Ethics in Research

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13.1 What Are Ethics, Medical Ethics, and Bioethics?

Ethics is a set of moral principles of 'what is right?' and 'what is wrong?' or, in simple words, 'what is good and what is bad?' When the same principles are applied to medicine, the subject is called medical ethics. It is expected that a doctor should act in a particular way and follow certain rules. Medical ethics are professional standards for physicians. Bioethics is a branch of medical ethics and deals with complex issues like euthanasia, transplant medicine, genetic medicine, assisted reproduction therapy, human cloning, and medical genomics. Medical ethics and bioethics concepts are guides for physicians and to ensure patient safety.

"Wrong is wrong even if everyone is doing it. Right is right even if no one is doing it." William Penn, American writer, (1644–1718).

S. Nundy et al., *How to Practice Academic Medicine and Publish from Developing Countries?*, https://doi.org/10.1007/978-981-16-5248-6_13

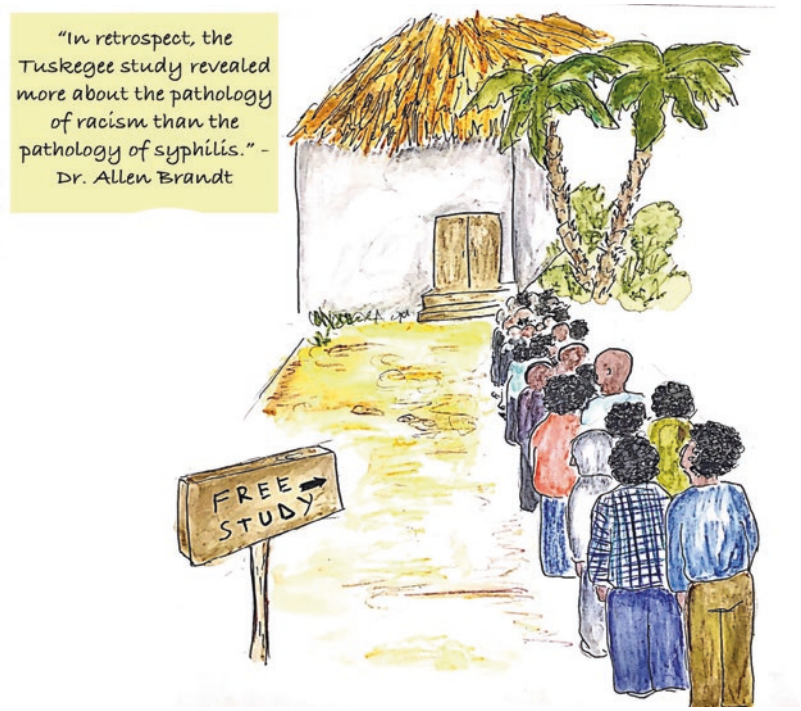
13.2 What Is the History of Medical Ethics?

Hippocrates is considered to be the father of medicine (as well as medical ethics) and enunciated what is now known as the Hippocratic oath around the fifth century BC, which most graduating doctors are required to take even today. In China, Confucius, the great philosopher, enunciated the concepts of ethics [1]. In 1947, after the Second World War a landmark court in Nuremberg, Germany which was investigating the atrocities of Hitler and the Nazis enunciated the Nuremberg Code which has now served as the foundation of modern-day ethics. This was followed in 1949, by the Geneva Declaration and subsequently, in 1964, there was a Declaration of Helsinki that modified the ethical code. 1n 1996, the International Conference on Harmonization of Technique Requirement and Good Clinical Practice Guidelines were published (ICH GCP) [2] involving 13 core principles which all investigators follow today.

In India, the history of medical ethics goes back to the Indus Valley civilization. Ayurveda is an ancient science and two of its manuscripts the 'Charak Samhita' and 'Shushrut Samhita' provide guidelines on ethical practice. More recently, in 2017, the Indian Council of Medical Research enunciated a set of guidelines on medical ethics which we will discuss later.

13.3 What Are the General Principles of an Ethical Clinical Trial?

These are based upon protecting the patients' rights, safety and ensuring his or her willingness to participate. The notorious Tuskegee study on Negro (African-American) males who had syphilis and were left untreated to observe the natural course of the disease was a landmark where no medical ethical principles were followed. It was supposed to last for 6 months but continued for 40 years (1932–1972) [3]. Although the drug penicillin, which could have cured them, was discovered in 1947, the trial patients were not given it or even informed about its existence. They were just given food, free treatment, and a burial [3]. Other studies which were unethical were done by the Nazis during the Second World Ward and in some of these they observed the physiological effects of immersing prisoners in ice-cold water. The Nuremberg code was a direct result of such gruesome experiments.



13.4 What Are the Principles of Medical Ethics?

The four principles are Autonomy, Beneficence, nonmaleficence, and Justice (Fig. 13.1).

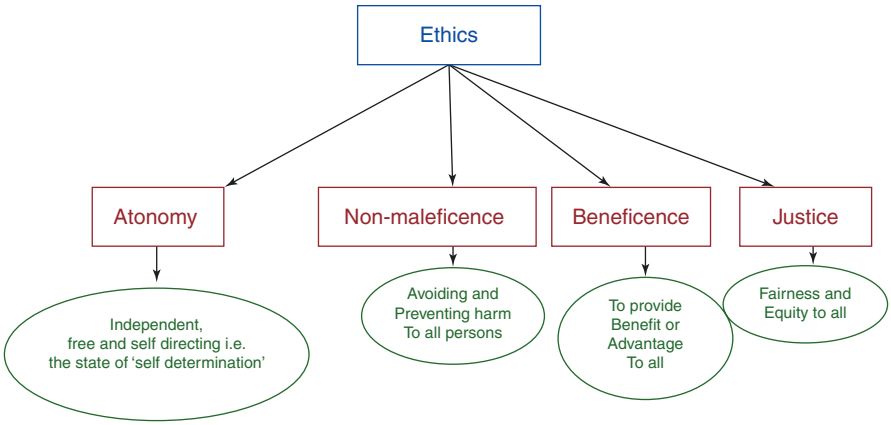


Fig. 13.1 Basic principles of Ethics

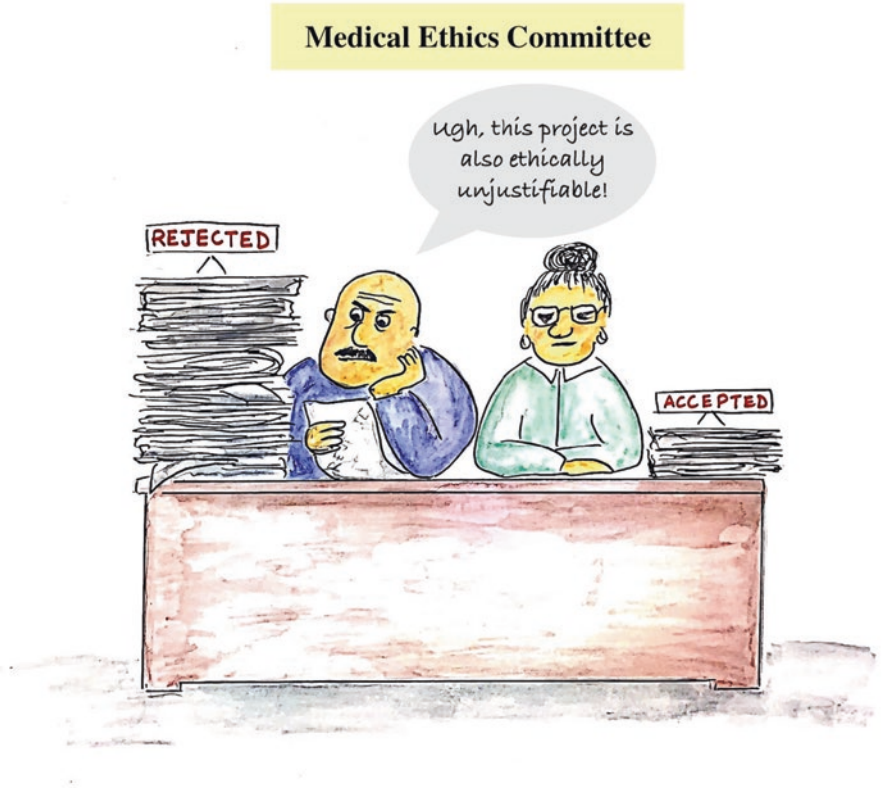
- *Autonomy* means patients should have a choice on whether they want to participate in a study [4]. They also have the right to information on the purpose of the clinical trial the right to withdraw midway, and also the right to know about the details of the drug used in the clinical trial. After stopping the trial, the patient has the right to be on an approved standard of care.
- *Beneficence* is derived from the Latin word meaning 'good deed'. It is to perform an act of 'charity, mercy, and kindness' with the strong implication of doing good to others including doing what is one's moral duty [5].
- *Nonmaleficence* means 'to do no harm'. Thus, the trial should benefit the participant rather than harm them. The principle of nonmaleficence supports the following rules—do not kill, do not cause pain or suffering, do not incapacitate, and do not cause offence [6].
- *Justice.* The fruits of the research should be for all sections of society and benefit the rich and poor equally. Each patient should be treated on his or her merit and need [6].

13.5 What Are the Duties of Ethics Committees?

Research is an important method of advancing medical knowledge but, at the same time, those who do research should not violate human rights. Every institution which does research should have an ethics committee which is a heterogeneous group of individuals whose aims are to monitor all research projects involving humans so that they are being done in the right way and on the right patients. They ensure patient safety and have the right to accept, modify, reject and stop any trial [7]. They should also look at the risk-to-benefit ratio to the participants and to their safety. Their specific duties are to:

- Review the scientific soundness of the trial.
- Accept or reject the proposed trial.

- Ensure the safety of the patient.
- Ensure the well-being of all the participants.
- Ensure travel reimbursements for the participants.
- Debar any group or individual which does not follow ethical principles.



13.6 What Is an Institutional Review Board (IRB)?

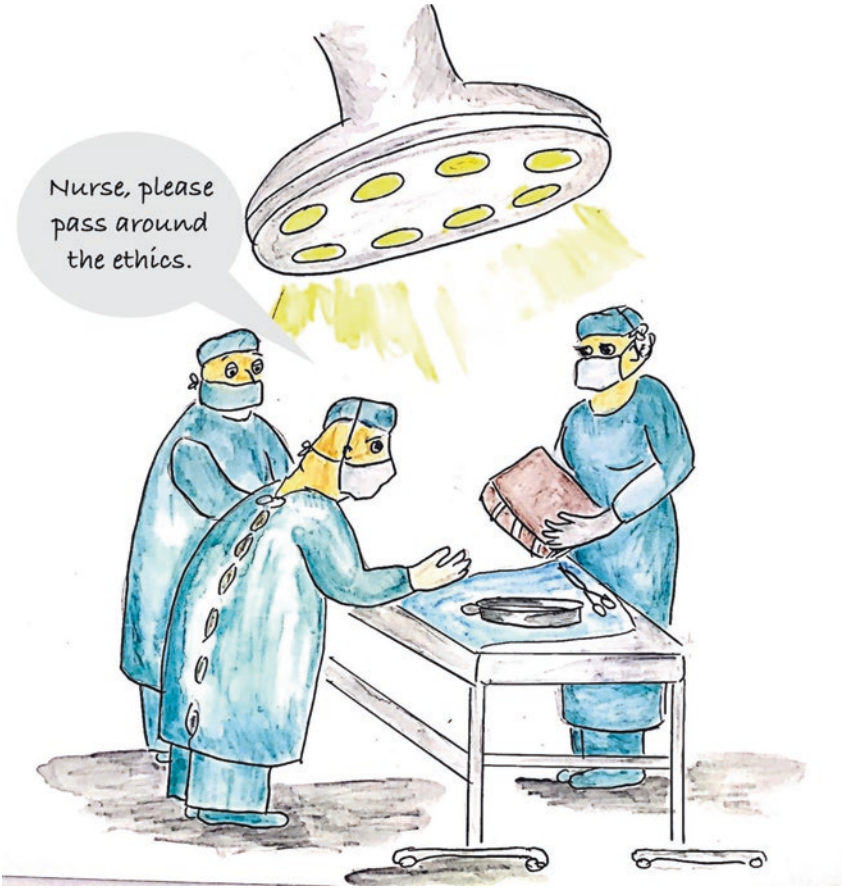
Sometimes an Ethics Committee is called an IRB which consists of members who ensure human safety during trials. There should be at least 5 members, according to good clinical practice, 7 according to the schedule Y of the Act, and 8–12 according to the Indian Council of Medical Research (ICMR) [8]. The members should be from different fields, one from civil society, one lawyer, one social worker, one basic medical scientist, one clinician, and one philosopher. It should have a Chairperson who is usually from outside and a Secretary from within the institution in which the project is proposed to take place. It must also include a woman. The quorum should be complete while addressing any issue. The IRB requires registration from the Central Drugs Standard Control Organization (CDSCO) and its registration requires renewal after every 3 years [9]. All records related to trials should be kept with the IRB for at least 3 years after their completion.

13.7 Which Documents Are Required to be Submitted to the Ethics Committee for Approval?

The list includes the following:

- Protocol of the trial.
- Any amendments related to the trial.
- Consent form given to the subjects.
- Investigators' details.
- Curricula vitae of the investigators.
- The Clinical Trial Agreement (CTA).
- Insurance papers that are site specific.
- Regulatory approval letter from the Drugs Controller (DCGI).
- Any advertisements related to the trial.
- Proof of travel reimbursements to the participants.
- Data collection form.

Besides these, the committee may ask for any other paper which is related to the trial.



13.8 What Happens in Case an Adverse Effect Occurs in a Clinical Trial?

All investigators are required to send regular recruitment-related updates, trial-related protocol deviation, report side effects, and serious adverse effects. In case a patient has any adverse effects, the primary investigator/sponsor should inform the ethics committee and treat the patient. The trial should be accompanied by insurance which covers any hospitalization or death. In case of death or serious adverse effect, the patient or his family needs to be awarded compensation based on a specified formula (Table 13.1) [10].

A serious adverse effect is defined by the Central Drugs Standard Control Organization as: [8]

- Death.
- Hospitalization of the participant in case the study was being conducted as an out-patient.
- Prolongation of hospitalization in case the study was being conducted on an in-patient.
- Persistent or significant disability or incapacity.
- A congenital anomaly or birth defect.
- Life-threatening condition.

The Drugs Controller General of India has issued a directive mentioning that any trial injury or death should be compensated by the sponsor. A compensation formula has already been proposed by the Independent Expert Committee for clinical trial-related death (Table 13.1).

13.9 What Is Medical Research Misconduct?

The Primary Investigator is the principal person who leads the research team. He or she needs to act in a way that is not influenced by his sponsors, pharmaceutical companies, or his peers. Research misconduct includes the following:

- Construction/making-up of data intentionally.
- Recording/reporting of fabricated data.
- Manipulating the research content.
- Omitting/suppressing data or results in the analysis.
- Overlooking scientific data without statistical justification.
- Plagiarism—'stealing of ideas' or using other authors' language for publication.

Table 13.1 Computation formula in case of adverse effect

$$\text{Compensation} = \frac{B \times F \times R}{99.37}$$

where,
B = Base amount (i.e., 8 lakhs)
F = Factor depending on the age of the participant (based on Workmen's Compensation Act)
R = Risk factor depending on the seriousness and severity of the disease, presence of comorbidity, and duration of disease of the participant at the time of enrolment in the clinical trial between a scale of 0.5 and 4 as under:

i. 0.50: Critically ill patient (expected survival not more than 6 months)
ii. 1.0: High-risk patient (survival expected between 6 and 24 months)
iii. 2.0: Moderate-risk patient
iv. 3.0: Mild-risk patient
v. 4.0: Healthy volunteers or participants of no risk.

However, in case of 90% expected mortality or more within 30 days, a fixed amount of Rs. 2 lakhs should be given.
In view of the above, a committee was constituted to work out a formula to be followed to determine the amount of compensation in case of clinical trial-related injury (other than death).
Serious adverse event causing permanent disability to the participant
The committee arrived at a conclusion that the amount of compensation to be paid in case of 100% disability should be 80% of the compensation which would have been due for payment to the nominee(s) in case of death of the participant. The amount of compensation for disability which is <100% will be calculated based on the presence of actual percentage disability. Accordingly, the committee arrived at the following formula:

$$\text{Compensation} = \frac{D \times 80 \times C}{100 \times 100}$$

D =Disability percentage
C = Compensation amount for payment to the participant's nominee(s) in case of death of the participant
Serious adverse event causing congenital anomaly or birth defect
The committee opined that the compensation in such cases should be a lump-sum amount such that if that amount is kept by way of fixed deposit or alike, it should bring a monthly interest amount which is approximately equivalent to half of the minimum wage of the unskilled worker (in Delhi). The committee noted that this aspect was duly considered while fixing Rs. 8 lakhs as the base amount for determining the amount of compensation in case of SAE resulting in death. Hence, the committee decided that the quantum of compensation in such cases of SAE should be half of the base amount as per the formula for determining the compensation for SAE resulting in death.
Serious adverse event causing life-threatening disease
The committee arrived at the following formula.

$$\text{Compensation} = N \times W$$

where,
N = Number of days for a life-threatening situation requiring medical care, irrespective of days of hospitalization
W = Minimum wage per day of the unskilled worker (in Delhi)
Reversible serious adverse event in case it is resolved
Compensation = $2 \times W \times N$.
where,
W =Minimum wage per day of the unskilled worker (in Delhi)
N = Number of days of hospitalization

13.10 Is Consent Important in Doing Research?

Written Informed Consent is a very important document that is required to be signed before starting or enrolling a patient. It means that the patient is willing to participate in the study. This document is signed by the patient who is explained about the risks, benefits, and side effects of the drug being tested. This is applicable for all adults of more than or equal to 18 years of age. If a child is involved in the study and has not attained legal age this is called 'assent'. This information can be given to the patient verbally or in the form of a written document or both. Figure 13.2 explains the need for three important aspects for taking consent [10].

Informed consent form must include the following:

- A declaration stating that it is research.
- Explaining the purpose of the study in simple language and how it will be done.
- Information about the probable duration of the involvement and the number of times the subject will be called for data collection.
- What benefits might accrue to the patient /subjects or to the community with the results expected from the research.
- Any predictable risks, distress, or awkwardness to the subject from participation in the trial.
- The level at which the privacy of the records will be maintained.
- Imbursement/reimbursement for subjects and accompanying relatives depending on the type of study.

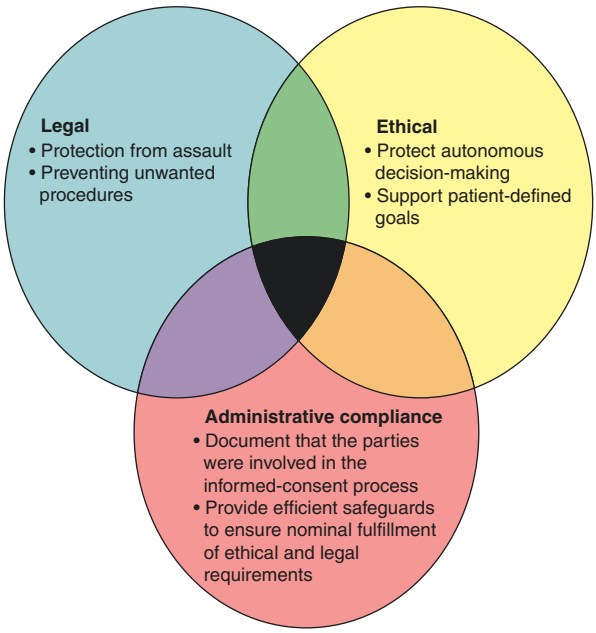


Fig. 13.2 Purpose of informed consent

Table 13.2 Ways to enhance informed consent

Simplification of informed conset documents
Assessment of patient comprehension
Use of printed brochure, information sheets
Use of multimedia and audio-video presentations
Extended discussions with patients
Use of decisional aids to help patients inn decision-making

- Free treatment and/or reimbursement of the subject for research-related injury and/or harm.
- Liberty of the subject to participate and/or withdraw from the trial at any time without consequence.
- Trial-related information of the Principal Investigator and other members of the team and of the Chairperson and Secretary of the IRB.

In addition, the following information may also be required depending on the type of study:

- Any different drugs/measures which may be beneficial to the participant.
- If there is a likelihood that the trial could lead to any defamation of the subject.
- Indemnification coverage if any, for research-related to serious adverse effects (SAE).
- Time for which the sample will be stored and used for secondary purposes.
- If the biological tissue will be shared with other researchers.
- Potential strategies to enhance the informed consent process.

13.11 What Are the Ways to Enhance the Informed Consent Process?

The various ways to enhance informed consent have been listed in Table 13.2. The process of consent should be voluntary, comprehensive, and informative. Additional audio-visual aids and printed sheets can help in decision-making [11].

13.12 Conclusions

- Ethics is an important aspect of the medical profession.
- The principles of ethics are autonomy, beneficence, nonmaleficence, and justice.
- Consent is an act of voluntary agreement between the patient and doctor.
- Consent is in simple language which the participant can understand. It gives details of treatment, possible side effects, and benefits to the patient.
- Compensation is given if there are adverse events in a clinical trial.

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