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REVIEW ARTICLE

ETHICAL PRINCIPLES AND PRACTICES IN CLINICAL RESEARCH: A BRIEF HISTORY AND GUIDELINES OF CURRENT RELEVANCE

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Abstract

Ethics is the science of moral values and standards. Scientific experiments, especially those in human subjects, need to be guided by specific ethical values in several aspects. Human experiments of newly discovered medicines or medicines under development, the clinical trials, have a fairly healthy ethical history in ancient and medieval times. However, between World War I and 1970s, the history of clinical trials is very disappointing and has often violated the ethical principles. As a result, several guidelines on ethical conduct of clinical trials have been formulated by various stakeholders covering more or less the same principles of ethics. The Nuremberg code, Declaration of Helsinki, the Belmont report, the ICH GCP guidelines, and the ICMR Guidelines on Ethics are some of the examples. All these documents have covered mainly three aspects of ethics of conducting research in human patients or subjects: a) the patient related aspects (protection, justice and beneficence); b) scientific standard and quality related aspects and c) documentation, publication and promulgation related aspects.

Keywords: Ethics, human subjects, clinical trials, guidelines

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Introduction

The word "ethics" finds its root in an ancient Greek word – *êthos* (ἦθος), which means character, moral nature, habit or custom. It has to also do with aesthetics or beauty – again relating to some purely human values. Ethics thus synthesizes, recommends, defends and sometimes re-defines the right moral conduct from the wrong one.

In last hundred years or so, medical, biomedical and pharmaceutical sciences have seen unprecedented advancement. And obviously this advancement was possible because of intense research and development activities. We would limit our focus in this paper to the ethics of clinical research in the aforesaid domains of knowledge.

It is kind of strange that the history of research involving human patients in ancient and mediaeval times of medicine and pharmaceuticals is relatively straightforward and mostly ethical. It is the stuff that has been done in the name of clinical research between World War I and late 1970s that is very bleak and shameful.

Earliest Mentions of Ethics in Ayurvedic Literature

Ayurveda (Charaka and Sushruta), among the ancient treatise, mentions the ethical principles of a medical or surgical practitioner which can be extended to the research in vogue at that time.[1,2]

While recommending ethics in practice, which was an integrated part of {long-term) research then, the Ayurveda says, "*'Having finished his studies… he should go about… with undeluded mind and with his eyes looking straight before him. He must be genial and take the initiative in a conversation. He must never resort to the patient's house uninvited.'*

'He should not administer the medicine in the wrong order nor should he delegate the responsibility to another… He must be versed in the knowledge of characteristics of constitution, drugs, disease and age.'[1]

Regarding the compensations to a qualified physician or researcher, the Ayurveda says, *'This science of life is permanent and yielding meritPractice of medicine is never fruitless, it sometimes gives money, sometimes religious merit, sometimes renown or sometimes the opportunity for study… .'*

In dealing with women, it says, *'His attitude to women should be particularly aloof and detached. When he enters a patient's house he should keep his head bent and not be curious about things and persons about him. If he has to enter to treat a woman, he should never go unaccompanied and he should never laugh nor smile nor exchange irrelevant words with her…. He should accept nothing from the woman without the knowledge of her husband. He should never enter without informing beforehand. He should neither talk nor sit with a woman in privacy. He*

should never look at her when she is uncovered nor laugh at her… .'

Finally, the Ayurveda insist that medicine is a lifelong study. It says that there is no limit at all to the Science of Life. So, further it says to the physician-investigator, '*So thou shouldst apply thyself to it with diligence. This is how thou shouldst act. Again thou shouldst learn the skill of practice from another without carping. The entire world is the teacher to the intelligent and foe to the unintelligent. Knowing this well, thou should listen and act according to the words of instruction of even an unfriendly person, when they are worthy… .* 'The ideal physician is the one who is well-born, of wide learning, of wide practical experience, skilful, pure, practised of hand, self-controlled, fully equipped with all the appurtenances (of healing), in full possession of his faculties, conversant with the normal course of nature, able to take prompt and appropriate decisions.[1,2]

Medical Ethics in Ancient and Medieval Europe

It appears that the medical licensure, guilds, universities, and a reciprocity of obligations and regulations thereof began in Europe in as early as 11th century CE. Far before that epoch, there were many references to medical ethics in ancient Greek and Roman texts. The Hippocratic Oath, for example, is well known in ancient Greek medical texts in its original form between fifth and third centuries BC. Greek and Roman medical literature also allude to the choice of treatment, patient cooperation, confidentiality and information given to the patient.[3]

In particular regards to the relationship with the patients, Desiderius Erasmus' views on medical ethics over 500 years ago is amazingly fitting even to the present day standards. He advocates for reciprocal attention to the patient's duties as well as those of the physician's. By treating this reciprocal relationship as a friendship between extreme unequals, Erasmus was able to maintain the nobility of the medical artandat the same time deal with the culturally sensitive issue of physicians'compensation. It is felt that as Erasmus' treatment of physician-patient reciprocity arose from a classical conception of friendship, there may be grounds for reconsidering the role of friendship in other discourses on medical ethics.[4]

Atrocious Violations of Medical Research Ethics during World War II and Following Few Decades

So called "medical experiments" were performed on thousands of concentration camp prisoners during World War II. These experiments included deadly studies and tortures such as injecting people with gasoline and live viruses, immersing people in ice water, and forcing people to ingest poisons.[5]

After the war was over, in 1947, a War Crimes Tribunal was set up at Nuremberg, Germany. The indictments included

conspiracy to commit crimes against peace; planning, initiating and waging wars of aggression; war-crimes and crimes against humanity. Out of 23 physicians and administrators who were accused, 16 were found guilty and imprisoned and 7 were sentenced to death. In the Tribunal's August 1947 verdict, a section called "Permissible Medical Experiments" became known as *the Nuremberg Code*. A summary of the ethical principles of the Nuremberg Code is provided in Table 1.[6]

The Tuskegee Syphilis Study from 1932-1972; the case of Harold Blauer (1953) at the New York State Psychiatric Institute; the New York City's Jewish Chronic Disease Hospital study of 1963; the Willowbrook Study of 1963-66 are some of the other examples of blatant violation of ethics and patients' rights.[5]

Table 1. Summary of the ethical principles of the Nuremberg Code

	Patient-Centric
1	Voluntary Consent is essential
2	Should be conducted by avoiding physical/mental suffering and injury
3	Adequate facilities should be used to protect subjects
4	Subject should always be at liberty to stop at any time
	High Quality & Scientific Ethics Centric
5	Should be based on previous animal experimentation
6	Risks should never exceed the benefits
7	Conducted only by qualified scientists
8	Scientist in charge must be prepared to terminate the experiment when injury, disability, or death is likely to occur
	Publication or Promulgation Centric
9	The results must be for the greater good of society
10	No experiments should be conducted if it is believed to cause death/disability

Declaration of Helsinki

After the declaration of the Nuremberg Code in 1947, the World Medical Association (WMA) issued a seminal document on the human research ethics, in 1964, in Helsinki Finland, called the Declaration of Helsinki. It has undergone as many as seven revisions, and the last one was issued in 2013 at the 64th WMA General assembly in Brazil.[7]

In addition to its General Principles the Declaration has clear-cut guidance on Risks, Burdens and Benefits; Vulnerable Groups and Individuals; Scientific Requirements and Research Protocols; Research Ethics Committees; Privacy and Confidentiality; Informed Consent; Use of Placebo; Post-Trial Provisions; Research Registration and Publication and Dissemination of Results; and on Unproven Interventions in Clinical Practice.[7]

Although the Declaration is primarily intended for the Physicians, the WMA encourages others who are involved in medical research involving human subjects to adopt these aforesaid principles.[7]

The Belmont Report

The Belmont Report (1978) summarizes ethical principles and guidelines for research involving human subjects. Three core principles are identified: *respect for persons, beneficence, and justice.* This report was issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research of the United States.[8]

ICMR 2017 and 2006: Ethical Guidelines for Biomedical Research on Human Subjects

These guidelines[9] have elaborated 12 general principles of Clinical and Biomedical research:

1. **Principle of essentiality:** research being carried out should be essential for the advancement of knowledge that benefits patients, doctors and all others in aspects of health care.

2. **Principles of voluntariness, informed consent and community agreement:** research participant should be aware of the nature of research and the probable consequences of the experiments. Participants then should make an independent choice without the influence of the treating doctor, whether to take part in the research or not.

3. **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…either through insurance cover or any other appropriate means to cover all foreseeable and hidden risks.

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

5. **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).

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

7. **Principle of accountability and transparency:** 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 for a period required by the regulatory authorities.

8. **Principle of the maximisation of the public interest and of distributive justice:** results of the research should be used for benefit of all humans, especially the research participants themselves and/or the community.

9. **Principle of institutional arrangements:** all institutional arrangements required to be made in respect of the research and its subsequent use. All applications should be made in transparent manner.

10. **Principle of public domain:** 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,

11. **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.

12. **Principle of compliance:** All those associated with the research work should comply by the guidelines pertaining to the specific area of the research.[9]

Ethics of Randomization in CTs

Randomized clinical trials pose a number of fundamental ethical questions: a) should they be placebo controlled? b) will control arms get standard treatment at all? can randomized trials of all kinds be cross-over?

Morally sensitive investigators must give careful consideration to these questions. In general, the randomized double-blind clinical trial (either with an active control or, in a few cases, with a placebo control) is ethically justified and the preferred method of demonstrating therapeutic effectiveness and safety. Use of randomized double-blind clinical trials

must assure adequate explanation of the research plan to the patient, the documentation of informed consent, adequate consideration of safety, and an acceptably low risk/benefit ratio.

Conclusions

Our medicines need to be evidence-based. And this evidence of efficacy, safety and quality has to be ethical in addition to being scientifically accurate and valid. History has witnessed that pharmaceutical and medicinal experiments on human subjects had had several departures from ethical standards. Since the publication of the Nuremberg Code, Declaration of Helsinki and similar ethical guidelines, we are trying to give our medicines ethical, scientific and universal legitimacy as a society

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