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Ethics in Biomedical Research and General Principles of Indian Council for Medical Research National Ethical Guidelines for Biomedical and Health Research involving Human Participants 2016

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Abstract

Knowing what constitutes ethical research is important for those who conduct research and the researcher should be familiar with the basic ethical principles and policies designed to ensure the safety of the research subjects. Research must be ethically conducted, trustworthy, and socially responsible for the results to be valuable. Ignorance of policies designed to protect research subjects is not considered a viable excuse and the researcher needs to fully understand the ethical code and guidelines to guarantee upstanding research practices. In the last decade medical research in India saw emergence of difficult ethical issues and intervention from the Supreme Court of India. The different socio-cultural ethos and the varying standards of health care in India pose unique challenges to the application of the universally prevailing ethical principles and guidelines. This necessitated the Indian Council of Medical Research (ICMR) to revise their 2006 ethical guidelines for biomedical research as 'National Ethical Guidelines for Biomedical and Health Research on Human Participants 2016'. These guidelines are applicable to all biomedical, socio-behavioral and health research conducted in India which involves human subjects. This article gives an overview of the evolution and principles of research bioethics, and helps to understand and disseminate the general principles of the Declaration of Helsinki 2013 of World Medical Association and the National Ethical Guidelines 2016 of ICMR.

INTRODUCTION

Ethics is the philosophical discipline that dates back to various religious writings and pertains to our notions to differentiate the good from bad, and the right from wrong.[1,2] It is the science of morality or moral philosophy that deals with our moral duties and obligations to the society, and seeks to address philosophical questions about morality.[1,2] Bioethics is the application of ethics in the field of healthcare and is the philosophical study of ethical controversies brought about by the advances made in the field of biology and medicine.[1,2] It incorporates philosophy, theology, anthropology, history, politics, and law, with ethical issues that arise in medicine, dentistry, biotechnology and other allied healthcare sciences.[1,2] The field of bioethics has grown over the last few decades from the 1960's to encompass ethical concern in the clinical settings, stem cell research, genetic cloning, and reproductive technologies, to broader concerns of human research participants, healthcare policy, and allocation of scarce resources.[1,2] This multidisciplinary interconnecting and overlapping evolving field may be broadly categorized under three headings: (1) Academic Bioethics: theoretical and practical biomedical aspects of the moral

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obligations and responsibilities of healthcare clinicians, researchers, and scholars; (2) Law Bioethics and Public Policy: legal and extra-legal regulation of clinical and research practices and framing world policies for the betterment of the universe as a whole; and (3) Clinical Ethics: incorporation of bioethics in clinical practice to improve patient care and management, and the code of conduct in the patient-healthcare-provider relationship.[1]

Research or biomedical research is defined by Council for International Organization of Medical Sciences (CIOMS) as "scientifically designed activity or activities to develop, contribute, and/or improve the theories, principles, relationships, and accumulation of information pertaining to betterment of human life and healthcare".[3] We need research to improve healthcare. Research bioethics is the branch of bioethics that deals with ethics in the field of research in medical and life sciences. It deals with the code of conduct in the relationship of participant-researcher, conflict of interest of sponsor-investigator, and supervision-monitoring of the research.[1] Biomedical research pertains to a broad range of systematic investigation on human subjects for developing and improving our knowledge to help improve our health, increase our understanding of the disease, and ethically justified by its social value.[4] Every form of research has some inherent risk and probabilities of harm to the participants and/or community.[4] Protection and safe-guarding the participants from the anticipated risks should be the highest priority and should be built into the study design.[4] 'Do no harm' has been the universal principle in all the systems of healthcare around the world.[4] The authors hope that this article helps a future budding researcher to understand the need, evolution, and the principles of research bioethics, and shall disseminate the general principles of the declaration of Helsinki 2013 of World Medical Association (WMA) and the national ethical guidelines 2016 for biomedical and health research involving human participants published by the Indian Council of Medical Research (ICMR).

EVOLUTION OF RESEARCH BIOETHICS

All the religions of the world preach ethics and give various codes of conduct for human beings to follow. The ancient Indian books of *Vedas, Sanatan Dharama, Sushrutha Samhita, Charaka Samhita, Bhagavad Gita,* among others promulgate various principles of ethics. The Hippocratic Oath about selfless service is traced back to the 3-5th BC renowned Greece physician. The modern version of this oath written in 1964 by the English physician Louis Lasagna is used all over the world by newly graduated physicians to publically pledge their commitment to health care and their responsibilities to the society.[5] With the rise of scientific human experimentation in the 17-18th century the need for self-regulation and medical ethics was first articulated by Scottish philosopher John Gregory and his younger associates the English dissenter Thomas Percival and American Benjamin Rush.[6]

The Nuremberg code was the first international document on the ethics of research which came into existence in 1947 as an aftermath of the inhuman treatment of Jews by the Nazi doctors in the concentration camps for various human experiments.[7] The Nazi doctors tortured, brutalized, crippled, and murdered thousands of Jews in the name of medical research. The key outlines of the code are as presented below.

1. Voluntary consent should be given by human subjects for the proposed research.
2. The study should yield fruitful results for the good of the society unprocurable by any other scientific methods.
3. Research must be based on sound theory and prior animal testing.
4. Anticipated results should justify the outcome of the experiment.
5. All unnecessary physical and mental suffering or injuries to the subjects are to be avoided.
6. No research is to be conducted if priori reason is present to believe that death or disabling injury shall occur to the subject.
7. Degree of risk taken cannot exceed anticipated benefits of the research.
8. The research can be conducted only by scientifically qualified persons.
9. Subject should be at liberty to end or opt out of experiment.
10. Scientist in charge must be prepared to terminate experiment at any stage to safeguard the health and wellbeing of the subject.

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PRINCIPLES OF RESEARCH BIOETHICS

Belmont report was drafted by the national commission for the protection of human subjects of biomedical and behavioral research in 1979 as a direct consequence of the 40 yr. (1932-1972) unethical Tuskegee clinical trials for syphilis in Alabama, on economically backward African-American people, sponsored and conducted by the Department of Public Health, Government of United States of America (USA).[8] The three cornerstones or pillars of healthcare research bioethics put forth in this report is universally accepted and is to be judiciously followed in all researches that recruit human participants.

1. Autonomy: This concept refers to the ability to take decisions for oneself, respect for the participant, special protection for people with diminished autonomy or vulnerable population (orphans, prisoners, students, people with special needs, and such others), voluntary participation, informed written consent, privacy and confidentiality, and consideration for cultural characteristics.[1,8-10]
2. Beneficence and non-maleficence: This principle refers to the obligation to do good always and never to do harm, assessment and calculation of risk-benefit ratio, and ensuring the scientific validity of the research.[1,8-10]
3. Justice: To ensure equal distribution of risks and benefits, equal distribution of resources, fair compensation and reimbursement, and declaration of any conflict of interest by the stakeholders.[1,8-10]

Ethics provides a framework for evaluating problems and determining an appropriate course of action and does not prescribe a specific set of rules or policies.[10] The principles of ethics are open-ended and often appear vague because if the principles are taken individually or collectively they might appear to be in conflict with each other depending on the prevailing situation and that period of time.[10] Decisions on the ethical issues should be based on sound, inductive and causative reasoning.[10] The core values and concepts of research bioethics include among others

1. Justifying the inclusion and need of human participants in the proposed research.
2. Ensuring the scientific value and validity of the research.
3. Showing respect for participant and maintaining their privacy and confidentiality.
4. Promoting and protecting the interests of research participants before the interest of science and society.
5. Voluntary participation and the right of the participant to discontinue participation, even after the study has begun.
6. Bringing about more good than harm for the betterment of the society.
7. Distributing the risks and the potential benefits, and ensuring that the sparse resources are used judiciously.
8. All vulnerable groups and individuals should receive specifically considered protection.
9. Upholding transparency and veracity (truthfulness) of the research.
10. Obtaining an independent and transparent ethical or review board certification prior to the enrolment of human subjects.
11. Registration in clinical trial registry to enable public dissemination of the obtained positive or negative results and outcome.
12. Ensuring that the participant and the associated community receive the post-trail benefits of the newer discovery, intervention or invention.

The Nuremberg Code 1947, United Nations Universal Declaration of Human Rights 1948, Deceleration of Helsinki 1964, and Belmont Report 1979, provided the foundation for the more recent internationally accepted important guidelines on bioethics.[7,8,11,12] Some of these are listed below.

1. Good Clinical Practice 1994 - World Health Organization (GCP-WHO).[13]
2. International Conference on Harmonization - Good Clinical Practice 1996 (ICH-GCP E6 R1).[14]
3. International Ethical Guidelines for Biomedical Research Involving Human Subjects 2002 - Council for International Organization of Medical Sciences (CIOMS).[3]
4. Universal Declaration on Bioethics and Human Rights 2005 - United Nations Educational, Scientific and Cultural Organization (UNESCO).[12]
5. Declaration of Helsinki 2013 - World Medical Association (WMA).[11]
6. The Ethics of Research Related to Healthcare in Developing Countries 2014 - Nuffield Council on Bioethics.[15]
7. European Group on Ethics in Science and New Technologies (EGE) 2015.[16]

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8. National Ethical Guidelines for Biomedical and Health Research involving Human Participants 2016 - Indian Council of Medical Research (ICMR).[4]

DECALARATION OF HELSINKI

In the late 1950s the drug thalidomide was not approved by the Food and Drug Administration (FDA) for use in USA. This unapproved drug was however used by well-meaning American physicians to treat nausea associated with pregnancy on unsuspecting mothers, due to the unethical marketing practice of the pharmaceutical company. Thalidomide was subsequently associated with limb-defects in more than 12,000 new-born.[2,11] Eventually this lead to the Declaration of Helsinki (Finland) in 1964 by the World Medical Association (WMA), and this document was revised in 1975, 1983, 1989, 1996, 2000, 2002, 2008 and 2013, and forms the basis of Good Clinical Practices (GCP).[11] The summary of the main issues addressed in the 64th WMA General Assembly held at Brazil in October 2013 are as below.[11]

1. While the primary aim of medical research is to generate new knowledge and understanding, it is the duty of the physician to follow all ethical standards that ensures and safeguards the health, dignity, wellbeing, privacy, confidentiality, and rights of his human subjects. The sole responsibility of protecting the participant rests with the physician, even though they have given consent to be part of the research.
2. Medical research should be conducted by and requires supervision by medically and scientifically qualified individuals who have received appropriate education and training in research bioethics. Research should be conducted with minimal harm to the environment.
3. Research protocols should be reviewed by an independent transparent scientific and ethics committee prior to the initiation of the trail, and should follow all international norms and any ethical standards or codes put forth by individual countries.
4. Physicians who combine research with medical care should involve their patients in research only if it is justified by its potential preventive, diagnostic, or therapeutic value and the study does not adversely affect the health of the patient. Risks should never exceed benefits and the importance of the research objective should outweigh the risks and burdens. All studies should be preceded by careful assessment of predictable risks and burdens to the subject or group and must be continuously monitored.
5. When risks outweigh the potential benefit the physician must assess whether to continue, modify, or stop the study. Appropriate compensation and treatment should be provided by the researcher to subjects who are harmed as a result of participation in the study. The physician should be confident that the risk can be adequately assessed and can be managed satisfactorily.
6. Medical research on vulnerable group and individuals shall only be justified if the research meets the health needs of that group and cannot be carried out in a non-vulnerable group. The vulnerable individuals should benefit from the knowledge, practice or intervention gained from that research. All vulnerable groups and individuals should receive specifically considered protection.
7. Research involving human subjects must confirm to all scientific principles and be based on the complete understanding of the earlier scientific literature and other sources of information on the area of research interest, and after adequate laboratory and animal experimentations.
8. The protocol of the proposed research should contain a statement of the ethical considerations involved and indicate how the principles of this declaration have been addressed. The protocol should contain all information's regarding funding, sponsors, institutional affiliations, conflict of interest, incentives provided, compensations, and arrangements for post-trail provisions.
9. The protocol should be approved by the concerned independent ethics committee prior to the start of the study. The researcher must report any adverse event (AE) and provide information for monitoring the study by the committee. No amendments to the approved protocol can be made by the researcher without prior approval of the committee for such modification or deviations. At the end of the study the researcher must submit a final summary of the study's findings and conclusion to the committee.
10. Privacy of the participants and confidentiality of their information must be protected at all times.
11. All participation must be voluntary and a freely given written informed consent must be obtained from the subjects after adequately informing them of the study aims, methods, anticipated benefits, potential risks, discomforts, compensation, incentives, post-study provisions and all the other relevant aspects of the

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proposed study. The potential participant should be informed about the right to refuse and the right to withdraw from the study at any given period of time without reprisal or denial of further standard treatment care. The consent should not be obtained under duress. If the potential research subject is incapable of giving an informed consent (e.g. vulnerable individual, minor) then consent from the legally authorized representative (LAR) should be obtained after seeking an assent from the participant. When the proposed research is on physically / mentally incapable or unconscious individuals then the informed written consent should be obtained from the LAR and later consent obtained from the subject as soon as possible.

12. Any new intervention must be tested and proven against the best known standard treatment protocol or the gold standard. Placebo may only be used when there are no proven intervention, or when compelling and scientifically sound methodological reason exists, and only if use of the placebo or no intervention will not cause any AE or irreversible harm to the participant.
13. After the completion of the research the identified beneficial intervention should be available for all the research participants. The stakeholders and the host country should make provisions for post-trail access to the beneficial intervention for the participants and the community.
14. All research involving human subjects should be registered in publicly accessible databases and clinical trial registry before recruitment of the first subject. The stakeholders and researchers have the moral duty to make public the complete and accurate results of their completed study.
15. Where proven interventions do not exist or if the current intervention is proved ineffective and if in the physician's judgment the unproven intervention offers hope of saving life, re-establish health, or alleviate suffering then the physician may provide the intervention. A research should be designed to validate scientifically the effectiveness of the intervention after seeking expert advice and conducted after obtaining informed written consent from the participant.

INDIAN COUNCIL OF MEDICAL RESEARCH GUIDLINES

For ethical research in India ICMR issued the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980.[4] Later in 2000 rapid advances made in biomedical science and technology necessitated the updating of these guidelines to 'Ethical Guidelines for Biomedical Research on Human Subjects', followed by a revision in 2006 to 'Ethical Guidelines for Biomedical Research on Human Participants'.[4] The honorable Supreme Court of India in its judicial order of November 2013 issued direction that all future clinical and drug trials to be conducted in any part of India shall have audio-visual recording of the process of obtaining the written informed consent of each trial subject, adhering to the principles of confidentiality and privacy and obtaining a prior consent for audio-visual recording.[17] Due to the emergence of difficult ethical issues over the last decade in many of the medical research and drug trials conducted in India the ICMR guidelines were further revised as 'National Ethical Guidelines for Biomedical and Health Research on Human Participants 2016'.[4] The three basic principles of research bioethics namely autonomy, beneficence, and justice has been expanded into the general principles and these are to be applied to all biomedical and health research involving human participants, or on research using their biological material or data.[4]

1. Rights, safety and well-being of the research participant/subject are the most important consideration in any biomedical research that involves human participants.
2. ***Principle of essentiality:*** The need for human participants in the proposed research is considered to be essential only if after diligent consideration of all the other alternative methods in the background of the existing knowledge in the proposed area of research has been looked into and evaluated. The proposed research should be carefully considered and peer reviewed by competent scientific committee followed by certification from the institutional review board or ethics committee (IRB/EC) prior to initiation of any research involving human subjects. The IRB/EC should acknowledge the necessity/essentiality for human participants, scientific validity, and benefits to the community in the proposed research. The benefits should justify the risk to the research subject after benefit-risk assessment.
3. ***Principle of voluntariness, informed consent and community agreement*:** All research participants should voluntarily give a written informed consent to take part in the proposed research, and should have the right to abstain from further participation if so desired at any time without any obligation or loss of benefit/treatment to

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which they are normally entitled. When the participant is deemed to have diminished autonomy or belongs to a vulnerable population, the informed consent shall be obtained from who is empowered to or has a duty to act on their behalf (e.g. LAR). If required for cultural characteristics / appropriateness adequate consent or agreement should be obtained from the head of the family or the community leader. Only the IRB/EC has the authority to permit waiver of informed written consent based on the degree of risk involved.

4. ***Principle of non-exploitation and distributive justice***: Burdens and benefit of research should be distributed without any discrimination between communities, groups or countries. The research participants should be equitably selected so that the burdens and benefits of the proposed research are distributed fairly and without arbitrariness or discrimination. Sufficient safeguards should be ensured to protect the vulnerable groups, and such group should not be used for benefit of those who are better off than them. Research should not lead to social, racial or ethnic inequalities.
5. ***Principle of privacy and confidentiality***: The identity, all records/report/data, and personal matters of the research subject shall be kept confidential at all times and its access limited to the authorized personal. The participant should never suffer from any discrimination, stigmatization or hardship as a consequence of having participated in the research. While conducting research with stored biological samples or medical records coding or anonymisation of personal information should be done. Any scientific publication arising out of research should uphold the privacy of the subject, and a specific re-consent would be required to publish any photographs that reveal the subject's identity. Only under specific circumstances such as (a) when required by the law or regulatory authorities, (b) threat to persons life, (c) public health risks, (d) when essential for providing intervention or treatment the confidentially can be breached. The right to life of an individual (suicidal/homicidal tendency, HIV infection, etc.) supersedes the right to privacy.
6. ***Principle of precaution and risk minimization***: At all the stages of research due care and caution should be taken by all stakeholders (principal investigator, institution, IRB/EC, sponsors, regulators) to ensure that the participant and community are put to minimum risk. The risk can be discomfort or harm which could be physical, psychological, social, economic or legal. The IRB/EC shall monitor the research and if required give necessary directions and specific guidelines to minimize all anticipated risks as the research progresses. An adequate mechanism should be established by the host institution and/or sponsor for providing required aftercare and treatment in the event of any unfortunate adverse event (AE) or harm due to the research and if the need arises to immediately provide compensation and/or rehabilitation either through insurance or any other appropriate means. It is the responsibility of the researcher to report any AE to the IRB/EC within 4-7 days along with a report on relatedness of the AE to the research.
7. ***Principle of professional competence***: All research shall be conducted by competent and scientifically qualified persons who can act with total integrity and impartiality. All research involving human subjects should be planned, conducted, evaluated and monitored by persons who are competent in that field and have the appropriate relevant qualification, experience and/or training.
8. ***Principle of accountability***: All research shall be conducted in a fair, honest, impartial and transparent manner after full disclosure of any conflict of interest by the stakeholders. Complete records of the research, data, and notes should be retained for a prescribed period for monitoring, evaluation, and for scrutiny by any appropriate legal or administrative authority. The researcher should take adequate precaution and appropriate steps that are necessary to ensure that the research reports, materials and data are duly preserved and archived. All stakeholders involved in the research are accountable for their actions.
9. ***Principle of maximization of benefit and of distributive justice***: Research should be designed and conducted for the benefit of all mankind and never for certain group of people or community. The direct and/or indirect benefit(s) should be shared with the participant and the community from which they are drawn or recruited. The benefits accruing from the research should be made accessible to individuals, community and the population of research.
10. ***Principle of institutional arrangements***: The researcher should comply with all the required procedures and institutional arrangement made in connection with the research and its subsequent use should be in a bonafide and transparent matter. Institutions where the research is being conducted should have policies for appropriate research governance and take the responsibility to facilitate the research by providing required infrastructure, manpower, funds and training opportunities.

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11. ***Principle of transparency***: All research result, data, outcome and evaluation emanating from the research should be placed in public domain through scientific publication and such methods (including clinical trial registry), so as to benefit all mankind and to avoid repetition of research and wasting of sparse resources, while ensuring the right to privacy of the participant. All stakeholders should disclose to the participants and the IRB/EC any conflict of interest or any financial or non-financial secondary interest, and should take all considerations to manage and mitigate them appropriately.
12. ***Principle of totality of responsibility***: It is the moral responsibility of all stakeholders who perform or profit from the research or product to ensure safety and scientific validly, and to subject themselves to monitoring and to take all due remedial action whenever required. The national and international ethical guidelines and related regulations are binding on all the stakeholders directly or indirectly.

CONCLUSION

The primary aim of medical research is to understand the cause, development and effects of the disease, and to improve preventive, diagnostic, and therapeutic interventions. Even the best proven intervention or diagnostic gold standard must be evaluated continuously for their safety, effectiveness, efficiency, accessibility and quality. It shall be the duty of all the stakeholders associated with the research to ensure that both the letter and spirit of the guidelines, modifications, regulations or notifications specifically prescribed for that area of research are scrupulously observed and duly complied with. The international code of medical ethics states that "a physician shall act in the patient's best interest when providing medical care." The three keywords for ethical research involving human participants are autonomy, beneficence, and justice.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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