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Review

Ethics in medical research

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ABSTRACT

Ethics, an essential dimension of human research, is considered both as discipline and practice. For clinical research, ethically justified criteria for the design, conduct, and review of clinical investigation can be identified by obligations to both the researcher and human subject. Informed consent, confidentiality, privacy, privileged communication, and respect and responsibility are key elements of ethics in research. A systematic literature search of English-language articles on Medline, ISI web of knowledge, Sciencedirect, Google scholar, the Cochrane database of evidence-based reviews, and the Database of Abstracts of Reviews of Effects was performed by connecting the Mesh terms ("ethics", "medical research", research ethics", "medical education", "research ethics principles". The abstracts of 461 articles were reviewed for the relevancy of topic and analyzed in terms of application and validity. Out of these, 21 studies were found relevant as they concentrated principles of ethics in medical research, their practical applications, and suggested guidelines for future research.

Research ethics committees must promote greater understanding of ethical issues on biomedical research. These committees function for submission, consideration, evaluation, and communication of findings. Application, research protocol, patient information leaflet and informed consent form, and any other supporting documentation are thoroughly reviewed by research ethics committees for legal and moral safety, integrity, and welfare of the research subjects.

Contents

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1. Historical background

In the early 1960s, most notably in the United States, instances of unethical medical research was reported over the volunteers, especially those who were vulnerable or terminally sick, were treated with obvious disrespect and exposed to significant risks of harm [1]. Among these were the infamous project conducted at the Brooklyn Jewish Chronic Disease Hospital in which elderly patients who had some disability were injected with live cancer cells in circumstances in which it was unclear whether consent was sought [2]. A study of infectious hepatitis C at the Willowbrook home for children with mental retardation, who were deliberately infected with hepatitis C, not only raised serious concerns in public, but also jeopardized the reputation of noble medical profession. In 1966, Henry Beecher's article, 'Ethics and Clinical Research,' in the New England Journal of Medicine reported 22 examples of medical research that involved suboptimal ethical treatment of human subjects [3]. For nearly 40 years (1932–1972), the U.S. National Health Service conducted a research titled the 'Tuskegee Study of Untreated Syphilis in the Negro Male.' The study was done on about 600 black men, of whom 399 had syphilis. The participants were never informed that they were involved in a research study, and their informed consent was not obtained [4]. Such unethical incidents necessitated the dire need of informed consent from participants and researchers' responsibility to be satisfied that the gain anticipated in any research project was commensurate with the risks involved.

This article explicitly reviews widely accepted ethical principles that govern the conduct of research with human participants. Application of research ethics committees to monitor and approve prior review of proposed research that involves human participants or subjects (human research) has been elucidated along with the legal and practical implications.

2. Research ethic's declarations and treaties

A number of treaties and declarations have been reported in the literature, which addressed fundamental principles of ethical conduct in biomedical research: the Nuremberg Code [5], the Declaration of Helsinki [6], EU Convention on Human Rights and Biomedicine [7] Convention on Human Rights and Biomedicine (the Oviedo Convention) [8] various guidelines promulgated by the Council for International Organizations of Medical Sciences [9], and a number of treaties and conventions [10–13]. Principles have been enunciated specifically to protect human subjects from harm and to demonstrate respect for their autonomy. The two comprehensive and pioneering documents about research ethical issues are considered to be the Nuremberg Code and the *Declaration of Helsinki.*

2.1. Nuremberg Code (1947)

In the nineteenth century, the judgment of the trial of the Nazi doctors at Nuremberg is the commonly recognized starting event for modern research ethics. It contained ten paragraphs, referred to as the Nuremberg Code [5], outlined in Table 1. In the modern world, this is regarded as the founding document of contemporary research ethics, which emphasizes on sound scientific research protocol and consent.

In the next two decades following Nuremberg Code, sporadic uses of prior review processes was implemented, but the prevailing view was that reliance on the primary

Table 1
Statements of Nuremberg Code [14].

No.	Statements
1	Voluntary consent to be based on sufficient knowledge of the nature, duration, purpose, methods, inconveniences, hazards, and effects of the research
2	Research would yield fruitful results for the good of society not procurable by other methods
3	Research to be based on animal research and prior knowledge
4	All unnecessary physical or mental suffering and injury to be avoided
5	No experiment be conducted in which death or disabling injury will occur (except where physicians were also subjects)
6	Degree of risk would not exceed that determined by the humanitarian importance of the problem to be solved
7	Preparation and facilities be provided to protect subjects against even the remote possibility of injury, disability, or death
8	The research be conducted by scientifically qualified persons and require the highest degree of skills and care
9	Subjects be free to bring an experiment to an end if they reached the physical or mental state where continuance seemed impossible
10	Researchers be prepared to terminate the experiment if they had cause to believe, in their good faith, skill, and judgment, that continuation was likely to result in injury, disability, or death to a subject

responsibility of researchers in the design and conduct of medical research offered ample protection of the involved participants.

2.2. Declaration of Helsinki (1964)

In 1964, the *Declaration of Helsinki*, published by the World Medical Association (WMA), introduced an authoritative attestation of the need for prior review of any kind of human research [6]. Although the *Declaration* emphasized the scientific standards that should govern scholarly research, it allowed more freedom to the physicians to omit the application of consent procedures in special circumstances [15]. This shortcoming of the *Declaration* indicated that the rights and safety of the research participants still lied with the individual investigator. Then came the revision of the *Declaration of Helsinki in 1975* [16] that required the assessment of research protocols by an independent research ethics committee. With the revised version, it seemed that biomedical research involving human subjects finally had been furnished with a firm system of internationally accepted norms and principles [17]. Today, the *Declaration of Helsinki* is considered as a document of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

3. Research ethics committees

The system of prior ethical review of medical research employs to protect the rights and welfare of human participants, ensuring the legal and ethical application of codes of practice of medical research conduct. US federal regulations for the protection of human research subjects define a "human subject" as "a living individual about whom an investigator obtains [1] data through intervention or interaction with the individual, or [2] identifiable private information" [18].

An institution's Research Ethics Committee (REC) aims to safeguard the welfare, dignity, and safety of the participants, ensures that ethically approved research is conducted in line with the approved protocol, and promotes public confidence in the conduct of human research. RECs play key roles in promoting ethical practices in biomedical research and in identifying solutions to ensure that the interests of researchers and society do not take precedence over the rights of the participants [19].

The committee performs the following functions [20]:

a. **Prior review** of human research proposals, scrutinizing the ethical standards for research conduct in legal framework
b. **Observations** to the investigators, to modify the research proposal to meet the required ethical standards
c. **Decision** to approve or reject the research proposal
d. **Monitoring** the conduct of approved research proposals, ensuring that their conduct continues to conform to the approved protocol
e. **Resolution**, or referral for resolution, of complaints in relation to the conduct of approved research projects or the conduct of the ethical review of those projects
f. **Premature termination** and/or suspension of the conduct of a research proposal whenever it becomes evident that continuing conduct will expose participants to greater levels of risk than those approved
g. **Accountability and quality assurance** by reporting to the relevant institution about its performance

Applications to the RECs follow the official review of the proposal, and one of the following decisions may be sought:

1. Accept without changes
2. Accept with suggested changes
3. Recommend submission to committee of another region
4. Revise and resubmit (with changes)
5. Reject (with reasons)

4. Research misconduct

Currently, majority of the research misconduct and irregularities are related to studies funded by the pharmaceutical industry and strongly linked with the financial interests of this industry. Technical faults in the research design, wrong recruitment process, insufficient sample size, and weak statistical analysis of the data often lead to non-publishable research. Another form of research misconduct is the procedural irregularities by misinterpreting the trial data, attempting to draw favorable conclusions than those warranted by the available data [21]. Reporting of fabricated favorable results due to the comparison of the drug under study only against placebo or a non-gold standard drug also leads to research misconduct.

5. Key issues of research ethics

5.1. Informed consent

Informed consent refers to an ethical and legal doctrine based on the understanding that all interventions (diagnostic, therapeutic, preventive, or related to scientific studies) in the medical field should only be performed after a participant has been informed about the purpose, nature, consequences, and risks of the intervention and has freely consented to it [22]. The primary focus of consent should be on informing and protecting research subjects, through disclosure and discussion of relevant information, meaningful efforts to promote participants' understanding, and by ensuring that decisions to participate, or to continue participating, are always made voluntarily.

Informed consent is the ethical cornerstone of randomized clinical trials (RCT), where volunteers are given the option to participate in a trial that includes randomization or to remain outside the trial and receive traditional medical treatment. Mandatory condition for an informed consent include; provision of detailed information to a subject; adequate understanding of the information provided; expression of consent and/or authorization of the intervention [23].

The researcher's primary moral responsibility is to design a clinical trial that will answer a research question without exposing human subjects to undue risks in the process [24]. When fully informed subjects give their consent, acknowledge their role as research participants and take responsibility for their designated roles. Assuming that the research question is significant, the trial is well structured, and the risks to the individual patient are justified, the tension between collective ethics and individual ethics is obviated when individual subjects give their informed consent. This holds true if the primary intent of the investigator is to compare two treatments, not to provide better overall care to the subject [25]. Implementation of informed consent can be considered as a sign of the growing patients' welfare and rights movement, protecting various dimensions of their integrity, safety, and confidentiality.

Obtaining consent does not necessarily employ disclosing the information; rather it demands comprehension of the information ensuring that the subject is, in fact, amicably informed. However the problems in attaining fully informed consent are well documented [26,27]. In some situations, despite researcher's sincere efforts, subjects often fail to understand the nature or rationale for the research and hence are incapable of providing an informed consent. In two separate studies that assessed biobank participants' understanding, more than one-third of participants answered questions incorrectly regarding the objective of the research, limitations to confidentiality protections, that their DNA would be stored as part of the research, that the research involved some risks, and whether they would receive individual genetic results [28,29]. This reflects an important understanding that genomic research presents challenges for traditional models of informed consent, and provides opportunities for new models of consent and communication [30].

5.2. Patient information sheet

Once informed consent is obtained, the research subject is given a patient information sheet [31], detailing the following aspects of the study:

1. Title of the research project
2. Invitation to participate in the research
3. Purpose and significance of research
4. Time commitments
5. Termination of participation, indication voluntary contribution
6. Risks involved
7. Costs and compensation
8. Anonymity and confidentiality

5.3. Confidentiality

Confidentiality means the nondisclosure of certain information except to another authorized person. The concept of confidentiality applies that the information a person reveals to a professional is private and has limits on how and when it can be disclosed to a third party [32]. Various dimensions of confidentiality described in the literature include human rights, confidentiality in young persons, domestic violence, true anonymisation of data, validity of consent for disclosure, cancer and genetic registers, fertility, involuntary disclosure, and safeguards [33].

There is no breach of confidentiality if the following recordings for any purpose were used, as long as they were effectively anonymised [34]:

a. Conventional X-rays
b. Images taken from pathology slides
c. Laparoscopic images of the inside of abdominal cavity
d. Images of internal organs
e. Ultrasound images

To maintain the subject confidentiality, the researcher should collect only the data that is really required, should collect anonymous data, store name and data separately by using identification numbers instead of names, use password to protect the data files, and secure the office and computer.

5.4. Privacy

Privacy is the quality of being secluded from the presence or view of others. Privacy in research refers to the right of an individual to make decisions concerning how much information about their physical status, health, social network, and thoughts and feelings will be shared with investigators [35]. To protect the privacy rights of family members, researchers must be careful in determining whether family members should be considered as research participants.

5.5. Privileged communication

Privileged communication includes conversations within the context of a protected relationship, such as that between doctor and patient, a therapist and client, an attorney and client, a husband and wife, or a priest and penitent; under common law, privilege involves a number of rules excluding evidence that would be adverse to a fundamental principle or relationship if it were disclosed [36]. Such communications are secure, reliable, and meant to be kept among the directly involved parties.

5.6. Respect and responsibility

Respect in research refers to respect for people and respect for truth. People have the right to dignity and privacy (informed consent and confidentiality). Respect for truth implies probity and respect for the intellectual rights of others. All possible efforts should be directed to avoid plagiarism and clinching false conclusions by over and under emphasizing the results [37].

Responsibility of the human subject involves voluntary informed consent, avoiding deception, rewards and incentives, privacy, and disclosure. Also the researchers are responsible for maintaining the reputation of educational research by adhering to the highest standards of quality research. When publishing the research, investigators should disclose any competing or financial interests.

6. Data Protection Act 1998

This act is applicable to the researchers residing in the UK and explicitly describes the legal ways and means to use the personal data. Briefly, the act can be viewed as having 7 standards outlined in Table 2.

6.1. Overview of research ethics in medical education

Medical research ethics is anchored in the Hippocratic Oath, in doing no harm, and tends to take the protection of the individual as its main objective [38]. Therefore, according to the *Declaration of Helsinki*, studies should be designed in the safest manner possible and every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens weighed against foreseeable benefits to the subject or to others.

General principles governing the ethics in research demand that research involving humans has merit and is beneficial, that researchers have integrity, that the benefits and burdens of research participation are justly shared, that risks to participants are minimized and are justified by potential benefits, and that participants are respected as people and their informed consent is given [1]. Recently, there is escalating attention to topics such as reasons for or against participants' satisfaction with informed consent procedures [39], comprehension of risks [40], views on compensation [41] and sources of trust or mistrust in the research enterprise [42]. Punch [43] challenged that the process of obtaining informed consent is inappropriate, because activity that cannot be interrupted is taking place, even though the mere presence of a researcher does change the situation. This is known as the "observer's paradox." Also psychiatric patients are not wholly free to choose when it comes to activities such as leaving the hospital, and cannot choose when visitors enter or leave the ward (these are some reasons for regarding this group as vulnerable) [44]. Hence, ethical guidelines, such as informed consent, the principle of voluntariness, and estimating the risk/benefit ratio, become substantial challenges when employed in special circumstances.

Table 2

Standards	Description
1	• The research subject must be informed that who will hold the data, who will have access to data and the reason for holding the data • If the data is collected from a third party e.g. physicians, then they must be informed about the research • Researchers must review the need to hold personal data
2	• The data should only be collected for the defined objective(s) and should not be further processed which is not consistent with the objective • An exception to this statement being the recycling of the personal data in a manner that it would not inflict damage or distress to the research subjects
3	The data must be only that which is required for the designed research
4	The data must be accurate and if necessary updated
5	• The data must not be maintained unnecessary longer than the planned research • An exception to this statement being the recycling of the personal data in a manner that it would not inflict damage or distress to the research subjects
6	Empowers the research subjects with the right to know what data is kept about them, the reasons for keeping the data, who will be told about the data, and purpose of this exercise
7	Data should be stored securely. Computer files should be password controlled and manual files should be secured in locked containers

6.2. Future vision and research potential

There are certain areas in research ethics, which need further investigations and analysis. Salient features are highlighted below:

1. There should be a consensus on the **right to withdraw by the researcher**. Due to the danger of rapid dissemination, this right to withdraw becomes impractical and invalid in no time, and current recommendations do not have enough regulatory control in such situations.
2. There is an urge for a fundamental and precise **risk/benefit analysis** of the public data sharing.
3. The existing and emerging **governance structures** and guidelines need to be explored and researched. This will facilitate the utility and constructive use of technologies within ethical frameworks.
4. The institutions need to organize workshops, seminars, and training **courses for the academia** and novice researchers for the education and knowledge about research ethics.

6.3. Conclusion

Ethics of medical research on human subjects must be clinically justified and scientifically sound. Informed consent is a mandatory component of any clinical research. Investigators are obligated to design research protocols that establish standards of scientific integrity, safeguard ethical and legislative issues of the human subjects, and follow the protocols for prospective review by independent research ethics committees.

Conflict of interest

Authors have no conflict of interest in this study.

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