Review Article

Indian Council of Medical Research's National Ethical Guidelines for biomedical and health research involving human participants: The way forward from 2006 to 2017

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Abstract

The Indian Council of Medical Research (ICMR) recently published the third revised guidelines "National Ethical Guidelines for Biomedical and Health-Related Research Involving Human Participants" in 2017. The changes to the guidelines were needed to acculturate the rapid advances in the research environment and advances in science and technology. The revised guidelines propose substantial changes/ modifications compared to the previous version. These include the introduction of broad consent, ethical issues related to deception, review of multi-centric research by a single ethics committee and ethical issues involved in implementation research and other issues related to public health research. The revised guidelines also incorporate modifications and minor changes to the previous version. Although most of the changes in the revised guidelines are in parallel to most of the international guidelines, we have also highlighted the minor differences compared to other international guidelines.

Keywords: Ethics, guidelines, human participants, Indian council of medical research, research

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INTRODUCTION

In October 2017, the "Ethical Guidelines for Biomedical Research on Human Participants (2006)"[1] [hereafter, Indian Council of Medical Research {ICMR (2006)} guidelines] by the ICMR has been updated as the "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017)"[2] [hereafter, ICMR (2017) guidelines]. In addition, ICMR has also published two separate guidelines for research in children[3] and research with stem cell.[4] ICMR came up with the revised version in parallel to 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 lines [hereafter, CIOMS (2016) guidelines][5] Federal Policy for the Protection of Human Subjects or the "Common Rule".[6] It is to be noted here that, although the "Common Rule" is used for the regulation of human research funded or conducted by US government,[7] the CIOMS Guidelines is particularly made to guide human research in the developing countries,[8] and are not legally binding. The ICMR (2017) guidelines include substantive changes to the conduct of research in human.

There are several factors behind updating the previous ICMR (2006) guidelines. The rapid expansion of research

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areas and use of new tools in research increases the possibility of exploitation of research participants.

With appraising of international guidelines, changes are needed at the national level to maintain uniformity to conduct of health-related research as many researches involve international collaboration. The growing concerns of legal aspects in health-related research require the changes in ethical guidelines at regular interval to safeguard the researchers from being penalized. The evolution of community acceptance for research involving humans needs highest standards in ethical practice. Public concern about individual privacy is a major emerging challenge to maintain privacy and confidentiality. Storage of medical records on the computer is also a threat to privacy. As the practical effects of these changes will be on the research participants and researchers, both appreciations and criticisms are needed from the research community for the updated revisions.

While most of the changes are drafted keeping recent updates of international guidelines in mind, the document is reticent in certain areas while some areas are less informative; but as a whole, these changes are a positive and a welcome move.

SECTION I

This section deals with the major new changes in ethical issues such as broad consent, deception, multicentric trials, and implementation research (IR).

BROAD CONSENT

The concept of broad consent has been recently updated in the CIOMS (2016) guidelines. Although the term broad consent has been mentioned and described in different sections of the ICMR (2017) guidelines, we here focus on the positive and negative aspects of it. Broad consent is defined as consent for an unspecified range of future research subject to a few contents and/or process restrictions.[9] In other words, it is the consent for secondary use of biological specimen in future with a particular purpose(s) (10). Studies have also mentioned that around 3-40% participants may not be willing to provide consent for unspecified future use.[10-12] It is also reported that broad consent may be more acceptable to older participants and not younger ones, and its acceptance to certain population may be less than other populations.[13,14] A recently published large multicentric experimental survey[15] involving 82,328 individuals in the US reported that 66% of respondents were willing to take part in a biobank and their willingness and attitudes did not differ between respondents when three different types of consents were used, namely; broad-open, broad-controlled, and tiered controlled consent. Rather, their willingness to participate was affected by race, educational level, religion, provision of research benefits, and need for a few information. The maintenance cost for broad consent system is low if proper infrastructure is available, and the burden on the participants is less.[9] As a majority of the participants are consistent with broad consent, it can be used if a proper framework is used such as (a) initial consent, (b) oversight of the future research projects, and (c) mechanism for maintenance of contact details and communications with the participants.[9]

DECEPTION

This is also a newly added ethical issue, which was also introduced in the CIOMS (2016) guidelines. Deception refers to any action designed to mislead others by distorting, falsifying, or misinforming individuals so that they are manipulated to react in a certain way.[16] Various way of carrying out deception in research are dissimulation, propaganda, beguilement, and mystification, etc., Deception in medical research is a matter of debate. There are certain situations where the use of deception in research can be justified; such as the use of deception is the only way to get information and to obtain reliable and unbiased results.[16] The National Bioethics Advisory Commission (NBAC) (volume 2) guidelines mentioned that Ethics Committees (ECs) should approve studies with deception only when it cannot be conducted without deception in some exceptional situations, and the ECs may approve such studies when the following criteria are satisfied; such as "full information may compromise the scientific validity of the project; the extent and detail of the deception is explained in the research protocol; there are no suitable alternatives to the deception; there is no increased risk to the participants; there will be disclosure as soon as possible after participation; the participants are free to withdraw their data; and the activity will not affect the relationship between researchers and research in general with the community at large."[17]

Benham mentioned that the psychological discomfort resulting out of deception is no more than the usual psychological stress that arises in the day-to-day life.[18] In fact, most of the study participants do not bother about deception[19] rather they enjoy the participation in research using deception.[20] The arguments against the use of deception in research are: use of deception in research is inappropriate as it plays with the faith and emotion of the participant,[21] it also directly affects the

dignity of the researchers, when the research participants are suspicious about the researchers, their response for a particular intervention or procedure will change, which may compromise the research findings, and it may put the research ethics under question as research ethics depends on integrity, accuracy, efficiency, and objectivity.[22]

Deception can be direct or indirect. Indirect deception has more ill effects than direct deception. In indirect deception, the participants are not provided the full information about the real purpose of research where deliberate misinformation is given to the participants in direct deception, which may include study instructions, and false feedback, etc.[23] Deception may also affect the validity of the study as it may result in suspicious participants who behave differently to the study question being asked.[24] Such ill effects of deception can be reduced by debriefing the procedure to the study participants.[25] Nuffield bioethics guidelines for developing countries mentioned that coercion, deception, manipulation, deliberate misdescription of what is proposed, lack of disclosure of material facts, or conflicts of interest are the hindrance to the genuineness of consent.[26] NBAC guidelines also suggest future consideration to allow the participants for withdrawing their data after debriefing the process.[17]

MULTI-CENTRIC TRIALS

The recent ethical guidelines proposed a common review for the participating sites in multicentric research. Although this is a welcome step, there are pros and cons to such a decision. The federal agencies and departments of US proposed the change in the "Common Rule" that mandates a central institutional review board (IRB) for federally funded multicenter research.[6] There are many advantages to have a common EC for reviewing multicentric studies such as, it will prevent delay in the review process; it prevents the duplication of efforts by various ECs, and it can streamline the review process. However, there are many challenges to this single review process like fear of not having a local EC by the investigator and institution for any deficiencies in main EC review, the main EC may not be familiar with the local situations.[27] In case of multicentric research involving academic institutions are involved, the main EC, if governed by an academic institution, needs sufficient resource, and expert EC members to review such proposal. The academic ECs may need extensive modifications to review this type of proposal,[28,29] and for this, they may be reluctant to review multicentric research proposal. On the other side, if it is decided to have a local EC review in addition to the main EC, it may delay the review process and the cost of review may be more.

The advantage of the Indian guidelines is that Indian guidelines are more flexible giving options for the local ECs to decide whether to undergo review by a single/common EC for multi-centric research or to have separate review by each local EC. This common review process is only applicable to ECs located in India for research involving low or minimal risk, survey or studies using anonymized samples or data or low or minimal risk public health research.

IMPLEMENTATION RESEARCH

It is the scientific study of methods to promote the systematic uptake of clinical research findings into routine clinical practice and hence to reduce inappropriate care.[30] The major ethical issues involved in IR can arise in various phases, such as planning phase, implementation phase, or postresearch phase. The issues in planning phase may be related to responsiveness to the local needs and priorities, contextual equipoise, study design, stakeholder and community engagement, and maintenance of balance between risks and benefits. Autonomy and informed consent, privacy and confidentiality, the standard of care, ancillary care, and community and health system empowerment are the ethical issues that can occur in the implementation stage of IR. In the postresearch stage of IR, the ethical issues involved are the dissemination of the research finding(s) to the participants/community, ownership of the data, translation of research finding(s) to public health action, scalability and sustainability, and benefit sharing.[31]

1. Responsiveness and equipoise in implementation research:
   IR should be planned based on the local needs and priority.[32] Engagement of the local health experts and community is needed to properly identify the priority needs of a particular community. ECs also should see these things while reviewing the IR project.[33] In IR, contextual or situational equipoise is more important than clinical equipoise. In contrast to clinical equipoise, contextual equipoise arises when there is doubt about the positive outcome of a new intervention in a specific context.[34]
2. Community engagement and research collaboration:
   There should be a fair selection process for selecting community representative irrespective of class, race, gender, or ethnicity.[35] Research collaboration between different institutions working on the same issue can be made to avoid competition between researchers and duplication of efforts.[36]
3. Risk-benefit balance:
   The balance between the risks and benefits experienced by two different groups of a study can be maintained by effective communication with research participants and

proper ethical deliberations. The ethical deliberation should be transparent involving communities and all stakeholders.[37] The extent of exposure of individuals to risks for the benefit of others should be decided on consultation with the community and stakeholders[38]

4. Autonomy and privacy and confidentiality:
   In IR, there may be difficulties in the operationalization of informed consent.[39] Fair selection of community representatives can be done by including the representative from various target groups and adopting transparent selection procedure.[40] However, the participant's decision by informed consent or assent cannot be replaced by gatekeeper's agreement.[5] The EC has the responsibility to ensure that the appropriate informed consent process is followed.[41] The privacy and confidentiality of the participants are of utmost importance. For this, it is better to use anonymized data where possible. The researcher can also obtain a waiver of consent from the respective EC where it is impossible to obtain consent. However, the researcher should inform the participants about the study procedures including data collection strategy to reassure them about privacy and confidentiality.[42]
5. Standard of care and ancillary care:
   The standard of care can be provided either by allocating existing local standard care which may not be ethically acceptable but acceptable to the community or new standard of care based on the agreement of the public health experts of that region and the acceptability to the community.[43] Ancillary care refers to the identification of problems that may contribute to ill-health that are beyond the scope of the study in question.[44] The provision of ancillary care although not mandatory, their need should be decided based on the urgency and severity of the conditions and the provision within the scope of IR. Sometimes, the researchers may not be able to provide ancillary care because of lack of proper expertise or lack of access to system level intervention. However, they should establish a process of accountability based on the identified need through their research.[45]
6. Dissemination of research findings and benefit-sharing:
   After the completion of research, the findings (negative or positive) should be disseminated widely to the public including the involved communities.[36] The benefits of the IR should be shared irrespective of its context in the community.[46]

SECTION II

In this section, we discuss the modifications of the ICMR (2017) guidelines as compared to the previous ICMR (2006) guidelines [Table 1], and in reference to other existing international guidelines.

INFORMED CONSENT

The revised "Common Rule" proposed changes in the requirement of informed consent and directed that it must include "information that a reasonable person would want to have to make an informed decision" to participate in a trial. However, this change is not highlighted in CIOMS (2016) guidelines and in ICMR (2017) guidelines. Hudson and Collins mentioned that the recent proposed changes in the "Common Rule" highlighted some important issues regarding informed consent documents (ICDs) such as, they are too long, too complicated, and filled with legal text designed more to protect institutions than research participants.[47] The proposed changes also include the content of the ICD short and limited to specific elements in the rule describing as "essential information that a reasonable person would want to know" and the nonessential information to move to a separate appendix.[8] The rule also proposed that all federally sponsored clinical trials should post one (1) IRB approved ICD on a publicly available federal website within 60 days of the last protocol-dictated subject visit.[48]

ETHICS COMMITTEE MEMBERSHIP AND REVIEW

Regarding EC membership, CIOMS (2016) guidelines mentions that "ideally, one or more members should have experience as study participants since there is growing recognition that knowledge gained through personal experience as a participant can supplement the professional understanding of illness and medical care."[5] The recent proposed changes in the "Common Rule" exempted the following research activities from review which include surveys, interviews, and other forms of free communications between investigators and human adults, aptitude testing, observation and recording of verbal and nonverbal behavior in schools and public places, benign behavioral interventions, secondary data analysis, and other low-risk projects and research procedures. For this type of research, the rule specified a "limited IRB review."[48]

PUBLIC ACCOUNTABILITY FOR HEALTH-RELATED RESEARCH

According to the recent ICMR guidelines, all the clinical trials conducted in India must be registered with the Clinical Trials Registry India (hereafter, CTRI) which was launched on July 20, 2007 and was made mandatory by Central Drugs Standard Control Organization (CDSCO) on June 15, 2009.[2] Although retrospective registration of clinical trials is not possible currently with CTRI in India, CIOMS guidelines mention the option for

Table 1: Comparison of salient features of Indian Council of Medical Research (2006) guidelines versus the Indian Council of Medical Research (2017) guidelines

Specific areas	ICMR (2006) guidelines	ICMR (2017) guidelines
Categories of risk	Three categories were mentioned (less than minimal risk, minor increase over minimal risk or low risk, and more than minimal risk or high risk).	Four categories are mentioned (less than minimal risk, minimal risk, minor increase over minimal risk or low risk, and more than minimal risk or high risk).
Number of EC members	8-12	7-15
Composition of EC	Eight different types of members were mentioned.	Seven different types of members are described [requirement of one social scientist/representative of non-governmental voluntary agency (NGO) and one philosopher/ethicist/ theologian are merged into one type].
Term of EC member	Specific duration was not mentioned, but it was mentioned that membership can be extended for one more term.	May be two to three years, but can be extended as specified in the standard operating protocol
Alternate member secretary	Option for alternate member secretary was not mentioned.	Alternate member secretary is optional.
Good clinical practice (GCP) training certificate for investigator	GCP training certificate for investigator was not mandatory.	GCP training certificate is mandatory for investigator conducting clinical trials (preferably within five years)
Common review of multi-centric research by a single/main EC	Common review process for multi-centric research by a single/main EC was not mentioned.	For multi-centric research involving more than one Indian centers, the main EC will conduct full review and the local EC should conduct only expedited review for site specific requirements
Permissible amount of blood to be collected	-For healthy adults and non-pregnant women of normal weight for their age: not more than 500 ml in 8 weeks' period, frequency should not be more than 2 times/week; -For other adults and children: not more than 50 ml or 3 ml/kg whichever is lesser in 8 weeks period and frequency not more than 2 times/week; -For neonates: not more than 10% within 48-72 h	-Drawing a small amount of blood for testing will fall under minor increase over minimal risk or low. No such limit is mentioned under more than minimal risk or high risk; -For BA/BE study: the amount of blood drawn should be within physiological limits irrespective of study design and the EC should take specific note on the amount of blood drawn depending on whether the individual is a healthy adult or a child or a patient.
Duration for record keeping	Minimum three years for all types of studies.	Same for other study, but minimum five years for regulatory clinical trial.
Women in research	Option for consulting husbands or family members was mentioned.	Women may consider consulting their husbands or family members whenever necessary
Vulnerable group	Under vulnerable groups, although economically or socially disadvantaged group was mentioned, specific examples were not mentioned.	Unemployed individuals, orphans, abandoned individuals, persons below the poverty line, ethnic minorities, sexual minorities – lesbian/gay/bisexual and transgender (LGBT) are included as examples under economically and socially disadvantaged group.
Assent for research involving children	Though assent was needed for mature minors (age 7-18 years), age-wise categorization for verbal/oral and written consent was not mentioned.	Verbal/oral consent should be obtained from children of age seven to twelve years, for children between twelve to eighteen years of age, written assent should be obtained.
Clinical trials of drugs and other interventions	Option for one member with adequate research experience in the required field was not mentioned.	At least one member of the research team must have the qualification and adequate research experience in the subject on which the trial is planned.
Trials with medical devices	Medical devices were classified into critical and non-critical devices.	Medical devices are classified into four classes, namely, A, B, C and D for low, low-moderate, moderate-high and high level of risk, respectively.
Regulatory approval for academic trials	Regulatory approval was needed for any type of clinical trial.	Academic clinical trial for off label use of drugs may not require regulatory approval.

retrospective registration in registries. However, the guidelines also mention that registration should be done before the enrollment of the first participant.[5] The ICMR (2017) guidelines also mention that other biomedical and health-related research, registration with CTRI is voluntary. For publication of research related to clinical trials, editors of the major biomedical journals in India also declared to publish trials registered on any public database. The Declaration of Helsinki clearly states that "every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject" in October 2013.

VULNERABLE GROUPS

In the recent ICMR (2017) guidelines, sexual minorities are added as the vulnerable population under economically and socially disadvantaged along with unemployed individuals, orphans, abandoned individuals, persons below the poverty line, and ethnic minorities. The CIOMS guidelines mention that the following members of groups that are traditionally considered as vulnerable such as people receiving welfare benefits or social assistance and other poor people and the unemployed; people who perceive participation as the only means of accessing medical care; some ethnic and racial minorities; homeless persons, nomads, refugees, or displaced

persons; people living with disabilities; people with incurable or stigmatized conditions or diseases; people faced with physical frailty, for example, because of age and comorbidities, individuals who are politically powerless; and members of communities unfamiliar with modern medical concepts. It also mentions that "in some contexts, vulnerability might be related to gender, sexuality, and age."[5] The NBAC guidelines mention that under particular circumstances, injection drug users, the seriously ill, the elderly, and undocumented immigrants could also be considered vulnerable. It also mentions that vulnerability is context sensitive, i.e., one individual who is vulnerable in one situation may not be considered vulnerable in another situation like people with low income who are ready to take the risk because of the provision of large financial incentive can be considered as vulnerable.[17]

CONCLUSION

The ICMR (2017) "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants" has been recently published by the ICMR. These guidelines include substantive changes to the conduct of research in human. The ethical issues related to some areas are added newly while some areas of the previous version of the guidelines are expanded into separate sections. Several other modifications in various areas are described in respective sections. Most of the ethical issues are drafted keeping most recent updates in international guidelines in mind. The concept of broad consent has been updated as per the recent update in the CIOMS (2016) guidelines. Use of deception in research has been added after the same has been mentioned in the CIOMS (2016) guidelines. It is mentioned that the ECs should approve studies with deception only when it cannot be conducted without deception. The section on multicentric research is at par with the "Common Rule" of the federal agencies and departments of US. It talks about the flexibility of the Indian ECs to review a multicentric study proposal for research involving low or minimal risk, survey, or studies using anonymized samples or data or low or minimal risk public health research. For IR, the ICMR (2017) guideline discussed on community engagement, collaboration, competition, and duplication, autonomy and informed consent, privacy and confidentiality, the standard of care or prevention, ancillary care, dissemination of research findings, and benefit sharing. This updated guideline will serve as a guide for the investigators/researchers, EC, and sponsors for conducting clinical research in India.

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Conflicts of interest

There are no conflicts of interest.

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