

Ethics in Biomedical Research

Vina Vaswani¹, Vinodkumar C.S²

¹Director, Centre of Ethics, Yenepoya University, ²Associate Professor, Department of Microbiology
S.S Institute of Medical Sciences and Research Centre, Davangere
[Received: 26/10/2014, Revised: 3/12/2014, Accepted: 11/12/2014]

Introduction

Research ethics provides guidelines for the responsible conduct of biomedical research. In addition, research ethics educates and monitors scientists conducting research to ensure a high ethical standard. Ethics in clinical research focuses largely on identifying and implementing the acceptable conditions for exposure of some individuals to risks and burdens for the benefit of society at large. Ethical guidelines for clinical research were formulated only after discovery of inhumane behavior with participants during research experiments¹.

History

The birth of modern research ethics began with a desire to protect human subjects involved in research projects. The first attempt to craft regulations began during the Doctors Trial of 1946-1947. The Doctors Trial was a segment of the Nuremberg Trials for Nazi war criminals. In the Doctors Trial, 23 German Nazi physicians were accused of conducting abhorrent and torturous “experiments” with concentration camp inmates. The accused physicians tortured, brutalized, crippled, and murdered thousands of victims in the name of research. Some of their experiments involved gathering scientific information about the limits of the human body by exposing victims to extreme temperatures and altitudes. The most gruesome and destructive experiments tested how quickly a human could be euthanatized in order to carry out the Nazi racial purification policies most efficiently. To prosecute the accused Nazi doctors for the atrocities they committed, a list of ethical guidelines for the conduct of research – the Nuremberg Code – were developed.

The Nuremberg Code consisted of ten basic ethical principles that the accused violated. The 10 guidelines were as follows:

1. Research participants must voluntarily consent to research participation
2. Research aims should contribute to the good of society
3. Research must be based on sound theory and prior animal testing

4. Research must avoid unnecessary physical and mental suffering

5. No research projects can go forward where serious injury and/or death are potential outcomes 6. The degree of risk taken with research participants cannot exceed anticipated benefits of results 7. Proper environment and protection for participants is necessary

8. Experiments can be conducted only by scientifically qualified persons

9. Human subjects must be allowed to discontinue their participation at any time

10. Scientists must be prepared to terminate the experiment if there is cause to believe that continuation will be harmful or result in injury or death².

The Nuremberg Guidelines paved the way for the next major initiative designed to promote responsible research with human subjects, the Helsinki Declaration. The Helsinki Declaration was developed by the World Medical Association and has been revised and updated periodically since 1964, with the last update occurring in 2000.² The document lays out basic ethical principles for conducting biomedical research and specifies guidelines for research conducted either by a physician, in conjunction with medical care, or within a clinical setting.

The Helsinki Declaration contains all the basic ethical elements specified in the Nuremberg Code but then advances further guidelines specifically designed to address 5 the unique vulnerabilities of human subjects solicited to participate in clinical research projects.

The unique principles developed within the Helsinki Declaration include:

- The necessity of using an independent investigator to review potential research projects.
- Employing a medically qualified person to supervise the research and assume responsibility for the health and welfare of human subjects.
- The importance of preserving the accuracy of research results.

Correspondence:

Dr. Vinodkumar C.S

Associate Professor, Department of Microbiology
S.S Institute of Medical Sciences and Research Centre
Mob: 9964402525 Email : vinodmicro@yahoo.com

Access this article online

Website : www.jermt.org

Quick
Response
Code :



- Suggestions on how to obtain informed consent from research participants
 - Rules concerning research with children and mentally incompetent persons
 - Evaluating and using experimental treatments on patients
- i The importance of determining which medical situations and conditions are appropriate and safe for research³.

Following the Helsinki Declaration, the next set of research ethics guidelines came out in the Belmont Report of 1979 from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The report outlines:

1. The ethical principles for research with human subjects
2. Boundaries between medical practice and research
3. The concepts of respect for persons, beneficence, and justice
4. Applications of these principles in informed consent (respect for persons), assessing risks and benefits (beneficence), and subject selection (justice)⁴.

Currently, the focus of research ethics lies in the education of researchers regarding the ethical principles behind regulations as well as the oversight and review of current and potential research projects. The field has expanded from providing protections for human subjects to including ethical guidelines that encompass all parts of research from research design to the truthful reporting of results.

Guidelines for functioning of Ethics Committee

A. Good Clinical Practice (GCP)

1. Ethics Committee

The sponsor and / or investigator should seek the opinion of an Ethics Committee regarding suitability of the protocol, methods and documents to be used in recruitment of subjects and obtaining their informed consent including adequacy of the information being provided to the subjects. The Ethics Committees are entrusted not only with the initial view of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the Ethics of the approved programs till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research.

i. Basic responsibilities

The basic responsibility of an IEC is to ensure a competent review of all ethical aspects of the project

proposals received and execute the same free from any bias and influence that could affect their objectivity.

The IEC should specify in writing the authority under which the committee is established, membership requirements, the term of reference, the conditions of appointment, the offices and the quorum requirement. The responsibilities of an IEC can be defined as follows:

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

ii. Composition

a. IEC should be multidisciplinary and multi-sectorial in composition. Independence and competence are the two hallmark of an IEC.

b. The number of persons in an ethical committee be kept fairly small (5-7 members). It is generally accepted that a minimum of five persons is required to compose a quorum. There is no specific recommendation for a widely acceptable maximum number of persons but it should be kept in mind that too large a Committee will make it difficult in reaching consensus opinion. 12 to 15 is the maximum recommended number.

c. The Chairperson of the Committee should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary who generally belongs to the same Institution should conduct the business of the Committee. Other members should be a mix of medical/non-medical, scientific and non-scientific persons including lay public to reflect the differed viewpoints. The composition may be as follows:

- Chairperson
- 12 basic medical scientists (preferably one pharmacologists)
- 12 clinicians from various Institutes
- One legal expert or retired judge
- One social scientist / representative of nongovernmental voluntary agency
- One philosopher / ethicist / theologian
- One lay person from the community
- Member Secretary

iii. Terms of Reference

The IEC members should be made aware of their role and responsibilities as committee members. Any change in the regulatory requirements should be brought to their attention and they should be kept abreast of all national and international developments in this regard. The Terms of Reference should also include a statement on Terms of Appointment with reference at the duration of the term of membership, the policy for removal, replacement and resignation procedure etc. Each Committee should have its own operating procedures available with each member.

iv. Review Procedures

The Ethics Committee should review every research proposal on human subjects. 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 subjects with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. The ethical review should be done through formal meetings and should not resort to decisions through circulation of proposals.

v. Submission of Application

The researcher should submit an appropriate application to the IEC in a prescribed format along with the study protocol at least three weeks in advance. The protocol should include the following:

- a. Clear research objectives and rationale for undertaking the investigation in human subjects in the light of existing knowledge.
- b. Recent curriculum vitae of the Investigators indicating qualification and experience.
- c. Subject recruitment procedures.
- d. Inclusion and exclusion criteria for entry of subjects in the study.
- e. Precise description of methodology of the proposed research, including intended dosages and routes of administration of drugs, planned duration of treatment and details of invasive procedures if any
- f. A description of plans to withdraw or withhold standard therapies in the course of research.
- g. The plans for statistical analysis of the study.
- h. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and vernacular languages.
- i. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory and animal research.

- j. For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury or toxicity due to over-dosage should be included.
- k. Proposed compensation and reimbursement of incidental expenses.
- l. Storage and maintenance of all data collected during the trial.
- m. Plans for publication of results - positive or negative – while maintaining the privacy and confidentiality of the study participants.
- n. A statement on probable ethical issues and steps taken to tackle the same.
- o. All other relevant documents related to the study protocol including regulatory clearances.
- p. Agreement to comply with national and international GCP protocols for clinical trials.
- q. Details of funding agency / Sponsors and fund allocation for the proposed work.

vi. 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 frequently intervals to review new proposals, evaluate annual progress of ongoing ones and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate.

- a. 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.
- b. A member must voluntarily withdraw from the IEC while making a decision on an application which evokes a conflict of interest which should be indicated in writing to the chairperson prior to the review and should be recorded so in the minutes.
- c. If one of the members has her/his own proposal for review, then the member should not participate when the project is discussed.
- d. A negative decision should always be supported by clearly defined reasons.
- e. An IEC may decide to reserve its positive decision on a study in the event of receiving information that may adversely affect the benefit/risk ration.
- f. 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.

- g. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.
 - h. 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.
 - I. If necessary, the applicant/investigator may be invited to present the protocol or offer clarification in the meeting. Representative of the patient groups or interest groups can be invited during deliberations to offer their viewpoint.
 - j. 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.
 - k. Meetings are to be minuted which should be approved and signed by the Chairperson.
- f. All correspondence with IEC members and investigators regarding application, decision and follow up
 - g. Agenda of all IEC meetings
 - h. Minutes of all IEC meetings with signature of the Chairperson
 - i. Copies of decision communicated to the applicants
 - j. Records of all notification issued for premature termination of a study with a summary of the reasons
 - k. 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 at least a period of 5 years if it is not possible to maintain the same permanently.

ix. Special Consideration

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 specialized 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 subjects and those with diminished autonomy besides issues pertaining to commercialization of research and international collaboration. The observations and suggestions of IEC should be given in writing in unambiguous terms in such instances⁵.

B. Schedule Y of Drugs and Cosmetics Act 1945

1. Responsibilities of the Ethics Committee

- i. It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and wellbeing of all trial subjects. The ethics committee should exercise particular care to protect the rights, safety and wellbeing of all vulnerable subjects participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent. Ethics committee should get document 'standard operating procedures' and should maintain a record of its proceedings.
- ii. Ethics Committee should make, at appropriate intervals, an ongoing review of the trials for which

vii. Interim Review

The IEC should decide and record the special circumstances and the mechanism when an interim review can be resorted to instead of waiting for the scheduled time of the meeting. However, decisions taken should be brought to the notice of the main committee. This can be done for the following reasons:

- a. Reexamination of a proposal already examined by the IEC
- b. Research study of a minor nature such as examination of case records etc.
- c. An urgent proposal of national interest.

viii. 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. Records should be maintained for the following:

- a. The constitution and composition of the IEC
- b. The curriculum vitae of all IEC members
- c. Standard Operating Procedures of the IEC
- d. National and International guidelines
- e. Copies of the protocol, data collection formats, CRFs, investigational brochures etc. submitted for review

they review the protocol. Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites.

- iii. In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Licensing Authority.

2. Studies in special population

I. Geriatrics

Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the Sponsor's option) in meaningful numbers, if

- The disease intended to be treated is characteristically a disease of aging; or
- The population to be treated is known to include substantial numbers of geriatric patients; or
- When there is specific reason to expect that conditions common in the elderly are likely to be encountered; or
- When the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

ii. Paediatrics

- The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.
- The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.
- If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are

currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

- If the new drug has a potential for use in paediatric patients – Paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited paediatric data at the time of submission of application – more data in paediatric patients would be expected after marketing authorization for use in children is granted.
- The paediatric studies should include–
 - Clinical trials,
 - Relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and
 - Definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.
- If the new drug is a major therapeutic advance for the paediatric population – the studies should begin early in the drug development, and this data should be submitted with the new drug application.
- Paediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/ legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/ legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, paediatric participants should additionally assent to enroll in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent(s)/ legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in

the study. In this situation, continued parental/legal guardian consent should be sufficient to allow participation in the study.

- h. For clinical trials conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about pediatric, ethical, clinical and psychosocial issues.

iii. Pregnant or nursing women

- a. Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant/nursing women or fetuses/nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.
- b. For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, fetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug⁶.

Registration of Ethics Committee, guidelines and process

In the Drugs and Cosmetics Rules, 1945, (hereinafter referred to as the said rules), after rule 122 DC, the rule “122 DD. Registration of Ethics Committee (EC) has been introduced in 08.02.2013 according to it – no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration of the

committee with the licensing authority as defined in clause (b) of rule 21. The registration, unless it is sooner suspended or cancelled, shall be valid for a period of five years from the date of issue.

The Ethics committee will review and accord its approval to a clinical trial and also carry ongoing review of the trial at appropriate intervals, as specified in Schedule Y, and the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable regulatory requirements for safeguarding rights, safety, and wellbeing of the trial subjects. In case of any serious adverse events occurring to the clinical trial subjects during the clinical trial, the ethics committee will analyze and forward its opinion as per procedures specified under APPENDIX XII of schedule Y.

References

1. Sanmukhani J, Tripathi C.B. Ethics in Clinical Research: The Indian Perspective. *Indian J Pharm Sci.* 2011;73(2): 125-30.
2. Mustafa KME. Nuremberg Code: A landmark document on medical research ethics. *Sud. J. Pub. Health*, 2008; 3(2):144-8.
3. Declaration of Helsinki. *Bulletin of the World Health Organization*, 2001; 79(4):32-4.
4. The Belmont Report. DHEW Publication No. (OS) 78-0014. Vol II.
5. Indian Good Clinical Practices. <http://cdsco.nic.in/html/GCP.htm> 1/54 accessed on 30-01-2015.
6. Schedule Y. The Drugs and Cosmetics Act and Rules (As amendment up to the 12th December 2014).

How to Cite this article :

Vaswani V, C S Vinodkumar. Ethics in Biomedical Research. *J Educational Res & Med Teach* 2014;2(2):29-34

Funding: Declared none Conflict of interest: Declared none