Ethics in Clinical Research: The Indian Perspective

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Sanmukhani and Tripathi: Ethics in Clinical Research

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 behaviour with participants during research experiments. The Nuremberg Code was the first international code laying ethical principles for clinical research. With increasing research all over, World Health Organization formulated guidelines in the form of Declaration of Helsinki in 1964. The US laid down its guidelines for ethical principles in the Belmont Report after discovery of the Tuskegee's Syphilis study. The Indian Council of Medical Research has laid down the 'Ethical Guidelines for Biomedical Research on Human Subjects' in the year 2000 which were revised in 2006. It gives twelve general principles to be followed by all biomedical researchers working in the country. The Ethics Committee stands as the bridge between the researcher and the ethical guidelines of the country. The basic responsibility of the Ethics Committee is to ensure an independent, competent and timely review of all ethical aspects of the project proposals received in order to safeguard the dignity, rights, safety and well-being of all actual or potential research participants. A well-documented informed consent process is the hallmark of any ethical research work. Informed consent respects individual's autonomy, to participate or not to participate in research. Concepts of vulnerable populations, therapeutic misconception and post trial access hold special importance in ethical conduct of research, especially in developing countries like India, where most of the research participants are uneducated and economically backward.

Key words: Clinical research, ethics, ethics committees, ICMR guidelines, informed consent

The word 'ethics' is derived from the Greek word, *ethos*, which means custom or character. Ethics is the systematic study of values, so as to decide what is right and what is wrong. In clinical research human beings are involved, as opposed to animals, atoms or asteroids, as the object of study. It focuses on improving human health and well-being, typically by identifying better methods to treat, cure or prevent illnesses. 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 the society at large.

HISTORY

The ethical guidelines in various parts of the world were formulated only after discovery of inhumane behaviour with participants during research experiments. In the pre World War II era, most of the research experiments were carried on own self or on one's own patients. World War II led the states to take more interest in science and research resulting in initiation of larger, systematic clinical investigations to gain knowledge for better treatment of patients, specially the soldiers. Most of the studies were carried out through defence efforts and used mainly the prisoners without concern of their consent and well being. The experiments by the Nazi doctors in their concentration camps were the cruellest of all of them. In some of the most dreadful of these experiments, they kept the prisoners in compression chambers, freezing water, created gunshot wounds and even transplanted grafts among twins to see the body's response in such adverse situations. Death was the end point in most of the experiments and when it was not so, the doctors did antemortum dissection to study changes in the body. The discovery of these experiments stunned the whole world which led to formulation of Nuremberg code[1] in Germany to prevent recurrence of such episodes. It was the first international code for ethics in clinical research laying down the guidelines for research on human subjects. It laid down ten clear principles to be followed by researchers and made voluntary consent essential, allowed subjects to withdraw from the

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experimentation at any time, banned experiments that could result in major injury or death of the subjects and made mandatory to have preclinical data before experimenting on humans.

DEVELOPMENT OF VARIOUS ETHICAL GUIDELINES - CHANGING SCENARIO

The Nuremberg code was not honored by some researchers and there continued to be abuses and exploitations of humans in research. The Willowbrook State Study[2] to know natural course of infective hepatitis in children and the Jewish Chronic Disease Hospital study[3] to understand body's ability to reject cancer cells in debilitated subjects were examples of unethical research. This led the World Medical Association (WMA) to develop a set of guidelines to safeguard the rights and well being of participants in clinical research. The set of guidelines was adopted by the 18th WMA General Assembly and was called the Declaration of Helsinki[4]. It was revised five times and the latest version was published in 2000 at the 52nd WMA, Edinburgh, Scotland. It contains 32 principles, which stress on informed consent, confidentiality of data, vulnerable population and requirement of a protocol, including the scientific reasons of the study, to be reviewed by the ethics committee.

In the United States the ethical guidelines were setup after the discovery of the Tuskegee Syphilis Study[3]. The study was started in 1932 with 399 syphilitic African American men to see the natural course of syphilis and was supposed to last for about six months but as the researchers were getting "good data" they decided to continue it. The participants were misled and deprived of treatment even after the introduction of penicillin in the 1940s. These ethical atrocities were exposed in 1972 resulting in discontinuation of the study, but till then it had already led to 28 deaths and permanent disability in 100 subjects; moreover 40 patients infected their wives resulting in 19 cases of congenital syphilis. To probe into the study the 'National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research' was formed which wrote the Belmont Report[5] in 1979 and laid the foundation for regulations regarding ethics and human subjects' research in the US. The Belmont report stressed upon three basic ethical principles: respect for person, beneficence and justice. These were applied in the form of informed consent, assessment of risks and benefits by ethics committees and selection of subjects.

With the increasing interest of pharmaceutical industries in carrying out research experiments in the developing and the under developed countries, in 1982, the Council for International Organizations of Medical Sciences (CIOMS)[6] in association with World Health Organization (WHO) developed 'International Ethical Guidelines for Biomedical Research Involving Human Subjects'. They especially stressed upon ethical issues in less developed countries like investigator's duties regarding consent, appropriate inducements, special/ vulnerable populations, therapeutic misconceptions and post trial access.

THE INDIAN PERSPECTIVE

The Indian Council of Medical Research (ICMR), in February 1980, released a 'Policy Statement on Ethical Considerations involved in Research on Human Subjects'. This was the first policy statement giving official guidelines for establishment of ethics committees (ECs) in all medical colleges and research centres. But as with other nations of the world, these guidelines were not respected by many researchers and India was not free of controversial research works. In 1970s and 1980s researchers at the Institute for Cytology and Preventive Oncology in New Delhi, carried out a study on 1158 women patients of different stages of cervical dysplasia or precancerous lesions of the cervix[7]. These patients were left untreated to see how many lesions progressed to cancer and how many regressed. By the end of the study seventy one women had developed malignancies and lesions in nine of them had progressed to invasive cancer. Sixty-two women were treated only after they developed localised cancer. After the controversy about the study became public in 1997, the ICMR started developing 'Ethical Guidelines for Biomedical Research on Human Subjects' and finalised them in the year 2000. These are a set of guidelines which every researcher in India should follow while conducting research on human subjects. Although not a law, these guidelines have been put into force through Schedule Y. With the changing scenario in the research field and development of modern techniques, the guidelines were revised in 2006[8]. These guidelines have elaborated the three basic ethical principles: respect for person,

beneficence and justice by inducting twelve general principles as follows:

Principle of essentiality:
The research being carried out should be essential for the advancement of knowledge that benefits patients, doctors and all others in aspects of health care and also for the ecological and environmental well being of the planet.

Principles of voluntariness, informed consent and community agreement:
The research participant should be aware of the nature of research and the probable consequences of the experiments and then should make a independent choice without the influence of the treating doctor, whether to take part in the research or not. When the research treats any community or group of persons as a research participant, these principles of voluntariness and informed consent should apply to the community as a whole and also to each individual member who is the participant of the research or experiment.

Principle of non-exploitation:
Research participants should be remunerated for their involvement in the research or experiment. The participants should be made aware of all the risks involved irrespective of their social and economic condition or educational levels attained. Each research protocol should include provisions of compensation for the human participants either through insurance cover or any other appropriate means to cover all foreseeable and hidden risks.

Principle of privacy and confidentiality:
All the data acquired for research purpose should be kept confidential to prevent disclosure of identity of the involved participant and should not be disclosed without valid legal and/or scientific reasons.

Principle of precaution and risk minimisation:
Due care and caution should be taken at all stages of the research and experiment (from its beginning as a research idea, formulation of research design/ protocol, conduct of the research or experiment and its subsequent applicative use) to prevent research participant from any harm and adverse events. EC has to play an active role in risk minimization.

Principle of professional competence:
Clinical research should be carried out only by competent and qualified persons in their respective fields.

Principle of accountability and transparency:
The researcher should conduct experiments in fair, honest, impartial and transparent manner after full disclosure of his/her interests in research. They should also retain the research data, subject to the principles of privacy and confidentiality, for a minimum period of 5 years, to be scrutinized by the appropriate legal and administrative authority, if necessary.

Principle of the maximisation of the public interest and of distributive justice:
The results of the research should be used for benefit of all humans, especially the research participants themselves and/or the community from which they are drawn and not only to those who are socially better off.

Principle of institutional arrangements:
It is required that all institutional arrangements required to be made in respect of the research and its subsequent use or applications should be duly made in transparent manner.

Principle of public domain:
The results of any research work done should be made public through publications or other means. Even before publication, the detailed information of clinical trials should be made public before start of recruitment via clinical trial registry systems that allow free online access like: www.ctri.in/; www.actr.org.au/; www.clinicaltrials.gov/ or www.isrctn.org/.

Principle of totality of responsibility:
All those directly or indirectly connected with the research should take the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down in respect of the research.

Principle of compliance:
All those associated with the research work should comply by the guidelines pertaining to the specific area of the research.

For research to be conducted ethically we need to follow these twelve general principles laid down by the ICMR. In order to follow these principles we should be aware about the informed consent process,

vulnerable population, therapeutic misconception, post trial access and structure and role of ethics committees. These concepts hold special importance in developing countries like ours, as most of the research participants are uneducated and economically backwards, hence we discuss them here.

INFORMED CONSENT[8,9]

A well-documented informed consent is the hallmark of any ethical research work. It is the responsibility of the investigator/researcher to obtain the informed consent of the prospective participant or in the case of an individual who is not capable of giving informed consent, the consent of a legal guardian. Informed consent respects individual's autonomy to participate or not to participate in research. Adequate information about the research is given in a simple and easily understandable vernacular language in a document known as the 'Participant/Patient Information Sheet' attached along with the 'Informed Consent Form (ICF)'. The patient information sheet should include: A statement that the study involves research; an explanation of the purpose of the research and the expected duration of the subject's participation; a description of the procedures to be followed and identification of any procedures which are experimental; a description of any reasonably foreseeable risks or discomforts to the subjects; a description of any benefits to the subjects or to others which may reasonably be expected from the research; trial treatment schedule(s) and the probability for random assignment to each treatment (especially in randomized placebo controlled trials); a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects; a statement describing the extent, if any, to which confidentiality of records identifying the subjects will be maintained; for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, and where further information may be obtained; an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subjects; a statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subjects are otherwise entitled, also the subjects may discontinue participation at any time without penalty or loss of benefits.

The ICF should specify that the participant has read and understood the patient information sheet; no further permission is required to look into his health records for study purpose until his identity is not revealed; the results arising from the study can be used only for scientific purposes and he voluntarily agrees to take part in the study. The ICF should have space for signature/thumb print of the participant, the principal investigator, a witness and a legally acceptable representative when required.

The ICF with participant/patient information sheet should be approved by the EC before use. The ICF should have the sign or thumb impression of the prospective participant before start of the experiment. If the participant is illiterate, the document should have the signature of a witness, who has seen that the contents of the patient information sheet were adequately explained to the participant. If the participant is a minor or not capable of giving consent, a verbal assent should be taken from him and the consent form should be signed by his legally acceptable representative. If the treating physician of a prospective participant is also the investigator, the informed consent should be taken by any other neutral physician to prevent biased decision of the participant. Informed consent if properly taken protects the rights of prospective participants and thus forms the basis of ethical research work.

VULNERABLE POPULATION

Persons who are relatively or absolutely incapable of protecting their own interests are termed as vulnerable research population. The very poor, illiterate patients, children, individuals with questionable capacity to give consent (including psychiatric patients), prisoners, foetuses, pregnant women, terminally ill patients, students, employees, comatose patients, tribals and the elderly are examples of vulnerable population. Declaration of Helsinki[4] states that 'Medical research involving a underprivileged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of that population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.' It is the responsibility of the EC to see whether the inclusion

of vulnerable populations in the study is justifiable or the population is just being exploited to generate clinical data. To prevent even minor exploitation the EC should consult the representative of vulnerable population that is to be researched upon while reviewing the protocol.

THERAPEUTIC MISCONCEPTION[10,11]

The therapeutic misconception (TM) is a vexing ethical issue for obtaining valid informed consent. A patient coming to a physician may misinterpret and enrol in a research study thinking it to be routine medical care without understanding the experimental nature of the treatment given. He may misinterpret the information given about the research, such that he believes that aspects of the research will directly benefit him.

Thus, it is important that investigators should make efforts to dispel the TM in order to promote ethical and valid informed consent. ICFs should clarify the salient features of research: The purpose of randomized controlled trials (RCTs), random selection of treatment, masking of treatment, meaning and rationale of placebo, restrictions on treatment flexibility and how treatment decision making differs in RCTs compared with routine medical care. Thus to safeguard the ethical rights of the participants therapeutic misconception needs to be taken care of.

POST-TRIAL ACCESS[8,12]

The concept of post trial access holds special importance for clinical research works in the less developed countries. Pharmaceutical companies from developed countries collect the clinical data for their new and experimental drugs from the population in less developed countries. Most of these drugs would never be used by the communities from where the experimental data are collected and here comes the importance of post trial access for safeguarding the rights of such communities. The Helsinki Declaration of WMA, 2000 states that at the end of the trial, every participant should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. The Declaration of the WMA in 2004 reaffirmed its position that "it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so that ethical review committee may consider such arrangements during its review." Therefore, whenever possible EC should consider such an arrangement in the *a priori* agreement. Sometimes more than the benefit to the participant, the community may be given benefit in indirect way through improving their living conditions, establishing counselling centres, clinics or schools and giving education on maintaining good health practices.

ETHICS COMMITTEE[8,13]

The first appearance of need of ethics committee (EC) was made in Declaration of Helsinki in 1964, while in India it appeared in 1980 in the ICMR Policy Statement. EC also called as the Institutional Review Board or the Ethics Review Board stands as the bridge between the researcher and the ethical guidelines of the country.

The establishment of EC requires 5-15 members with at least one basic medical scientist (preferably one pharmacologist), one clinician, a legal expert, a social scientist / representative of NGO / philosopher or theologian and a lay person from the community. Every institute, where research is going on should have its own EC with its head preferably from outside the institute.

Individuals carrying out research can approach to independent ECs. The decisions of EC should be taken only after quorum formation with a minimum of five members having at least one basic medical scientist, one clinician and one legal expert or retired judge. The ECs should have independence from political, institutional, professional, and market influences, in their composition, procedures, and decision-making. As there are no laws governing the registration, formation or working of ethics committees in India, each ethics committee should have their own standard operating procedures for proper functioning.

ECs are responsible for carrying out the review of proposed research before the commencement of the research. The basic responsibility of EC is to ensure an independent, competent and timely review of all ethical aspects of the project proposals received in

order to safeguard the dignity, rights, safety and well-being of all actual or potential research participants. The scientific design and conduct of the study should also be reviewed at the outset as poor science is poor ethics. The appropriateness of the study design in relation to the objectives of the study, the statistical methodology (including sample size calculation) and the potential for reaching sound conclusions with the smallest number of research participants should be assessed. The EC should also look into matters like informed consent process, qualifications of principal investigator and supporting staff, adequacy of infrastructure and facilities, risk benefit ratio, plans to maintain confidentiality and plans for post trial access and compensations. They also need to ensure that there is regular evaluation of the ongoing studies that have received a positive decision. EC is the most important check point for promoting ethical research in the country.

THE WAY AHEAD

Though we have formulated many ethical guidelines for clinical research, are we adequately following them? The answer is 'No'. This is because the ethical guidelines in India are just the recommendations and not a law. For proper enforcement of these guidelines should be made a part of the law as has been done in US and other countries of the world. Another issue lies with the training of doctors and research scientists in our institutions. Doctors are specially trained to be good clinicians but are never taught even the fundamentals of ethical clinical research. The post graduate dissertation or the PhD thesis is a precious opportunity to train tomorrow's investigators in the elements of ethical clinical research. Undergraduates should also be involved in simple observational research.

Finally if we can overcome these challenges, we will make India a competent and credible place of ethical clinical research.

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