CHAPTER II

ETHICAL REVIEW PROCEDURES

The need for evaluation of research proposals has been emphasized under the Statement of General Principles at item no. 5 pertaining to precaution and risk minimisation. It is mandatory that all proposals on biomedical research involving human participants should be cleared by an appropriately constituted Institutional Ethics Committee (IEC), also referred to as Institutional Review Board (IRB), Ethics Review Board (ERB) and Research Ethics Board (REB) in other countries, to safeguard the welfare and the rights of the participants. There are also independent ethics committees [IEC(Ind)] functioning outside institutions for those researchers who have no institutional attachments or work in institutions with no ethics committee. The Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring of the approved programmes to foresee the compliance of the ethics during the period of the project. Such an ongoing review shall be in accordance with the international guidelines wherever applicable and the Standard Operating Procedures (SOP) of the WHO available at www.who.int

BASIC RESPONSIBILITIES

The basic responsibility of an Institutional Ethics Committee (IEC) is to ensure a competent review of all ethical aspects of the project proposals received by it in an objective manner. IECs should provide advice to the researchers on all aspects of the welfare and safety of the research participants after ensuring the scientific soundness of the proposed research through appropriate Scientific Review Committee. In institutions where this is lacking, the IEC may take up the dual responsibility of review of both, the scientific content and ethical aspects of the proposal. It is advisable to have separate Committees for each, taking care that the scientific review precedes the scrutiny for ethical issues. The scientific evaluation should ensure technical appropriateness of the proposed study. The IECs should specify in writing the authority under which the Committee is established.

Special situations

Small institutions could form alliance with other IECs or approach registered IEC(ind). Large institutions / Universities with large number of proposals can have more than one suitably constituted IECs for different research areas for which large number of research proposals are submitted. However, the institutional policy should be same for all these IECs to safeguard the research participant's rights. A sub-committee of

the main IEC may review proposals submitted by undergraduate or post-graduate students or if necessary, a committee may be separately constituted for the purpose, which will review proposals in the same manner as described above. The responsibilities of an IEC can be defined as follows :-

1. To protect the dignity, rights and well being of the potential research participants.
2. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.
3. To assist in the development and the education of a research community responsive to local health care requirements.

COMPOSITION

The IECs should be multidisciplinary and multisectorial in composition. Independence and competence are the two hallmarks of an IEC. The number of persons in an ethics committee should be kept fairly small (8 - 12 members). It is generally accepted that a minimum of five persons is required to form the quorum without which a decision regarding the research should not be taken.The IEC should appoint from among its members a Chairman who should be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary should be from the same Institution and should conduct the business of the Committee. Other members should be a mix of medical / non-medical, scientific and non-scientific persons including lay persons to represent the differed points of view. The composition may be as follows:-

1. Chairperson
2. One - two persons from basic medical science area
3. One - two clinicians from various Institutes
4. One legal expert or retired judge
5. One social scientist / representative of non-governmental voluntary agency
6. One philosopher / ethicist / theologian
7. One lay person from the community
8. Member Secretary

As per revised Schedule Y of Drugs & Cosmetics Act, 1940, amended in 2005, the ethics committee approving drug trials should have in the quorum at least one representative from the following groups:

1. One basic medical scientist (preferably one pharmacologist).
2. One clinician
3. One legal expert or retired judge

4. One social scientist / representative of non-governmental organisation / philosopher / ethicist / theologian or a similar person
5. One lay person from the community.

The Ethics Committee (EC) can have as its members, individuals from other institutions or communities with adequate representation of age and gender to safeguard the interests and welfare of all sections of the community / society. If required, subject experts could be invited to offer their views, for instance, a pediatrician for pediatric conditions, a cardiologist for cardiac disorders etc. Similarly, based on the requirement of research area, for example HIV, genetic disorders *etc.* it is desirable to include a member from specific patient groups in the Committee.

TERMS OF REFERENCE

The Terms of References should include Terms of Appointment with reference to the duration of the term, the policy for removal, replacement, resignation procedure, frequency of meetings, and payment of processing fee to the IEC for review, honorarium / consultancy to the members / invited experts *etc.* and these should be specified in the SOP which should be made available to each member. Every IEC should have its own written SOPs according to which the Committee should function. The SOPs should be updated periodically based on the changing requirements.

The term of appointment of members could be extended for another term and a defined percentage of members could be changed on regular basis. It would be preferable to appoint persons trained in bioethics or persons conversant with ethical guidelines and laws of the country. Substitute member may be nominated if meetings have been continuously missed by a member due to illness or other unforeseen circumstances. For this the criteria for number of missed meetings may be defined in the SOP.

TRAINING

The EC members should be encouraged to keep abreast of all national and international developments in ethics through orientation courses on related topics by its own members or regular training organized by constituted body(ies), so that they become aware of their role and responsibilities. For drug trial review it is preferable to train the IEC members in Good Clinical Practice. Any change in the regulatory requirements should be brought to their attention and they should be aware of local, social and cultural norms, as this is the most important social control mechanism. .

REGULATION

Once the legislation of guidelines occurs which is currently under active consideration by the Ministry of Health, a Biomedical Research Authority will be set up under

the proposed Bill on Biomedical Research on Human Participants(Promotion and Regulation) which would require that all IECs register with this Authority. It will also evaluate and monitor functioning of the IECs, and develop mechanisms for enforcing accountability and transparency by the institutions.

REVIEW PROCEDURES

The IEC should review every research proposal on human participants before the research is initiated. It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the participants with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and the justice issues.

The IEC's member-secretary or secretariat shall screen the proposals for their completeness and depending on the risk involved categorise them into three types, namely, exemption from review, expedited review and full review (see below for explanation).

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 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 every day life.

An investigator cannot decide that her/his protocol falls in the exempted category without approval from the IEC. All proposals will be scrutinised to decide under which of the following three categories it will be considered :

1. Exemption from review

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

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

Exceptions:

i. When research on use of educational tests, survey or interview procedures, or observation of public behavior 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.

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

2. Expedited Review

The proposals presenting no more than minimal risk to research participants may be subjected to expedited review. The Member- Secretary and the Chairperson of the IEC or designated member of the Committee or Subcommittee of the IEC may do expedited review only if the protocols involve -

1. Minor deviations from originally approved research during the period of approval (usually of one year duration).
2. Revised 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.
3. Research activities that involve only procedures listed in one or more of the following categories :

   a. Clinical studies of drugs and medical devices only when -

      i. research is on already approved drugs except when studying drug interaction or conducting trial on vulnerable population or

      ii. adverse Event (AE) or unexpected Advcerse Drug Reaction (ADR) of minor nature is reported.

4. Research involving clinical materials (data, documents, records, or specimens) that have been collected for non-research (clinical) purposes.
5. 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.

   a. 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 -

i. 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;

ii. when the intervention has undergone testing for safety prior to its use in emergency situations and sponsor has obtained prior approval of DCGI;

iii. only if the local IEC reviews the protocol since institutional responsibility is of paramount importance in such instances.

iv. if Data Safety Monitoring Board (DSMB) is constituted to review the data;

b. 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, and therefore, the following points need to be considered when reviewing such research:

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

ii. Disaster-affected community participation before and during the research is essential and its representative or advocate must be identified.

iii. Extra care must be taken to protect the privacy and confidentiality of participants and communities.

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

v. 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.

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

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

3. Full Review

All research presenting with more than minimal risk, proposals/ protocols which do not qualify for exempted or expedited review and projects that involve vulnerable population and special groups shall be subjected to full review by all the members. While reviewing the proposals, the following situations may be carefully assessed against the existing facilities at the research site for risk/benefit analysis:

a. Collection of blood samples by finger prick, heel prick, ear prick, or venipuncture:
   i. 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;
   ii. 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;
   iii. from neonates depending on the haemodynamics, body weight of the baby and other purposes not more than 10% of blood is drawn within 48 - 72 hours. If more than this amount is to be drawn it becomes a risky condition requiring infusion/blood transfusion;
   iv. prospective collection of biological specimens for research purposes by noninvasive means. For instance:
      1. skin appendages like hair and nail clippings in a non-disfiguring manner;
      2. dental procedures - deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction of permanent teeth; supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth;
      3. excreta and external secretions (including sweat);
      4. uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum or by applying a dilute citric solution to the tongue;
      5. placenta removed at delivery;
      6. amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

7. mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
8. sputum collected after saline mist nebulization and bronchial lavages.

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

i. 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;

ii. weighing or testing sensory acuity;

iii. magnetic resonance imaging;

iv. electrocardiography, echocardiography; electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow,

v. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

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

SUBMISSION OF APPLICATION

The researcher should submit an application in a prescribed format along with the study protocol as prescribed in SOP of IEC concerned. The protocol should include the following : -

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.

3 Recent curriculum vitae of the Investigators indicating qualification and experience.

4. Participant recruitment procedures and brochures, if any.

5. Inclusion and exclusion criteria for entry of participants.

6. 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.

7.Plan to withdraw or withhold standard therapies in the course of research.

8.Plan for statistical analysis of the study.

9.Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and local languages.

10. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory, animal and human research.

11. For research involving more than minimal risk, an account of management of such risk or injury.

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.

14. Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.

15. 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..

16. All other relevant documents related to the study protocol like investigator's brochure for trial on drugs/ devices/ vaccines/ herbal remedies and statement of relevant regulatory clearances.

17.Agreement to comply with national and international Good Clinical Practices (GCP) protocols for clinical trials.

18. Details of Funding agency/ Sponsors and fund allocation.

19. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee(HMSC) or appropriate Committees under other agencies/ authority like Drug Controller General of India (DCGI)
20. For exchange of biological material in international collaborative study a MoU/ Material Transfer Agreement between the collaborating partners.
21. A statement on conflict-of-interest (COI), if any.

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 at frequent intervals to review new proposals, evaluate annual progress of ongoing ones, review serious adverse event (SAE) reports and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate. 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 Member Secretary should communicate the decision in writing to the PI.
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 reason
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 goals 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:

a. any amendment to the protocol from the originally approved protocol with proper justification;

b. serious and unexpected adverse events and remedial steps taken to tackle them;

c. 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.

REVIEW PROCESS

The method of review should be stated in the SOP whether the review should be done by all reviewers or by primary reviewer(s) in which case a brief summary of the project with informed consent and patient information sheet, advertisements or brochures, if any, should be circulated to all the other members.

The ethical review should be done in formal meetings and EC should not take decisions through circulation of proposals. The committee should meet at regular intervals and should not keep a decision pending for more than 3 - 6 months, which may be defined in the SOP.

PERIODIC REVIEW

The ongoing research may be reviewed at regular intervals of six months to one year as may be specified in the SOP of the ethics committee.

CONTINUING REVIEW

The IEC has the responsibility to continue reviewing approved projects for continuation, new information, adverse event monitoring, follow-up and later after completion if need be.

INTERIM REVIEW

Each IEC should decide the special circumstances and the mechanism when an interim review can be resorted to by a sub-committee instead of waiting for the scheduled time of the meeting like re-examination of a proposal already examined by the IEC or

any other matter which should be brought to the attention of the IEC. However, decisions taken should be brought to the notice of the main committee.

MONITORING

Once IEC gives a certificate 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. Additionally, periodic status reports must be asked for at appropriate intervals based on the safety concerns and this should be specified in the SOP of the IEC. SAE reports from the site as well as other sites are reviewed by EC 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.

RECORD KEEPING

All documentation and communication of an IEC are to be dated, filed and preserved according to written procedures. Strict confidentiality is to be maintained during access and retrieval procedures. The following records should be maintained for the following:

i.the Constitution and composition of the IEC;

ii. signed and dated copies of the latest the curriculum vitae of all IEC members with records of training if any;

iii. standing operating procedures of the IEC;

iv. national and International guidelines;

v. copies of protocols submitted for review;

vi.all correspondence with IEC members and investigators regarding application, decision and follow up;

vii. agenda of all IEC meetings;

viii. minutes of all IEC meetings with signature of the Chairperson;

ix. copies of decisions communicated to the applicants;

x. record of all notification issued for premature termination of a study with a summary of the reasons;

xi final report of the study including microfilms, CDs and Video recordings.

It is recommended that all records must be safely maintained after the completion/ termination of the study for a period of 3 years if it is not possible to maintain the same for more than that due to resource crunch and lack of infrastructure.

ADMINISTRATION AND MANAGEMENT

A full time secretariat and space for keeping records is required for a well functioning IEC. The members could be given a reasonable compensation for the time spared for reviewing the proposals. A reasonable fees can be charged to cover the expenses related to review and administrative processes. Every institution should allocate reasonable amount of funds for smooth functioning of the IEC.

SPECIAL CONSIDERATIONS

While all the above requirements are applicable to biomedical research as a whole irrespective of the specialty of research, there are certain specific concerns pertaining to specialised areas of research which require additional safe guards / protection and specific considerations for the IEC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable participants and those with diminished autonomy besides issues pertaining to commercialisation of research and international collaboration. The observations and suggestions of IEC should be given in writing in unambiguous terms in such instances. Details on these issues are described in the next Chapter on General Ethical Issues.