GUIDANCE DOCUMENT FOR INSTITUTIONAL ETHICS COMMITTEE REVIEWING CLINICAL TRIALS ON HUMAN PARTICIPANTS

December 2015
This document containing operational guidance has been developed for the benefit of Institutional Ethics Committee that reviews Study/ Research Protocols of Clinical Trials in Human. This document is designed with requirements from Schedule Y of the Drugs and Cosmetics Act., CDSCO Good Clinical Practice Guidelines for Clinical Trials on Pharmaceutical Products (2001), ICMR Ethical Guidelines for Biomedical research on Human Subjects (2006), WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants (2011).

The Institutional Ethics committee has to ensure that the clinical trial is conducted and data generated, documented and reported are in compliance with the study protocol and Good Clinical Practice Guidelines issued by CDSCO, Directorate General of Health Services, Ministry of Health & Family Welfare, Govt. of India; Ethical Guidelines issued by ICMR, Department of Health Research, Ministry of Health & Family Welfare, Govt. of India as well as all applicable statutory provisions of Drugs and Cosmetics Act and Rules and there under. Standard operating procedures should ensure compliance with applicable regulations and guidelines.

Based on this document, SOP templates are being developed that can be used by the IEC for their functioning.

This is intended as general guidance only. It must not be regarded as a definitive interpretation of any Act or Guidelines. Anyone in doubt should refer to applicable rules and regulations, and guidelines.
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GLOSSARY

Act: Wherever relevant, the Act means Drugs & Cosmetics Act 1940 (23 of 1940) and the Rules made thereunder.

Adverse Event (AE): Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given. Also see Serious Adverse Event

Adverse Drug Reaction (ADR):

- In case of approved pharmaceutical products: A noxious and unintended response at doses normally used or tested in humans
- In case of new unregistered pharmaceutical products (or those products which are not yet approved for the medical condition where they are being tested): A noxious and unintended response at any dose(s)

The phrase ADR differs from AE, in case of an ADR there appears to be a reasonable possibility that the adverse event is related with the medicinal product being studied. In clinical trials, an untoward medical occurrence seemingly caused by overdosing, abuse/ dependence and interactions with other medicinal products is also considered as an ADR. Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic). Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are, therefore, readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

Approval by EC: Affirmative decision of the EC that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the EC, the institution, good clinical practice (GCP), and the applicable regulatory requirements. (ICH GCP-E6)

Audit of a Trial: A systematic verification of the study, carried out by persons not directly involved, such as:
- Study related activities to determine consistency with the Protocol
- Study data to ensure that there are no contradictions on Source Documents. The audit should also compare data on the Source Documents with the interim or final report. It should also aim to find out if practices were employed in the development of data that would impair their validity.
- Compliance with the adopted Standard Operating Procedures (SOPs)

Autonomy: Legally effective informed consent is obtained, unless the requirements for waiver of informed consent are met by adequate and appropriate methods in accordance with the provisions of applicable regulations.

Beneficence: The sum of the benefits to the subject and the importance of the knowledge to be gained so outweigh the risks to the subjects as to warrant a decision to allow the subject to accept these risks.

Bias: Inclination or prejudice for or against one person or group, especially in a way considered to be unfair
**Bio bank:** A bio bank/repository is collection of resources that can be accessed to retrieve human biological material and data.

**Blinding/Masking:** A method of “control experimentation” in which one or more parties involved are not informed of the treatment being given. Single blind refers to the study subject(s) being unaware, while Double blind refers to the study subject(s) and/or investigator(s), monitor, data analyst(s) are being unaware of the treatment assigned

**Case Record Form:** A document designed in consonance with the Protocol, to record data and other information on each trial subject. The Case Record Form should be in such a form and format that allows accurate input, presentation, verification, audit and inspection of the recorded data. A CRF may be in printed or electronic format.

**Clinical Trial:** A systematic study of pharmaceutical products on human subjects – (whether patients or non-patient volunteers) – in order to discover or verify the clinical, pharmacological (including pharmacodynamics/pharmacokinetics), and/or adverse effects, with the object of determining their safety and/or efficacy.

**Contract:** A written, dated and signed document describing the agreement between two or more parties involved in a biomedical study, namely Investigator, Sponsor, and Institution. Typically, a contract sets out delegation/distribution of responsibilities, financial arrangements and other pertinent terms. The “Protocol” may form the basis of “Contract”.

**Confidentiality:** Maintenance of privacy of study subjects including their personal identity and all medical information, from individuals other than those prescribed in the Protocol. Confidentiality also covers the prevention of disclosure of sponsor’s proprietary information to unauthorized persons.

**Comparator (Product):** A pharmaceutical product (including placebo) used as a reference in a clinical trial.

**Compliance:** Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements. (ICH GCP-E6)

**Conflict of Interest:** is a situation in which a person or organization is involved in multiple interests (financial, emotional, or otherwise), one of which could possibly corrupt the motivation of the individual or organization.

**Essential Documents:** The Documents that permit evaluation of the conduct of a study and the quality of the data generated.

**Genetic Material/ Genome:** Genetic material refers to DNA or any other material carrying hereditary information in each cell of an organism. It consists of unique, single copies of genes, which make up approximately 10% of the DNA. The total informational content of an individual is known as ‘genome’.

**Good Clinical Practice (GCP):** It is a standard for clinical studies or trials that encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures that the studies are implemented and reported in such a manner that there is public assurance that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects are protected. GCP aims to ensure that the studies are
scientifically authentic and that the clinical properties of the “Investigational Product” are properly documented.

**Final Report:** A complete and comprehensive description of the study after its completion. It includes description of experimental and statistical methods and materials, presentation and evaluation of the results, statistical analyses and a critical ethical, statistical and clinical appraisal. The Investigator’s declaration closing the study is a part of the Final Report.

**Impartial Witness:** An impartial independent witness who will not be influenced in any way by those who are involved in the Clinical Trial, who assists at the informed consent process and documents the freely given oral consent by signing and dating the written confirmation of this consent.

**Informed Consent:** Voluntary written assent of a subject’s willingness to participate in a particular study and in its documentation. The confirmation is sought only after information about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available and of the subject’s rights and responsibilities has been provided to the potential subject.

**Interim Clinical Trial/Study Report:** A report of intermediate results and their evaluation based on analyses performed during the course of a trial. (ICH GCP-E6)

**Investigational Product:** A pharmaceutical product (including the Comparator Product) being tested or used as reference in clinical study. An Investigational Product may be an active chemical entity or a formulated dosage form.

**Investigator:** A person responsible for the conduct of the study at the trial site. Investigator is responsible for the rights, health and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator.

**Investigator’s Brochure:** A collection of data (including justification for the proposed study) for the Investigator consisting of all the clinical as well as non-clinical information available on the Investigational Product(s) known prior to the onset of the trial. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new substantially relevant data is generated during the trial, the information in the Investigator’s Brochure must be updated.

**Justice:** The selection of subjects is equitable and is representative of the group that will benefit from the research.

**Legally Acceptable Representative:** An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial. (ICH GCP-E6)

**Medical Device:** A medical device is defined as an inert diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action, within or on the body.

**Medicated Device:** These are devices that contain pharmacologically active substance which are treated as drugs.
Minimal Risk: Defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of the general population or during the performance of routine physical or psychological examinations or tests. However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant undergoing these interventions since it would be undertaken as part of current everyday life.

**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). (ICH GCP-E6)

**Multi-Centric Study:** A clinical trial conducted according to one single protocol in which the trial is taking place at different investigational sites, therefore carried out by more than one investigator.

**Nonclinical Study:** Biomedical studies not performed on human subjects.

**Placebo:** an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (as a drug).

**Protocol:** A document that states the background, objectives, rationale, design, methodology (including the methods for dealing with AEs, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed. A list of items to be included in the Protocol is compiled in a subsequent chapter.

The content and format of the protocol should take into consideration the adopted SOPs, the regulatory requirements and the guiding principles of GCP. The term Protocol, unless otherwise specified, relates to the latest amended version of the document, read in conjunction with all its appendices and enclosures.

**Randomisation:** The process of assigning study subjects to either the treatment or the control group. Randomisation gives all subjects the same chance of being in either group in order to reduce bias.

**Regulatory Authority:** The Drugs Controller General of India or an office nominated by him is the regulatory authority for the purpose of carrying out Clinical Trials in India. The Regulatory Authority approves the study Protocol, reviews the submitted data and conducts inspections.

**Serious Adverse Event (SAE):** An AE or ADR that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (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.

**Sponsor:** An individual or a company or an institution that takes the responsibility for the initiation, management and / or financing of a Clinical Study. An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a Sponsor.

**Sponsor-Investigator:** An individual who both initiate and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person...
other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-Investigator include both those of a sponsor and those of an Investigator. (ICH GCP-E6)

**Study Subject (Subject):** An individual participating in a clinical trial as a recipient of the Investigational Product. A Study Subject may be a healthy person volunteering in a trial or a person with a medical condition that is unrelated to the use of the Investigational Product or a person whose medical condition is relevant to the use of the Investigational Product.

**Vulnerable Subjects:** Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. (ICH GCP-E6)

**Well-being (of the trial subjects):** The physical and mental integrity of the subjects participating in a clinical trial. (ICH GCP-E6)
**ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR(s)</td>
<td>Adverse Drug Reaction(s)</td>
</tr>
<tr>
<td>AE(s)</td>
<td>Adverse Event(s)</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunization</td>
</tr>
<tr>
<td>CDSA</td>
<td>Clinical Development Services Agency</td>
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<td>CDSCO</td>
<td>Central Drugs Standard Control Organization</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>DCG(I)</td>
<td>Drugs Controller General (India)</td>
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<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
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<tr>
<td>HMSC</td>
<td>Health Ministry Screening Committee</td>
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<tr>
<td>ICH</td>
<td>International Conference for Harmonization of Technical Requirements for</td>
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<td></td>
<td>Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<td>ICMR</td>
<td>Indian Council of Medical Research</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>IW</td>
<td>Impartial Witness</td>
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<tr>
<td>LAR</td>
<td>Legally Acceptable Representative</td>
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<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<td>SAE(s)</td>
<td>Serious Adverse Event(s)</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>UMC</td>
<td>Uppsala Monitoring Center</td>
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<tr>
<td>URL</td>
<td>Uniform Resource Identifier</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1 PURPOSE

An Institutional Ethics Committee (IEC) is established to formalize and specify institution’s commitment to the promotion of high scientific and ethical standards in patient care, professional education, clinical research, and community interests. The purpose of the Guidance Document is to describe the standard procedures to be followed when constituting an IEC, the role and its effective functioning to provide approval for new drug clinical trials.

2 SCOPE

The guidance document applies for review of all phases of clinical trials and should be subject to review by IEC and Institution policies and procedures.

3 RESPONSIBILITY

The responsibility of the IEC is to review studies that are to be conducted in humans. The committee will make unbiased recommendations on all types of research proposals with a view to safeguard the dignity, rights, safety and well-being of all actual and potential research subjects. The goals of research, however important, should not be permitted to override the health and well-being of the research subjects. The committee shall take care that all the cardinal principles of research ethics viz. Autonomy, Beneficence, Non-maleficence, Proportionality and Justice. These should be adequately taken care during planning, conduct and reporting of the proposed research as stated in the ICMR Ethical Guidelines for Biomedical Research on Human Subjects. For this purpose, it will look into the informed consent process, study/ protocol risk benefit ratio, distribution of burden and benefit and provisions for appropriate compensation process, wherever required.

It will review the proposals before start of the study and monitor the research throughout the study until and after completion of the study through appropriate well documented procedures, for example annual reports, final reports and site visits, assessment of all SAE and advise for compensation to regulatory authority, etc. The committee will also examine compliance with all regulatory requirements, applicable guidelines and laws.

The mandate of the committee will be to review all research projects involving human subjects/ materials to be conducted at the institute, irrespective of the funding agency. In addition, each Investigator shall be responsible to the committee, for proving the benefit of placing human subjects at risk. All studies need to be approved before study procedures begin.

The ethics committee’s opinion must be free from pressures of:

- Political influence
- Institutional affiliation
- Profession-related interests
- Direct or indirect financial inducement or any impression thereof
- Coercion

4 IEC REGISTRATION

As per Rule 122DD of Drugs and Cosmetics Rule, 1945; no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with CDSCO. An application for registration of Ethics Committee shall be made to the CDSCO in accordance with the requirements as specified in the Appendix VIII of Schedule Y.
The application submitted to CDSCO office should have all the required administrative as well as technical information in proper manner as per the checklist. The checklist as per the format is given in Annexure 1. The registration of IEC with the licensing authority is for a period of three years. Therefore, IEC shall submit renewal application within three months prior to the expiry of registration, to the DCG(I) office. CDSCO shall be informed in writing in case of any change in the IEC membership or constitution.

The checklist for submission of application for registration of IEC is in Annexure I.

4.1 REVIEW FEES

The Institutional Ethics Committee (IEC) shall charge an application fee for reviewing study protocol. The IEC may decide to exempt review fee for government-funded research; Investigator-initiated research or research supported by grants from non-profit foundations or organizations.

4.2 INITIAL REVIEW FEE

The IEC shall charge a non-refundable, initial one-time review fee (irrespective of the clinical phase of the trial. This fee could be inclusive or exclusive of applicable taxes.

4.3 STUDY RENEWAL FEE

In addition to the initial review fee, the IEC shall charge a yearly fee (for e.g. Rs. 10,000) for ongoing review of the study from the second year. The study renewal review fee funds the costs of the Committee renewal review of the ongoing review of adverse events, protocol variances and site visits. The committee examines each Investigator’s progress reports and activities for the previous year.

All applications need to be mandatorily accompanied by application fee before it can be processed. The fee shall be paid by cheque or by demand draft drawn in favor of IEC and accounts thus maintained.

5 COMPOSITION OF INSTITUTIONAL ETHICS COMMITTEE

The Institutional Ethics Committee (IEC) shall be multidisciplinary and multi-sectorial in composition. The institution shall constitute the IEC. The institute should have a procedure and policy to establish or oversee the establishment of IEC and provides support to IEC activities including training, resources and infrastructure. Name of IEC should have reference to the institution under whose authority it is established. It should be reflected in all documentation and communications.

Independence and competence shall be the characteristics of IEC and a policy statement should be issued by the institute authorizing the IEC of its independence. This shall be done by the Head of Institute. The number of members in the committee should be in odd numbers; seven as minimum and 15 maximum, including the chairperson and the secretary.

The committee shall have adequate representation of gender, age, community etc. to safeguard the interests and welfare of all sections of community / society. Members shall be aware of local, social and cultural norms, as this is the most important social control mechanism.
The EC formation and functioning shall adhere to existing applicable guidelines and rules and regulations [Schedule Y of the Drugs and Cosmetics Act, CDSCO-GCP Guidelines for Clinical Trials on Pharmaceutical Products (2001), ICMR Ethical Guidelines for Biomedical research on Human Subjects (2006), WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants (2011)].

5.1 CHAIRPERSON

The chairperson of the committee should not be a current or retired employee of the institute, he or she should be from outside of the institute to maintain the independence of the committee.

5.2 SECRETARY

The secretary shall be from the institute and will be in charge of the secretariat of the IEC and responsible for reporting to the chairperson on all matters related to the IEC.

5.3 OTHER MEMBERS

The other members should represent an appropriate balance of professional, ethical, legal, cultural, educational, and community interests. It would be good to take people from all walks of life that are typical of the community and general population, whether employed, unemployed or retired.

The committee should have adequate representation of age, gender, community, etc. to safeguard the interests and welfare of all sections of the community/ society. Members are expected to be aware of local, social and cultural norms, as this is the most important social control mechanism.

For appointment to the committee, basic medical scientist and clinicians should have postgraduate qualification and should have sufficient years of work experience at positions of significant responsibility and be aware of their role and responsibilities as committee members. Professional integrity and commitment to human welfare would be important criteria for inclusion as members. A member should be willing to disclose his/her full name, profession, designation and affiliations.

Members include individuals with scientific expertise, including expertise in behavioral or social sciences; healthcare providers; members who have expertise in legal matters and/or ethics; and lay person (whose primary background is not in health research with human participants whose primary role is to share their insights) about the communities from which participants are likely to be drawn.

The IEC member shall have demonstrated an understanding of the purposes and operations associated with institute’s Human Research Protection Program, and shall have demonstrated an understanding of the policies and procedures with respect to designing, receiving approval for, and conducting human research.

The composition of IEC should be as follows:

1. Chairperson
2. Clinicians
3. Basic Medical Scientist preferably a Medical Pharmacologist
4. Legal Expert
5. Social Scientist/ Representative of Non-Governmental Voluntary Agency/ Philosopher, Ethicist or Theologian
6. Lay Person from the community
7. Member Secretary

Expert Member/ Independent Consultants: Subject matter experts may be invited to offer their views on review of research protocols, therapeutic area and causality assessment for SAE, however the expert members or independent consultants will not be voting members. Their inputs shall be maintained on record and considered when reaching a decision. This is to ensure that scientific review is appropriate, approval of the trial meets regulatory requirements and vulnerable participants are protected from undue risk. For example, a cardiologist for cardiac disorders and a pediatrician for review of pediatric studies. Similarly based on requirements of research areas like HIV, genetic disorders, etc., it is desirable to invite an expert from specific patient groups to the committee meeting, like a social worker who has experience in working with HIV patients can be invited.

Some non-health care professionals with clinical research experience may also qualify as expert members, for example: statisticians, data managers, academic scientists, e.g. biochemists, molecular biologists, immunologists, geneticists, medical devices experts and laboratory staff.

If an IEC regularly reviews research involving vulnerable populations (children, pregnant women, cognitively impaired persons, or prisoners), at least one member should be knowledgeable about and experienced in working with these subjects.

5.3.1 BASIC MEDICAL SCIENTIST

- A basic medical scientist should have post-graduate qualifications and adequate experience in his/her respective field.
- A basic medical scientist should be an MD in one of the basic sciences. Basic sciences include anatomy, physiology, biochemistry, pharmacology, microbiology, and pathology.

5.3.2 LAY PERSON

Lay person’s primary role is to share their insights about the communities from which participants are likely to be drawn. The role of lay person is to emphasize on aspects like the comprehensibility of the informed consent and other study documents to be used for participants, the study schedule and related activities and caregiver involvement.

- The term 'lay' is used to cover people with a diversity of backgrounds outside of the specific science being reviewed or conducted. This could include individuals with expertise in ethics, animal welfare, social sciences as well as members of the local community. Ideally, individuals should have no vested interest in the research and be independent of the particular science faculty or establishment
- Represent the interests of the community/participant at large
- Be able to take a balanced view of the likely harms and benefits of a research project bringing a lay perspective to bear.

5.3.3 LEGAL PERSON
Role of Legal expert is as primary reviewer of the contract to review the insurance, compensation and trial agreements.

- A legal person can be a retired expert in law (judge) or medico-legal expert
- The clear articulation of law by legal person improves the ethical analysis of study
- Law can help physicians and others in decision-making and legalized approaches are similarly said to foster deliberation and careful weighing of evidence as well as playing a fundamental role in tempering subjective discretion and minimizing arbitrariness
- Should review agreements and insurance in clinical trials.

5.3.4 **Social Scientist/ Representative of Non-Governmental Voluntary Agency/ Philosopher/ Ethicist / Theologian**

Role of theologian is to understand if there are any religious implications to any of the trial activities.

- A graduate with specialization in social ethics, intercultural ethics, and the ethics of gender and vulnerable population
- Serve as resource persons to religious beliefs and faith concerning the spiritual and value dimensions and values of illness and health even if patients or their families have no apparent religious affiliation
- Bring expertise in spiritual, theological, ethical, and moral values to the multi-disciplinary team in the clinical setting.

6 **SECRETARIAT**

The Secretariat consist of IEC Secretary and administrative/support staff.

To support the smooth functioning of the IEC, administrative staff shall be appointed by the chairperson of IEC or the head of the institute.

- IEC must have proper address and telephone numbers.
- There should be proper storage facility for record keeping.
- Support staff should be adequate in number and training to enable the IEC to carry out its technical and administrative responsibilities
- Adequate resources for the staff to fulfil its assigned functions, including office space and equipment and supplies (e.g. computers, stationery, telephones, photocopying machines, shredding machine).
- IEC must have proper SOPs for its all the activities.

7 **APPOINTMENT**

The head of institute shall appoint the Secretary and other members of the IEC. The head of institute shall appoint the Secretary. The IEC members shall appoint from among its Chairperson and co-chairperson. Independent consultants are appointed by the chairperson of the IEC.

For all the members as well as experts invited for meetings, files should be maintained by the secretariat. The files should have details of qualification, area of expertise, organization details (to which member is affiliated), role in ethics committee, complete contact details and updated CV.
For the expert members, evidence of invitation of particular meeting should also be retained and documented.

**7.1 CRITERIA FOR SELECTION OF MEMBERS**

Members shall be selected in their personal capacities, based on their interest, ethical and/or scientific knowledge and expertise, experience in the domain field and profile and availability of time for spending to review and monitor the progress of the studies.

The members representing medical scientist and clinicians should have graduate qualification and adequate experience in their respective fields. Conflict of interest should be avoided while making appointments, with transparency with regard to financial and non-financial interests. The conflict of interest if any shall be disclosed and confidentiality agreement shall be signed by all members.

Listed below are some criteria that can be applied when assessing candidates for becoming a member of the IEC. The potential members must be able to demonstrate that they have the qualities, skills and experience to meet the criteria as below:

- Have a strong personal commitment to the interests of research participants who take part (or are asked to) in health care research.
- Have a strong personal commitment to ensuring the highest standards for health care research.
- Be able to read, understand and analyse complex issues from research proposals and weigh up conflicting opinions.
- Be able to take an objective stance, looking at a situation from different perspectives.
- Be a good communicator with a practical approach and confidence to voice his/her opinions.
- Be able to discuss issues with people who may not agree with the member including being able to influence others from a range of backgrounds.
- Be committed to the public service values of accountability, probity, openness and equality of opportunity.
- Be able to demonstrate an ability to contribute to the work of the IEC.
- Understand the requirement for confidentiality in issues faced by an IEC.
- Be willing to undertake training to equip to carry out his/her role.
- Need to be confident about expressing and supporting their own opinions.
- Live in, or close to, the geographical area of the institution and IEC.
- Have experience of conducting research projects.
- Flexibility, excellent communication skills and a desire to ‘make a difference’

**7.2 TRAINING OF EC MEMBERS**

Training on the ethical aspects of health-related research with human participants, how ethical considerations apply to different types of research, and how the IEC conducts its review of research, is provided to IEC members when they join the committee and periodically during their committee service.

- A new member shall be inducted one month prior to his/her formal appointment and shall be requested to be an “observer” for the first meeting.
- The IEC members should be trained in Research Bioethics.
- An introductory training shall be imparted by the Secretary to new members.
• The IEC members shall be encouraged to receive ongoing training by attending workshops at least once every year.
• The IEC shall conduct workshops from time to time to impart training to the IEC members and Institutional faculty members.
• Requirements and updates from relevant guidelines (E.g.: ICMR, CDSCO-GCP, Schedule-Y)
• IEC Secretariat shall maintain training records of each IEC member

Note: When training is supported by research sponsors, mechanisms should be in place to ensure that the sponsor has no control, direct or indirect, over the content of the training.

Also all the members should be trained on rights and responsibilities of research participants. As per rules and regulation the charter should be prepared by the IEC secretariat and should be made available to all stake holders including the research participants.

7.3 TERM OF OFFICE

The membership of IEC shall be for a period of two to three years and shall be renewed after the stated term. At the end of the term, at least one third of the IEC members shall be replaced such as to maintain the composition. Extension of membership may be considered due to non-availability of members of similar stature, qualification and intent to contribute to ethical human testing.

In case of the resignation/ discontinuation/ disqualification/ death/ chronic absenteeism of any member, before the completion of the tenure of the existing appointed committee, the Chairperson, Head or other administrative authorities of Institute may appoint a replacement. This appointment will be effective for the remaining tenure of the existing committee.

7.4 RENEWAL OF MEMBERSHIP

The membership shall be renewed after the stated term. Selection of members shall be done at least one month in advance. Designated members of the IEC who wish to attend IC meetings as observers shall read, understand, accept and sign the agreement contained in the Confidentiality/ Conflict of Interest form at the beginning of the IEC meeting and/or before scientific and ethical review tasks.

7.5 SELF-EVALUATION

EC should conduct self-evaluation periodically, at least annually. The evaluation should be done for the appropriateness of its composition, attendance of members, adequate resources for functioning of EC, the review process, etc.

If there is any process failure, root cause analysis should be done to identify the process failure and the corrective and preventive action taken should be documented.

7.6 RESIGNATION

If any member wishes to discontinue from the EC, he/she would be required to inform the Chairperson, in writing. Members may voluntarily resign from the committee at a month’s notice citing appropriate reasons.
7.7 TERMINATION/ DISQUALIFICATION PROCEDURE

During the tenure, Chairperson shall have the authority to terminate/ disqualify any of the members in the event that the member has not complied with the conditions of appointment, is absent without prior information for three consecutive meetings or on an occurrence of any event that casts a serious doubt on the integrity or ethics of the member.

In all such situations/ circumstances, the Head of Institute shall be informed of such termination to the member prior or within 15 calendar days of termination. Documentation of the termination shall be recorded in the minutes of the next duly constituted IEC meeting and the EC membership roster and circulars shall be revised.

8 SCHEDULE OF MEETING

The IEC should meet regularly. The frequency of IEC meetings shall depend on number and the type of protocols reviewed. An IEC meeting roster should be maintained by the IEC secretariat and there should be SOP for this activity.

9 CONFIDENTIALITY

All IEC members should maintain absolute confidentiality of all discussions during the meeting, including the documents circulated for review, unless required by law. All members have to sign a Confidentiality and Non-Disclosure Agreement at the time of appointment regarding meeting deliberations, applications, information on research participants and related matters, the term of which shall be binding on them even after the termination of the contract.

10 CONFLICT OF INTEREST

IEC members shall disclose to the committee all conflicts of their own, their spouse/ domestic partner, and their dependent children with regard to a research project involving human participants.

After the initial constitution, subsequent appointment to the committee shall be guided by the quorum requirements and activity of the members involved. Any members who have obvious undue influence on the decisions of other members by the way of their institutional association, financial liability, kinship or authority would need to voluntarily excluded themselves from the quorum. In case, this is not done voluntarily, exclusion may be suggested (if deemed necessary) by at least 2 other members.

A member should declare at the first meeting in which he/she participates, all conflicts or potential conflicts, of interest that may compromise his/her position on the IEC. It would be up to the rest of the IEC to take an appropriate decision.

A member who has direct involvement or self-affirmed conflict of interest with a proposal being considered shall not form a part of the quorum.

Conflicting interest includes, but is not limited to, the following:

- The IEC member or his/her family member:
  - Is or will be an investigator in the research
  - Supervises an investigator on the protocol
o Holds a significant financial interest in the business entity sponsoring the research
o Has a proprietary interest in the research, such as a patent, trademark, copyright, or licensing agreement
o Holds a close personal relationship with an investigator
o Participates in a potentially competing research program or study
o Has any other personal/financial biases or interests that may interfere with the exercise of impartial judgment and objective review of the research.

Each member, including immediate family’s financial and non-financial interest shall complete a Financial Disclosure Form with a limit for having financial interests in the study sponsoring company.

To counter balance internal and institutional pressures, more non-scientific and non-institutional members shall be appointed to the IEC. The committee, in order to maintain sufficient independency shall keep the investors/equity owners of the institute from participating in the EC review process.

11 INFRASTRUCTURE

The parent institution of the IEC shall provide the IEC with sufficient resources (meeting space, secretariat office, computers, archival room and fund) and administrative staff to support the IEC’s review and record keeping duties. There should be a clear term of reference and budget for resource allocation by the Institute.

12 ROLES AND RESPONSIBILITIES OF THE IEC AND ITS MEMBERS

The Committee shall:

- Provide independent and competent review of all ethical aspects of research proposals.
- Review research proposals submitted to it within a reasonable time and document its views in writing to the applicant(s).
- To assist in the development and education of a research community responsive to local health care requirements.
- Safeguard the dignity, rights, safety, and well-being of all study participants and communities paying special attention to investigations that may involve vulnerable participants.
- Request the Investigator(s) to explain any aspect of the study that may require personal appearance at its Committee meeting.
- Provide guidance to the Investigator on all aspects of the welfare and safety of research participants.
- Ensure scientific soundness of the proposed research.
- Make available acceptable standard format accepted by the committee for submissions of research proposals.
- Obtain relevant documents including but not limited to the following:
  o Trial Protocol (including protocol amendments)
  o Patient Information Sheet and Informed Consent Form (including updates if any) in any in English and/or vernacular language.
  o Investigator’s Brochure
  o Proposed methods for patient accrual including advertisement (s) etc. proposed to be used for the purpose.
  o Principal Investigator’s current CV.
12.1 ROLE OF CHAIRPERSON

- Chair the meetings
- Facilitate and participate in IEC educational activities
- Keep abreast of regulations and policies governing IEC review of research and the conduct of human subjects research
- Appoint IEC members

12.2 ROLE OF SECRETARY AND THE SECRETARIAT

- Organization of an effective and efficient tracking procedure for each proposal received.
- Preparation, maintenance and distribution of study files.
- Organization of regular IEC meetings.
- Preparation of the agenda and the minutes of the meetings.
- Maintenance of the IEC records and archives.
- Communication with IEC members and Investigators.
- Arrangement of trainings/workshops for personnel and IEC members.
- Receipt of IEC processing fees.
- Maintain financial records which includes details of IEC fee for their services, honorarium payment to members and other expenses incurred.
- Prepare for financial audits and maintain the financial audit reports.
- Organizing the preparation, review, revision and distribution of SOPs
- Providing the necessary administrative support for IEC related activities to the Chairperson of the Committee.
- Correspondence with Chairperson and IEC members, with Investigator and with Regulatory Authority.

12.3 ROLE OF ALL MEMBERS

The members’ (including Chairperson and Secretary) primary responsibilities will be determining the scientific and ethical validity of the research and the protection of the safety, rights and confidentiality of the research subjects.

- Participate in the IEC meeting.
- Review and discuss research proposals assigned for evaluation.
- Review progress reports and monitor ongoing studies.
- Monitor site for adverse events and recommend appropriate action(s).
- Maintain confidentiality of the documents and deliberations of the IEC meetings.
• Declare conflict of interest, if any - Such disclosure shall be sufficiently detailed and timely to allow the IEC Administration to transfer the project to another IEC member or allow time for an alternate member to attend the IEC meeting to meet quorum.
• The IEC member/consultant shall evaluate whether a conflict of interest exists, and he/she shall disclose any identified conflicts to the IEC at the next IEC meeting. If an IEC member discovers that he/she has a conflict of interest during the conduct of a study over which the IEC provides oversight, the IEC member/consultant shall report the conflict to the IEC. Other IEC members shall cooperate with the IEC and other officials in their review of the conflicts of interest issues and shall comply with all requirements of the IEC.
• Carry out work delegated by the Chairperson, Co-Chairperson and/or Member Secretary.
• Participate in continuing education activities in biomedical ethics and biomedical research.

Provide information and documents related to training obtained in biomedical ethics and biomedical research to the IEC secretariat.

12.4 ROLE OF IEC SECRETARIAT

• Organizing an effective and efficient tracking procedure for each proposal received.
• Preparing, maintaining and distributing study files.
• Assisting Member Secretary in performing his/her duties
• Providing necessary administrative support for IEC related activities to the Member Secretary, IEC.
• Receiving IEC processing fees and issuing official receipts for the same.
• Making the pre and post arrangements of IEC meetings.
• Filing study related documents i.e., Archiving and maintaining the study files.
• Preparation for accreditation, audits
• Participate in the development, revision and subsequent implementation of SOPs.

13 COMPENSATION AND REIMBURSEMENTS TO EXTERNAL MEMBERS

All external members, and experts invited (if any) will be paid an honorarium (for e.g. Rs. 1000) for each meeting attended and may also be reimbursed for travel and other actual costs incurred towards contributing to the workings of the IEC.

Appropriate bills will have to be submitted together with the claim form to the Secretary.

14 INDEMNIFICATION

Any member acting responsibly within the Committee should be ‘indemnified’ by the institution. That is, the institution will protect members against civil legal action that might arise from the business of the committee. This is with the provisos that the member informs the institution and co-operates with them in respect of any claim made against them and has not acted in bad faith, willfully defaulted on their responsibilities or been grossly negligent.

15 TRANSPARENCY, ACCOUNTABILITY, AND QUALITY OF IEC

The entity establishing the IEC employs reliable means to evaluate whether the staff and members of the IEC routinely follow the IEC’s policies, rules, and written procedures, with
special attention to whether the ethical considerations articulated in international guidelines and national standards are being considered and applied consistently and coherently.

Knowledgeable and unbiased people at regular conduct such evaluations, pre-defined intervals using a pre-defined format; internal assessments are supplemented periodically by independent external evaluations.

The entity (Institution) establishing the IEC is committed to consider and, when appropriate, follow up on the findings and recommendations of the internal and external evaluations.

The results of the evaluation are of a type that can aid the IEC in reviewing its practice and appraising performance (rather than apportioning blame), while also assuring the public that research is being reviewed according to established standards.

Researchers, research participants, and other interested parties have a means of lodging complaints about the IEC; such complaints should be reviewed by an entity other than the IEC itself, and appropriate follow-up actions should be taken.

Researchers should have a means of discussing concerns with IEC members, both on general matters and in response to IEC decisions on particular research studies.

IEC decisions, excluding confidential information, are made publicly available, through mechanisms such as clinical trial registries, web sites, newsletters, and bulletin boards.

16     PROCEDURE FOR SUBMISSION OF PROPOSAL

- The proposals shall be addressed to the chairperson of the Ethics Committee, and shall be submitted to the IEC Coordinator/ Secretariat.
- The IEC Coordinator/ Secretariat will communicate with the applicant and will acknowledge receipt of the application with supporting annexes.
- The Secretary shall screen the proposals for their completeness as well as with regard to any clarifications or additional documentation that may be required, within a week of receiving the application (or earlier in case of exemption or expedited review).
- Appropriate number of copies of each document should be submitted.
- Application should be submitted at least two weeks prior to the next review meeting.
- A unique submission number shall be assigned to proposals submitted for review.
- Investigators shall be notified via letter to present the protocol and offer clarification during the IEC meeting.

Review with suggestions for amendments may be returned to the submitter and the final submission updated accordingly.

16.1     ESSENTIAL DOCUMENTS TO BE SUBMITTED

For a thorough and complete review, all research proposals (XX copies) should be submitted in the following manner:

- Study Submission Form with CTRI registration number.
- Patient Information Sheet & Informed Consent Forms (ICFs), for studies in children, parental consent form and in case of children between age 7-18 years of age- Child Assent Forms and Parent consent forms - in language understandable are mandatory along with certificate of back translations.
• Study Protocol
• Investigator’s Brochure
• Case Record Form (CRF) or paper copy of electronic CRF
• A recent, signed and dated curriculum vitae of the Investigators indicating qualifications and relevant experience
• Investigator’s Undertaking
• Agreement to comply with national regulations and guidelines and study protocol
• Regulatory clearance from appropriate regulatory authorities i.e. CDSCO approval/ICMR/ Health Ministry Screening Committee (HMSC) (if applicable)
• For international collaborative study Memorandum of Understanding between the collaborating institutes
• Clinical Trial Agreement (if applicable)
• Insurance/ Indemnity policies, indicating who are covered (if applicable)
• Participant recruitment and enrollment procedures/advertisement (if any).
• A statement describing any reimbursement and compensation for study participation (including expenses and access to medical care) to be given to research participants; a description of the arrangements for indemnity, if applicable (in study-related injuries); a description of the arrangements for insurance coverage for research participants, if applicable; all significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other IECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of the modification(s) to the protocol made on that account. The reasons for negative decisions should be provided.
• Any other important information relevant to the study
• Decision of other Ethics Committees (If required/ asked for)

The checklist for various documents should be provided in Study Review Form.

16.2 RESUBMISSION OF STUDY WITH CHANGES AS PER IEC SUGGESTIONS

For resubmission, the Investigator should submit copies of the amended study related documents along with justification for amendment or modification, and clearly highlight/demarcate sections that have undergone change.

The documents shall be verified by the secretariat for the completeness and reconfirm that the copies contains the modification highlighted with respect to the earlier submission.

The unchanged study-related documents need not be re-submitted (IEC can decide as per policy).

16.3 ANNUAL CONTINUING REVIEWS OF APPROVED RESEARCH STUDIES

The IEC secretariat shall send reminders for annual report to investigators at least a month or two prior to lapse of approval.

The IEC shall receive a copy of Annual Status/ Continuing Review Report in the prescribed format and related documents for the approved research study.

For periodic review, the investigator should submit relevant details like, number of participants recruited, adverse events and serious adverse events, protocol deviations, non-compliance
and summary of amendments (if any). All continued reviews shall be discussed in full board meeting.

The IEC secretariat shall verify the completeness of the Continuing Review Application i.e., Progress report/Request letter for extension of approval of the project.

The progress or continuing review report shall be discussed in the expedited review meeting or full board meeting of IEC.

16.4 RESEARCH STUDY COMPLETION/TERMINATION

The IEC should receive a copy of Study Completion Report in the prescribed format (as per Schedule Y and ICH-E3)/ termination report.

The study completion/ termination report will be discussed in the full board meeting of IEC.

17 PROCEDURE FOR MEETING

Meetings shall be scheduled approximately every week, month or quarter based on the load of the proposals. Exact meeting date shall be notified at least 3 weeks in advance so that all members can make themselves available for the purpose.

The Secretary shall be the convener with responsibility for organizing the meetings, maintaining the records, laying out the agenda and communicating with all concerned for the meeting. He/she shall prepare the minutes of the meetings after incorporating the comments of all the members and get it approved by the Chairperson before communicating decision of the IEC to the Investigators.

The meetings must demonstrate and document the following deliberations:

- The presence of full quorum
- Declaration of conflict of interest
- Confirmation of Last meeting’s Minute
- Details of risk-benefit assessment decision of review (initial, continue review) of study
- Any changes requested
- Protocol deviations
- AE/SAEs
- Non-compliance
- Monitoring sites, reports and Corrective and Preventive Action (CAPA) plan
- Any other relevant discussions/updates.

17.1 BEFORE MEETING

- IEC Secretary prepares the agenda a week prior to the IEC meeting and circulates the agenda via email

- Schedule studies on the agenda. The number of items is based on available expertise (members and consultants), urgency, order of submission to the IEC and IEC workload.

- Secretary prior to the meeting will identify IEC members who may have a conflict of interest due to their participation as key personnel on a current or proposed research project.
• An IEC member who has a conflict of interest with regard to a research project that will be reviewed at a convened IEC meeting must notify the IEC office of the conflict prior to the meeting.

• Once the IEC office receives notice of recuse, the IEC Secretary will seek an alternate IEC member to join the meeting for the review of that project if necessary to meet quorum.

• The copies of the protocols/documents shall be sent to the IEC members by either electronic mail (in case of electronic submission of protocols) or by courier of hard copies and CD (soft copy) preferably 10 days in advance of the scheduled meeting.

17.2 CONDUCT OF MEETING

• At the beginning of each convened IEC meeting, the IEC Chair or designee will ask the members if anyone has a financial or non-financial conflict of interest with regard to any of the research projects that will be reviewed at the meeting. The IEC Chair or designee will announce that members with a conflict of interest must excuse themselves from deliberation and decision on that research protocol. Regular meetings shall be held at least quarterly.

• Research involving vulnerable populations (vulnerable to coercion or undue influence) will be placed on the agenda only when at least one individual (IEC member or independent consultant) who is knowledgeable about or experienced in working with the population will participate in the meeting (or an independent consultant has been obtained). If expertise with a specific vulnerable population is needed but not available from the IEC members, an expert member will be obtained or the item will be scheduled for a later meeting when expertise is available.

• Secretariat shall obtain signatures on Confidentiality, Conflict of Interest, Agreement, Attendance etc.

• Chairperson will initiate the meeting and Secretary shall discuss the minutes of the previous meeting of IEC as well as major issues/policies discussed in minutes of the other IEC and present the agenda for the current meeting

• The IEC shall inform Investigators to attend the full board meeting related to their studies, and clarify doubts, if any

• IEC completes the adequate review of the research studies submitted. The committees will review new studies, amendments, annual /continuing review of ongoing studies, SAE reports, any other documents and assess final reports of all research activities through a scheduled agenda

• The decisions shall only be made at meetings where a quorum is present.

• Only IEC members who attend the meeting will participate in the decision. Decisions will be arrived at through consensus/unanimous opinion amongst the members of IEC. The decision-making is thus concerned with the process of deliberating and finalizing a decision. IEC will approve when all participating members will give consensus and quorum will be present, without quorum the decision cannot be made.
17.3 **AFTER THE MEETING**

- The Secretary shall compile the proceedings of IEC meeting. The minutes of the meeting will be compiled and sent to Chairperson for review within 7 working days.

- Once finalized, the IEC meeting will be signed by Member Secretary and Chairperson and shall be circulated to all IEC members within 15 days.

- The minutes of the IEC meeting will be ratified in the subsequent IEC meeting

- Secretary shall email the minutes of the meeting (MoM) to IEC members after obtaining approval from the chairperson.

- Place the original version of the minutes in the minutes file and copy of the minutes shall be filed in the corresponding research protocol file.

- A copy of decision letter along with all project related correspondence shall be placed in the appropriate project files and communicated to investigators.

- The Secretary shall communicate IEC decisions to the Investigators in writing.

18 **FUNCTIONS OF IEC**

18.1 **QUORUM REQUIREMENTS**

All research projects for approval by the full board of the IEC shall be reviewed at convened meetings at which a majority of the members of the IEC are present. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting. The presence of the following five (5) members is required to form part of the quorum without which a meeting cannot be convened and a decision regarding the project cannot be taken. (Schedule Y)

For review of each protocol, the quorum of Ethics Committee should be at least one members from the following representations:

- Basic medical scientists (preferably one pharmacologist)
- Clinician
- Legal expert
- Social scientist or representative of non-governmental voluntary agency or Philosopher or ethicist or theologian or similar person
- Lay person from the community

**Point to Note:**

- The quorum is the count of the number of members present in the IEC meeting.
- The quorum means: The minimal number of officers and members of a committee or organization, usually a majority, who must be present for valid transaction of business.
- If the number present falls below the required number, the quorum fails.
- If any member as defined in Schedule Y Appendix VIII is absent, the requirement of quorum will not be met.
- If an investigator is part of the quorum of five members, and if he is unable to vote for his own study, the quorum will fail.
18.2 MANAGEMENT OF RESEARCH STUDY SUBMISSIONS

It is the responsibility of the secretariat to receive, record and distribute the study documents for IEC review.

For the initial review of study, Investigators should submit all study related documents to the IEC, no fewer than 4 weeks before the next scheduled meeting. The investigator should submit research proposal to the IEC for review and approval under any of the sections mentioned below:

- Initial Review Application
- Resubmission of Study with Corrections
- Study protocol
- Protocol Amendment or any other amendments
- Annual Status Reports/ Continuing Review of the study
- Study Completion/ Termination
- On the receipt of the study related documents at IEC office all the applications shall be verified for their completion along with required documents.
- Other related documents necessary for initial review

The missing documents or incomplete applications shall be notified to the Investigator via letter for necessary actions.

The hard copies and soft copy of the research project shall be stored. The paper copies shall be stored under controlled access storage in IEC office. The soft copy of the study accepted will be stored electronically.

18.3 REVIEW OF PROPOSALS

The Secretary shall screen the proposals for their completeness. Depending on the risk, as defined in "Ethical guidelines for Biomedical Research on Human Participants, ICMR 2006; involved in the research proposals, the Secretary shall categories them into three types, viz.

1. Full board review
2. Expedited review
3. Exemption from review

The checklist for review of Protocol, Patient Information Sheet and Informed Consent Form, and Investigator’s Brochure are provided as annexure documents.

18.3.1 ETHICAL BASIS OF REVIEW

The IEC bases its decisions about research that it reviews on a coherent and consistent application of the ethical principles articulated in international guidance documents and human rights instruments, as well as any national laws or policies consistent with those principles.

The IEC makes clear the specific ethical guidelines on which it relies in making decisions and makes them readily available to researchers and the public. To aid in determining the ethical acceptability of research protocols, an IEC may utilize a checklist to ensure that all relevant criteria are considered during review and that, as a general rule, similar protocols are treated similarly. When an IEC determines that an approach it has taken on a particular ethical issue
in the past is no longer appropriate, it provides an explicit rationale for its change in position. In communicating decisions about particular protocols to researchers, the IEC explains its analysis of any significant ethical issues that arose in the review.

As articulated in more detail in ethics guidelines and the research regulations, key criteria include, but are not limited to, the following sections:

**18.3.1.1  SCIENTIFIC DESIGN AND CONDUCT OF THE STUDY**

Research is ethically acceptable only if it relies on valid scientific methods. Research that is not scientifically valid exposes research participants or their communities to risks of harm without any possibility of benefit. IEC should have documentation from a prior scientific review, or they should determine that the research methods are scientifically sound, and should examine the ethical implications of the chosen research design or strategy. Unless already determined by a prior scientific review, IEC should also assess how the study will be conducted, the qualifications of the researcher(s), the adequacy of provisions made for monitoring and auditing, as well as the adequacy of the study site (e.g. availability of qualified staff and appropriate infrastructures).

**18.3.1.2  RISKS AND POTENTIAL BENEFITS**

In ethically acceptable research, risks have been minimized (both by preventing potential harms and minimizing their negative impacts should they occur) and are reasonable in relation to the potential benefits of the study. The nature of the risks may differ according to the type of research to be conducted. IEC members should be aware that risks may occur in different dimensions (e.g. physical, social, financial, or psychological), all of which require serious consideration. Further, harm may occur either at an individual level or at the family or population level.

**18.3.1.3  SELECTION OF STUDY POPULATION AND RECRUITMENT OF RESEARCH PARTICIPANTS**

Ethically acceptable research ensures that no group or class of persons bears more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research; these benefits include the direct benefits of participation (if any) as well as the new knowledge that the research is designed to yield. Thus, one question for research ethics review to consider is whether the population that will bear the risks of participating in the research is likely to benefit from the knowledge derived from the research. In addition, ethically acceptable research includes recruitment strategies that are balanced and objectively describe the purpose of the research, the risks and potential benefits of participating in the research, and other relevant details.

**18.3.1.4  INDUCEMENTS, FINANCIAL BENEFITS, AND FINANCIAL COSTS**

It is considered ethically acceptable and appropriate to reimburse individuals for any costs associated with participation in research, including transportation, child care, or lost wages. Many IEC also believe that it is ethically acceptable to compensate participants for their time. However, payments should not be so large, or free medical care or other forms of compensation so extensive, as to induce prospective participants to consent to participate in the research against their better judgment or to compromise their understanding of the research.
18.3.1.5 PROTECTION OF RESEARCH PARTICIPANTS’ PRIVACY AND CONFIDENTIALITY

Invasions of privacy and breaches of confidentiality are disrespectful to participants and can lead to feelings of loss of control or embarrassment, as well as tangible harms such as social stigma, rejection by families or communities, or lost opportunities such as employment or housing. IEC should therefore examine the precautions taken to safeguard participants’ privacy and confidentiality.

18.3.1.6 INFORMED CONSENT

The ethical foundation of informed consent is the principle of respect for persons. Competent individuals are entitled to choose freely whether to participate in research, and to make decisions based on an adequate understanding of what the research entails. An authorized surrogate decision-maker should make decisions for children or adults who lack the mental capacity to provide informed consent.

IEC should examine the informed consent document, assent form (if applicable), translations process through which informed consent will occur, as well as the information that will be provided.

IEC may waive the requirement of informed consent only when doing so is consistent with international guidelines and national standards. While informed consent to research is important, the fact that a participant or surrogate may be willing to consent to research does not, in itself, mean that the research is ethically acceptable.

18.3.1.7 COMMUNITY CONSIDERATIONS

Research has impacts not only on the individuals who participate, but also on the communities where the research occurs and/or to whom findings can be linked. Duties to respect and protect communities require examining by the IEC and, as far as possible, are aimed at minimizing any negative effects on communities such as stigma or draining of local capacity, and promoting, as relevant, positive effects on communities, including those related to health effects or capacity development.

Researchers should actively engage with communities in decision-making about the design and conduct of research (including the informed consent process), while being sensitive to and respecting the communities’ cultural, traditional and religious practices.

18.4 ELEMENTS OF REVIEW

The emphasis is on ethical guidance, grounded in the core principles of Respect for Persons, Concern for Welfare, and Justice. The welfare of participants takes precedence over the interests of researchers and sponsors. The primary task of the IEC is to review research proposals and their supporting documents with special attention to safety of participants involved in research.

18.4.1 STUDY PROTOCOL

The protocol should include the following and as per Appendix X of the Schedule Y of the Drugs and Cosmetics Act:
1. The title with signature of Principal Investigator (PI) and Co-Investigators as attestation for conducting the study.
2. Clear research objectives and rationale for undertaking the investigation in human participants in the light of existing knowledge. Does the study address an important research question or is it a predominantly service proposal? If the objectives of the application will be achieved, how will scientific knowledge or clinical practice be advanced?
3. Participant recruitment procedures and inclusion and exclusion criteria for entry of participants. The characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status, and ethnicity) the means by which initial contact and recruitment is to be conducted; the means by which full information is to be conveyed to potential research participants or their representatives; inclusion criteria for research participants; exclusion criteria for research participants; students or staff recruitment in research; healthy volunteers; information contained in the advertisement and mode of its communication; final copy of printed advertisements; final audio or video taped advertisements.
4. Precise description of methodology of the proposed research, including sample size (with justification), type of study design (observational, experimental, pilot, randomized, blinded etc.), intended intervention, dosages of drugs, route of administration, duration of treatment and details of invasive procedures if any.
5. Plan to withdraw or withhold standard therapies in the course of research. Protocols using placebo requires careful consideration before approval. Denial of available treatment to control (placebo) arm of participants is unethical. The justification of predictable risks weighed against the anticipated benefits for the research participants and the concerned communities.
6. A statement on probable ethical issues and steps taken to tackle the same like justification for washout of standard drug, or the use of placebo control.
7. Plan for statistical analysis of the study.
8. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and local languages.
9. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory, animal and human research.
10. For research involving more than minimal risk, an account of management of such risk or injury.
11. Criteria for termination of a study must be defined in the protocol and plan of interim analysis must be clearly presented. This is important when on interim analysis the test drug is found to be clearly more effective or less effective than the standard drug. The study can be discontinued thereafter and better drug should be given to the patients receiving less effective drug. Also, in the event of safety concerns to the participants, the participants can be withdrawn from the study.
12. Proposed compensation and reimbursement of incidental expenses and management of research related and unrelated injury/ illness during and after research period.
13. An account of storage and maintenance of all data collected during the trial. The provisions made for monitoring and auditing the conduct of study and hence generating the data.
14. Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.
15. Agreement to comply with national and international Good Clinical Practices (GCP) protocols for clinical trials.
**EXAMPLE:** In studies where participants are randomly assigned to different groups (e.g., treatment A; treatment B; no treatment), ethical issues relevant to the principle of justice arise when one group may fair better or worse than another (placebo-controlled clinical trials). For this reason, clinical equipoise may be considered as a starting point for the design and review of clinical trials.

Clinical equipoise means a genuine uncertainty exists on the part of the relevant expert community about what therapy or therapies are most effective for a given condition. This uncertainty necessitates the conduct of research to determine the comparative therapeutic merits of existing interventions (not all of which may be represented in a given clinical trial). Clinical equipoise provides a link between the duty of care of a clinician with the need to do research to ensure that the therapies or interventions offered are demonstrably safe and effective.

### 18.4.2 INFORMED CONSENT FORM AND PATIENT INFORMATION SHEET

#### 18.4.2.1 CARE AND PROTECTION OF RESEARCH PARTICIPANTS

The IEC will assess the adequacy of safeguards of the rights and welfare of research participants, and the appropriate inclusion of women, minorities, and children, based on the information in the application. The IEC should evaluate the involvement of human subjects and proposed protections according to the following review criteria:

1. Risk to subjects
2. Adequacy of protection against risks
3. Potential benefits of the proposed research to the subjects and others.
4. Importance of the knowledge to be gained
5. Data and safety monitoring for clinical trials
6. Required qualifications and experience of the Investigators’ for the proposed study
7. Any plans to withdraw or withhold standard therapies for the purpose of the research, and the justification for such action
8. Plans to withdraw subjects from the study by the Investigator
9. Medical care to be provided to research participants during and after the course of the research
10. Adequacy of medical supervision and psycho-social support for the research participants
11. Steps to be taken if research participants voluntarily withdraw during the course of the research
12. Criteria for extended access to, the emergency use of, and/or the compassionate use of study products
13. Arrangements, if appropriate, for informing the research participant’s general practitioner or family doctor, including procedures for seeking the participant’s consent to do so
14. Description of any plans to make the study product available to the research participants following the research and description of any financial costs to research participants
15. Rewards and compensations for research participants (including money, services, and/or gifts)
16. Provisions for compensation/treatment in the case of the injury/ disability/ death of a research participant attributable to participation in the research (as per institutional policy/ ICMR guidelines/ existing national legislation (CDSCO)
17. Insurance and indemnity arrangements.
18. Translations for appropriateness of language, accuracy and completeness of information.

**18.4.2.2 PROTECTION OF RESEARCH PARTICIPANT CONFIDENTIALITY AND PRIVACY OF THEIR DATA**

A description of the information which should be given to participants and the persons who will have access to personal data of the research participants, including medical records and biological samples; and measures taken to ensure the confidentiality and security of personal information concerning research participants.

**18.4.2.3 INFORMED CONSENT FORM**

Every investigator should recognize the importance of obtaining valid and appropriate informed consent as an important protection of the rights and welfare of human subjects. Indeed, the very first principle of the Nuremberg Code, which represents the genesis of research ethics, states, “The voluntary consent of the human subject is absolutely essential.” Obtainment of informed consent involves both the process which is the consent dialogue and the documentation of obtaining informed consent on the IEC approved informed consent form (ICF).

One of the most advanced international guidelines on the informed consent process was put forth by the Council for International Organizations for Medical Sciences (CIOMS). The Organization’s commentary on Guideline states “obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in doing so manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others.” The CIOMS commentary further states “informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information...in language that suits the individual’s level of understanding...the investigator must then ensure that the prospective subject has adequately understood the information”.

One of the difficulties that investigators and other research personnel often encounter, both during and after the informed consent process, is “therapeutic misconception” which can literally render informed consent invalid. Therapeutic misconception can be defined as the situation where a subject or his/her Legally Acceptable Representative (LAR) either over-estimates the direct therapeutic benefits which may be gained by participation in the research and/or under-estimates the risks thereby compromising their ability to provide and/or maintain a voluntary and knowing informed consent. Research personnel who are The process of informed consent involved in the consent process should take all necessary steps to minimize the possibility that subjects will consent to participate in research because of therapeutic misconception.

Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability) the above information should be provided to the legally acceptable representative (LAR). If the subject or his/her legally acceptable representative is unable to read/write – an Impartial witness (IW) should be present during the entire informed consent process.
The Investigator has the duty to communicate to the subjects/LAR/IW, all the information necessary for informed consent. There should not be any restriction on subject’s right to ask any questions related to the study as any restriction on this undermines the validity of informed consent.

The required elements of informed consent (as listed below) should be presented and discussed with the prospective subject in a sequential manner utilizing the approved ICF as a guide. The presentation should be structured to facilitate a dialogue with reinforcement and elaboration of important information (e.g., the risks of the research). The person(s) involved in obtaining the subject’s consent should constantly evaluate whether the process is achieving the goal which is to obtain of legally effective informed consent from the subject. In addition to paying attention to general signs of information receptivity, it is often helpful to ask open-ended questions in order to identify points of confusion which require clarification.

18.4.2.3.1 Essential Elements

As per Appendix V of Schedule Y:

a. Statement that the study involves research and explanation of the purpose of the research
b. Expected duration of the Subject’s participation
c. Description of the procedures to be followed, including all invasive procedure and
d. Description of any reasonably foreseeable risks or discomforts to the Subject
e. Description of any benefits to the Subject or others reasonably expected from research.
   If no benefit is expected Subject should be made aware of this. 28
f. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
g. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject’s medical records
h. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
i. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
j. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
k. The anticipated prorated payment, if any, to the Subject for participating in the trial
l. Subject’s responsibilities on participation in the trial
m. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled
n. Any other pertinent information

18.4.2.3.2 Additional Elements, Which May Be Required

a. Statement of foreseeable circumstances under which the subject’s participation may be terminated by the investigator without the subject’s consent.
b. Additional costs to the subject that may result from participation in the study.
c. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by Subject.
d. Statement that the Subject or Subject’s representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.

e. A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or foetus, if the Subject is or may become pregnant), which are currently unforeseeable

f. Approximate number of Subjects enrolled in the study per site and the study.

18.4.2.3.3 AUDIO-VISUAL (AV) RECORDING

- Audio-visual recording of Informed Consent Process shall only be mandatory for cases where vulnerable population is involved & the trial is of New Chemical Entity or New Molecular Entity
- For clinical trials of Anti-HIV and anti-Leprosy drugs, only audio recording of the informed consent process shall be mandatory.
- The Investigator must provide the subject/LAR/IW with the information described in section 18.4.2.3 before signing the informed consent by the subject. The language of information should be non-technical and understandable by the study subjects/ LAR/ IW and the same shall be recorded through audio-visual means. Details of questions if any, asked by the subject/ LAR/ IW and his/her understanding on consent are also to be recorded through the audio video recording. The process of signing/ putting thumb impression by the subject/LAR/IW should also be video recorded.
- During the audio-visual recording of informed consent process, the identity and records of the trial subjects are as far as possible should be kept confidential.
- The Investigator must safeguard the confidentiality of trial data, which might lead to the identification of the individual subjects.
- The trial data of subjects can be disclosed only in a court of law under the orders of the presiding judge or in some cases may be required to communicate to Drug regulatory/ Health authority.
- To maintain the confidentiality, the videographer should also be recruited as part of the study team.
- Prior to initiation of the study, the Investigator should define and allocate the activities of audio-video recording of informed consent process to the respective identified person as videographer and should be mentioned in the study log of roles and responsibility of research staff.
- Prior consent of the subject should be taken for audio-visual recording of informed consent process and the same should be documented by the investigator. Such consent may be taken orally. Only those subjects who give the consent for the AV recording shall be included in the clinical trial.
- Audio-visual recording of informed consent process and other related documents should be preserved safely after the completion / termination of the study for at least a period of 5 years if it is not possible to maintain the same permanently.

18.4.2.4 ADVERTISEMENTS

The EC reviews advertising to ensure that advertisements do not:

1. State or imply a certainty of favourable outcome or other benefits beyond what is outlined in the consent document and the protocol
2. Include exculpatory language. Example: In the event that you suffer a research-related injury, your medical expenses will be covered by your medical insurance.
3. Emphasize the payment or the amount to be paid, by such means as larger or bold type
4. Promise “free treatment” when the intent is only to say participants will not be charged for taking part in the investigation
5. Advertisements are limited to the information prospective participants need to determine their eligibility and interest, such as: The name and address of the researcher or research facility, The purpose of the research or the condition under study, In summary form, the criteria that will be used to determine eligibility for the study
6. A brief list of benefits to participants, if any
7. The time or other commitment required of the participants
8. The location of the research and the person or office to contact for further information.

18.4.3 PROPOSAL INVOLVING VULNERABLE POPULATION AND SPECIAL GROUP

18.4.3.1 VULNERABLE GROUPS

Efforts may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed.

a. Research on genetics should not lead to racial inequalities;
b. Persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them;
c. Rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioural disorders must be protected. Appropriate proxy consent from the legal guardian should be taken after the person is well informed about the study, need for participation, risks and benefits involved and the privacy and confidentiality procedures. The entire consent process should be properly documented;
d. Adequate justification is required for the involvement of participants such as prisoners, students, subordinates, employees, service personnel etc. who have reduced autonomy as research participants, since the consent provided may be under duress or various other compelling reasons.
e. Individuals whose willingness to volunteer in a research study may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate may also be considered vulnerable. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention.

Vulnerable subjects include as listed below:

a. Persons who are economically or socially disadvantaged
b. Mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders
c. Prisoners, students, subordinates, employees, service personnel etc. who have reduced autonomy as research subjects.

18.4.3.2 RESEARCH INVOLVING CHILDREN
EC shall ensure the following while reviewing the research proposal involving children:

- Children will not be involved in research that can be carried out equally well with adults.
- The purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase 3 clinical trials in adults.
- For studies prior to phase 3 the drug has a therapeutic value in a primary disease of the children.
- The settings of the research provide the child and parent adequate medical and psychological support.
- Interventions intended to provide direct diagnostic, therapeutic, or preventive benefit for the individual child participants must be justified in relation to potential risks involved in the study and potential benefits to society.
- The risk presented by interventions not intended to benefit the individual child participant is low when compared to the importance of the knowledge that is to be gained.
- Interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child participant as any available alternative interventions.
- A parent or legal guardian of each child has given proxy consent.
- The assent of the child should be obtained to the extent of the child’s capabilities such as in the case of mature minors or adolescents, unless there is no medically acceptable alternative to the therapy provided or tested, and consent has been obtained from at least one parent or guardian.

### 18.4.3.3 Research Involving Adults Unable to Consent

If research involves adults unable to consent, the ethics committee must consider additional safeguards to protect their rights and welfare: when conducting non-therapeutic research, consent must be obtained directly from the participant, unless:

- The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally. The foreseeable risks to the participants are low.
- The negative impact on the participant’s wellbeing is minimized and low.
- The clinical trial is not prohibited by law.
- The opinion of the ethics committee is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

When adults are unable to consent, the IEC shall ensure that a non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written consent document.

Non-therapeutic clinical trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
• The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally.
• The foreseeable risks to the participants are low.
• The negative impact on the participant’s wellbeing is minimized and low.
• The clinical trial is not prohibited by law.
• The opinion of the IEC is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.
• Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

18.4.3.4 Research Involving Pregnant and Nursing Women

The following is required when pregnant or nursing women are enrolled in research:

• Pregnant or nursing women should in no circumstances be the participant of any research unless the research carries no more than minimal risk to the foetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation.
• As a general rule, pregnant or nursing women should not be participants of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable participants.
• Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast-feeding to the nursing child should be properly assessed except in those studies where breast feeding is harmful to the infant. Compensation in terms of supplying supplementary food such as milk formula should be considered in such instances.

The justification for participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting foetal abnormalities and for conditions associated with or aggravated by pregnancy etc.

18.4.3.5 Research Related to Termination of Pregnancy

Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made participants for such research as per The Medical Termination of Pregnancy Act, Government of India, 1971.

18.4.3.6 Research Related to Pre-Natal Diagnostic Techniques

In pregnant women such research should be limited to detect the foetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, Government of India, 1994 and not for gender determination.

If the research includes a vulnerable population that is not covered in the above list or there are no national or international guidelines for ensuring protections. IEC shall evaluate the research proposal to ensure that they consider precaution to protect such participants.
18.4.4 CONSIDERATIONS WHILE REVIEWING THE STUDY

The qualifications of the Investigator should be considered when reviewing proposals. The Investigator’s professional competence should be taken into account and related to the degree of protocol complexity and risk to human subjects. IECs may require less experienced research investigators to be supported by seasoned researchers. Proposals that require skills beyond those held by the Investigator should be modified to meet the Investigator’s skills, have additional qualified personnel added, or be disapproved.

Investigators shall prepare protocols giving complete descriptions of the proposed research. The research plan must include provisions for the adequate protection of the rights and well-being of prospective subjects and ensure that pertinent laws and regulations are observed. Samples of informed consent documents must be included with protocols. Investigators are responsible for obtaining informed consent and ensuring that no human subject will be involved in the research prior to obtaining the consent.

External standards are of particular concern for research conducted in clinical facilities. Appropriate reviews for scientific merit must be conducted before the research is approved. Mechanisms for monitoring the progress of the research must be in place.

Investigators, through their research design, determine whether the proposed research will involve human subjects. Some IECs, for example, require that all research protocols involving human subjects be submitted to the IEC for review. The IEC then determines whether the research is exempted from IEC review under the applicable regulations and institutional policies, and whether full or expedited IEC review is appropriate.

Other points to consider are:

- Does the investigator have the appropriate qualifications, experience, and facilities to ensure that all aspects of the project and follow-up will be conducted rigorously and with due regard for the safety and well-being of the subjects?

- Are adequate procedures in place through which the researcher will monitor the project and report problems to the IEC?

- What is the Investigator’s past record with regard to approved research?

Researchers are responsible for complying with all the IEC decisions, conditions, and requirements. Investigators are responsible for reporting the progress of the research to the IEC and/or appropriate institutional officials as often as and in the manner prescribed by the IEC but no less than once per year.

18.5 FULL BOARD REVIEW

All research presenting with more than minimal risk, proposals/protocols that do not qualify for exemption from review or expedited review, and projects that involve vulnerable persons such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons shall be subjected to a full review.

Minimal risk would be defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of the general population or during
the performance of routine physical or psychological examinations or tests. However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant undergoing these interventions since it would be undertaken as part of current everyday life.

Research proposals that have undergone expedited review and are referred to full board as no decision could be reached.

While reviewing the proposals, the following situations may be carefully assessed against the existing facilities at the research site for risk/benefit analysis:

1. Collection of blood samples by finger prick, heel prick, or venepuncture:
   - From healthy adults and non-pregnant women who weigh normal for their age and not more than 500 ml blood is drawn in an 8 week period and frequency of collection is not more than 2 times per week
   - From other adults and children, where the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected has been considered and not more than 50 ml or 3 ml per kg, whichever is lesser is drawn in an 8 week period and not more than 2 times per week;
   - From neonates depending on the haemodynamics, body weight of the baby and other purposes not more than 10% of blood is drawn within 48 - 72hours. If more than this amount is to be drawn it becomes a risky condition requiring infusion/blood transfusion;
   - Prospective collection of biological specimens for research purposes by noninvasive means. For instance:
     a) Hair and nail clippings in a non-disfiguring manner
     b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction
     c) Permanent teeth, if routine patient care indicates a need for extraction
     d) Excreta and external secretions (including sweat)
     e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax, or by applying a dilute citric solution to the tongue
     f) Placenta removed at delivery
     g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labour
     h) Supra- and sub-gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques
     i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings
     j) Sputum collected after saline mist nebulization.

2. Collection of data through non-invasive procedures routinely employed in clinical practice. Where medical devices are employed, they must be cleared/approved for marketing, for instance -

   - Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy
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- Weighing or testing sensory acuity
- Magnetic resonance imaging
- Electrocardiography, echocardiography; electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow
- Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

3. Research involving clinical materials (data, documents, records, or specimens) that will be collected solely for non-research (clinical) purposes.

4. Collection of data from voice, video, digital, or image recordings made for research purposes.

5. Research on individual or group characteristics or behaviour not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behaviour or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

18.5.1 STUDY REVIEW APPLICATION PROCESS

The copies of the protocols/documents shall be sent to the IEC members by either electronic mail (in case of electronic submission of protocols) or by courier of hard copies and CD (soft copy) preferably 4 weeks in advance of the scheduled meeting.

The members will review the documents and use assessment form as a checklist while reviewing each research project.

The duly filled, signed and dated assessment forms shall be returned to the IEC office prior to meeting.

18.6 EXPEDITED REVIEW

Proposals that involve no more than minimal risk and those that do not satisfy the criteria for exemption will be eligible to apply for expedited review.

The Secretary and the Chairperson or designated member of the Committee may do expedited review only if the protocols involve:

- Deviations from originally approved research during the period of approval (usually of one year duration) which do not affect the safety of research participants.

- Proposal previously approved through full review by the IEC or continuing review of approved proposals where there is no additional risk or activity is limited to data analysis.

- Research activities that involve only procedures listed in one or more of the following categories:
- Clinical studies of drugs and medical devices only when research is on already approved drugs except when studying drug interaction or conducting trial on vulnerable population
  - Adverse Event (AE) or unexpected Adverse Drug Reaction (ADR) of minor nature is reported

- Research involving clinical materials (data, documents, records, or specimens) that have been collected for non-research (clinical) purposes.

- When in emergency situations like serious outbreaks or disasters a full review of the research is not possible, prior written permission of IEC may be taken before use of the test intervention. Such research can only be approved for pilot study or preliminary work to study the safety and efficacy of the intervention and the same participants should not be included in the clinical trial that may be initiated later based on the findings of the pilot study.

- Research on interventions in emergency situation –
  - When proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, physicians may use new intervention as investigational drug (IND)/ devices/ vaccine to provide emergency medical care to their patients in life threatening conditions.

- Research in such instance of medical care could be allowed in patients
  - When consent of person/ patient/ responsible relative or custodian/ team of designated doctors for such an event is not possible. However, information about the intervention should be given to the relative/ legal guardian when available later

- When the intervention has undergone testing for safety prior to its use in emergency situations and sponsor has obtained prior approval of CDSCO

- Only if the local IEC reviews the protocol since institutional responsibility is of paramount importance in such instances

- If Data Safety Monitoring Board (DSMB) is constituted to review the data

- Research on disaster management (A disaster is the sudden occurrence of a calamitous event at any time resulting in substantial material damage, affecting persons, society, community or state(s). It may be periodic, caused by both nature and humans and creates an imbalance between the capacity and resources of the society and the needs of the survivors or the people whose lives are threatened, over a given period of time. It may also be unethical sometimes not to do research in such circumstances. Disasters create vulnerable persons and groups in society, particularly so in disadvantaged communities), the following points need to be considered when reviewing such research:

  - Research planned to be conducted after a disaster should be essential culturally sensitive and specific in nature with possible application in future disaster situations.

  - Disaster-affected community participation before and during the research is essential and its representative or advocate must be identified.
• Extra care must be taken to protect the privacy and confidentiality of participants and communities.

• Protection must be ensured so that only minimal additional risk is imposed.

• The research undertaken should provide direct or indirect benefits to the participants, the disaster-affected community or future disaster-affected population and a priori agreement should be reached on this, whenever possible, between the community and the researcher.

• All international collaborative research in the disaster-affected area should be done with a local partner on equal partnership basis.

• Transfer of biological material, if any, should be as per Government rules taking care of intellectual property rights issues.

18.6.1 PROCEDURE FOR EXPEDITED REVIEW

It is the responsibility of the Investigator to:

• Indicate in the application for review if he/she believes it qualifies for expedited review; indicate the category under which the review qualifies for expedited consideration
• In the case of minor protocol amendments of approved research studies clearly specify the amendments that need expedited review.

The Chairperson will decide whether the proposal satisfies the criteria for expedited review. The guidelines for review are same as those to be followed for full review. If required, expert opinion may be sought, keeping in mind confidentiality, but the expert will not play any role in making the final decision. Chairperson frames a subcommittee for expedite review which reviews the study within 5 days of protocol submission to IEC. Expedite review should not take longer than 2 weeks.

The decision of the expedited review is to be sent in writing by the Secretary to the investigator. A list of all research proposals approved using expedited review procedures is provided to the IEC at its next convened meeting. A record must be maintained of category under which the expedited review was justified.

18.7 EXEMPTION FROM REVIEW

18.7.1 CATEGORIES FOR EXEMPTION

Proposals which present less than minimal risk fall under this category as may be seen in following situations:

• Research on educational practices such as instructional strategies or effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

18.7.1.1 EXCEPTIONS

1. When research on use of educational tests, survey or interview procedures, or observation of public behaviour can identify the human participant directly or through
identifiers, and the disclosure of information outside research could subject the participant to the risk of civil or criminal or financial liability or psychosocial harm.

2. When interviews involve direct approach or access to private papers.

18.7.2 **Procedure for Exemption from Review**

- It is the responsibility of the Investigator to identify the application for review, the exemption he/she believes is applicable to the research under consideration.
- Provide a justification for the exemption(s) with sufficient information about the involvement of human subjects to allow a sufficient assessment that the claimed exemption(s) is appropriate.
- A brief description of the proposal (adequate to evaluate risks to subjects and explain criteria under which exemption is applied for) and the full proposal (with copies of all instruments to be used, informed consent form) is to be submitted to the Secretary.
- The proposal shall be screened by the Secretariat for completeness and sent to the Chairperson.
- The Chairperson will decide whether the proposal satisfies the criteria for exemption from review. The IEC members can request the Investigator for clarifications on the proposals if required.
- If the IEC agrees that the proposal should be exempt from IEC review, the Secretary records IEC's decision and thereafter notifies the Investigator in writing.
- If there is a disagreement between reviewers regarding the exemption, and the proposal cannot be exempt from review, a recommendation for expedited review or full review shall be made.

18.8 **Continued Review**

The ethics approval is provided to a proposal only for a limited time period, usually for a period of one year. In order to renew approval the Investigator shall be required to request for a Continuing Review of the proposal and submit the annual report of the trial.

The procedure for continue review takes the following into consideration:

- Documents to be reviewed, including but not limited to: progress reports (no of participants recruited, their follow ups, protocol deviation), final report, safety reports, audit reports independent of the research and the sponsor (e.g. institutional internal audits)
- Experiences of the participants and potential participants (e.g. independent observation of the informed consent discussion, independent surveys of participants experiences)
- Notification from the applicant with regard to suspension/premature termination or completion of the study
- Quorum requirements, and communication procedure for continue reviews, which may vary from requirements and procedures for the initial review of the application
- The intervals for continue reviews, which should be determined by the nature of the research project but should generally be at least once a year
- Circumstances that will trigger follow-up reviews, in addition to those that are regularly scheduled, including the following:
  - Any protocol amendment likely to affect the rights, safety, and/or well-being of the research participants or the conduct of the study
- Serious unexpected adverse events related to the conduct of the study or study product
- Any event or new information that might affect the potential benefits or risks of harm involved in the study
- Decisions made by a data safety monitoring board (DSMB) or other monitoring or regulatory authorities to suspend a study in whole or in part

### 18.8.1 Procedure for Continued Review

The Secretariat will look through the master file of projects approved by the IEC for the due date of continuing reviews. The Secretary should receive the continuing review application well in advance i.e. 10 months after IEC final approval and at least annually.

Reminder notices are sent to the Investigator in writing/email one to two months before the expiration date of each protocol approval. Investigator is requested to submit the completed study status report along with a copy of the current Informed Consent.

Investigator should submit hard copies of the report and a soft copy.

The Secretary will receive and verify the contents of the Continuing Review Application submitted by the Investigator for each approved study.

The report must be reviewed and approved by the IEC prior to the expiration of the previous study approval. If approval is given, an e-mail/letter is sent to the Investigator, and the continuing review expiration date is updated for another term’s approval.

EC members could arrive at any one of the following decisions at the IEC meeting:

- Approval to continue the study; or not approved
- Approved with modifications: Studies for which modifications have been suggested by the IEC cannot proceed until the conditions set by the IEC have been met. Studies should be amended and submitted to the IEC within one month for re-review
- Not Approved

The decision will also include any significant findings that have arisen during review process and this will be communicated to Investigator. It is the responsibility of Investigator to provide this information to the participants and once done submit the report to IEC.

The decision regarding the approval/recommended modifications/disapproval will be noted and documented in the minutes of the meeting is recorded by the Secretary.

The Secretary will maintain minutes of the meeting relevant to the continuing review as part of the official record of the review process.

A decision resulting from a continued review should be issued and communicated to the applicant, indicating either that the original decision is still valid or that there has been a modification, suspension, or withdrawal of the IEC’s original decision.

If the study is not approved by the date specified, the study approval automatically expires and all research must stop including recruitment, advertisement, screening, enrolment, consent, interventions, interactions, and collection of private identifiable information until
approval of the study. There is no grace period. Interventions and interactions on current participants may continue only when the IEC finds an over-riding safety concern or ethical issue involved such that is in the best interest of individual participants. Under no circumstances can enrolment of new participants occur.

The Secretariat shall send reminder notice by email to the Investigators prior to expiration date. If there is still no response, a letter is then sent to the Investigator with copies distributed to the Head of Institute, and funding agency if applicable. At that point, the study approval expires, the study is closed and any data collected during expiration must not be included. A new application will then be required before work can commence again. Patterns of non-compliance by the Investigator can trigger formal inquiries by the IEC.

In addition to required Protocol Status Reports, the IEC may conduct other types of post-approval reviews including, but not limited to, self-assessment by the Investigator, document review by IEC staff, interview with the Investigator, interview with research staff and surveys of past participants.

18.9 AMENDMENTS AND REVISIONS

Any proposed change or revision to a currently approved study that affects human participants must be reviewed and approved by the IEC prior to the implementation of that change. Only administrative changes do not require approvals, but they must be notified to IEC.

A change which require approval is one which, in the judgment of the IEC reviewer, makes substantial alteration in:

- The level of risks to participants and hence may involve increased risk to participants or that substantially change the nature of the study
- The research design or methodology such as replacement of or significant changes to study instruments including surveys and questionnaires or adding/revising eligibility criteria or changes to the study population
- The number of participants enrolled in the research
- The informed consent to include a newly identified risk related to the study (this may require that participants sign a new consent form)
- The qualifications of the research team
- The facilities available to support safe conduct of the research
- In advertisement
- Addition or deletion of sites (due to non-recruitment or SAE, fraud and misconduct)
- Any other factor, which would warrant review of the proposed changes by the convened IEC. In addition, revised procedures must involve no more than minimal risk, and

Some examples of administrative changes are: changes in telephone numbers; addition/deletion of associates or staff; the deletion of questions in a survey; changes in funding; alteration of the project title; addition or deletion of Investigators.

18.10 DECISION MAKING PROCESS

The IEC should be able to provide complete and adequate review of the research proposals submitted to them. It should meet periodically to review new proposals, evaluate annual progress of ongoing ones, review SAE reports and assess final reports of all research activities
involving human beings through a previously scheduled agenda. The following points should be considered while doing so:

1. The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend / reject / suggest modification for a repeat review or advice appropriate steps. The Secretariat should communicate the decision in writing to the Investigator.

2. If a member has conflict-of-interest (CoI) involving a project then s/he should submit this in writing to the chairperson before the review meeting, and it should also be recorded in the minutes.

3. If one of the members has her/his own proposal for review or has any CoI then s/he should withdraw from the IEC while the project is being discussed.

4. A negative decision should always be supported by clearly defined reasons.

5. An IEC may decide to reverse its positive decision on a study if it receives information that may adversely affect the risk/benefit ratio.

6. The discontinuation of a trial should be ordered if the IEC finds that the objectives of the trial have already been achieved midway or unequivocal results are obtained.

7. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.

8. The following circumstances require the matter to be brought to the attention of IEC:
   - Any amendment to the protocol from the originally approved protocol with proper justification;
   - Serious and unexpected adverse events and remedial steps taken to tackle them;
   - Any new information that may influence the conduct of the study.

9. If necessary, the applicant/Investigator may be invited to present the protocol or offer clarifications in the meeting. Representative of the patient groups or interest groups can be invited during deliberations to offer their viewpoint.

10. Subject experts may be invited to offer their views, but should not take part in the decision making process. However, her / his opinion must be recorded.

11. Meetings are to be minuted which should be approved and signed by the Chairperson/alternate Chairperson/designated member of the committee.

**18.11 DOCUMENTATION OF REVIEW**

The proceedings of all meetings shall be documented and shall be kept in confidence. The IEC Coordinator/Secretariat shall securely maintain the documentation.

The IEC shall undertake the review of proposals at its meetings. After the discussion the committee may make one of the following recommendations:

- **Approval** - indicating that the proposal is approved as submitted;

- **Conditional Approval** - indicating that the proposal is approved in principle, subject to the submission of certain clarifications, minor revisions or additional documents. In this case, the investigator may have to satisfy certain conditions set out by the IEC. This may include the submission of certain documents. The duration of time by which the investigator responds needs to be specified in the approval letter – and in no case should exceed 3 months. The study can only begin once the Secretary issues an approval letter.
• **Approval after amendment(s)** - indicating that the proposal is approved subject to the incorporation of the specified amendment(s) verified by committee members.

• **Deferment** - indicating that the proposal is not approved as submitted but it can be re-assessed after revisions, justifications or additional information to address the specified reason(s) for deferment. The issues of concern are usually of a fundamental nature (e.g. with regard to the risk/benefit ratio or issue related to participant protection). However, resubmitted proposals will go under expedited review.

• **Disapproval** - indicating that the proposal is not approved because members' concerns for the protection of the participants have not been satisfactorily addressed even after the revision. Regardless of the reason for rejection, the IEC must invite the PI to present her/his views/justification and the same are discussed by the members of the IEC with the PI, and also among themselves. The rejection letter should explain the reasons underlying the IEC decision. In case the applicant considers the reasons for disapproval contentious, he/she may appeal for reconsideration providing justification for appeal. The same application may be reconsidered if the chairperson believes there is sufficient evidence for the recommendation to be revised.

The deliberations and decisions made during the meetings should be documented, approved, signed and maintained as minutes of meeting. The decision should be notified to investigator in writing.

**18.12 NOTIFICATION OF AMENDMENTS TO RESEARCH PROPOSALS**

The investigator should not implement major amendments until they have been reviewed and the decision of the IEC conveyed to the investigator in writing. An exception to this situation is when an immediate change is essential to prevent apparent hazards to research subjects. The IEC may then be informed as soon as possible of the change that will be reviewed taking usual considerations into account. In other situations the procedure is as follows:

Amendments may also be requested at the time the follow-up report is submitted. The procedure for submission of the follow-up report is as detailed below. The original proposal must be resubmitted with the proposed changes (in addition to the follow-up report if submitted as part of this). An attached list should however mention the changes proposed and the sections and page numbers in the protocol where these have been detailed. The original proposal needs to remain unmodified with additions and justifications of changes in the appropriate sections, being clearly marked so as to be distinguishable from the original. In the situation where the amendments are sufficiently many/substantive enough to cause fundamental alterations to the protocol, the IEC may recommend the rewriting of the proposal.

When considering the amendments, the IEC may ask for fresh or re-consent to be taken under the following conditions:

• Availability of new information that necessitates deviation from the earlier protocol.
• When a research participant regains consciousness from an unconscious state or is mentally competent to understand the study. If such an event is expected then procedures to address it should be spelt out at the start itself in the informed consent form.
• In case of studies where a long term follow-up or extension is planned.
• When there are changes to the modality of treatment/procedures/site visits.
If there is possibility of disclosure of identity through data presentation or photographs that should be camouflaged adequately) in publications, the fresh/re-consent is to be taken prior to publication.

The decision on approval/change of status of technical/ethics approval if any given the proposed amendments, and if necessary, the requirement for a full ethics review, will be conveyed in writing to the Investigator by the Secretary.

To apply for approval of a revision, submit an Amendment/Modification form by to the IEC Office and described on the Amendment/Modification form. Approval of a revision does not change the approval or expiration date of the protocol. It merely approves the modification to the study and allows the PI to begin using the modified or new procedures/documents. The PI must receive the approved Amendment/Revision form from the IEC Office prior to implementing the new changes.

18.13 MONITORING

Once IEC gives a letter of approval it is the duty of the IEC to monitor the approved studies, therefore an oversight mechanism should be in place. Actual site visits can be made especially in the event of reporting of adverse events or violations of human rights. IEC should monitor site for all approved studies at least once. During the site visit, source documents, Case report forms (CRF), Investigation product (IP) storage, informed consent process and SAE management can be reviewed.

Additionally, periodic status reports must be asked for an appropriate intervals based on the safety concerns. SAE reports from the site as well as other sites are reviewed by IEC and appropriate action taken when required. In case the IEC desires so, reports of monitoring done by the sponsor and the recommendations of the DSMB may also be sought.

IEC should document all the findings and suggestions during the site visit and report should be shared with the investigator. And a follow up of corrective actions should be done with the investigator and should be documented and presented during the next IEC meeting.

19 NON-COMPLIANCE BY INVESTIGATORS, SITE AND IEC

19.1 INVESTIGATORS

The common lapses in Investigator compliance may include unreported changes in protocols, misuse or non-use of the informed consent document, and failure to submit protocols to the IEC in a timely fashion. Problems such as these are often caused by communication difficulties.

Occasionally, an Investigator will either avoid or ignore an IEC. Such cases present a more serious challenge to the IEC and to the institution. Regardless of Investigator intent, unapproved research involving human subjects places those subjects at an unacceptable risk. When unapproved research is discovered, the IEC and the institution should act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the Investigator's fitness to conduct human subject research. Beyond the obvious need to protect the rights and welfare of research subjects, the credibility of the IEC is clearly at stake.
The IEC is required to inform the Head of the Institution and the Licensing Authority immediately of non-compliance by the Investigator and harming the subjects.

19.2 SITE/ INSTITUTION

Although institutions are accountable for the actions of individual Investigators and the IEC, institutional noncompliance is more broadly described as a systemic failure of the institution to implement practices and procedures. Prime examples are the failure of the institution to ensure that the IEC is appropriately constituted and functions in accordance with the regulations, that the IEC receives appropriate institutional support and staffing, and that Investigators meet their obligations to the IEC.

19.3 IEC

IEC non-compliance occurs whenever the IEC deviates from the duties imposed upon it by the regulations. Such deviations include the inadequate review of research protocols by failing to ensure that the consent document and process provide sufficient information to allow prospective subjects to make an informed decision whether to participate in the research; failing to ensure that the research design includes adequate monitoring of the data and any additional safeguards necessary to protect the welfare of particularly vulnerable subjects; and failing to conduct continuing review of research at intervals appropriate to the degree of risk.

IECs also breach their regulatory responsibilities by failing to maintain adequate records of IEC business and to hold their meetings with a majority of members present, including a non-scientific member.

20 NOTIFICATION OF ADVERSE EVENTS/ SERIOUS ADVERSE EVENTS

Any untoward medical occurrence (including a symptom/ disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given.

An AE or ADR that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (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.

An adverse reaction, the nature or severity of which is not consistent with the applicable product information, is unexpected AE.

An adverse event is considered to be associated with the research intervention if there is a reasonable possibility that the reaction may have been caused by the research intervention (i.e., a causal relationship between the reaction and research intervention has a reasonable likelihood).

All serious, unexpected and associated events shall be notified to the Ethics committee as per the 122 DAB rule in the Drugs and Cosmetics Rules 1945.

In case of SAE, the chairperson may decide to call an emergency meeting and discuss the SAE(s).
Following are the possible decisions that the committee may take regarding the continuation of the study:

- Continue without protocol changes
- Continue with protocol amendments
- Put the study on hold with a methodical withdrawal of suspected treatment(s) till the cause of events is identified. Such decision may be revised in a subsequent emergency meeting
- Termination of the study
- Opinion on financial compensation

20.1 GUIDING PRINCIPLES

- If the serious events are a result of breach of protocol, the committee may recommend disciplinary action against those responsible while allowing the continuation of the study without changes in the protocol.

- If the research intervention has a reasonable possibility of being the cause of the serious events in question, the study must be put on hold with a systematic reversal, safeguarding the health and well-being of the subject while the cause is being determined. After the cause is identified, the study may continue with appropriate changes in the study protocol or the committee may recommend termination as appropriate.

- If the event leads to an SAE, the clinical trial participants shall be given the compensation as per the 122 DAB rule in the Drugs and Cosmetics Rules 1945

- If statistical significance of endpoints has been reached and meaningful inferences can be drawn, termination of the study should be considered.

- If the cause of events cannot be ascertained and the seriousness of adverse events is such that continuation of the study may pose a significant threat to life or may cause permanent disability, the committee is obliged to recommend termination.

- If the sponsor and the Investigators desire termination, the same may be recommended noting the specific reasons for termination as provided by them.

- In case of Death occurring to the clinical trial subject, Investigator will report all the serious adverse events to IEC, sponsor and CDSCO within 24 hours of occurrence of the event. Sponsor will submit the detailed report of SAE to IEC, CDSCO and Head of Institute within 14 calendar days of occurrence of the SAE. The investigator will also submit the detailed report of SAE to IEC, CDSCO and Head of Institute within 14 calendar days of occurrence of the SAE. The IEC shall forward it’s report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the sponsor or his representative within 30 calendar days of the occurrence of the SAE (a lay out of SAE timelines is presented in Annexure 2).

- CDSCO will send all reports (Investigator, IEC, Sponsor) to Expert committee (in case of SAE of Death)

- The timeline of Expert Committee to give its recommendation to CDSCO are 105 calendar days (CD) of the occurrence of the serious adverse event of death.
• The order of CDSCO on the quantum of compensation to be paid by sponsor (for SAE of death and other than death) will be sent within 150 CD of occurrence of serious adverse event by CDSCO to Sponsor.

• Sponsor will pay the compensation to subject within 30 calendar days of order from CDSCO.

21 ASSESSMENT OF RELATIONSHIP OF SAE(S) & ADVERSE EVENTS TO CLINICAL TRIAL

Causality is the relationship between two events (the cause and the effect), where the second event (effect) is a consequence of the first (cause).

The causality assessment is a systematic review of the data to determine the likelihood of a causal association between the event and investigational product. While classifying relationship of adverse event to the treatment, these adverse events are rarely “certain” or “unlikely”, most of the times they are somewhere in between these two extremes. Many systems have been developed to harmonize the causality assessment, however the reliable quantitative relationship is not precise.

WHO-UMC causality categories are as given in table below:

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
</tr>
</thead>
</table>
| Certain                   | • Event or laboratory test abnormality, with plausible time relationship to drug intake  
• Cannot be explained by disease or other drugs  
• Response to withdrawal plausible (pharmacologically, pathologically)  
• Event definitive a recognized pharmacological phenomenon  
• Re-challenge satisfactory, if necessary |
| Probable/Likely           | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
• Unlikely to be attributed to disease or other drugs  
• Response to withdrawal clinically reasonable  
• Re-challenge not required |
| Possible                  | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
• Could also be explained by disease or other drugs  
• Information on drug withdrawal may be lacking or unclear |
| Unlikely                  | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)  
• Disease or other drugs provide plausible explanations |
| Conditional/Unclassified  | • Event or laboratory test abnormality  
• More data for proper assessment needed, or  
• Additional data under examination |
| Un-assessable/Unclassifiable | • Report suggesting an adverse reaction  
• Cannot be judged because information is insufficient or contradictory  
• Data cannot be supplemented or verified |

The information about the adverse event may be adequate or inadequate. Even with the adequate information, precision of causality is largely determined by the expertise, experience
and skills of reviewers. It may be possible that there will be more than one conclusion on causality by the same reviewers. The IEC shall design a checklist to assemble information on the participant-investigational product-event relationship.

The information should be sought for following key areas:

- Evidence of other causes
- Evidence against a causal relationship
- Other qualifying factors for classification such as the background rate of the event, present and past medical history and health conditions, potential risk factors, medication, biological plausibility, etc.

22 FORMULA FOR COMPENSATION

22.1 QUANTUM OF COMPENSATION IN CASE OF CLINICAL TRIAL-RELATED DEATHS

22.1.1 AGE OF THE SUBJECT

The factor ranges from 99.37 (for age of 65 or more) to 228.54 (of age not more than 16) depending upon the age of the injured. The table of the Workmen Compensation Act is at Annexure 3.

22.1.2 RISK FACTOR

Risk factor depends on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial.

Risk factor is divided in a scale of 0.50, 1.0, 2.0, 3.0 and 4.0. However in case of patients whose expected mortality is 90 % or more within 30 days, a fixed amount of Rs. 2,00,000 may be given. The five grade of the scale is divided as follows:

- 0.5 Terminally ill patient (expected survival not more than 6 months)
- 1.0 Patient with high risk (expected survival between 6 to 24 months)
- 2.0 Patient with moderate risk
- 3.0 Patient with mild risk
- 4.0 Healthy Volunteers or subject of no risk

22.1.3 BASE AMOUNT

A base amount of Rs. 9.0 Lakhs is kept. It is evident that the base amount will increase/change with the revision of minimum wage.

Computing the 3 factors viz. Age, Risk and Base amount, following formula is suggested by CDSCO for deciding the quantum of compensation in case of SAE (death) related to clinical trial:

\[
\text{Compensation} = B \times F \times R \\
99.37
\]

Legend:

- B = Base amount (i.e. Rs. 9 Lakhs)
• \( F = \text{Factor depending on the age of the subject based on Workmen Compensation Act} \)
• \( R = \text{Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4} \)

**NOTE:** However, in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of Rs. 2 lakhs should be given.

### 22.2 QUANTUM OF COMPENSATION FOR SAE OTHER THAN DEATH

#### 22.2.1 TRIAL RELATED SAE CAUSING PERMANENT DISABILITY TO THE SUBJECT

\[
\text{Compensation} = \frac{(D \times 90 \times C)}{100 \times 100}
\]

\( D = \% \text{ of Disability} \)
\( C = \text{Quantum of Death compensation as calculated above} \)

#### 22.2.2 TRIAL RELATED SAE CAUSING CONGENITAL ANOMALY OR BIRTH DEFECT

Compensation in such cases should be a lump sum amount such that if that amount is kept by way of fixed deposit or alike, it should bring a monthly interest amount which is approximately equivalent to half of minimum wage of the unskilled worker (in Delhi). Hence, the Committee decided that quantum of compensation in such cases of SAE should be half of the base amount as per formula for determining the compensation for SAE resulting into death.

In case of **deformity that can be corrected fully & permanent mental or physical disability, the medical management as long as required** would be provided by sponsor or his representative that will be over and above the financial compensation.

#### 22.2.3 TRIAL RELATED SAE CAUSING LIFE-THREATENING DISEASE

\[
\text{Compensation} = 2 \times N \times W
\]

- \( N = \text{No of days the subject under life threatening Situation requiring medical care, irrespective of number of days of hospitalization} \)
- \( W = \text{Minimum Wages per day of Unskilled worker (in Delhi)} \)

#### 22.2.4 TRIAL RELATED REVERSIBLE RESOLVED SAE

\[
\text{Compensation} = 2 \times N \times W
\]

- \( N = \text{No of days of hospitalization} \)
- \( W = \text{Minimum Wages per day of Unskilled worker} \)

The minimum wages per day of unskilled worker in Delhi are available at website of Ministry of labor, Delhi Govt. The URL of website is given below:

http://www.delhi.gov.in/wps/wcm/connect/doit_labour/Labour/Home/Minimum+Wages/

**NOTE:** In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of non-permanent injury and loss of wages of the subject.
An excel sheet is provided in Annexure 4 to calculate the quantum of compensation.

23 MAINTENANCE AND ARCHIVAL OF FILES

- A Study Master File is the file comprising all essential documents and correspondence related to the study/protocol. Study files should be established at the time of initial submission in the EC office.

- The study files are assigned unique identifiers (serial project no.)

- All documents related to the study file are gathered, classified and combined together appropriately.

- All active files are kept in a secured file cabinet with controlled access. Only authorized individuals' i.e. Secretary/Chairperson, will have access to the files.

- The study files are maintained in an easily accessible and secure place for at least 5 years after the study closure.

- All closed study files shall be separately archived.

- The completed/closed project files will be stored in archive boxes that are clearly labelled with the project number and title, name of PI and disposal date. The archive boxes will be sent to a secure, dry location. The access to the files should be restricted to the IEC and the regulatory authorities. The details of the archiving location should be recorded in a location register stored in the IEC office. This register should record the project number and title, name of PI and the disposal date.

24 DISPOSAL OF FILES

The study file will be maintained in the IEC office for a period of five years following closure of the study. After completion of the archival period the closed files will be shredded and disposed off. However, all the copies of the research projects and documents submitted for IEC review shall be shredded by the authorized IEC personnel after the IEC meeting without any notification to the PI. A logbook of disposed documents will be maintained.

25 DISSOLUTION OF COMMITTEE

The committee shall be considered non-functional and dissolution considered in the following instances:

- No meeting is convened for a continuous period of 12 months

- Meeting attendance is below 5 independent members for four consecutive meetings

26 AMENDING SOP

Any amendments to the SOP shall be approved under the same procedure as for other proposals under the preview of IEC.

27 REFERENCES

1. Schedule Y of the Drugs and Cosmetics Act
2. ICMR Ethical Guidelines
3. CDSCO-GCP
4. WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants
5. WHO-UMC system for standardized case causality assessment
6. Causality Assessment of an Adverse Event Following Immunization (AEFI). User manual for the revised WHO classification

28 ANNEXURES

Annexure-1: Checklist for Submission of Applications for Registration of Ethics Committee
Annexure-2: Lay out for timelines of SAE reporting
Annexure-3: Excel sheet for compensation calculation