STANDARD OPERATING PROCEDURE [SOP]

PROCESS OF REVIEW

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1. Purpose

The purpose of this standard operating procedure (SOP) is to describe the initial review of research proposals prior to their initiation and regular monitoring of the approved research project to ensure ethical compliance during the conduct of research. By this the committee also ensures to safeguard the dignity, rights, safety and well-being of all research participants.

2. Scope

This SOP applies to all studies submitted to IEC for establishment of an appropriate and sustainable system for quality ethical review and monitoring.

3. Review by formal meeting

All proposals that are submitted for full committee review will be deliberated and the decision about the proposal will be taken at a full committee meeting. A meeting will be considered valid only

if the quorum is fulfilled. This will be maintained throughout the meeting and at the time of decision making. If a member has declared a conflict of interest for any research proposal, then it will be taken in writing by the Chairperson before beginning of the meeting and shall be recorded in the minutes of the meeting. The member who has declared conflict of interest will be asked to withdraw from the EC meeting (leave the room) while the research proposal is being discussed upon, if he/ she is not an investigatory. If the IEC Member is an investigator, he/ she shall be present for review process only. At the time of discussion amongst members and final decision, the concerned member shall leave the meeting. This will be minuted and the quorum rechecked. A list of absentee members as well as members leaving or entering in-between the meeting will be recorded. Proposals will be taken up item-wise, as given in the agenda. Number of proposals reviewed in a meeting will justify that there is ample time devoted for review of each proposal. If there are more number of proposals for consideration per meeting, meetings will be more frequently arranged to review them. Time allotted for the meeting will be reasonable to allow ample discussion on each agenda item. The minutes of the previous meeting and list of protocols that underwent expedited review will be ratified. The contents of the patient/participation information sheet including the local language translations back translations of the informed consent document in English, wherever required; provision for audio-visual recording of consent process, if applicable, as per relevant regulations; and if consent waiver or verbal/oral consent request has been asked for, this will be specifically reviewed.

Apart from research proposals taken for Full Committee/ Board Meeting, investigator [s] can submit their research projects any time to the IEC, in the same way as mentioned above, with justification as to why their research project should be considered for an expedited review.

Project [s] will be considered eligible for Expedite Review where they involve:

a. Minor amendments and extensions of approved protocols
b. Urgent amendments to approved protocols for safety reasons
c. Urgent proposal of national interest
d. Research on interventions in emergency situations i.e. epidemic
e. Research on Disaster management

Few examples that may be eligible for Expedited Review:

- Revised proposal with minor modifications previously approved through full review by the IEC
- Change in the name, address of sponsor
- Change in contact details of Principal Investigator, and Member- Secretary, IEC
- Request for change in Principal Investigator, Co-Investigator, change in any member

involved in the research etc.

- Minor corrections in budget
- Other administrative changes in the investigator brochure, informed consent document etc.

Expedited Review [s] of research projects may be undertaken between scheduled meetings at the discretion of the Member Secretary, depending upon the need. The Member Secretary will be free to seek advice from other IEC members or suitably qualified experts, as appropriate [usually 2-3 members/ experts], before reaching a decision. Any research that is deemed to have potential risk/ raises ethical issue after such expedite review may be slotted for review in the next full committee meeting and the decision of the same will be communicated to the investigator, in hard as well as soft copy. Methodology for conduct of the meeting, review procedure, noting of minutes and communication with the PI will remain same as stated above. The decision and minutes of this review will be noted down for ratification at the next IEC meeting.

Any research with the potential for physical or psychological harm to the trial participant will generally be not considered for expedited review. This includes, and is not limited to, regulated clinical trials, research involving invasive physical procedures and research exploring sensitive personal or cultural issues. Where any research involves a departure from the ethical principles of integrity, respect for persons, beneficence and justice, the protocol will be considered in the Full Committee/ Board Meeting and not dealt with Expedited Review.

[Annexure 5, 5.1]

4. Initial review of proposed clinical trial

EC members will undergo initial and continuing training in Human Research Protection, IEC SOPs and related regulatory requirements. All trainings will be documented. The EC will perform its function through competent initial and continuing review of all scientific, ethical, medical and social aspects of research proposals received by it in an objective, timely and independent manner by attending meetings, participation in discussion and deliberations. Only the full committee will do initial and continuing review of such proposals. IEC may have empowered representatives from the specific populations during deliberations. Meetings of IEC shall be held on scheduled intervals as prescribed (once in 2 months, for which the dates will be finalized at the end of previous meeting). Additional meetings will be held as and when necessary especially for reported Serious Adverse Events and Expedite Reviews. Last date for receipt of new research proposals shall ordinarily be 3 weeks prior to scheduled meeting but never less than 2 weeks. IEC Manager is the software being

used by IEC for electronic submission. Apart from it, a hard copy [master file] of the whole proposal need to be submitted to IEC Office too. On receipt of hard copy as well as electronic version, IEC Co-ordinator shall forward the project [s] to Member Secretary. After MS review for completion of submitted documents, he/ she shall forward the project to all the members. About 2 weeks' time shall be ordinarily be given for each member to review the project. In case where a subject expert is needed, it shall be identified from already available pool of experts [within/ outside the institution] and the documents of the project shall even be forwarded to him. Primary reviewers may be identified for reviewing specific components of a given research proposal.

After initial review of the project, all members shall enter their comments/ suggestions in the online software that automatically reach the Member Secretary. Upon receiving suggestions from all the members, MS then prepares a consolidated suggestion sheet for forwarding it to the Principal Investigator.

PI will be available during the meeting and will be invited to offer clarifications. Decisions will be taken by consensus after discussions, and voting will be done if necessary. If a decision is reached by voting, specific comments of minority votes shall specifically be included in the minutes of meeting. The decisions of the meeting shall be recorded as minutes of meeting. It then shall be circulated on email to all members for suggestions or corrections, to be replied within a stipulated time frame. On receiving replies from all members, MS shall then finalize the minutes of meeting and put to Chairperson for signature. These minutes of meeting shall be archieved as a separate file and confirmed during the next meeting.

[Annexure 17, 18]

5. Review of informed consent document, assent form (as applicable) and translations

The informed consent process will be reviewed keeping in mind the following:

- The process used for obtaining informed consent, including the identification of those responsible for obtaining consent and the procedures adopted for vulnerable populations
- The adequacy, completeness and understandability of the information to be given to the research participants, and when appropriate, their LARs;
- Contents of the patient/participation information sheet including the local language translations;
- Back translations of the informed consent document in English, wherever required;
- Provision for audio-visual recording of consent process, if applicable, as per relevant regulations;

- If consent waiver or verbal/oral consent request has been asked for, this will be reviewed by assessing whether the protocol meets the criteria.

[Annexure 16]

6. Review of the informed consent processes

In a reviewed research project, verbal/oral consent/waiver of consent/re-consent may be obtained under certain conditions after due consideration and approval by the EC. It is the responsibility of the IEC to review and approve a request for verbal/written consent waiver. The Member Secretary will record this decision in the minutes. If the proposal has undergone expedited review, the waiver of consent will be granted only after full board review. The final decision whether to grant the waiver will be taken at a full board meeting unless the project is considered under expedited review. Criteria shall be as per existing ethical guidelines and regulatory requirements confirmed with entries as per predetermined checklists. The decision regarding approval / disapproval of waiver will be informed to the Principal Investigator in writing. If the waiver is not granted, the IEC will provide reasons for the same. In certain circumstances audio/audio-visual recording of the informed consent process will be required, for example in certain clinical trials as notified by CDSCO. These shall be approved as per the existing regulatory requirements for the same.

[Annexure 16]

7. Evaluation of recruitment strategies

Recruitment strategies will be evaluated to ensure equitable inclusion of participants without any skew towards particular patient population with regard to socio-economic class, gender or literacy. Particular emphasis will be placed on following aspects of recruitment strategies:

a. The characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status, and ethnicity)
b. The means by which initial contact and recruitment is to be conducted
c. The means by which full information is to be conveyed to potential research participants or their representatives
d. Inclusion criteria for research participants
e. Exclusion criteria for research participants
f. Students or staff recruitment in research
g. Healthy volunteers
h. Information contained in the advertisement and mode of its communication.
i. Final copy of printed advertisements

j. Final audio or video taped advertisements

k. Compensation being provide for travel as well as daily wages on case to case basis

[Annexure 10, 22, 23]

8. Evaluation of proposals involving special group and vulnerable population

Ethics Committee will evaluate the specific context-dependent characteristics that may place study participants at increased risk of being harmed or wronged (CIOMS). Ethics Committee will ensure special protections for groups considered to be vulnerable, including allowing for no more than minimal risks for research procedures that offer no potential individual benefits for participants, or requiring that the research be carried out only when it targets conditions that affect these groups. Ethics committee will enable the participation of vulnerable individuals by protecting their rights and interests through special safeguards and protections. The Member Secretary with Secretariat will maintain up-to-date tools, like checklists, for reviewing research concerning vulnerable groups based on new and evolving applicable regulations and guidelines. IEC Chairperson / Member Secretary will be responsible for ensuring that IEC members are well-versed in new and evolving regulations and guidelines pertaining to vulnerable populations, through regular training programmes. The Member Secretary/ Chairperson will be responsible for selecting primary reviewers with appropriate expertise to conduct the reviews of such research and for securing consulting expertise as and when required for selected reviews. IEC member will be responsible for conducting review of research planned for vulnerable populations, including an assessment of potential for coercion.

In such research projects, subject experts from identified pool within the institution or as the case may by specific population groups will be invited for the meeting. Subject expert will be selected from the ones who meet criteria as for specific EC member mentioned in EC composition. They will be asked to submit confidentiality and conflict of interest document prior to meeting and shall not have voting rights.

[Annexure 18]

9. Evaluation of budget with regards to indemnity, compensation, roles and responsibilities

IEC will review the proposed plan for tackling any medical injuries or emergencies. Source and means for compensation for study related injury will be ascertained. Plans for payment for participation, reimbursement of incurred costs, such as travel or lost wages, incidental expenses and other inconveniences will be reviewed. After the approval from IEC, the Sponsor/CRO will submit the Clinical Trial Agreement [CTA]/ Memorandum of Understanding and Indemnity Agreement document on Rs. 100 stamp paper separately (two copies) to the Institute which will be signed by sponsor and the CEO of the institution with the counter signature of PI. All CTAs shall be evaluated with

predetermined checklist to confirm required inclusions/ exclusions. The drug trial will be started by the PI after the agreement is signed by both the parties as well as DCGI and required regulatory approvals are available for the concerned trial.

IEC will approve travel costs to tune of Rs. 500/- [from within Anand District] and Rs. 1000/- [from outside Anand District] where actual travel bills are not available. In cases where actual bills are available, the same amount would need to be reimbursed to a maximum of a specific amount as agreed with Sponsor and mentioned in CTA.

[Annexure 17, 18]

10. Review of amendments to the originally approved protocol, consent forms and investigators brochure

a. Post decision communication

After review of any research protocol, IEC will give one of the following decisions:

- Letter of suggestions – for revision with minor modifications/amendments
- Approval with or without mandatory regulatory instructions [as the case may be]
    - Approval will be given after examination by the Member Secretary or expedited review, as the case may be;
- Revision with major modifications for resubmission
    - This will be placed before the full committee for reconsideration for approval; or not approved (or termination/revoking of permission if applicable)
- Disapproval/ revoking of permission
    - Clearly defined reasons will be given for not approving/ terminating/ revoking of permission.

b. Amendments submitted

Amendments will be incorporated in the proposal(s) to align to the research needs arising from the emergency including issues related to re-consent from participants. IEC will ensure that the clinical trials should be conducted in accordance with the ethical principles described in these guidelines, Indian GCP as well as applicable regulations for medical and medicated devices, that is, GSR 78 (E) dated 31.1.2017 or as per amendments/modifications issued from time-to-time.

- Any proposed changes to approved projects will require to be reported by the PI to the IEC for review. All amended documents [submitted in hard as well as online] will have the changes highlighted and contain revised version numbers and dates [where applicable]. Additionally, summary of changes outlining the nature of the proposed changes, reasons for the changes, and an assessment of any ethical implications arising from the request on the conduct of the research

will also need to be submitted.

- Expedited Review of requests for minor amendments and urgent amendments to approved protocols for safety reasons may be undertaken by the Member Secretary between scheduled meetings at the discretion of the Chairperson [as above], which will be ratified at the next IEC meeting. MS shall ensure that such requests do not hamper patient safety and fall within the ambit of IEC mandate for expedited reviews.
- All other requests for amendments will be reviewed by the IEC at its next scheduled Full Committee/ Board meeting, provided the request has been received by the Member Secretary by the agenda closing date. The procedure of review of amendment shall remain the same as to be followed for reviewing a new research project.
- The decision of the IEC will be communicated in writing to the PI, advising whether the proposed amendment and/or request for extension has been given ethical approval within 15 working days of the meeting at which the request was considered [this may be the Full Committee meeting or Expedited Review Meeting].
- Notification of the approval of amendments and extensions will be conveyed in writing in the standard format as per Schedule Y [as stated above].
- If the IEC determines that further information, clarification or modification is required for the consideration of the request for amendment or extension, the correspondence to the investigator will clearly articulate the reasons for this determination, and will clearly set out the information that is required.
- All received and approved requests for amendments and extensions will be recorded, and the status of the project updated in the IEC's data of received and reviewed applications.
- In cases of re-consenting or use of newly updated consent forms, IEC shall ask for submission of a copy of re-consented document or a copy of newly update consent form.

[Annexure 18]

11. Periodic review of trial

IEC will review the ongoing research at six-month interval (or more often, if deemed necessary depending on the level of risk). It will make sure that the progress report, safety report [s] and the final reports will be submitted at the regular intervals.

- Progress reports:
  - In those cases, where the IEC has requested the submission of progress reports, these will be submitted to the IEC, generally within six weeks of the anniversary of the IEC approval.

- The progress report consists of a simple declaration notifying the IEC of any ethical problems or adverse events which may have occurred during this period.

- SUSAR & CIOMS Reports:
  - IEC expects to be regularly updated with SUSAR and CIOMS reports of ongoing trials indicating adverse events or newly identified risk factors at other sites or any relevant published data in reference to the investigational drug
- Safety reporting:
  - A Serious Adverse Event (SAE) occurring to a research participant will be reported to the IEC as per existing regulatory requirements.
- Protocol deviations and violations:
  - In case where deviation/ violation from or changes to the protocol [s] occur, they are to be reported by the PI within 15 days of such deviation/ violation.
  - Along with its report, it needs to be clearly stated whether such protocol deviation or violation has/ had any impact on participant safety and what measures have been initiated by PI to ensure that such deviations or violations are prevented in future.
- Final reports:
  - The IEC will receive a final report as soon as the research gets completed.
  - It would include information on whether the study achieved its objectives, the main findings and arrangements for publication or dissemination of the research including any feedback to participants.

[Annexure 10]