The New Indian Ethical Guidelines for Biomedical and Health Research-Delving New Vistas

The Indian Council of Medical Research (ICMR), the apex body in India for the formulation, coordination, and promotion of biomedical research, recently updated the ethical guidelines for pursuing research involving human subjects. These guidelines are titled as the "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017."[1] The present statement is the 4th of its kind released by the ICMR after a gap of 11 years.

India is a global hub for clinical trials and the remarkable progress witnessed in the field of biomedical research fittingly calls for the current changes in ethical practice. The release of these 2017 Indian guidelines appropriately coincides with the other two internationally acclaimed guidelines on biomedical research, namely, the "International Ethical Guidelines for Health-related Research Involving Humans" prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization in 2016 and the "Federal Policy for the Protection of Human Subjects or Common (Final) Rule" in 2017.[2]

This commentary deals with the some of the substantial modifications made in the current guidelines in comparison to the previous one ("Ethical Guidelines for Biomedical Research on Human Participants, 2006") and other International Guidelines.

The Structure

Broadly, the following amendments are conspicuous in the presentation style. First, there are sequential multilevel numberings of the various headings and subheadings which make the location of a particular section easier.[3]

Second, there are 12 sections compared to the eight chapters in the previous edition; all the sections are sufficiently revised and updated despite which there seem to be some lacunae. The newer sections included are the sections on "Responsible conduct of research (Section 3)" and the "Social and behavioral sciences research for health (Section 9)." The chapters on "Statement of specific principles for research in transplantation (Chapter VII)" and "Statement of specific principles for assisted reproductive technologies (Chapter VIII)" are completely removed from the current version.

Third, the most significant one is the utilization of "Boxes" and "Tables" for better representation of the data, which succinctly convey the message.[4] The document contains 43 Boxes and eight Tables; which are also aptly numbered sequentially [Tables 1 and 2].

Fourth is the inclusion of "Abbreviations and Acronyms" (51 items) and "Glossary" (68 items) at the end which act as ready reckoner for the abbreviated terms and definitions used in the document.

However, the lack of indexing is very much felt. An alphabetically listed "Index," at the end of the document, would have made things much easier. Although the list of "Standard Operating Procedures (SOPs)" for ethics committees (ECs) is appended, templates for each of these 28 SOPs could have been provided for better clarity. Another suggestion is to hyperlink the "Table of Contents," individual "Tables" and "Boxes" for easy maneuvering between the texts. The inclusion of charts or algorithms presented in a way to help all the stakeholders involved in research could have been beneficial in the various decision-making processes like that existing with the US.[5]

The Content

At the outset, the scope of these guidelines is precisely stated as "these guidelines are applicable to all biomedical, social, and behavioral science research for health conducted in India involving human participants, their biological material and data"– which was lacking in the previous statements. However, what amounts to "research" or the definition of research is not explained, as "medical research" and "medical practice" tend to be at crossroads many times. Furthermore, the present title is modified and more refined than the previous one.

All the 12 general principles are condensed and rearranged more appropriately. The "Principle of social responsibility (1.1.4)" and the "Principle of environmental protection (1.1.12)" are the two newer principles which discuss pursuing research without disturbing the social harmony and protecting environmental resources; as it is known that research can harm the individual and the community differently.[6] The "Principles of accountability and transparency (VII)" is merged with the "Principles of public domain (X)" and the "Principles of compliance (XII)" is removed.

General ethical issues including the informed consent process

With regards to "compensation for research participants," the statements like "may be reimbursed for expenses incurred relating to their participation in research" or "may also be paid for inconvenience incurred, time spent, and other incidental expenses" are not as vehement as the revised CIOMS guidelines[7] which state "must, therefore, be reasonably reimbursed" and "participants must be appropriately compensated for the time spent and other inconveniences resulting from the study participation."

Table 1: List of "Boxes" present in the "National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017"

Box number	Section	Caption	Page number
3.1	Responsible conduct of research	Identifying, mitigating and managing COI	15
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4.4 (b)		Details of documents to be included in the protocol	35
4.5		Types of decisions by EC	42
4.6		Examples of "for cause" monitoring	46
5.1	Informed consent process	Essential and additional elements of an informed consent document	50
5.2		Conditions for granting waiver of consent	54
6.1	Vulnerability	Characteristics of vulnerable individuals/populations/group	56
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6.3		Risks for women participants in clinical trials/intervention studies	60
6.4		Conditions for research on children	62
6.5		Consent of parent/LAR	63
6.6		Considerations for assent	64
7.1	Clinical trials of drugs and other interventions	Phases of drug development	71
7.2		Risks of Phase I clinical trials	73
7.3		Types of vaccines	75
7.4		Conditions where a placebo may be used	77
7.5		Precautions to be taken when a placebo is used	77
7.6		Conditions for sham surgery	82
7.7		Classification of drugs/formulation under AYUSH	84
7.8		Criteria for research involving pregnant women and fetuses	89
8.1	Public health research	Public health research proposal review	95
8.2		Types of consent	101
8.3		Waiver of consent in public health research	102
9.1	Social and behavioural sciences research for health	Ethical issues in social and behaviour sciences studies	105
9.2		Consideration for appropriate design and conduct of study	106
9.3		Considerations by the EC for ethical review	106
9.4		Informed consent in social and behavioural sciences research on health	108
9.5		Types of deception	110
11.1	Biological materials, biobanking and datasets	Confidentiality and privacy of donors related to biological materials and/or data	129
11.2		Example of multiple options in a multi-layered consent	130
11.3		Types of consent processes and their implications	131
11.4		Use of stored samples	133
11.5		Considerations for benefit sharing	134
11.6		Measures to ensure privacy and confidentiality of individuals	136
12.1	Research during humanitarian emergencies and disasters	Considerations for fair selection of participants	139

EC=Ethics committee, COI=Conflict of interest, LAR=Legally acceptable/authorized representative

The risk involved in research has been categorized and described elaborately as "less than minimal risk," "minimal risk," "low risk" and "high risk" whereas, in the 2006 edition, only the minimal risk category had been defined. Some of the other newer inclusions are the necessity of the researcher to administer a "test of understanding" particularly for sensitive studies, the requirement of partner/spouse to give additional consent in some types of studies and to get consent from another member of a family (secondary participants) in genetic research.

An essential element of an informed consent document (ICD), namely, "Statement mentioning that it is research"– was not mentioned previously. In accordance with the latest amendments to the "Declaration of Helsinki (DoH)– Ethical Principles for Medical Research Involving Human Subjects,

Table 2: List of "Tables" present in the "National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017"

Table number	Section	Caption	Page number
2.1	General ethical issues	Categories of risk	6
4.1	Ethical review procedures	Composition, affiliations, qualifications, member specific roles and responsibilities of an EC	28
4.2		Types of review	36
4.3		Ethical issues related to reviewing a protocol	38
4.4		Documents to be maintained by EC for record	47
6.1	Vulnerability	Obligations/duties of stakeholders	59
7.1	Clinical trials of drugs and other interventions	Classification of medical devices	79
11.1	Biological materials, biobanking and datasets	Types of samples	129

EC=Ethics committee

2013"[8] the information on post-trial access in the ICD is to be included– which is not updated appropriately; rather "post research plan/benefit sharing" is included which can be misconstrued. Nevertheless, the ICD based on the current guidelines can very well end up to many pages, burying the vital information and can appear complex to a reasonable participant; hence, the need for a concise and focused presentation of the important information at the outset could have been stressed like that of the US' "Final rule, 2017."[9]

Granting "waiver of consent" for "retrospective studies, where the participants are de-identified or cannot be contacted" is a welcome move. However, a drastic change is "waiver of consent" can no longer be granted for studies involving minimal risk; as it is clearly stated that for the research involving less than minimal risk to participants a "waiver of consent" can be justified. In sharp contrast, the CIOMS guidelines state that "waiver of consent" can be granted for "the research which poses no more than minimal risks to participants"– which encompasses research involving minimal risk.[7]

The intricacies surrounding the research involving pediatric population is well emphasized, and recently the ICMR had released the "National Ethical Guidelines for Bio-medical Research involving Children, 2017" for the first time. A child becoming an adult during the course of the study requires a fresh consent or "Re-consent" to continue in the study and at times the partner/spouse may also be required to give additional re-consent in some situations are the other newer updates.

Compensation for research related harm is discussed more extensively though how a participant who withdraws halfway from the study is to be compensated, is not provided. The implication of conflict of interest on biomedical research though mentioned is not elaborate-like the "finder's fee" to the researchers for recruiting patients and scenarios in which the researcher is also the treating clinician for the participant.[7]

Responsible conduct of research

The concept and importance of "data sharing"[10] are deliberated. Under the sub-head "Responsible authorship and publication," the importance of primary (or) first authorship-"Research performed as part of a mandatory requirement of a course/fellowship/training program including student research should have the candidate as the primary author" and peer reviewing system are discussed.

Though the various aspects of research publication are well covered, incorporation of a phrase like that in the CIOMS guidelines[7] or the DoH[8] stressing on the importance of publication of negative and inconclusive research results would have been better.

All clinical research involving human participants should be registered prospectively with the Clinical Trials Registry–India (CTRI), a free and online public record system for registration of clinical trials, post-graduate thesis and other biomedical research being conducted in the country. For the first time registering of clinical trials is discussed, understandably so, as the CTRI was launched by ICMR in 2007[11] just after the release of the 2006 guidelines.

Ethical review procedures

The section on "Ethical review procedures" is exhaustively revamped. An institution that does not have its own EC (user institution) can now utilize the services of the EC of another institution (host institution) preferably in the adjoining/nearby area. The move to have multiple ECs in a single institution is remarkable, as it is obvious that some of the institutional ECs are overburdened due to the introduction of stringent regulatory amendments recently.[12] Though the number for making a quorum remains to be five the number of members in an EC can now be 7–15. More elaboration on the quorum requirements like minimum one nonaffiliated member should be part of the quorum, and preferably the layperson should be part of the quorum are found. However, the statement "Preferably 50% of the members should be nonaffiliated or from outside the institution" is a tough act to follow. Nevertheless, the necessity to have a research participant as a member of the EC as described by the CIOMS guidelines[7] as "ideally, one or more members should have experience as study participants" is not stressed in this Indian variant which is to be acclaimed as it appears to be more impractical.

Registration and accreditation of ECs are now recommended to uphold the quality of the ethical review. ECs dealing with

clinical trials are now to be registered with the Central Drugs Standard Control Organization (CDSCO). However, the guidelines state that accreditation is only a voluntary process and not a mandatory one– which is not in line with the recent cry for regulatory oversight of ECs.[13] Similarly, although the essentiality of training of EC members is mentioned, who has to train them is not specified and the veracity of training programs conducted by the Indian Society for Clinical Research[14] and the Clinical Development Services Agency[15] is not discussed; the kind of strategies or approaches needed for ethics education, like case-based learning, role-play, expert instruction or small group-based active learning, is also not detailed.[16] In fact, the EC members act as one of the stakeholders for achieving the 1st Pillar (strengthen health research capacity) under the ICMR Strategic Plan-2017-24 (ISP 2017-24).[17]

Strict oversight systems can at times backfire and halt the progress of research.[2] The current guidelines appear to be more flexible regarding requirement of continuing review; the frequency of which is now based on the risk involved in the research. However, the requirement of continuing review of studies which have completed patient recruitment or study interventions and solely involved in analyzing the data or only observational follow up is yet to be clarified.

For multicentric research within India, it is not elucidated whether to go for multi-institutional review or a single review by a designated EC; discussions on both types of review are given without a final suggestion.

Vulnerability

The clause "a woman who becomes pregnant must not automatically be removed from the study when there is no evidence showing potential harm to the foetus" shows enhanced pliability compared to the previous edition which states "pregnant or nursing women should in no circumstances be the participant of any research unless the research carries no more than minimal risk to the fetus or nursing infant."

A radical change with regards to research in children is the removal of an erstwhile statement "For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults." The current version also defines the legal age of consent as 18 years and various types of assent such as verbal/oral assent (from 7 to 12 years) and written assent (from 12 to 18 years) and provision of waiver of assent. Vulnerable groups like lesbian/gay/bisexual and transgender (LGBT) community and particularly vulnerable tribal groups (PVTG) are discussed for the first time. In recent times, there is an underrepresentation of these vulnerable populations in clinical research resulting in profound knowledge gaps. In line with the DoH,[8] a move toward participation and away from protectionism is to be encouraged and which is only partially dealt with in these present guidelines.

There is no discussion of research conducted in low-resource settings, as it is evident by the recent CIOMS guidelines that low-resource settings are not restricted to low-income countries.[18]

Clinical trials of drugs and other interventions

Discussion about "Phase 0" studies occurs in this current version for the first time. In contrast to the previous edition, "Phase IV" of drug development is described as a general term encompassing post-marketing surveillance, Phase IV clinical trials, outcomes research and registries adding more clarity. The requirement of a clinical pharmacologist is no more stressed in Phase II/III trials.

Two more conditions are added where a placebo may be used, namely, "withholding an established effective therapy would not expose participants to serious harm, but may cause temporary discomfort or delay in relief of symptoms" and "the use of an established effective therapy as a comparator would not yield scientifically reliable results and the use of placebo would not add any additional risk of serious or irreversible harm to the participants." However, the presence of "compelling scientific reasons" for using placebo as discussed in the CIOMS guidelines is not dealt here. Some of the examples of "compelling scientific reasons" are the clinical response to the established effective intervention is highly variable, the symptoms of the condition fluctuate and there is a high rate of spontaneous remission, or the condition under study is known to have a high response to placebos.[7]

Academic clinical trials, as defined by the CDSCO recently,[19] are clinical trials intended for academic purposes in respect of approved drug formulations for any new indication or new route of administration or new dose or new dosage form. Regulatory approval is currently not required for pure academic clinical trials; however, they have to be registered in CTRI. The guide and the academic institution should take up the responsibilities of the sponsor for students conducting clinical trials as part of their academic thesis.

The clause "Phase I trials are not necessary for trial on medicated devices" is currently removed. Clinical trials on phytopharmaceutical drugs, biologicals and biosimilars, contraceptives, oncology, synthetic biology; and investigator-initiated clinical trials are newly described in the present version.

For oncology-related trials, if the trial is an add-on design, the sponsor need not pay for the background standard of care– this statement clears the air around this burning issue.

Public health research and social and behavioral sciences research for health

Public health research ethics deals with four additional principles such as the principle of social justice, the principle of reciprocity, the principle of solidarity, and the principle of accountability and transparency. The guidelines propose the requirement of two levels of consent, i.e., the first level is the gatekeeper, and the other level is the individual participant. However, the issues related to obtaining consent in cluster randomized trials (CRTs) are not clear; the guidelines are of the thought of going with the group consent invariably for all the CRTs which is not recommended by the CIOMS counterpart.[7]

Researchers should be alert to cultural symbols of refusal, such as body language, silence, monosyllabic replies, or restlessness that communicate discomfort. They must not persist with the research under these circumstances. The aforementioned phrases stress the relevance of participant refusal in social and behavioral sciences research on health. Deception occurs when researchers provide false or incomplete information to participants for the purpose of misleading them to achieve the study objectives and for larger public good. The various types of deception defined are active deception, incomplete disclosure, and authorized deception. However, the implications of "pseudo-patients" or "mystery clients" are not mentioned.[7]

Human genetics research and biobanking

Some of the new information included, under the section on "Human genetics testing and research," is about whole exome sequencing, whole-genome sequencing, direct to consumer testing, population screening, noninvasive prenatal screening/testing, pre-implantation genetic screening and diagnosis, genome-wide association study and the gene editing technology, Clustered, regularly interspaced, short palindromic repeat (CRISPR). The new improvised move is to disregard newborn screening when treatment may not be available or affordable (such as in lysosomal storage disorders). A path-breaking statement under gene therapy is "All gene therapies are considered as research, and all protections for human research participants should be in place."

The definition of repository or biobank along with its activities has been improved. The two additional requirements such as clarity on custodianship and post-research benefit sharing are included along with the individual informed consent, approval of the EC and repository governance committee to avoid exploitation and safeguard the rights of donors. The application of multi-layered consent wherein consent needs to be administered during multiple stages, i.e., storage, analysis of the biospecimens/samples, use of data linked to the sample, return of results to the participant, sharing of the sample/data with other researchers/national or international institutions, multicenter and multinational collaborations and potential commercialization are mentioned. The provision of "broad informed consent" and informed "opt-out/in" practices replacing the conventional method of obtaining informed consent (specific) is an essential change in line with the increasing number of studies dealing with the big data. The newly promulgated "Final Rule" by the US also does not include the use of unidentified bio-specimens under its purview which means studies on these samples can be done without an EC review.[9,18] It should also be noted that "blanket consent" and "broad consent" are not the same; "blanket consent" is open-ended permission without any limitations whereas "broad consent" is less specific yet more narrow than "blanket consent"– in this document both these terms are used interchangeably.[2]

Previously, it was discussed that the "ownership of the sample lies with the individual, family or community as the case may be." However, the present version precisely states that the "participant owns the biological sample and data collected from her/him and therefore, could withdraw both the biological material donated to the biobank and the related data" and the "researchers have no claim for either ownership or custodianship." Another update is that there should be a technical authorization committee with representation of both science and ethics and external members for every biorepository; and this committee should function in tandem with the EC.

In conclusion, there is a reasonably good balance among the members involved in the generation of these guidelines concerning their field of expertise, region of origin and gender. The concept of biomedical research, now the preferred term is "health-related" research,[18] has grown very broad and so its ethical principles. At present, bioethics requires a multidisciplinary approach from professionals of diverse fields which is well reflected in the current guidelines. However, the involvement of experts from several domains may at times be counterproductive disturbing the harmony in the conduct of biomedical research, which should be addressed; limited participation of personnel with requisite expertise as and when required could be a solution. These strict codes of guidelines may not be adhered to always as there can be unpredictable situations arising in the actual field of study; not under the purview of these guidelines. In those times, it is for all the stakeholders to enact what is called as the "situational or relational ethics" as opposed to the "procedural ethics."[20] Hence, like in other "standard treatment guidelines" or "clinical practice guidelines" where the treating physician makes the final call based on his "clinical judgment," these ethical guidelines are ought to be followed supported by the "ethical judgment" of the stakeholders on a trial-to-trial basis.

As stated in the fag-end of the document, the ICMR guidelines are widely sought after by researchers, institutions, medical colleges, universities, EC members, and sponsors engaged in health-related research in the country. Hence, it is the obligation of the Council to draft these national ethical guidelines abreast with the flourishing biomedical research over the years and protect research integrity, which we suppose they have achieved hands down!

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