

INSTITUTIONAL ETHICS COMMITTEE
H. M. PATEL CENTRE FOR MEDICAL CARE & EDUCATION
KARAMSAD, GUJARAT -388325

[Reg. No. ECR/ 331/ Inst/ GJ/ 2013/ RR-16]

STANDARD OPERATING PROCEDURE [SOP]

DECISION MAKING AND POST REVIEW ACTIVITIES

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1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe how the Institutional Ethics Committee (IEC) members will objectively reach to a decision after full review of a submitted research project and perform post review activities.

2. Scope

This SOP applies to the initial review and assessment of all research study protocols submitted for review and approval from the IEC, amendments, SAE Review, handling of complaints as well as expedite reviews.

3. Decision making process

The Member Secretary will appoint two or more primary reviewers for each study on the basis of expertise in the related field and experience. They should include one clinician and one non-technical person as applicable. More than two may be appointed, if necessary.

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Primary reviewers will have to mandatorily review the assigned protocol and put forth their comment [s] first at the review meeting. The protocol will be reviewed by the member [s] as per guidelines to review a study protocol with existing checklists.

An IEC member will consider the following criteria when performing the review of the study protocol and the study related documents:

- Scientific design and conduct of the study
- Investigators brochure about the trial product
- Risks and potential benefits
- Selection of study population and recruitment of research participants
- Inducements, financial benefits, financial costs, provision of compensation
- Data analysis and reporting
- Protection of research participants' privacy and confidentiality
- Community considerations [availability of the investigational product after trial is over]
- Qualifications of Investigators and assess adequacy of study sites
- Disclosure or declaration of potential conflicts of interest
- Compliance to national and international guidelines and existing regulatory requirements

An IEC member will consider the following criteria when performing the review of the Informed Consent Document [including assent]:

- Voluntary, non-coercive recruitment, participation/ withdrawal
- Procedures for obtaining informed consent
- Contents of the patient information sheet - title, objective, study design and procedures
- Contents and language of the informed consent document
- Translation of the informed consent document in the local languages
- Language used – plain and easy to understand by general public
- Contact persons with address and phone numbers for questions about research participant' rights and study or injury
- Privacy and confidentiality of study participants
- Risks and discomforts – physical / mental / social of study participants
- Alternative treatments availability [their efficacy or toxicity]
- Benefits – to participants, community, institution and society
- Compensation for participation (whether it will act as undue inducement)

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- Involvement of vulnerable participants
- Provisions for medical/ psychosocial support
- Treatment for study related injuries
- Compensation for study-related injuries: as per applicable local regulations
- Use of biological specimens for research purposes
- Check for provision for signatures with dates of participant, person conducting informed consent discussion, investigator and witness
- Provision for audio visual recording of consent process in case of regulatory drug trials

4. Participant recruitment process

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

5. Conflict of interest declaration including voluntary withdrawal during decision making process

- In cases of declared conflict of interest [of member/ investigator], the IEC will determine whether a conflict of interest does exist or not, and if it exists, will require the member to withdraw from the meeting until the IEC's consideration of the relevant matter has been completed. The concerned member [s] will not be permitted to adjudicate on the research or be part of the decision making process and shall be asked to be out of the meeting hall.

[Annexure 2.1]

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- All such declarations of conflict of interest and the absence of the member concerned will be noted in minutes of the meeting.

6. Basis of decisions for the initial and periodic approvals

Based on above, members will fill out the respective checklists and write their comments related to review of the research proposal. The duly filled, signed and dated assessment forms will be submitted during the full committee meeting. The IEC Secretariat will collect the checklists, review forms from each reviewer and file in the original study file.

During the discussion at the meeting:

- The primary reviewer shall brief the members about summary of the study protocol and read out the comments and evaluation provided on the review form [s].
- The comments of an independent subject expert (if applicable) will be put forth by the Member Secretary.
- The other IEC members shall give their comments right after the presentation.
- The investigator/sub-investigator shall always be called in to provide clarifications on the study protocol that he/she has submitted for review to the IEC.
- The IEC members will discuss and clarify the comments and suggestions.
- The Member secretary (assisted by the Secretarial staff) shall record the discussions
- The final decision on the study will be recorded as either Approved/ Disapproved/ Suggested to comply or any other (as per a given instance) in the meeting and shall be made by voting or by majority consensus and will be recorded in the IEC Minutes of the meeting. Voting or consensus shall be recorded by asking the members to raise their hands, if consenting to the decision put forth [approval/ rejection/ compliance].
- A majority vote for approval, disapproval or request for modifications of a study suspension or termination of an ongoing study is defined as 2/3rd of the voting members present at the meeting.
- The following will not be eligible to vote:
 - Member(s) of the committee who is/are listed as investigator(s) on a research proposal
 - An investigator or study team member invited for the meeting.
 - The Subject Expert invited for the meeting to provide opinion
 - Specific patient groups invited for the meeting will not vote or participate in the decision making procedures of the committee.

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The Committee will decide whether responses to IEC queries and (if applicable) revised protocol will go only to Member Secretary, to primary reviewers or to Full Board before final approval. The response and changes carried out may be considered for discussion at a future IEC meeting. If the IEC decision is 'Disapproved' or any other, the decision should be made on the basis of specific reasons, which are communicated by the IEC to the principal investigator in the letter of notification.

7. Approval of deliberations and decisions during the meetings and maintenance of minutes of meeting.

- The Secretariat will obtain the signature of all the members and of the Chairperson of the IEC on the IEC Meeting Attendance List during each meeting. If the study is approved, the Committee will recommend additional monitoring for a study if it is so determined at the meeting depending on factors like risk is high in the protocol, the PI has a history of repeated protocol violations, PI has many protocols and any other reason so deemed.
- The Secretariat will list participating members in the meeting and summarize the guidance, advice and decision reached by the IEC members. With the study protocol, the relevant checklists and review forms from all members will be filed in the study file by the Co-ordinator.
- It will be the duty of Member Secretary to prepare and maintain minutes of all meetings of the IEC. The format will include: Attendance of members, brief agenda, notification of approval of minutes of previous meeting, Suggestions for new proposals/ amendments, conflicts of interest, if any, monitoring reports, if any and any other issues [e.g. any expedited review undertaken/ concerns or complain received etc.], if required.
- The minutes will also include the recording of decisions taken by the IEC as well as a summary of relevant discussion. This will include reference to views expressed by absent members also, if necessary. In relation to the review of new applications or amendments, the minutes will record a summary of the main ethical issues considered [if any apart from expected elements of review], including any requests for additional information, clarification or modification of the project etc.
- While recording a decision made by the IEC after voting [in a particular case], any significant minority views (i.e. 2 or more members) if any, will also be noted in the minutes. To encourage free and open discussion and to emphasis the collegiate character of the IEC, particular views will not attribute to particular individuals in the minutes, except in circumstances where a member seeks to have his/her opinions or objections recorded.
- Declarations of conflicts of interest by any member of the IEC and the absence of the member concerned during the IEC consideration of the relevant application will be included in the minutes

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too.

- The minutes will be circulated to all, following the respective meeting on email and any suggestions/ corrections sought. Corrections/ suggestions [if any by members] will be incorporated and approved by Chairperson/ Deputy Chairperson. The same will be officially read out in subsequent meeting for approval by all the members; which again will be recorded in the minutes of that particular meeting.
- The original copy of each meeting's minutes will be retained in a confidential 'Minutes of meeting' file at the IEC Office.

8. Protocol deviations and non-compliances shall be evaluated and appropriate actions shall be taken as per rules & regulations

- 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.

A protocol deviation occurs when the activities during a study diverge from the IRB - approved protocol; a variance from protocol

Examples of protocol deviations:

- Vital signs obtained prior to informed consent
- Weighing participant with shoes on
- Urine dipstick is completed, but not sent for formal U/A
- Targeted physical exam documented instead of complete PE
- Conjugated bilirubin, part of the protocol, is left off the lab request form, but total bilirubin was drawn and is normal

A protocol violation occurs when there is divergence from the IRB - approved protocol (a deviation) that also: – reduces the quality or completeness of the data impacts a subject's safety, rights or welfare – affects the scientific integrity

Examples of Protocol Violations

- Inadequate informed consent
- Enrolment of subjects not meeting the inclusion /exclusion criteria
- Initiation of study procedure prior to completion of informed consent
- Unreported SAE's
- Improper breaking of the blinding of the study
- Use of prohibited medication
- Incorrect or missing tests

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- Mishandled samples
 - Multiple visits missed or outside permissible windows
 - Inadequate record – keeping
 - Intentional deviation from the protocol, GCP or regulations by study personnel in a non - emergency setting
 - Repeated noncompliance by the subject
 - Repeated deviations of the same nature
 - Falsification
- On the other hand, if any deviation is needed to be implemented without prior written approval of Ethics Committee [as in to eliminate immediate hazards to the trial subject (s) or when change (s) involve (s) only logistic or administrative aspects of the trial], they should be notified to the Ethics Committee within 30 days of such deviation/ change in protocol [time limits subject to change as per the latest regulations].
 - All such deviations/ violations reported will clearly indicate the effect of such deviation has any adverse effect on participant safety or not?

The IEC requires, as a condition of approval of each project, that the researchers immediately report any deviation or violation of protocol with regards to the ongoing approved research project. In cases of protocol deviation/ violation reported by the PI, they will be reviewed in the next Full Committee/ Board Meeting, unless any such deviation/ violation has a risk on participant wellbeing/ safety. In case of a risk on participant wellbeing/ safety, the Member Secretary will convene an Expedite Review Meeting to deal with the reported matter. Procedure for conduct of meeting, review, minutes as well as communication with the PI will remain the same as above. Depending upon the deviation or violation risking patient safety or PI misconduct, appropriate action shall be undertaken as per existing regulatory guidelines and actions as listed earlier in process of review.

9. Analysis and reporting of Serious Adverse Events

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR) refers to an adverse event (AE) or adverse drug reaction (ADR) that is associated with death, inpatient hospitalization (in case the study was being conducted on out-patients), prolongation of hospitalization (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

Any injury or death of the subject occurring in any approved research project [including clinical

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trial] due to following reasons will be considered as clinical trial related injury or death and the subject or his/ her nominee (s), as the case may be, are entitled for financial compensation for such injury or death [7 criteria as mentioned under Rule 122 DAB and Appendix XII of Schedule Y to the Drugs and Cosmetics Rules]:

- a. adverse effect of the investigational product [s]
- b. violation of the approved protocol, scientific misconduct or negligence by Sponsor or his representative or the investigator
- c. failure of investigational product to provide intended therapeutic effect
- d. use of placebo in a placebo-controlled trial
- e. adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol
- f. for injury to a child in-utero because of the participation of the parent in clinical trial
- g. any clinical trial procedures involved in the study

Reporting of a SAE:

1. Principal Investigator will, within 24 hours, report [by telephone/ email/ in hard copy to the Chairperson, IEC] all Serious Adverse Events in clinical trials to the IEC in accordance with the reporting conditions required by Schedule Y, Drugs and Cosmetic Rules, 1945 [Subparagraph (3) relating to the 'Responsibilities of the Investigator (s)] as per Appendix XI of the said rules.
2. In case there is a holiday/ weekend on the day of electronic reporting, PI will report the same in hard copy on next 1st working day.
3. The Sponsor and Investigator are expected to forward the reports on all the serious adverse event [s], after analysis to the Ethics Committee and Head of the Institution [CAM], along with a copy of the report to the Licensing Authority within 14 calendar days after occurrence of the serious adverse event [s] of death
4. The same [serious adverse events and the response to those events] will be included in the periodic and final reports for the project also.

IEC Analysis, Causality Assessment & Justification and Opinion:

1. In case of serious adverse event occurring to the clinical trial subject, the IEC will convene either a Full Committee/ Board Meeting or SAE Sub-Committee [if it exists] meeting within 30 days of date of reporting by PI.

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2. As stated earlier, to complete a quorum, minimum of 5 [five] members [as per Schedule Y] will be required for the meeting to review the SAE.
3. The reported SAE will be reviewed in presence of PI or Co-Investigator [Co-I]. [If none of the investigator [s] attends the meeting, the Committee will review the matter based on available documents. If deemed necessary, the Committee may approach the participant or his/ her legally acceptable representative, before arriving at any decision. In such an event, the decision of the Committee will be binding to the PI and Sponsor].
4. Necessary document [s] will be reviewed and investigator may even be asked to submit a copy of relevant documents too.
5. The Committee will ensure during the review that trial participant has been provided with adequate medical care as per applicable rules and regulations. For the same, it may even direct the Sponsor to bear the costs of the medical treatment of reported SAE till it is proved that current medical condition has no relation the trial in question [as per current CDSCO Regulations].
6. Causality assessment & justification will be done using WHO/ Naranjo Causality Assessment Tool.

[Annexures 11, 12]

7. As usual, minutes of meeting will be prepared by Member Secretary [with all required elements as stated above and additional SAE reporting requirements] and got approved by the SAE Sub-Committee Members.
8. Once minutes approved, IEC Report will be prepared and forwarded to CDSCO with its recommendations so as to reach it by mail/ post within 30 days of reporting of the SAE.

[Annexure 13]

- a. The report will include copy of Appendix XI, Duly Analysis Report by Investigator, Sponsor's Report, WHO/ Naranjo Causality Assessment Tool [with signatures of attending members] and Minutes of Full Committee/ Board or SAE Sub-Committee Meeting wherein the SAE was reviewed.
 - b. The report will also include a request to Expert Committee [for review of SAE at CDSCO] to forward a copy of its decision for record purposes.
 - c. In case the Expert Committee decides to award compensation to the study participant/ legally acceptable representative, the committee will request to be provided an acknowledgement of disbursement of compensation for confirmation and record purposes.
8. The compensation amount [if deemed necessary] will be determined based on the guidelines provided by CDSCO as available at:

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- a. Formula to determine the quantum of compensation in case of clinical trial related serious adverse events [SAE] of deaths occurring during clinical trials;
<http://www.cdsco.nic.in/writereaddata/formula2013SAE.pdf> **[Annexure 14]**
- b. Formula to determine the quantum of compensation in case of clinical trial related injury [other than death];
[http://www.cdsco.nic.in/writereaddata/ORDER%20and%20Formula%20to%20Determine%20the%20quantum%20of%20compensation%20in%20the%20cases%20of%20Clinical%20Trial%20related%20serious%20Adverse%20Events\(SAEs\)%20of%20Injury%20other%20than%20Death.pdf](http://www.cdsco.nic.in/writereaddata/ORDER%20and%20Formula%20to%20Determine%20the%20quantum%20of%20compensation%20in%20the%20cases%20of%20Clinical%20Trial%20related%20serious%20Adverse%20Events(SAEs)%20of%20Injury%20other%20than%20Death.pdf) **[Annexure 15]**

10. Notification of all decisions/opinions to the stake holders especially investigator [s]

- Following online review by members of IEC, a query letter prior to the scheduled meeting may be sent online through eEC Software, where needed.
- After the review meeting, The IEC will report in writing to the Principal Investigator (PI) the decision of the committee after the minutes are approved by all members and signed by the Chairperson/ Deputy Chairperson. A copy of the same will also be sent through eEC Software too.
- If the IEC determines that further information, clarification or modification is required for the consideration of a project, the correspondence to the PI will clearly articulate the reasons for this determination, and clearly set out the information that is required.
- If the requested information is not received from the applicant within 3 months of issue of suggestion letter, the project may be dismissed and the applicant will be required to resubmit the project at a later date as fresh application.
- Once a compliance to suggestions of reviewed proposals is received, it will be the discretion of the Member Secretary to get the re-submission reviewed by one/ more members of IEC without convening a Full Committee/ Board Meeting **[Annexure 8]**
- After receipt of the comments of the IEC members, depending upon them, approval may be granted to the concerned research project.
- In all cases, IEC will notify the PI of the ethical approval of a project only when all outstanding requests for further information, clarification or modification have been satisfactorily resolved. Ethical approval letter will be issued in Schedule Y Format, Appendix VIII [2].

[Annexure 9]

- Under no circumstance, IEC shall approve a study, pending approval from regulatory

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authorities. No conditional approvals are to be given for want of required documents

- The approval letter shall clearly state that PI needs to submit the copy of ICD of 1st participant screened/ recruited into the study to ensure that participants are included only after submitted protocol is approved by IEC.
- If the IEC determines that a project is ethically unacceptable or the approval needs to be revoked, the notification of the IEC's decision will include the grounds for the same while communicating to the PI, in hard copy as well as soft copy.
- The status of the projects will be regularly updated in the IEC's data of received and reviewed applications for record purposes.
- Communication from IEC to Investigator regarding decision on the proposal will ordinarily be done within 15 working days after review of the application in the full committee/ in cases of Exempt from Full Committee/ in cases of Expedite Reviews/ in cases of case report or series.