11. In case of minor protocol violations, the Principal Investigator should document all minor protocol violations occurring since the previous institutional ethics committee review and submit the information to Institutional Ethics Committee in a summary document at the time of continuing review.
12. While writing the protocol, the Statistical Analysis Section should indicate how protocol deviations will be analyzed.

Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

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13. The final study report should state the frequency and type of protocol deviations and explain their impact on the results.
14. All documentation related to non-compliance with the protocol should be available for inspection by the institutional ethics committee, regulatory authorities and the sponsor.
15. Repeated violations or a single major violation seriously impacting patient's safety can lead to termination of study staff and/or the study coordinator without any notice.

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Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

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Appendix:

Illustrative examples:

Protocol exception and amendment:

In a clinical study if the inclusion criteria state that individuals aged between 18 and 40 yrs 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 the Institutional ethics committee 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 yrs. then this would qualify as a protocol amendment.

Other examples of protocol amendment

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

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

W
1-1-28
Dr. Parthiv Gogoi
Professor & Head,
Department of Clinical Pharmacology,
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012

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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 participants 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 subject, investigator, or study staff and not due to conscience 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 subject, missing signature of person obtaining consent, incorrect date on consent)
4. Study visits outside the protocol-prescribed visit window (for example. if the subject was on vacation or was ill and was 1 week late for a visit)
5. Failure of the subject to return study medication or diary card
6. Enrollment numbers that exceed specifications


1.1.26
Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
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Seth GS Medical College & KEM Hospital, Parel, Mumbai 400012.

Reviewer as appropriate:

Signature with date

Roopa Parida
01/Jan/2026

Dr. ROOPA PARIDA
Department of Clinical Pharmacology
Seth GS Medical College & KEM Hospital,
Parel, Mumbai-400 012.

Approved by Head of Department:

Dr. Nithya Gogtay
Professor and Head

Signature with date

Nithya Gogtay
1-1-26
Dr Nithya Gogtay
Professor & Head
Department of Clinical Pharmacology
1st Floor, MS Building
Seth GS Medical College & KEM Hospital
Parel, Mumbai 400 012