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REVIEW PAPER

Ethical requirements in the clinical drug trial: Indian perspective

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ABSTRACT

Advances in Biomedical Science and Technology and their application in medicine are provoking anxiety among the public and society with new ethical dilemmas. Society is concerned about what it fears would be abused in scientific investigation and biomedical technology. Biomedical research (BMR) involving human participants (HPs) raises many unique and complex ethical, legal, social, and political issues. Research scholars in medical education need sound knowledge and a clear perspective in their relevant field. The academic curriculum hardly includes such experiences and skills, neither taught nor shared. Mastery and proficiency on the topic shall assist researchers in dealing with research misconduct issues challenging legal and ethical aspects in their experiments, studies, and publication. There are national and international guidelines, regulations, and acts to curb any unhealthy BMR, including clinical drug trials (CDTs). All research involving HPs should be conducted per three basic ethical principles: respect for the person, beneficence and justice. The present guidelines are directed at applying these principles to research involving HPs. The scholars need to remember those defined ethical and legal issues failing which legal intervention will come into force. In this regard, relevant ethical and legal issues for carrying out BMR-like CDT will be focused.

Keywords: Indian Council of Medical Research; Central Licensing Authority; Indian Medical Council Regulations.

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INTRODUCTION

Research ethics guides us in responsibly conducting BMR, defined by principles, regulations, and laws. The objectives of it are to protect the HPs, research to serve the interests of individuals, groups, and society as a whole, scrutinise specific actions of research proposals for ethical soundness like supervision of risk, guarding privacy and the procedure of informed consent, and lastly, to builds trust, public accountability, and public support for science.[1]

Continued educational support on legal and ethical research might help medical graduates and scholars prevent their research and publication difficulties.[2] The commonly encountered ethical issues by the medical fraternity ranges from the initial decision to undertake the project, the selection and application of the various research procedures, and data management, analysis and publication.[3]

It may also be remembered that failure to comply with ethical norms may invite legal action. Hence the sound knowledge of ethical and legal guidelines is the prerequisite for any research to initiate, mainly the CDT. Therefore, this review paper aims to determine whether the existing ethical and legal bindings are enough to curb the unhealthy practice of CDTs or sufficient to promote CDT in India.

ETHICAL PRINCIPLES

It is essential to resolve ethics-related matters while engaging people in BMR. Therefore, with the HPs, BMR

must follow the four fundamental ethical principles: autonomy (respect for person/HPs), beneficence, non-maleficence (not harm), and justice.[4]

BACKGROUND OF THE ETHICAL RESEARCH

The Hippocratic oath was the exemplar of medical etiquette through the centuries and, as such, determined the professional attitude of generations of physicians in modern medicine for 2500 years in its moral and ethical flavour. The Caraka Samhita, the Indian Ayurvedic Medicine treatise dating from about the first century AD, instructs doctors to "endeavour for the relief of patients with all thy heart and soul; thou shall not desert or injure thy patient for the sake of thy life or living".

In 1772, a physician, Thomas Percival, drew up a comprehensive scheme of medical conduct.[5] His work was published with the title "Medical Ethics". Percival advised doctors "to unite tenderness with steadiness, and condescension with authority" to inspire the minds of their patients with gratitude, respect, and confidence.[6]

The American Medical Association (AMA) have recognised that its "Code of Medical Ethics", issued in 1847, was primarily derived from Percival's work.[7]

During the post-second world war (1939-45), medical practitioners of Germany conducting tests on the individual without consent was the most astounding, subjecting the HPs to serious risk of death or permanent impairment. It raised grave concerns about subjecting human subjects to medical research.[8]

Consequently, the earliest international code on human experimentation appeared as the Nuremberg Code in 1947. Although HP's informed consent was mentioned in 1900, the Nuremberg Code highlighted the essentiality of voluntariness of participation.[6]

The World Medical Association (WMA) is the guardian of 'The Declaration of Helsinki', consisting of bundles of ethical principles on human experimentation;[9] was widely regarded as the cornerstone of human research ethics.[10-13] This set of moral principles is not legally binding to international law. Instead, it draws its mandate from the degree to which it has been codified or influenced by national or regional legislation and regulations.[13] This statement of Helsinki is the responsibility of the WMA, yet the declaration is considered the property of all humankind, as stated in the Brazilian Forum, 2000. It has gone for five revisions and two clarifications since its conception in 1964. The WMA recently invited submissions for further revision.[14]

The Belmont Report of the US in 1979 defined the ethical principles for protecting HPs in biomedical and behavioural research. Besides these, some more relevant documents guided the BMR to avoid any ethical or legal inflict, as shown in **Table 1**.

Table 1 Relevant ethical declaration on Biomedical research

Sl No	Title of declarations	Year
1	Schedule Y of the Drugs and Cosmetics Rules	1945
2	The Universal Declaration on Human Genome and Human Rights	November 11 1997
3	The Indian Medical Council (Professional Conduct, Ethics & Etiquettes) Regulations	March 11 2002
4	The International Declaration on Human Gene Data	October 16 2003
5	Universal Declaration on Bioethics and Human Rights	October 19 2005
6	ICMR Guidelines on Research of Human Subjects	2006
7	Prof. Ranjit Roy Chaudhury Expert Committee Report	2013
8	The Drug and Cosmetic Bill	2013
9	The New drugs and Clinical trials rule 2019	March 19 2019

In collaboration with the WHO, the **Council for International Organizations of Medical Sciences** (**CIOMS**) published 1982 "The International Ethical Guidelines for Health-related Research" in Geneva. This guideline emphasised the ethical issues in less developing nations. The present scope of it is restricted to the typical activities of health-related research with human participants, viz., observational research, clinical trials, biobanking and epidemiological studies.

THE INDIAN MEDICAL COUNCIL REGULATIONS[15]

This regulation is known as Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 (Amended Up to October 8, 2016). A few relevant regulations for registered medical practitioners regarding BMR are:

Chapter (6.2): Defines the patent and copyright items. For the greater interest of humanity, copyrighted or patent appliances must be made available. However, a medical practitioner may patent or copyright those products, such as instruments, medicines, or procedures.

Chapter (6.6): It defines the Human Rights violation. Under no circumstances does the medical practitioner aid, abet torture, or lobby in the annoyance of mental or bodily hurt to anyone.

Chapter 6.8 (e): This chapter prescribes the ethical principles of BMR. The physician may conduct projects funded by the medicinal company, but they must follow the criteria (i) to (vii) laid down under this regulation. It must be transparent and accountable for everyone involved and should not have any conflict of interest of the funded institute. Follow-up of all the ethical principles is necessary, from obtaining permission from the appropriate authority, ethical approval, and disclosures of the funding amount at the beginning.

Regulation (7.22): Graceful compliance with ICMR guidelines while conducting any BMR is mandatory. It also defines consent as misconduct if not taken per the ICMR guidelines.

CLINICAL DRUG TRIALS (CDT) AND LEGAL ISSUES

Randomised controlled trials (RCTs) existed better than clinical research over the years. For the controlling authority, it has become a concerning issue. CDT is a closely regulated trial research in India that must comply with many ethical requirements.[16]

Recently, in India, as many as 211 people died between January and June 2012 due to serious adverse events (SAE) during CDTs. Many demand strict regulations with rigorous monitoring to ensure that patients do not become the unfortunate victims of CDT.[17] It has also been alleged that many medical professionals carry CDT violating ICMR and other ethical guidelines. Even the sexual malfunction drug was tried out on mentally ill patients in Indore without the ethics committee (EC)s' proper approval as alleged. The issues of informed consent, adequate documentation of medical records, etc., were also ignored.[18]

The WHO in 2014 issued a statement strongly advocating public disclosure of all CDTs and their results in India. When data is not released, doctors, patients and medical regulators cannot make informed decisions.[19] Hon'ble Supreme Court of India has advocated safeguarding the HPs to minimise SAE and death. In the said trial, the issues of compensating the victims were not solved. A Public Interest Litigation (PIL) was recorded in the Supreme Court of India in 2012. Consequently, a committee has been formed by the Government of India to investigate compensation.[20,21]

Recently, the Drugs and Cosmetics Rules formed a committee to define the amount of compensation in cases of SAE and death following CDTs.[20]

In the direction of the regulatory bodies, it is said that the researchers must comply with all the ethical aspects and have been warned not to indulge in professional misconduct by violating any regulation thereof.[8,20,22]

Though CDT research is essential for humanity, not at the cost of the regulatory, ethical guidelines from the appropriate authority, even non-governmental agencies come up to monitor the progress of CDTs. The National

Human Rights Commission (NHRC) investigated the human rights issues of the HPs. The HPs are to get adequate compensation with the intervention of the different courts.[20] So, the researchers must follow all the regulatory guidelines with letters and spirits as follows:

PRINCIPLES IN ETHICAL RESEARCH

The study aims to improve people's well-being (Social Value). The outcome is to produce valuable results and increase understanding (Scientific Validity). The selection of the participants should be reasonable. The risks involved must be balanced by benefits the subjects. An independent review is to be obtained. There must be informed consent, and enrollment should be respectful.[23]

ETHICAL GUIDELINES FOR BMR

The ethical declaration on BMR is the ICMR Code, which has a statement of General Principles on ethical considerations involving HPs in BMR and a statement of Specific Principles on Research using HPs in specific areas of BMR.[8]

All institutions in the country, which carry out any form of BMR involving HPs, must comply with this declaration of ICMR with the utmost respect to protect all individuals' safety and well-being. EC must approve all proposals on BMR involving HP.

TERMS OF REFERENCE

The Standard Operative procedures (SOP) should specify the terms of reference mentioning all operative procedures.[8]

Duty of Principal Investigator (PI)

The PI is accountable for undertaking the research and observing the HPs recruited for the study's rights, health, and welfare. He should be competent and qualified to conduct methodological analysis for the study's proper conduct. He should follow the study protocol's ethical, legal and scientific requirements.

REVIEW PROCEDURES

EC should review every BMR proposal. The scientific review should be carried out beforehand. The ECs should verify the ethical matters related to the participants' threats and benefits with proper justification with documentation of their secrecy, confidentiality, and justice issues. The committee shall also screen the proposals for completeness and, depending on the risk involved, categorise them into three types: exemption from the review, expedited, and complete review.[8]

Exemption from review

The EC decides whether the research project will be exempted from review but not the researcher to decide. Hence, every BMR proposal should be submitted to the EC Proposals that have less than minimum risk fall under this category, i.e., classroom teaching technique, etc.

The exceptions to exemptions for ethical review of research proposal come when research on educational examinations, investigation or discussion events that can reveal the identity or through identifiers and disclosing information outside research could subject the participant to the risk of civil or criminal financial liability psychosocial harm. Also, when interviews involve a direct attempt or entry to private papers.[8]

STATEMENT OF GENERAL PRINCIPLES

The clinical researchers need to understand and follow the statements laid down in the ICMR declaration like principles of essentiality; principles of voluntariness, informed consent and community agreement; principles of non-exploitation; principles of privacy and confidentiality; principles of precaution and risk minimisation; principles of professional competence; principles of accountability and transparency; principles of the maximisation of the public interest and distributive justice; principles of institutional arrangements; principles of the public domain; principles of the totality of responsibility and at the end the principles of compliance.[8]

STATEMENT OF SPECIFIC PRINCIPLES

Furthermore, the clinical evaluation of drugs, devices, vaccines, diagnostics, herbal remedies; epidemiological studies; human genetics and genomics research; research in transplantation research, and assisted reproductive technologies, statements come up to be followed as specific principles.[8]

THE NEW DRUGS AND CLINICAL TRIALS RULES, 2019

This rule will apply to all new drugs, EC and investigational new drugs relevant for human use,

bioequivalence studies and clinical trial in India. This new rule prescribes certain specific requirements for the institutional EC. The EC must follow the requirements set per the new rules and forward their report to the Drugs Controller, India, the Central Licensing Authority. The primary aims are to encourage clinical trials in India.[24]

REGULATORY MECHANISM IN INDIA

The CDTs in India are governed by the "Drugs and Cosmetics Act of 1940", "The Medical Council of India Act of 1956", and "The Central Council for Indian Medicine Act of 1970". The prerequisites for carrying out a CDT in India are: "Permission from the Drugs Controller General, India (DCGI)", "Approval from the respective EC where the study is planned", and "Mandatory registration on the ICMR maintained website".[24]

THE CENTRAL DRUGS STANDARD CONTROL ORGANISATION (CDSCO)

CDSCO is India's National Regulatory Authority (NRA) under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. It may be mentioned that the Drugs & Cosmetics Act, 1940 and Rules 1945 have assigned different tasks to state and central regulators to regulate all issues of drugs & cosmetics. The consistent execution of all obligations of the Act & Rules is made throughout this country.

Transparency, accountability, and uniformity is the responsibility of CDSCO regarding all aspect of newer drugs starting from manufacturing, import and distribution. CDSCO grants permission to carry out the CDTs under the Drugs and Cosmetics Act and prescribes the standards and its control. The State Drug Control Organizations may advise implementing the Drugs and Cosmetics Act. Both jointly grant the licenses of specific specialised categories of critical Drugs such as blood and blood products, IV Fluids, vaccines, etc.[24]

The ethical and legal obligations bind to BMR, integral to producing scientific papers. Violation of it may invite judicial scrutiny.[25] The five years of preservation of all data of CDT are also of paramount importance.[26]

REGISTRATION OF THE EC FOR CDT

EC shall only review and approve a clinical trial protocol with prior registration with the Central Licensing Authority.[24] The EC shall be required to register under rule 7, with an application to CLA designated by the Central Government, Ministry of Health and Family Welfare, Department of Health Research (DHR) in Form CT-01. The EC must provide the following (**Table 2**) data and details, as mentioned in the third schedule to be accompanied by Form CT-01.[27]

Table 2 List of mandatory papers for the ethics committee (EC) registration

Sl no	Required papers
1	Constitution and composition of the EC
2	Biodata of all members of the EC
3	SOPs of EC
4	National and international guidelines followed by the EC
5	Copies of the protocol, data collection formats, case report forms, investigators' brochures, etc., presented for review
6	All correspondence with committee members and investigators regarding the application, decision, and follow-up
7	Plan of all EC meetings and minutes of all EC meetings with the signature of the chairperson
8	Copies of decisions communicated to candidates
9	Records relating to any order issued for premature termination of study with a summary of the reasons thereof
10	Final report of the study, including microfilms, compact disks, or video recordings
11	EC recommends the determination of compensation
12	Records relating to the Serious Adverse Effects (SAE), medical management of trial subjects, and compensation paid

Grant of registration certificate

Provisional registration with two years validity is granted upon receipt of such details and Form CT-01. A final registration may be given in Form CT-03 on satisfactory verification of the paper submitted by the EC.

Rejection of registration certificate

However, if satisfied, the application may be accepted within 45 days, mentioning the reason behind it. The EC may again appeal to the Central Government, the Ministry of Health and Family Welfare, within 60 days of receiving such an order of rejection. The Central Government may investigate allowing the applicant (EC) to dispose of the case within 60 days of receipt of such an application.

Renewal of registration

The EC must apply in the same Form CT-01 for renewal with the documents mentioned in Table 3 three months before registration expiry. Upon scrutinising the data and documents, the CLA renew the registration. Submitting a new set of documents is required only when there is a change of some information of EC. In contrast, the renewal may be rejected for non-compliance with the requirement.

REGISTRATION OF THE EC FOR HEALTH AND BMR

The institution should have an EC to conduct BMR to look after all the ethical requirements per the National Ethical Guidelines for Biomedical and Health Research Involving HPs laid down by the ICMR.[27]

Registration with authority designated by the Central Government, the Ministry of Health and Family Welfare, and the DHR should be done with the online portal at: https://naitik.gov.in/DHR/Homepage. The National EC Registry for Biomedical and Health Research under the DHR assists in accepting and handling such applications looking for registration and helps the authority execute duties. They issue a provisional registration certificate with two years of validity. The final registration is for five years which is granted in Form CT-03. The activities of the EC have to be as per ICMR guidelines for research involving HPs.

Thus, if done in letter and spirit, the available guidelines, regulations, and acts are sufficient to conduct BMR, viz., CDTs.

CONCLUSION

Therefore, ethics is needed in research and publication. If somebody violet ethics, then the law comes into force as nobody is above the law. The CDTs in India are on a gradual rise but leg behind many miles from the advanced countries. Violations of ethical guidelines have created legal hurdles among researchers. To avoid all legal worries, the researchers must follow ethical guidelines, national and international treaties.

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