Title: Site Monitoring Visit and Audit of Protocols

SOP Code: SOP16/v3

Effective Date: 03/10/2019

Prepared by:

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Dr. Vikram Shetty, Chairperson, YEC-1	Signature with Date 3/10/19

Notified by:

Registrar, Yenepoya deemed to be University	Signature with Date 3/10

Table of Contents:

1. **Purpose:** The purpose of this standard operating procedure (SOP) is to describe the procedures for site monitoring and post-approval activities of the protocols approved by Yenepoya Ethics Committee-1 (YEC-1).
2. **Scope:** This SOP applies to all protocols approved by YEC-1 for which a routine or for-cause on-site monitoring should be undertaken.
3. **Responsibilities:**

3.1. **YEC-1 Chairperson will:**

3.1.1. Approve the formation of a site monitoring subcommittee and its constituent members

3.1.2. Oversee and approve all site monitoring visits (scheduled and unscheduled)

3.1.3. Oversee and approve all audits initiated by YEC-1

3.2. **YEC-1 Member-Secretary will:**

3.2.1. Ensure that the resolution to fix a site monitoring visit schedule for the protocols that are determined as eligible for site monitoring, is done in the YEC-1 meeting.

3.2.2. Ensure that the decision and frequency of site monitoring visits are recorded in the minutes (as resolution), in the decision form and in the site monitoring roster.

3.2.3. Organize the formation of a site monitoring subcommittee and its constituent members

3.2.4. Ensure that the communications are sent to all concerned stakeholders in a timely manner.

3.3. **YEC-1 Secretariat will:**

3.3.1. Maintain the site monitoring roster and update it regularly from time to time.

3.3.2. Remind the Member-Secretary of upcoming scheduled site monitoring visits

3.3.3. Prepare the communications and necessary files required for a site monitoring visit

3.3.4. Inform all the members on the day of the site monitoring visit

3.3.5. Coordinate with the on-site representative of the PI for smooth conduct of the site monitoring visit.

3.4. **YEC-1 members will:**

3.4.1. Cooperate with the Chairperson/Member-Secretary/Secretariat in the smooth conduct of the site monitoring visit.

3.4.2. Actively take part in the site monitoring visit

3.4.3. Compile the site monitoring visit report in a timely manner and submit to the YEC-1 Secretariat.

3.4.4. Assist the Member-Secretary in assessing the audit reports submitted by the PIs, in a timely manner, as recommended by the YEC-1.

4. Mandate:

4.1. **Indian Council of Medical Research (ICMR):** "It is recommended that ECs should follow mechanisms described in a SOP to monitor the approved study site until completion of the research to check for compliance or improve the function."[1]

4.2. **Indian GCP Guidelines:** "The Ethics Committees are entrusted not only with the initial view of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the ethics of the approved programmes till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research."[2]

5. Definitions:

5.1. Site monitoring: Site monitoring is a post-approval activity of the YEC-1 in which the Site monitoring sub-committee will visit the research site, inspect the site for availability of requirements as per the approved protocol, verify documents to confirm protocol adherence and interview participants or observe recruitment/informed consent process, if possible.

[1] ICMR's National Ethical Guidelines for Biomedical Research involving Human Participants 2017 (4.12.1).

[2] Indian GCP Guidelines (2.4.2) http://www.cdsco.nic.in/html/GCP1.html accessed on 13 August 2019 at 1145 hours

5.1.1. **For cause:** When the site monitoring is conducted for a specific reason(s) (listed below) as determined during the research period.

5.1.2. **Routine:** When the site monitoring is planned at the time of approval of the protocol based on the risk assessment

5.2. **Audit of the files:** Audit is a post-approval activity of the YEC-1 in which the YEC-1 members conduct an audit of the protocol to look for protocol adherence and identify protocol deviations in the data collection/informed consent forms in the given protocol.

6. Detailed instructions:

6.1. **Decision for Routine site monitoring:**

6.1.1. For all full review protocols, the decision of routine site monitoring visit and its frequency will be made depending on the level of risk to the participants at the time of approval in the YEC-1 meeting

6.1.2. The YEC-1 may conduct site-monitoring at the time of first or subsequent recruitment of participants for clinical trials with high risk or when involves vulnerable population in order to ensure fair selection and recruitment of participants.

6.2. The site monitoring schedule for the protocol will be recorded in the resolution, decision form and in the site monitoring roster

6.3. **Decision for "for-cause" monitoring:** For-cause monitoring visit may be decided in the following circumstances:

6.3.1. To observe the PI or a designated research team member carry out the informed consent process, in a regulatory clinical trial (whenever possible).

6.3.2. High number of or frequent protocol violations or violations that significantly and unjustifiably increase the risk to the research participants.

6.3.3. Large number of studies carried out at the study site or by the same investigator

6.3.4. Large number of Serious Adverse Events (SAE) reports

6.3.5. High recruitment rate

6.3.6. Failure to submit the required documents despite repeated requests

6.3.7. Non-compliance of the Principal Investigator to the standards of care in research as based on the Indian GCP guidelines.

6.3.8. Receipt of complaints about the research trial from a participant or any other stakeholder.

6.3.9. Any adverse media report regarding a research proposal approved by YEC-1

6.3.10. Adverse information regarding a research proposal approved by YEC-1 - received from any other source

6.3.11. Non-compliance with EC directions/current regulations

6.3.12. Misconduct by an investigator of a research proposal approved by YEC-1

6.3.13. Any other cause as decided by YEC-1.

6.4. **Preparation for site monitoring visit**

6.4.1. The Member-Secretary will identify one or more YEC-1 members to conduct monitoring of a site and after the approval of the Chairperson, will constitute the site monitoring subcommittee.

6.4.2. When an SAE is reported at the site, the lay person will be included in the SAE subcommittee to monitor the compensation issues.

6.4.3. The subcommittee members will be informed about this monitoring schedule by email.

6.4.4. The tentative date and agenda of monitoring will be decided by the subcommittee and communicated to the PI - at least 2 calendar days prior to the visit date - with a request to be available at the site, at the date and time agreed upon.

6.4.5. If the PI is unable to be present during the site monitoring visit, then he/she will designate another responsible member of the research team to be present on the decided day.

6.5. **During the site monitoring visit:**

6.5.1. The subcommittee members will review the relevant protocol documents and reference material (if requested) and make appropriate notes before visiting the site.

6.5.2. The subcommittee members will carry the site monitoring visit report form (Ann01/SOP16/v3 and Ann02/SOP16/v3) and the respective protocol file after entering in the document access log.

6.5.3. The members will meet with the Principal Investigator upon reaching the site and begin the process of site monitoring.

6.5.4. In case, the PI is not available during the site visit, the PI may designate another member of the research team who is well versed with the research protocol and recruitment and the site.

6.5.5. In case the study site is deserted or closed and the PI or any other designated person is unavailable and not contactable, the monitoring subcommittee shall wait for a period of 15 minutes before returning and file the report stating “Unavailable for monitoring”.

6.5.6. Suitable immediate action may be recommended by the YEC-1 site monitoring subcommittee.

6.5.7. The Member-Secretary will obtain approval from the Chairperson and communicate this to the PI, and then ratify this decision in the next meeting in this regard and the same will be minuted and conveyed to the PI.

6.5.8. The following will be checked as per the checklist:

6.5.8.1. The log of delegation of responsibilities of study team

6.5.8.2. Whether the site is using the latest YEC-1 approved version of the protocol, informed consent documents, case record forms, diaries, advertisements, etc.

6.5.8.3. The informed consent process, if possible, by observation

6.5.8.4. Randomly-selected participant files to ensure that the documentation is as per standards laid down in Indian GCP guidelines and that the participants are signing the informed consent forms, using the correct version and the correct language.

6.5.8.5. Investigational product accountability is adequately controlled and documented throughout the product flow at the study site (arrival, dispensing, use, return from the subject and return/destruction after the study), access log, storage times, conditions, expiry dates, and sufficient supplies available (wherever applicable)

6.5.8.6. Whether the investigator is following the approved protocol and all approved amendment(s), if any

6.5.8.7. That the investigator and the investigator's trial staff are adequately informed about the trial.

6.5.8.8. Whether the investigator and the investigator's trial staff are performing the specified study functions, in accordance with the approved protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

6.5.8.9. That the investigator is enrolling only eligible subjects, as per the inclusion and exclusion criteria.

6.5.8.10. Whether all serious adverse events (SAEs) are appropriately reported within the time as per the applicable regulatory requirement(s). Case record forms would be checked to review the safety data i.e. adverse events (AEs) and SAEs for the volume or severity of adverse events.

6.5.8.11. The lay person will check whether the compensation issues have been adequately and appropriately addressed

6.5.8.12. The project files of the study to ensure that documentation is filed appropriately

6.5.8.13. The source documents for their completeness

6.5.8.14. The views of the study participants, if possible and participant rights display

6.5.8.15. Security issues of the data, archival, restriction of access, maintenance of logs, etc

6.5.8.16. The member(s) will fill the site monitoring visit report form (Ann01/SOP16/v3) and Ann02/SOP16/v3 (if applicable), sign and date it.

6.6. **Preparation of the report:**

6.6.1. The Site Monitoring subcommittee will submit the completed site monitoring visit report form (Ann01/SOP16/v3 and Ann02/SOP 16/v3 - if applicable) to the YEC-1 Secretariat within 7 calendar days of conducting a site monitoring visit or at the time of immediate next meeting of the YEC-1 (whichever is earlier).

6.6.2. The report should describe the findings of the monitoring visit in an objective manner specifying protocol adherence and protocol deviations/violations.

6.7. **Decision making on an urgent ground:**

6.7.1. If the site monitoring subcommittee has findings that directly or indirectly impact on the safety of the participants, the subcommittee will inform the Member-Secretary on the same day.

6.7.2. The Member Secretary will take up the matter with the Chairperson, and call for an Emergency meeting within calendar 2 days.

6.7.3. In the Emergency meeting, after assessing the seriousness of the impact on the safety of participants, the research may be terminated, or suspended or allowed to continue with appropriate amendments, or

allowed to continue with a reprimand.

6.7.4. The final decision taken by the Chairperson, will be informed at the next YEC-1 meeting and will be recorded in the site monitoring visit report form (Ann01/SOP16/v3) and in the minutes.

6.8. **Decision in the YEC-1 meeting:**

6.8.1. The Member-Secretary will present the monitoring report at the subsequent YEC-1 meeting

6.8.2. The subcommittee members will provide additional inputs, so as to enable a proper assessment of the report.

6.8.3. YEC-1 will deliberate on the issues and take appropriate specific action or combination of actions, by voting, some of which are listed in 6.8

6.9. **Final decision:**

6.9.1. Note the report and recommend continuation of the project without changes

6.9.2. Recommend continuation of the project with one or more of the following changes

6.9.3. Restrict further enrollment of participants

6.9.4. Recommend additional training of the PI or trial staff

6.9.5. Recruit additional members in the study team

6.9.6. Cause the PI to amend the methodology such that the risks are mitigated.

6.9.7. Temporary suspension of study until further decision at YEC-1

6.9.8. Termination of the study

6.10. **Communication of the final decision:**

6.10.1. The Secretariat will convey the decision of the YEC-1 to the Principal Investigator in writing within 7 calendar days of the meeting for decisions as in 6.8.1 and 6.8.2.1 to 6.8.2.4

6.10.2. The Secretariat will inform the decision of the YEC-1 to the Principal Investigator within 2 calendar days of the meeting for decisions 6.8.2.5 and 6.8.2.6

6.10.3. A copy of the report will be kept in the protocol file

7. Reference to other applicable SOPs:

7.1. SOP7A/v3: Initial Full-Board Review of Research Study Protocol

8. Annexures:

8.1. Ann01/SOP16/v3: Site Monitoring Visit Report

8.2. Ann02/SOP16/v3: Monitoring of informed consent process

8.3. Ann03/SOP16/v3: Monitoring of Audiovisual recording of AV consent Process

Ann01/SOP16/v3

Site Monitoring Visit Report

1	**YEC-1 Protocol No.**	Date of visit:
2	**Title:**	
3	**Name and affiliation of PI:**	
4	**Type of Study:** Investigator initiated Sponsored/funded	
5	Date of YEC-1 approval:	
6	Date of initiation of the study:	
7	Duration of study:	
8	Reason for monitoring: Routine/ For-cause:	
9	Protocol violations/deviations	
10	SAE reporting: Recruitment rate Others	
11	Last site monitoring:	1. Date: 2. Decision:
12	Status of the study:	1. Ongoing 2. Completed 3. Recruitment completed 4. Follow up/Extension 5. Suspended 6. Terminated

13	Recruitment details	1. Recruited (so far): 2. Screened 3. Screen failures 4. Enrolled 5. Withdrawn 6. Reasons for withdrawing 7. Discontinued 8. Reasons for discontinuing 9. Completed 10. Active
14	Are the present study team members as per the list approved by the YEC-1	Yes/No Comment
15	Are the site facilities appropriate	Yes/No Comment
16	Is the recent version of Informed Consent Document (ICD), after YEC-1 approval used?	Yes/No Comment
17	Whether consent has been taken from all patients in their native language?	Yes/No Comment
18	Any other findings noted about the ICDs?	Yes/No Comment
19	Is recent YEC-1 approved version of protocol used?	Yes/No Comment
20	Have the eligibility, inclusion exclusion criteria been adhered to?	Yes/No Comment
21	Any adverse events found?	Yes/No Comment
22	Any SAEs found?	Yes/No Comment

23	Were the SAEs informed to YEC-1 within timelines specified by CDSCO?	Yes/No Comment
24	No. of deaths reported Deaths unrelated to trial participation Deaths possibly related to trial participation Deaths due to trial participation Any other non-death study-related injury	Comments (if any):
25	Compensation paid for study related injury or death	Yes/No Comment
26	Are there protocol non-compliance deviations/violations?	Yes/No Comment
27	Have protocol non-compliance deviations/violations been informed to YEC-1?	Yes/No Comment
28	Are all Case Record Forms up to date	Yes/No Comment
29	Are storage of data and investigating products locked?	Yes/No Comment
30	If participant recruitment has been observed/ monitored, was the recruitment process fair and free?	Yes/No/ Not observed Comments:
31	If informed consent process was observed/ monitored during the visit, was the informed consent appropriately obtained in terms of providing information, testing comprehension, ensuring voluntariness and agreement?	Yes/ No/ Not observed Comments:

32	How well are the participants protected?	Good/Fair/Not good Comment
32	Any other remarks	Yes/No Comment
33	Duration of visit:_____ hours	Start time: End time:
34	Study team member(s) present:	Signature of team member(s) with date
35	Name(s) of YEC-1 members who attended monitoring visit:	Signature of YEC-1 members with date
36	Provisional decision	Discussion in the next YEC-1 meeting
37	Completed by:	Signature with date:

Extract of resolution of minutes:

YEC-1 meeting NO: Date of the meeting	
Discussion in the YEC-1 meeting:	
Final decision at the YEC-1 meeting	
1. Noted the report and recommended continuation of the project without changes	
2. Recommended continuation of the project with one or more of the following changes a. Restrict further enrollment of participants b. Recommended additional training of the PI or trial staff c. Recruit additional members in the study team d. Cause the PI to amend the methodology such that the risks are mitigated.	
3. Temporary suspension of the study until further decision at the YEC-1	
4. Termination of the study	

Signature of Chairperson with date:

Ann02/SOP16/v3: Monitoring of informed consent process

Elements	**Yes/ No**	**Remarks**
The informed consent process was taken by the research team member designated to take the informed consent		
The informed consent was carried out in the room with privacy		
Informed consent document was the same version as approved by YEC-1		
The informed consent was obtained in the regional language that the participant is conversant with		
The participant was made to feel at ease and no coercion was applied by the PI or the research team		
Adequate privacy was provided		
PI's demeanor was open and friendly, inviting participant to ask questions		
The PI reconfirmed whether the participant had understood the nuances of the research and that this was different from therapy		
PI described (in simple language) the choice to enroll or not; right to refuse; possible alternative; risks and benefits		

The PI made it clear about reimbursement for time spent; compensation in the event of adverse event; and the role of nominee in case of SAE (including death)		
PI provided a copy of the participant information sheet to the participant and encouraged him/her to read it		
The PI gave ample time to the participant to consider the risks and benefits before signing IC document		
PI gave one copy of the informed consent form to the participant to keep	`	
In the case of a minor, parent/LAR was present and included in the discussion		
In case of a minor (between 12 and 18 years) assent form was explained and signature of the participant taken		
The overall time taken for the PI to complete the IC process (in minutes)		

Name of YEC-1 member: Sign: Date:

Ann02/SOP16/v3: Monitoring of Audiovisual recording of Informed Consent Process

Sl No	Checklist item	Response
1	Facility where an informed consent process should be carried out is well lit, noise-free, privacy-ensured?	Yes/No Comment
2	Is the consent process and the consent form in a language the participant/LAR understands best and is literate in?	Yes/No Comment
3	Introduction of each person (person conducting the informed consent discussion participant/ legally acceptable representative (LAR) / impartial witness) involved during the informed consent process was done?	Yes/No Comment
4	Was information provided to the participant/ LAR/ witness (as applicable) that the process of taking the consent is being recorded for the purpose of documentation as required by the government rules?	Yes/No Comment
5	Was information provided to the participant/ LAR/ witness (as applicable) that the confidentiality of information and privacy of participants is assured?	Yes/No Comment
6	Was information provided to the participant/ LAR/ witness (as applicable) that the recording may be shown to government agencies or members from the YEC-1?	Yes/No Comment
7	Was explanation or narration provided by the person conducting the informed consent discussion?	Yes/No Comment
8	Were the questions asked by the potential participant/LAR answered satisfactorily?	Yes/No Comment
9	Did the PI allow ample time and opportunity to read/understand the information in the informed consent document or discuss the same with family members?	Yes/No Comment
10	Did the PI or a member of the study team encourage reading out by the participant/LAR (or having read out by impartial witness) the statements mentioned in informed consent and stating whether participant agrees or not for each statement?	Yes/No Comment
11	Was there appropriate documentation of signatures of all those involved in the informed consent process?	Yes/No Comment

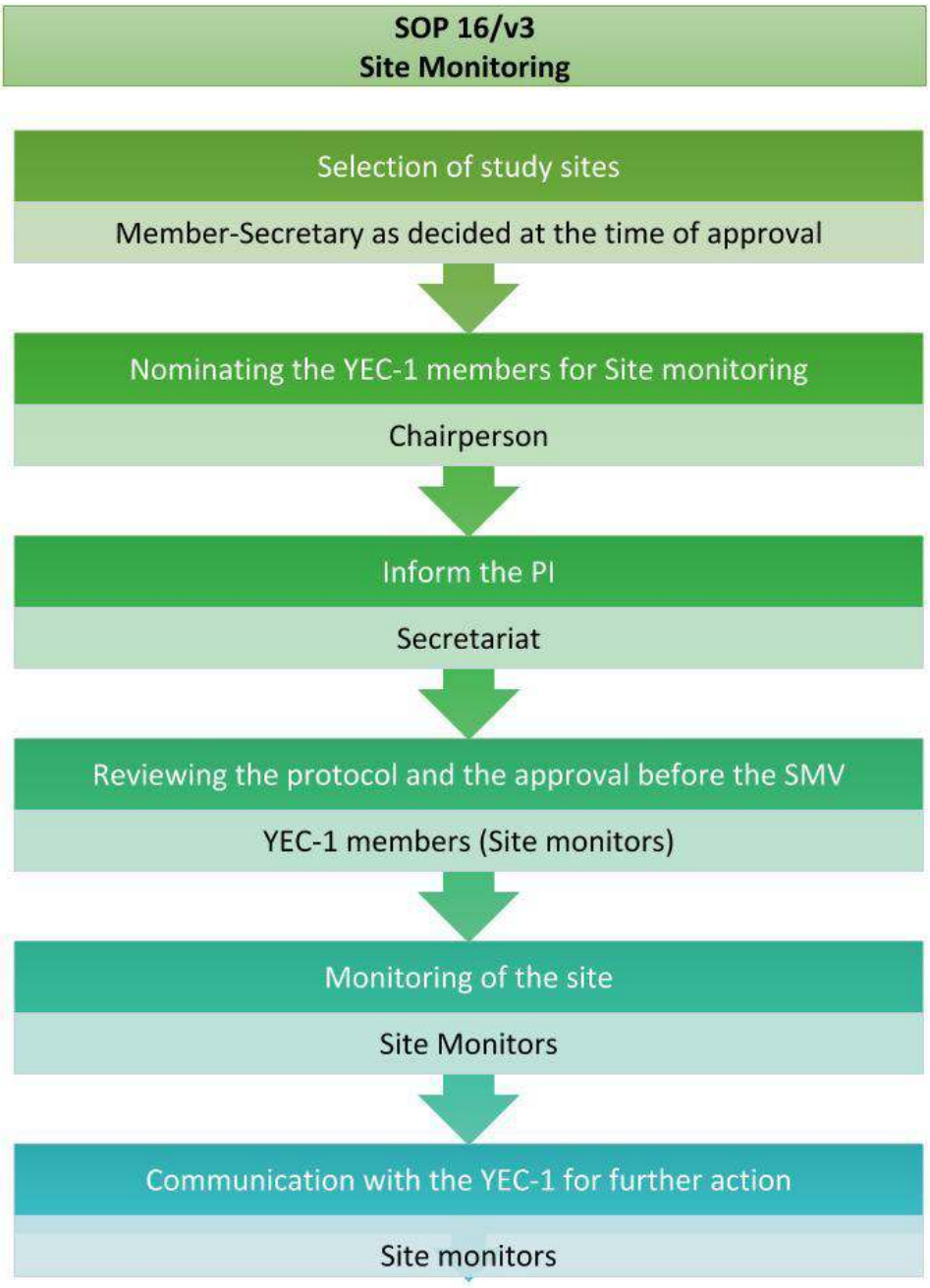
12	Was there adequate clarity and completeness of the AV recording of the informed consent process?	Yes/No Comment
13	Was the recording stored in password protected laptop/desktop computer and/or hard drive and/or labeled CD with access allowed only to the principal investigator and designated members of study team?	Yes/No Comment

Name(s) of the study team members carrying out the informed consent process with signature and date:

Name(s) of the YEC-1 monitor(s) observing the informed consent process with signature and date:

Final decision at the YEC-1 meeting held on (date)	Extract of resolution of minutes:
	Signature of Chairperson with date:

9. Flowchart:


SOP 16/v3
Site Monitoring
Selection of study sites
Member-Secretary as decided at the time of approval
Nominating the YEC-1 members for Site monitoring
Chairperson
Inform the PI
Secretariat
Reviewing the protocol and the approval before the SMV
YEC-1 members (Site monitors)
Monitoring of the site
Site Monitors
Communication with the YEC-1 for further action
Site monitors