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Evolution of ICMR Ethical Guidelines for Biomedical Research

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ABSTRACT

The Indian Council of Medical Research (ICMR) felt the need for standard national guidelines for conduct of biomedical research, and issued the "Policy statement on ethical considerations involved in research on human subjects" in 1980. With the rapid evolution and adoption of scientific and technological innovations in the field of biomedical research and changes in concepts of morality and philosophy, the guidelines incorporated many changes and revised versions were released in the years 2000, 2006 and 2017. The latest 2017 ICMR guidelines for biomedical research has been titled "National ethical guidelines for biomedical and health research involving human participants". It was designed to cater to the needs of the advancing technological development and also adopted International guidelines with modifications that suit our population with varied social, cultural and religious backgrounds. Also, separate guidelines were formulated by the ICMR for biomedical research involving children, and revised the guidelines for stem cell research in the year 2017. These guidelines have become the reference documents for the researchers, Ethics Committee members and other stakeholders involved in biomedical research in India.

INTRODUCTION:

Although there was existence of International guidelines like "The Nuremberg Code of 1947"[1] , Universal declaration of Human rights, Geneva (1948)[2] , Declaration of Helsinki (1964) [3], and Belmont report (1979) [4], the need for a standard national guidelines for conduct of research on humans was felt by the Indian Council of Medical Research (ICMR) inorder to protect and safeguard the rights, dignity, and wellbeing of the research participants and to prevent them being exploited by unethical experiments.

Evolution of the ICMR ethical guidelines:

ICMR issued a "Policy statement on ethical considerations involved in research on human subjects" in the year 1980.[5] With advancements in science and technologies in the field of biomedical research and better insights about disease pathogenesis paving way for the discovery of newer medical treatments, there was a need to modify the ethical guidelines from time to time. In addition, changes in concepts of morality and philosophy as to what is right and wrong also drove the guidelines to undergo drastic revisions from time to time. As guidelines evolved, it also adopted relevant aspects from the existing international ethical guidelines after modifying them to suit the varied social, cultural and religiously diverse populations of India.

After release of the ethical guidelines in 1980, it was revised periodically in the years 2000, 2006 and 2017. [6-8] The title of the document was also revised with time. The 2000 ICMR guidelines was titled "Ethical Guidelines for Biomedical Research on Human Subjects" and in the title of 2006 ICMR guidelines, the word "subjects" was replaced with "participants". The latest 2017 ICMR guidelines is titled "National Ethical Guidelines for biomedical and health research involving human participants".

Although the ICMR ethical guidelines underwent repeated revisions, the basic ethical concepts remained the same. With each revision, additional care was given to the finer details and was represented more elaborately. Many new topics were added, irrelevant topics removed and many concepts elaborated.

Overview of the contents of the ICMR ethical guidelines with changes incorporated in revised versions:

Contents of "Policy statement on the ethical considerations involved in research on human subjects" in 1980 [5]

The 1980 guideline document was only 9 pages and outlined the major rules to be followed in biomedical research. It covered the need for the constitution of the Institutional Ethics committee (IEC) and implementation of the ethical committee's guidelines. Topics like the support of clinical research by the council and other agencies, drug trials, clinical trials with plants, and indigenous systems of medicine were covered. The importance of Informed consent was highlighted and guidance on clinical research on vulnerable population like children, mentally deficient subjects, prisoners, medical students, and laboratory personnel were provided. It also mentioned provision of financial reimbursements to the study subjects participating in the clinical research projects and the need for publication of research papers in the Indian Journal of Medical Research.

Changes incorporated in "Ethical Guidelines for Biomedical Research on Human Subjects" in 2000 [6]

The 2000 ICMR ethical guidelines document was more elaborate with the inclusion of many new topics and it runs to 77 pages. Although the 1980 guidelines, mentioned about evaluation of drugs, devices and herbal remedies, there was a lacuna with regard to ethical guidance on clinical evaluation of medical diagnostics/ vaccines. This lacuna was fulfilled in the 2000 guidelines. Moreover, it included many new topics which were not dealt with in the earlier version, like ethical principles involved in epidemiological studies, human genetics research, transplantation including fetal tissue transplantation, and assisted reproductive technologies. Thus, it provided greater insights into the ethical aspects involved in research involving the newly included topics.

Changes incorporated in "Ethical Guidelines for Biomedical Research on Human Participants" in 2006 [7]

The 2006 ICMR ethical guidelines document was much more elaborate with 120 pages. The various topics were classified into chapters with a total of 8 chapters. The topics were similar to the 2000 guidelines with the following changes:

- Two new subtopics on "conflict of interest" and "post-trial access" were included in the topic on "General ethical issues".

- "Bioavailability studies" were included in drug trials in the chapter on the "Statement of specific principles for clinical evaluation of drugs/devices/diagnostics/vaccines/herbal remedies".

- "Community participation" was added to the specific principles in the chapter "Statement of specific principles for epidemiological studies".

- The term "genomics research" was added to the chapter on genetic research since an important milestone i.e., completion of the human genome project was achieved in the year 2003.[9] Thus, the chapter was titled "Statement of specific principles for human genetics and genomics research". Also, "biobanking" was included in detail in this chapter.

- A sub-topic on "Stem cells" was included as a part of the "Statement of specific principles for research in transplantation".

Changes incorporated in "National Ethical Guidelines for biomedical and health research involving human participants" in 2017 [8]

The 2017 guidelines document has many new topics added, some deleted and some topics written in a more detailed manner. It consists of 187 pages and the various topics were classified into 12 sections with sub-sections. New topics like responsible conduct of research; public health research; and social and behavioral sciences research for health (for first-time ethical guidelines on qualitative research has been formulated in 2017 ICMR guidelines) were incorporated. Also, the topic "datasets" was added newly in the section on "Biological Materials, Biobanking and Datasets".

The topics that were deleted from 2017 ICMR guidelines were as follows:

- Statement of specific principles for research in transplantation including fetal tissue transplantation

- Statement of specific principles for assisted reproductive technologies

This is because separate guidelines named "ICMR -DBT Guidelines for Stem Cell Research and Therapy" [10] were formulated, for research using stem cells in the year 2006 and later

revised in 2017 as "National guidelines for stem cell research" [11] and hence title on principles for research in transplantation was removed. The title on principles for assisted reproductive technologies (ART) was also deleted in 2017 guidelines because ART is mainly therapeutic and hence it need not be included in guidelines for biomedical research. Moreover, a separate "National Guidelines for Accreditation, Supervision, and Regulation of ART Clinics in India" was formulated in the year 2005.[12]

The topics/sections that were further elaborated and formulated as separate sections in 2017 ICMR guidelines are:

- Informed consent process
- Vulnerability
- Research during humanitarian emergencies and disaster
- "Biological materials, biobanking" in section on "Biological Materials, Biobanking and Datasets"

Modifications in salient ethical issues mentioned in the ICMR guidelines with time:[5-8]

General statement

The general statement included in the 2000 and 2006 ICMR guidelines were removed in the 2017 guidelines.

Statements of general principles

The basic 12 statements of general principles formulated in 2000 guidelines remained the same till 2006. In 2017, minor alterations were made. Out of the 12 general principles in 2006 ICMR guidelines, 3 principles - the Principles of the maximization of the public interest and distributive justice; Principles of public domain; and Principles of compliance were removed and replaced by Principle of Social Responsibility; Principle of Maximization of Benefit; and Principle of Environmental Protection.

General Ethical Issues

In the "general ethical issues" section of 2017 ICMR guidelines, an additional risk category called "minor increase over minimal risk" has been added compared to previous 2006 guidelines. Also in this section, subsections like "distributive justice", "payment for

participation" and "ancillary care" were included in 2017 guidelines. Also the subsection on "post-trial access" was modified as "post research access and benefit-sharing" in 2017 guidelines.

Institutional Ethics committee or Ethical review procedures

The need for an independent institutional ethics committee was recognized as early as 1980. The ICMR 1980 guidelines states that every institute involved in research must constitute an Institutional Ethics Committee (IEC) which should scrutinize the research proposals of researchers from their institute for preserving the health and safety of the potential research participants (subjects).

In 2000 guidelines, elaborate details of composition, quorum requirements, terms of reference, review procedures, submission of application, decision making process, interim review and record keeping (mentioned as up to 15 years after study completion, which was changed to 3 years in 2006 guidelines) were mentioned.

In 2006 guidelines, additionally following aspects were included:

- Training of the ethics committee members
- Registration of ethics committee approving clinical trials with authority
- Review procedures - explained in detail with classification into exempt, expedited and full board review.
- Administration and management – requirement of full time secretariat

Compared to the 2006 ICMR guidelines, the following subtopics have been added/modified in the section on "ethical review procedures" in the 2017 ICMR guidelines.

- Table on "Composition, affiliations, qualifications, member specific roles and responsibilities of an Ethics Committee" has been added.
- Table on "Ethical issues related to reviewing a protocol" has been added.
- A box on "Types of decisions by Ethics Committee" has been added.
- A subsection on "Review of multicentric research" has been added.

- In site monitoring – "cause monitoring" and a box on "examples for cause monitoring" has been added.

- "Documents to be maintained by EC for record" has been modified and classified based on "type of document" into "administrative related documents" and "proposals-related documents".

- "Registration and accreditation of Ethics committees" has been added.

Although these changes were made in the guidelines for Institutional ethics committee, the basic motto or responsibility of the IEC remains the same and has stood the test of time. It is to safeguard the dignity, welfare and rights of potential research participants and to ensure that research on humans is conducted in an ethical manner.

Clinical trials of drugs and other interventions

In this section on "Statement of specific principles for clinical evaluation of drugs/devices/diagnostics/vaccines/herbal remedies", the following topics which were not present in the previous 2006 ICMR guidelines, were added in the 2017 guidelines:

- Biologicals and biosimilars
- Clinical trials with stem cells
- Surgical interventions (including conditions for sham surgery)
- Community trials (public health interventions)
- Clinical trials of interventions in HIV/AIDS
- Investigator-initiated clinical trials
- Clinical trials on contraceptives
- Clinical trials in oncology
- Clinical trials of products using any new technology
- Synthetic biology

Human genetics testing and research

In this section in 2017 ICMR guidelines, the following topics have been added and they were not present in the 2006 guidelines.

- Culturally sensitive issues
- Storage of samples for future genetic research
- Results of genetic testing
- Publication aspects
- Commercialization and conflict of interest (COI)
- Misuse of genetic technology
- Population screening
- Pre-implantation genetic screening and diagnosis (PGS and PGD)
- Screening for carrier status
- Use of newer technologies - Chromosomal micro array; Whole exome sequencing and whole genome sequencing; Gene editing technology – Clustered, regularly interspaced, short palindromic repeat (CRISPR); Genome-wide association study (GWAS)
- Research on human embryos
- Foetal autopsy

Highlights of current 2017 ICMR guidelines:

The following are the highlights of the current 2017 ICMR guidelines:

- Previous grey zones in the area of ethics have been clarified.
- These guidelines can be used as a reference document by the researchers, Ethics Committee members and other stakeholders involved in biomedical research in India.
- It is more organized, thus making it easy to reference or quote clause(s) from the 2017 guidelines. It is also more colorful and visually appealing, compared to the previous versions.

- At the end of the guidelines, separate segments like "Suggested further reading", "Abbreviations and acronyms", and "Glossary" are included to further guide the readers. Moreover, annexure 1 contains a list of "Standard Operating procedures" and annexure 2 contains "a list of members of committees involved in the revision of guidelines (2015-2017)".

- The language of the guidelines is simple so that even the layperson in the ethics committee can understand it.

- Even undergraduate students can understand the guidelines and especially students who do STS projects can be instructed to read them and follow them.

CONCLUSION:

Thus, with the evolution to address the contemporary and emerging ethical issues, the ICMR guidelines became more organized, refined, and elaborate. Also, many ambiguities present in the previous guidelines were clarified. The guidelines incorporated many additions and deletions to cater to the needs of the advancing technological development and recent advances in the field of medicine. Also, the guidelines were developed to suit our population with varied social, cultural, and religious backgrounds. Thus, it has become the reference document for all biomedical research conducted in India.

However, revision of the ICMR ethical guidelines is an ongoing continuous process and publication of separate guidelines document for some topics which require more elaboration has become a norm. In the year 2017, the ICMR has revised the guidelines for stem cell research and also formulated a separate guidelines for biomedical research involving children.[11,13] In addition, in the year 2018, ICMR published a short and user-friendly "Handbook on National Ethical Guidelines for Biomedical and Health Research Involving Human Participants" for quick and easy reference of the major ethical issues invoved in biomedical research.[14] Similarly in the year 2019, the ICMR published the "ICMR Policy on Research Integrity and Publication Ethics (RIPE)" inorder to "ensure highest professional and ethical standards for biomedical and health research at all stages right from inception, conduct, review, reporting and publication".[15] Moreover, in the year 2020, with the emergence of Covid-19 pandemic, the on-going research came to a standstill and there increasing proposals on research in Covid; thus opening up new ethical dimensions and dilemmas. The ICMR issued the "SOP Template for Ethics Review of Biomedical and Health

Research During Covid-19 Pandemic" and the "National Guidelines for Ethics Committees Reviewing Biomedical & Health Research During Covid-19 Pandemic" recognizing the need for a guidance on review of research proposals during the times of humanitarian emergencies like the urrent Covid pandemic.[16,17]

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