SOP on Monitoring by Ethics Committees

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Follow SOP numbering, revision numbering and date convention process as per institution/hospital.

SOP on Monitoring by Ethics Committees

Disclaimer statement:

This SOP on Monitoring by Ethics Committee (EC) is prepared by Ethics Council of Indian Society for Clinical Research (ISCR) to promote common harmonised guidance document/template for Ethics Committees to conduct monitoring activities at clinical study sites. There are seven attachments to this SOP. The document was designed in alignment to applicable Indian and ICH guidelines/regulations. The SOP and appendices are easy to use, adaptable and can be customized as per requirements of ECs across the country. The attachments are published in pdf and word file documents. Word document files provide the freedom to different ECs to modify, incorporate the EC details (like name, address, institutional affiliation and logo) and make changes as per other additional ECs requirements. This comprehensive approved SOP is prepared based on discussion, review and suggestions received from different EC members and sponsor members.

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1. Purpose

To provide process related to the monitoring procedures carried out by Ethics Committees (EC)

2. Scope

This SOP applies to all clinical trials approved by EC i.e. studies related to clinical trial, bioavailability and bioequivalence study, academic clinical trials for which a routine or remote or for-cause on-site monitoring may be undertaken by the EC.

3. Abbreviations, Definitions and Background

Sr. No.	Abbreviations and Acronyms	
1.	AE	Adverse event
2.	AV	Audio Video
3.	CIOMS	Council for International Organizations of Medical Sciences
4.	CRO	Contract research Organisation
5.	DSMB	Data safety Monitoring Board
6.	EC	Ethics Committee
7.	IP	Investigational product
8.	ICU	Intensive care unit
9.	ICF	Informed consent form
10.	SAE	Serious Adverse event
11.	SOP	Standard Operating Procedure

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Sr. No.	Definitions
1.	**Ethics Committee:** "Ethics Committee" means, for the purpose of, - (i) Clinical trial, Ethics Committee, constituted under rule 7 and registered under rule 8; (ii) Biomedical and health research, Ethics Committee, constituted under rule 16 and registered under rule 17. *Reference-NDCT Rules 2019* **Ethics Committee** An independent review board or committee comprising of medical / scientific and non-medical / non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards. *Reference -CDSCO GCP guidelines*
2.	**Independent Ethics Committee (IEC):** An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and

	documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance *Reference- ICH E6(R2)*
3.	**Institutional Review Board (IRB):** An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocols and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. *Reference - ICH E6(R2)*
4.	**Monitoring:** The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s). *Reference - ICH E6(R2)*

Background
The Ethics Committee for a clinical trial shall make at appropriate intervals, an ongoing review of the clinical trials for which it has accorded approval and such review may be based on periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or by visiting the study sites. *Ref-NDCT Rules 2019, Rule 11 of CHAPTER III*

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Ethics committee should make, at appropriate intervals, an ongoing review of the trials for which they have reviewed the protocol. Such a review may be based on the periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or visiting the study sites *Ref-NDCT Rules 2019, THIRD SCHEDULE, CONDUCT OF CLINICAL TRIAL*
It is necessary for all research proposals on biomedical, social and behavioral science research for health involving human participants, their biological material and data to be reviewed and approved by an appropriately constituted EC to safeguard the dignity, rights, safety and well-being of all research participants. ECs are entrusted with the initial review of research proposals prior to their initiation, and also have a continuing responsibility to regularly monitor the approved research to ensure ethical compliance during the conduct of research. The EC should be competent and independent in its functioning *Reference-ICMR 2017, Section 4 -EC Review process*
Continuing Review & Monitoring: The EC should continually evaluate progress of ongoing proposals, monitor approved study site for compliance, review SAE reports, protocol deviations/violations/ non-compliance/ DSMB reports/ any new information/assess final reports. *Reference-ICMR 2017, Section 4 -EC Review process*

4. Procedure

4.1 Selection of study, site and team for EC monitoring activity:

4.1.1. The EC shall reviews all new research study and ongoing research study at interval of at least one year depending upon the nature, design, safety aspects, Protocol deviations, non-compliance (if any) etc. of the study.

4.1.2. Each EC shall develop EC monitoring annual calendar and tracker as per attachment-5 encompassing the studies which will be reviewed during a given year. EC shall prepare the list of studies to be monitored in a year at the start of the annual year. EC shall prepare this calendar based on the studies approved by the EC in previous year.

4.1.3. At minimum EC chairperson, Member secretary shall discuss and prepare the list of studies to be monitored and shall communicate the same to EC monitors.

4.1.4. EC shall form a sub-committee of two to three members for periodic review or monitoring of study as per attachment 6 i.e. template for composition of sub-committee for EC monitoring activity. EC monitoring activity is performed to ensure that subjects rights, safety and well-being is protected.

4.1.5. Member secretary and chairperson shall constitute a sub-committee of ethics committee members to perform the site monitoring exercise and those members of sub-committee shall be referred as EC monitors. At least one selected member shall have expertise and understanding of the clinical aspects of the disease/ patient population, statistical aspects, clinical trial conduct and methodology.

4.1.6. The EC Member Secretary shall decide the date of the EC monitoring in consultation with the EC monitors and the PI and final date of EC monitoring shall be communicated to PI.

4.1.7. The agenda of EC monitoring shall be prepared by the identified EC monitors in consultation with the Member Secretary and Chairperson as per attachment 1-Template for EC monitoring visit agenda.

4.1.8. EC monitoring can be performed through routine mode of monitoring i.e. onsite monitoring or through remote monitoring activity as per EC discussion. Type of monitoring can be based on type of study design, population included in the study, type of investigational product used, emergency situation in the country, any restriction imposed by government and others.

4.2 Types of monitoring:

EC Monitoring can be performed either through Routine monitoring/onsite mode of monitoring or through remote mode of monitoring.

4.2.1 Routine Monitoring:

Routine Monitoring/Onsite monitoring involves the review of overall processes including data at the investigator site by EC monitors as per EC monitoring checklist i.e. attachment 2-Template for EC monitoring checklist.

4.2.2 Remote monitoring:

4.2.2.1 Remote review of study data can be performed based on availability of study documents with the EC with/without requiring access to the source documentation at the site. This can be done by review of but not limited to:

- Review of the protocol deviation/violations/non-compliance, cross checking study protocol/ plans against data reported,
- Review of DSMB reports
- Process of providing reimbursements for travel/procedures/investigations etc.
- Monitoring of safety data, half yearly status reports of clinical studies,

quarterly/earlier enrolment status reports of subjects

4.2.2.2 Methods of conducting remote monitoring activity:

Remote monitoring can be done through review of shared PDF copies of documents through email; through suitable virtual software platform, preferably a video conference (like Zoom, Microsoft Team, Go To meeting etc.) to enable face to face discussion or teleconference if connectivity is an issue, through uploading of documents in SharePoint with access control provision.

4.2.2.3 Selection of studies for remote monitoring activities:

The EC shall decide about the type of monitoring required (i.e. remote or onsite monitoring) based on the type of risk involved in a study:

Type of Risk	**Examples of studies**	**Type of EC monitoring (Recommended)**
High risk	• Studies which involves principal investigator with less than 5 years of overall clinical trial experience on DCGI approved clinical trials. • Studies on COVID related clinical trials, Biologics • Studies which involves vulnerable population (pediatrics, Neonates, geriatrics) • Studies involving Direct to patient, Health home care services and telemedicine	Onsite monitoring visit (If on-site visit per schedule is not possible due to unprecedented situation (Pandemic, epidemic, natural disasters) then remote

	• Study which uses digital wearables, electronic Clinical Outcome Assessment (eCOA) or assessment, medical devices	evaluation can be performed)
Low risk	• Studies which do not fall under high risk category • Academic clinical trial or Investigator initiated clinical trials • Non-interventional/observational studies • Public health trial programmes by Government agencies • Post Marketing commitment studies • Studies which can be utilized for Marketing Authorization application.	On-site visit or remote visit

Table 1: Types of Risks:

4.2.3 **For Cause Monitoring**:

4.2.3.1 Certain studies can be considered for "For cause" monitoring by the EC Chairperson & secretary. On their instructions, EC monitors shall do the "For cause monitoring".

4.2.3.2 The criteria for selecting a study for "For Cause" monitoring will be based on the following but not limited to:

- High number of protocol deviations/violation
- High number of serious adverse events when compared to the number of subjects enrolled
- Any significant non-compliance issues noted by Sponsor and reported

to Ethics Committee

- Very low number of SAEs reported in comparison to other participating sites in a particular study.
- High number of study participant drop out
- Studies involving specialized population e.g. pediatric, geriatric, terminally ill population or vulnerable population
- Non-compliance to reporting requirements as per ethics committee SOPs or Indian Clinical trial guidelines
- Others

4.3 Activities to be conducted Before, During and After the EC monitoring activity:

4.3.1 Before the conduct of EC monitoring

4.3.1.1 The EC co-ordinator/secretariat shall notify the PI at least a week in advance regarding the EC monitoring visit agenda with details like scheduled EC monitoring visit dates, studies that will be reviewed, team members who will be interviewed and documents that will be reviewed.

4.3.1.2 Acknowledgement by Investigator is required either through a wet ink signed document or email confirmation of monitoring notification and the same shall be filed in the ethics committee folder by EC co-ordinator/secretariat.

4.3.1.3 It is the responsibility of the investigator to ensure regarding availability of documents and staff who have participated in the studies under monitoring scope.

4.3.1.4 Member secretary shall provide all study related documents to EC monitors involved in EC monitoring activity of any study at a site.

4.3.2 During the Conduct of EC Monitoring activities:

4.3.2.1 Opening meeting shall be conducted by EC monitors with the site staff before initiation of monitoring activity. Opening meeting shall address following activities but not limited to: provide introduction, discussion of monitoring agenda, facility tour & objective, availability of team members and documents etc.

4.3.2.2 EC monitors shall perform facility visit of investigational site like IP storage area, laboratory, imaging facility (if applicable), ICU, document storage, archival area, study staff sitting area, participant screening and study activity area etc. EC members can also review any ongoing study activity process like ICF process, screening process as per protocol, lab. Sample collection and processing activity, IP handling and dispensing activity and other.

4.3.2.3 EC members shall review site staff training record and delegation process to ensure that the site staff are adequately qualified by education, experience and are trained on various study related activities to perform the delegated tasks.

4.3.2.4 EC members can also interact with study participants if it feels necessary. The monitoring team can use this information to confirm that study participants are aware of study activities and to crosscheck whether participants have received specified patient reimbursement amount on time for their study participation.

4.3.2.5 Review of protocol and study documents: The EC monitoring team will be required to review documents pertaining to the study under review such as

protocol, informed consent forms, patient facing information including advertisements, protocol deviation logs, Adverse Event summaries etc. Review of amendments of protocol and study documents if any during the study.

4.3.2.6 Review of Patient Informed Consent/assent forms: It is recommended to review atleast 10 % ICF of subjects. These ICFs can be selected by taking few subjects from start of study, few from in-between and few from the latest screened subjects in the study. Selection of subjects shall include ICFs of illiterate subject/ vulnerable patients/ patients who have experienced any AE/SAE can be taken on priority. EC monitors shall verify if the current version of EC approved ICF are the ones which are in use

4.3.2.7 Review of ICF and AV or audio CDs of vulnerable population: EC monitors shall see AV recording of minimum 10 % subjects.

4.3.2.8 Subject recruitment process i.e. any advertisement, letters, poster, notices which were used for recruitment of subject

4.3.2.9 Review of all important communications with regulatory authority, sponsor and other stakeholders.

4.3.2.10 Review of patient source documents:

- Random review of patient source (at least 10%) specially focusing on Adverse Event/ Serious Adverse Event management
- Study subjects meet all the inclusion and none of the exclusion criteria
- Data reported in the Case Report Form is in line/ consistent with the source data

4.3.2.11 Review of IP supply, dispensing, accountability process, storage and overall management process along with IP related documentation with IP expiry date.

4.3.2.12 Review of safety reports. EC members shall also check for SAE data occurring at other sites.

4.3.2.13 Notification of safety events/ protocol non-compliance to regulatory and ethics committee are done as per local regulatory requirements.

4.3.2.14 Periodic review of accumulated study data and review of CSR in case if any study gets completed.

4.3.2.15 Review of reimbursement documents of participants

4.3.2.16 Insurance validity and lab accreditation information should be checked

4.3.2.17 Interview with PI and study team members shall be done to confirm the proper understanding of study activity and uniformity in study as per protocol.

4.3.2.18 Review of study communications from sponsor and sponsor monitoring reports.

4.3.3 After the conduct of EC monitoring activity:

A. Preparation and review of EC monitoring report:

4.3.3.1 EC monitors shall discuss internally, compile all their observations which are observed and include all observations in EC monitoring report.

4.3.3.2 Once the EC monitoring report is prepared after receipt of feedback from all involved EC members then the significant findings form the EC monitoring report shall be presented during the full board EC meeting and the concerned EC monitor shall provide additional details/clarifications to members, as required.

B. Report finalisation and distribution of EC monitoring report:

4.3.3.3 EC monitors shall finalise EC monitoring report as per attachment 3 i.e. Template for EC monitoring report and shall submit this EC monitoring report to EC Chairperson for approval.

4.3.3.4 EC monitor shall share this EC monitoring report with the PI and other involved site staff and request a response/ action plan to the findings within a stipulated

timeframe. Final approved EC monitoring report shall be submitted to site principal investigator (PI) within 14 working days after conduct of EC monitoring activity.

C. Compliance review and closure of EC monitoring report

4.3.3.5 Once EC members receive compliance to observations noted in EC monitoring report then the same will be discussed with EC chairperson for proper closure based on compliance review. In case if any point is open and not proper action is taken for the same then the same will discussed with PI and EC monitor for further course of action (if any) in follow-up reports.

4.3.3.6 EC members shall send follow-up monitoring report for any open observation and ask for clarification within stipulated timeline. If the response is not satisfactory then committee members can also recommend to either: continue with or without modification; suspend; terminate; recommend.

4.3.3.7 PI shall respond to follow-up reports to the findings with evidence of action completion.

4.3.3.8 EC members shall check for recurrence of issues in subsequent monitoring visits.

4.3.3.9 EC secretariat shall be responsible to place all important communications, documents i.e. EC monitoring agenda, EC monitoring report in respective EC file.

Note: PI shall provide response to all observations within 60 working days from receipt of the EC monitoring report.

4.4 Record keeping and Archival process of EC monitoring activity:

4.4.1 All documents and communication pertaining to EC monitoring should be appropriately dated, compiled in EC files and preserved as per written procedures

by EC staff. These documents shall be maintained under access control to ensure confidentiality and integrity of all study related documents.

4.4.2 All the documents and records shall be archived for a period of atleast five years after completion /termination of the study or as per applicable regulatory guidance.

4.4.3 Process for retrieval of documents shall be in place to ensure access to information for audits, inspection, and continual protection of study subjects and for post-study closure with prior permission in writing.

4.5 Non-Compliance to planned monitoring visits:

4.5.1 EC monitors shall review EC monitoring annual calendar and if monitoring activity is not performed as per calendar then the same shall be appropriately documented i.e. Memo/Note to file as per attachment 4 i.e. Template for Memo/Note to File and shall be filed along with proposed actions to mitigate such cases in future.

5. References

5.1 Internal

a. None

5.2 External

a. G.S.R.227(E)- New Drugs and Clinical Trials Rules 2019
b. CDSCO Good Clinical Practices For Clinical Research In India
c. ICMRs Ethical Guidelines for Biomedical research on Human Participants, ICMR (2017)
d. National guideline for Ethics Committees reviewing biomedical and health research during COVID-19 Pandemic, April 2020

e. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), March 2018

f. FERCI Model SOPs- Site monitoring and post monitoring activities.

6. Associated Templates and Attachments

Attachment 1 – Template for EC monitoring visit agenda

Attachment 2 – Template for EC monitoring checklist

Attachment 3- Template for EC monitoring report

Attachment 4 - Template for Memo/Note to File

Attachment 5- Template for EC Monitoring Annual Calendar and Tracker

Attachment 6- Template for composition of sub-committee for EC monitoring activity

Attachment 7- SOP Flowchart

7. Document Amendment History

SOP No.	**Revision No.**	**Amendment Description**	**Next Review Date**
SOP-EC-01 *(Mention SOP naming convention by institute/hospital*	01.00	Initial version	*(Mention SOP revision cycle as per institute/hospital practice i.e. 2 years or 3 years)*