**Ethics in Biomedical Research on Human Participants: Needs Emphasis to Save Naive Subjects**

**Abstract:**

Bioethics is a field of ethical enquiry to examine issues and dilemmas of ethics arising from health care and research of humans. Inadequate knowledge of ethical review procedures has made India an emerging global hub for clinical trials. Some shocking histories like Nazi human experimentation, Tuskegee syphilis experiments have led to development of some international regulations of ethics in medical research. The Indian Council of Medical research (ICMR) brought out the ‘Policy Statement on Ethical Considerations involved in Research on Human Subjects,’ in 1980. Still India was not free of controversial research works. So ICMR developed ‘Ethical guidelines for Biomedical Research on Human Subjects’ in 2000. All proposals on biomedical research involving human participants should be reviewed and cleared by an appropriately constituted multidisciplinary and multi sectoral Institutional Ethics Committee (IEC). Independence and competence are the two hallmarks of an IEC. Research should be conducted with the four basic ethical principles - autonomy (respect for person /participant), beneficence, non-maleficence (do no harm) and justice. The Principal Investigator is responsible for observing the health, rights, and welfare of the participants. Today’s undergraduate and postgraduate students are the researchers of tomorrow. There is a need to include the fundamentals of ethics in medical research for undergraduate academic curriculum. The post graduate and the PhD thesis is a precious opportunity to train upcoming researchers in the principles of ethics. Awareness of ethics among researchers and study participants is the key to overcome the challenges and make India a credible place for ethical medical research.

**Key words:** Ethics, Biomedical research, Informed consent, Institutional Ethics Committee

**Introduction**

Research is the systematic collection, analysis and interpretation of data to answer a certain question or solve a problem.1 It consists of three steps: keep a question, data collection to answer the question, and display an answer to the question.2In the areas of research, widely cherished valued are in potential conflict. The researcher's need to gather sensitive information necessary for meaningful program evaluation may conflict with the subject's right of privacy.3 A combination of moral values and principles that are applied to take judgements in medical practice, academic curriculum and research are termed as medical ethics4 Bioethics is a field of ethical enquiry to examine issues and dilemmas of ethics arising from health care and research of humans.5 Research is acceptable ethically only if it relies on valid scientific methods.6

**The need for ethical guidelines:** The Hippocratic Oath contains the Pythagorean duties of justice, secrecy, respect for teachers and solidarity with peers.7 Several sayings from Hippocratic works became for millennia the emblems of medical profession. The famous mottos “Life is short but the art is long” and “Do good or at least do not harm” 8 Historically, for scientific investigation ethical guidelines to protect human subjects were developed after recognizing past exploitation of human subjects and the acknowledged need to protect individual human rights. Federal regulations governing the protection of human subjects were published in 1974 in America.9

**Some shocking histories in Medical research which led to development of some regulations of ethics in medical research**

**Nazi Experiments**

Nazi human experimentation was a series of [medical experiments](https://en.wikipedia.org/wiki/Human_experimentation) on prisoners, including children, during early 1940s, in [World War II](https://en.wikipedia.org/wiki/World_War_II) . [Nazi Physicians](https://en.wikipedia.org/wiki/List_of_Nazi_doctors) and their assistants [forced](https://en.wikipedia.org/wiki/Coercion) prisoners into participating voluntary [consent](https://en.wikipedia.org/wiki/Informed_consent). It resulted in death, [trauma](https://en.wikipedia.org/wiki/Trauma_%28medicine%29), [disfigurement](https://en.wikipedia.org/wiki/Disfigurement) or permanent [disability](https://en.wikipedia.org/wiki/Disability).10 After the war, these crimes trial were carried out to punish physicians what became known as the [Doctors' Trial](https://en.wikipedia.org/wiki/Doctors%27_Trial) and judges included a section called Permissible Medical Experiment in 1947 **.** This section became known as the [Nuremberg Code](http://www.nihtraining.com/ohsrsite/guidelines/nuremberg.html). Basic principles of this code is to satisfy **moral**, **ethica**l, and **legal** concepts in medical research. It highlights some rules to carry out a research which include animal experiments first, voluntary consent, to anticipate scientific benefits, benefits should outweigh risks, no intentional death or disability, protection from harm, the human subject should be at liberty to bring the experiment to an end, qualified investigators to carry out a research and investigator should stop if harm occurs.11,12

**Tuskegee syphilis experiment**

The **Tuskegee Syphilis Experiment** is the [clinical study](https://en.wikipedia.org/wiki/Clinical_trial) conducted between 1932 and 1972 by the [U.S. Public Health Service](https://en.wikipedia.org/wiki/U.S._Public_Health_Service) in collaboration with [Tuskegee University](https://en.wikipedia.org/wiki/Tuskegee_University). Total 600 impoverished, African American [sharecroppers](https://en.wikipedia.org/wiki/Sharecroppers) were enrolled in this study. None were treated with [penicillin](https://en.wikipedia.org/wiki/Penicillin) even after its validation as an effective cure for the disease in 1947. In 1972, a leak to the press resulted in its termination on November 16 of that year. The victims of the study, included numerous men who died of syphilis, 40 wives who contracted the disease, and 19 children born with [congenital syphilis](https://en.wikipedia.org/wiki/Congenital_syphilis). [National Research Act](https://embryo.asu.edu/search?text=National%20Research%20Act) (Public Law 93-348) was passed on 12 July 1974 that a federal policy existed and these regulations were codified as 45 CFR 46. The [National Research Act](https://embryo.asu.edu/search?text=National%20Research%20Act) created the [National Commission](https://embryo.asu.edu/search?text=National%20Commission%20for%20the%20Protection%20of%20Human%20Subjects%20of%20Biomedical%20and%20Behavioral%20Research) to evaluate the ethical principles underlying the use of human research subjects and create guidelines both for **medical, behavioral** and **psychological research**. Their evaluation was ultimately published in 1979 as the Belmont Report*:* Ethical Principles and Guidelines for the Protection of Human Subjects of Research.13,14

**Basic Principles of the Belmont Report:**

**Respect for Persons** has at least two ethical considerations. The first is that the individual human research participant be treated as an autonomous being. The second is that those persons who are not able to make and carry out decisions for themselves must be protected from coercion by others and from activities that harm them. **Beneficence** is to do no harm and to “maximize possible benefits and minimize possible harms” to the individual research participant. **Justice,** the benefits and burdens of research should be uniformly distributed. The selection of research participants needs to be constantly monitored.15

**Milestones of ethics in Biomedical research**

**Some Salient Milestone Of International Ethical Guidelines and Regulations In World**

* 460BC- 377 BC: Oath of Medical ethics for Physician to Follow 7
* 1947: Nuremberg Code 11
* 1948 : Universal Declaration on Human Rights( adopted by General

Assembly of United Nations).6

* 1962 : Kefauver-Harris amendments,( disaster of thalidomide in Europe and

Canada was largely averted in the United States.5

* 1964 : Helsinki Declaration 16
* May 1974: Ethical guidelines, and basic regulations protecting human subjects in [US . Department of Health and Human Services](https://embryo.asu.edu/search?text=US%20Department%20of%20Health%20and%20Human%20Services) 3
* July 1974: [National Research Act](https://embryo.asu.edu/search?text=National%20Research%20Act) (Public Law 93-348)3
* 1977 : National Research Act  3
* 1979 : Belmont Report (USA) 3
* 1982/1992 : Proposed International Guidelines for Biomedical research involving

Human Subjects by (WHO/CIOMS) 5

* 1991 : International Guidelines for Ethical Review in Epidemiological studies 6
* 1993 : International Ethical Guidelines for Biomedical Research Involving

Human Subjects 6

* 1995 : WHO Guidelines for Good Clinical Practice (GCP) 17
* 2000 : WHO Operational Guidelines Ethics Committee that review Biomedical

Research 5

* 2002 : International Ethical Guidelines for Medical Research Involving

Human Subjects(CIOMS)5

2003 : Nuffield Council on Bioethics: The Ethics of Research related

to Healthcare in Developing Countries 5

* 2005 : Universal Declaration on Bioethics and Human Rights. 18
* 2007 : Ethical Consideration in Biomedical HIV Prevention Trial **18**

**Some salient milestone of Ethical Guidelines and Regulations in India at a glance**

* 1940 : Drug and Cosmetic Act 19
* 1956 : Indian Medical Council Act, 1956 , the Medical Council of India,20
* 1980 : Policy Statement on Ethical Considerations involved in research on

Human Subjects by ICMR .21

* 2000 : ‘Ethical guidelines for Biomedical Research on Human Subjects’22
* 2002 : Indian GCP Guidelines (Central Drugs Standard Control Organization . . . . (CDSCO) **23**
* 2002 : Indian Medical Council (Professional Conduct, Etiquette and

Ethics) Regulations. 24

* 2006 : Revised ‘Ethical guidelines for Biomedical Research on Human Subjects’ 25
* 2013 : The Drugs And Cosmetics (Amendment) Bill. 26
* 2013: National Guidelines for Stem Cell Research. 27

**Ethical guidelines in Indian Perspective**

Ethical guidelines are guidance documents which assist with decisions relating to the responsibility to adhere to established and relevant standards of ethical principles and practice.5 India too has developed national guidelines for research involving human beings. In our country the guidelines, which are often cited and followed, are those issued by the Indian Council of Medical Research, New Delhi.28Clinical drug trials or other research involving patients or volunteers as per the guidelines of ICMR can be undertaken, provided ethical considerations are borne in mind. Violation of existing ICMR guidelines in this regard shall constitute misconduct. Consent taken from the patient for trial of drug or therapy which is not as per the guidelines shall also be construed as misconduct.24 The Indian Council of Medical research brought out the ‘Policy Statement on Ethical Considerations involved in Research on Human Subjects,’ in 1980.21 But these guidelines were not followed by many researchers. 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. 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 localized cancer. Like this India was not free of controversial research works. So ICMR started developing ‘Ethical Guidelines’ and finalized them in the year 2000 as the ‘Ethical guidelines for Biomedical Research on Human Subjects’.22,28, 29 Since then it has been revised and the latest version has been published in 2006.25 This statement of Ethical Guidelines is known as the ICMR Code and consist of the **Statement of General Principle**s and **Statement of Specific Principles.**

# General principles gives thrust on25

* Essentiality
* Voluntariness, informed consent and community agreement
* Non-exploitation
* Privacy and confidentiality
* Precaution and risk minimisation
* Professional competence
* Accountability and transparency
* Maximization of the public interest ,distributive justice
* Institutional arrangements
* Public domain
* Totality of responsibility
* Compliance

**Statement of Specific Principles**

* For human genetics and genomics research
* For clinical evaluation Drugs / Vaccines/ devices/ diagnostics/ herbal remedies
* For epidemiological studies
* For research in transplantation
* For assisted reproductive technologies

**Ethics Review Procedure**

Evaluation of research proposals has been emphasized under the Statement of General Principles pertaining to precaution and risk minimization. It is mandatory that proposals of research involving human beings should be cleared by an appropriately constituted Ethics Review Board (ERB), Institutional Ethics Committee (IEC), also referred to as Institutional Review Board (IRB), and Research Ethics Board (REB) in other countries, to safeguard the welfare and the rights of the participants. 25 It is a group of individuals who undertake the ethical review of research protocols involving humans, applying agreed ethical principles.5  In India the Ethics Committee, constituted for the purpose of giving approval to a clinical trial protocol and other related matters, shall be registered with the Central Licensing Authority in such manner as may be prescribed.26,

**Composition of Institutional Ethics Committee (IEC)25**

The IECs should be multidisciplinary and multi sectoral 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).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 one Chairman from its members 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 work 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 aspects 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

**GENERAL ETHICAL ISSUES**

Research should be conducted with the four basic ethical principles - **autonomy (**respect for person /participant) **beneficence, non-maleficence** (do no harm) and **justice.** The Principal Investigator is liable for undertaking the research and observance of the rights, health and welfare of the participants recruited for the study. **Informed Consent of Participants** protects the individual’s freedom and respect for individual’s autonomy. Adequate information about the research is given in a simple and easily understandable language in a document known as the **Informed Consent Form with Participant/ Patient Information Sheet**.25 **Assent** is a variation on consent where a person who does not possess full competence to give informed consent gives affirmative agreement to participate in research. For instance, a child or person with dementia should give assent before being enrolled in biomedical research. However, it is important to note that assent does not eliminate the need for obtaining the permission of a parent or other legally authorized decision-maker. The assent should be obtained to the extent of the child’s capabilities such as in the case of mature minors from the age of seven years up to the age of 18 years. 5, 25

**Specific principles of this guidelines are for**

1. Drug trials

2. Vaccine trials

3. Surgical procedures / medical devices

4. Diagnostic agents - with special reference to use of radioactive materials and X-rays

5. Trials with herbal remedies

**Way of approach to Institutional Ethics Committee**

**SOP\*+ Protocol+ Application + consent form**

**Principal Investigator**

**Office of Research**

**Institutional Ethics Committee**

**Discuss at Convened Formal Meeting \***

**Approve**

**Modification**

**Not approve**

**Decision communicated to Principal Investigator**

**\*Standard Operation Procedure**

**Review Procedure by IEC:**

### Project Proposal

**Scientific Review**

**IEC**

**No more than minimal to risk**

**More than minimal risk**

**Less than minimal risk**

**Full review**

**Expedited review**

**Exemption from review**

**Phases of Clinical Trials25,26, 30,31**

All phases require approval from EC. The first three of the following four phases of clinical trials of drug require DCGI's clearance:

Phase I

Phase II

IEC

DCGI

Phase III

Phase IV

**Impact of recent regulatory notifications on an institutional ethics committee**

The Government of India came out with a slew of notifications to streamline clinical research in the beginning of 2013 in response to the Supreme Court’s orders and a Parliamentary Standing Committee’s report. The notifications greatly influenced the structure, review process, outcomes and administration of ethics committees across India.32

**The new regulations issued for clinical trials in India with timeline**

**GSR No. Date Notification**

53 E 30th Jan, 2013 SAE reporting and compensation 33

63 E 1st Feb, 2013 Conditions to be fulfilled by the sponsor

to conduct the clinical trial 34

72 E 28th Feb, 2013 Registration of ethics committees 35

GCT/20/SC/Clin./2013 DCGI 19 Nov,2013 Audiovisual recording of written . informed consent 36,37,38

**Challenges to Safeguard the research participants**

* Availability of naive subjects and ignorant researchers.
* Inadequate knowledge of ethical review procedures when India is emerging as a global hub for clinical trials.
* Participation in research for access to drugs, payment/ compensation.
* Compliance with the new regulations is a challenge.
* Lack of regulatory jurisdiction over private trial site.
* While ethics and law are different in certain ways, ethics remains a foundation for law, and often provides a justificatory basis for legal norms.

**Way forward:**

Autonomy, beneficence, non-maleficence and justice, the four pillars of ethics in medical research should be inherent feeling of researchers. Today’s undergraduate and postgraduate students are the researchers of tomorrow. So there is a need felt to include the fundamentals of ethics in medical research for undergraduate academic curriculum. The post graduate dissertation or the PhD thesis is a precious opportunity to train upcoming researchers in the principles of ethics clinical research. There is a need to give momentum for prompt and strict implementation of the Biomedical Research on Human Subjects (Promotion and Regulation) Bill, 2005 which is in budding stage. Awareness of ethics among researchers and study participants is the key to overcome the challenges and make India a credible place for ethical medical research.

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