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National Guidelines for Ethics Committees Reviewing Biomedical & Health Research during COVID-19 Pandemic: An analysis

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Abstract

The world currently faces an unprecedented pandemic outbreak of coronavirus disease (Covid-19). The novel nature of the virus and very high infection rates have not only increased the urgency to find a vaccine or cure but have also led to drastic changes in the mode of conduct of research. Thus, the Indian Council of Medical Research has developed the "National Guidelines for Ethics Committees Reviewing Biomedical & Health Research during Covid-19 Pandemic" for guidance during the review of research. Here, we attempt to analyse the strengths and limitations of these guidelines to assess if the unique ethical challenges faced during research in the current situation are adequately identified and addressed and if foundational values and principles of research ethics have been taken into account in these guidelines.

Keywords: *national guidelines, ethics committees, biomedical research, health research, Covid-19 pandemic,*

Introduction

The world is currently facing a pandemic outbreak of coronavirus disease (Covid-19) caused by the novel severe acute respiratory syndrome coronavirus 2. The novel nature of the virus, the very high infection rates (R0), and the increased mortality, especially among the elderly and those with comorbidities, have led to drastic changes in the mode of conduct of research. Trials are now being categorised as those dealing with Covid-19-related research, ongoing trials dealing with non-Covid-19 research, and new trials dealing with non-Covid-19 research. Under these circumstances, the Indian Council of Medical Research (ICMR) has developed guidelines regarding the conduct of research, namely the National Guidelines for Ethics Committees Reviewing Biomedical and Health Research during COVID-19 Pandemic (henceforth, ICMR- Covid-19 EC guidelines) (1). These guidelines have extensively drawn upon the 2017 National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (henceforth, ICMR 2017 guidelines) (2). They have been adapted to respond to anticipated specificities of research ethics issues that arise during the Covid-19 pandemic. In this article, we attempt to analyse the strengths and limitations of the new Guidelines. For doing so, we adopted the approach of comparing these new research guidelines with the most recent ICMR 2017 guidelines. Three specific objectives of the critical review of the ICMR-Covid-19 EC guidelines are: (a) to assess if ethical issues in research undertaken during the current situation, specific or related to Covid-19, are adequately identified and comprehensively addressed in the ethics review process; (b) to assess if the foundational values and principles of research ethics are taken into account while discussing specific research ethics challenges in a pandemic context; and (c) to help the peer community appreciate the novel ethical issues involved in undertaking research during the Covid-19 pandemic and understand and comply with the relevant guidelines.

ICMR-Covid-19 EC guidelines: Context, motivation, and overview

These guidelines have been developed for ethics committees (ECs) reviewing research in the ongoing Covid-19 era. Given the novel and contagious nature of the virus, there is an urgent need for extensive research to explore therapeutic options, deal with clinical challenges related to patient management and care, undertake epidemiological studies, fast track development of new diagnostic tools and vaccines, and conduct social–behavioural–cultural studies. Furthermore, carrying out research in the current scenario poses additional challenges and hurdles stemming from containment strategies, such as physical distancing and travel restrictions, and stigma attached to the disease and to those who either

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contract or are exposed to it. The high R0 combined with the novel nature of the virus has led to extreme measures, such as extended lockdown, by governments across the world, inducing public anxiety and paranoia, which has led to avoidable human loss and a negative impact on the global economy. Taken together, this underscores the urgency of undertaking research during the pandemic. The ethical principles and guidelines that were applied to research in the non-Covid era would still be applicable, along with additional guidelines to overcome the new hurdles and challenges.

The ICMR-Covid-19 EC guidelines have been developed by the ICMR Bioethics Unit of the National Centre for Disease Informatics and Research (NCDIR), Bengaluru, with this aim in mind; however, these guidelines are intended specifically for the Ethics Committees (ECs). A number of segments of the ICMR-Covid-19 EC guidelines are extracted from relevant portions of Chapter 12 on "Research during humanitarian emergencies and disasters" and other sections of the ICMR 2017 guidelines, with some Covid-specific additions.

The ICMR 2017 guidelines are meant for all stakeholders (sponsors, researchers, and the ECs), whereas the new guidelines, as the title suggests, are focused exclusively on meeting the needs of research ECs. It is intriguing that other stakeholders have been excluded from the purview of this document.

We observe that these guidelines have been developed with inputs from a handful of experts only. The rapid spread of the pandemic and the resultant social disruption may explain the restricted approach of not drawing upon multidisciplinary perspectives and reaching out to the wider peer community. A consultative approach is however much needed for two reasons: (a) the virus is novel, implying a number of unknown factors, unpredictability, and uncertainty; and (b) most guidelines are developed through extensive consultation and wider participation as required by the commitment to procedural justice. In the current situation, given the need for social distancing, this could have been achieved through online consultation.

The general ethical principles (Chapter 1) are the same as those for research in the non-Covid era. These include the principles of essentiality, professional competence, voluntariness, maximisation of benefits, non-exploitation, institutional arrangements, social responsibility, transparency and accountability, privacy and confidentiality, totality of responsibility, risk minimisation, and environmental protection. We offer a brief critical comparison between the ICMR-Covid-19 EC guidelines and the ICMR 2017 guidelines (Supplementary Table 1).

Critical analysis of the guidelines

In this section, we critically analyse the ICMR-Covid-19 EC guidelines to assess whether they capture all the specificities of the research that will be conducted during this Covid-19 period and whether they are founded on the core values and principles of research ethics. This analysis has been presented chapter wise to enhance its practical value for the peer community.

In the chapter on general ethical issues, section 2.1 (risk–benefit assessment) presents the type of review required according to the categories of harm. This is taken from the ICMR 2017 guidelines. However, in the Covid-19 era, the risks associated with normal activities have changed, thereby making "less than minimal risk" and "minimal risk" categories redundant/or to be used with caution. The earlier mentioned categories may apply only to very select types of research, such as epidemiological research or research using medical records. However, any research activity involving physical proximity, even something as simple as history taking, which under normal circumstances would have been considered minimal risk, will now be fraught with danger.

Section 2.5 deals with compensation for research-related harm. Although the new guidelines have mentioned "insurance as per norms", they have failed to recognise the challenges in insurance coverage of clinical trials in the Covid-19 era. While clinical trial insurance is mandatory, the Covid-19 pandemic has created an unprecedented situation with several unknown risks for participants. Insurance coverage is therefore bound to have several restrictions and exclusions, thereby creating gaps in the coverage. Sponsors and researchers may need to find ways and means to mitigate the harm to participants, arising from these gaps, when studying the safety and efficacy of the drug or vaccine.

Section 2.7 on community engagement talks of the importance of educating the community and avoiding the spread of false information. However, the applicability of this guideline to the functioning of ECs is unclear. Section 2.9 lays emphasis on safeguards in the storage of biological materials and datasets; however, in a Covid-19 pandemic, safeguards are needed at all levels, from collection, through storage and usage, to disposal.

Section 2.10 deals with collaborative research and data sharing which are considered good clinical practices. It is important for data to be made public, to avoid repetition of research and wastage of human resources. Data in the public domain needs to be anonymised. However, the ICMR-Covid-19 EC guidelines have failed to address this issue.

Section 2.11 uses the term "social distancing", as opposed to "physical distancing". The use of this term is not appropriate, especially in the context of the Indian value system, which is different from that of the West. The Indian culture views family as an extension of the individual and community as an extension of the family. Section 2.12.3 also talks of preparation of public educational material and community consultations. However, their applicability to ECs, other than for ECs to look

into these aspects during review, is unclear.

Section 2.12.6 has mentioned "monitored emergency use of. unregistered and investigational interventions" (MEURI) and the requirements that go with it. The ICMR-Covid-19 EC guidelines talk of informed consent, EC review, and approval. However, they do not mention the need for randomised control trials to test MEURI drugs at the earliest to provide generalisable evidence on its efficacy. MEURI should not be continued indefinitely, and all efforts must be made by the physician using MEURI to collect evidence on efficacy and side effects with as much rigour, as in a trial. ECs play a very important role in ensuring this.

The ICMR-Covid-19 EC guidelines have raised the issue of confidentiality in dealing with research on biological materials and data sets (section 2.9), in collaborative research (Section 2.10), and when reporting to public health authorities (section 3.4.9). Since Covid-19 is a notifiable disease, there is likelihood of breach of privacy and confidentiality in the process of notification. The new guidelines have failed to address this issue, apart from mentioning the importance of ensuring privacy and maintaining confidentiality. In Covid-19 research, security of all data, both digital and hard copies, should be ensured, with additional safeguards like coding to provide anonymity. The security of the code should be ensured by the sponsor/researcher. This is essential to prevent stigmatisation of and discrimination against the participant.

In the chapter on ethical review procedures, section 3.2.3 states that all Covid-19 related research should be registered with the Clinical Trial Registry of India (CTRI). It is unclear whether this guideline also applies to non-clinical Covid-19 related research. For example, is it relevant to register laboratory and animal research with CTRI as implied by the broad term "all COVID-19 related research" in the new guidelines? Section 3.4.1 talks about the submission of research proposals as soft or hard copies. As fomite transmission has still not been ruled out conclusively as a mode of transmission of the Covid-19 virus, with evidence pointing to the contamination of surfaces in the vicinity of the infected person, it would be preferable to restrict submission to soft copies only in the current situation (WHO scientific brief dated 9 Jul 2020-Transmission of SARS- CoV-2: Implications for Infection Prevention Precautions) (3). Section 3.2.4 talks of fast-tracking the review procedure for early initiation of research. However, fast-tracking of the review process by the ECs alone is insufficient, and the research cannot be started till approval is obtained from the Central Licensing Authority for clinical trials. Section 3.4.4 talks of the possible acceptance of electronic copies of documents; however, the word "maybe" should be revised to a more definite term. Apart from the added benefit of acceleration of the process, electronic submission also serves to reduce the risk of transmission. Thus, it should be made mandatory until more conclusive evidence is obtained on the mode of transmission of the virus.

The ICMR-Covid-19 EC guidelines make no mention of standard of care in Covid-19 related research and the role of placebo in the control arm. To the best of our knowledge, there is no specific standard of care for Covid-19 at present. All interventions being performed, such as remdesivir, hydroxychloroquine, and plasma therapy, are included under MEURI. Covid-19 related research, testing the efficacy of any specific intervention, may use any of the above treatments under MEURI or a placebo in the control arm. Currently, the non-specific standard of care for Covid-19 includes steroids, anticoagulants, and oxygen therapy, as and when required. Therefore, clinical trials on Covid-19 management will need to use one or more of the general or non-specific standard of care in both arms, to which a placebo may be added in the control arm.

In addition to all of the above, the sections have not been numbered correctly; hence, there will be difficulty in referring to the right section. These guidelines will be referred to by other countries in framing their own guidelines. In such situations, the typographical errors and the poor editing reflect poorly on the ICMR. These printing errors need to be rectified. Further, the terms used appear to be a mix of old and new. It is essential to restrict the use of terms to those used in the New Drugs and Clinical Trials Act, 2019. The text of the guidelines also needs to be edited for language to improve clarity and reduce ambiguity.

Lacunae in the guidelines

In this section, we wish to present some of the areas that have not been dealt with in the ICMR-Covid-19 EC guidelines. Bhatt (4) has highlighted the challenges of conducting any study in a Covid-19 pandemic situation. The challenges range from selection of investigational product, participants, and sample size, through methodology and review by ECs, to dissemination of results; these have been discussed below. The present ICMR- Covid-19 EC guidelines have not addressed them adequately.

Drug trials in human participants require to be supported by adequate pre-clinical and animal study data. However, this may not be feasible in Covid-19 studies, wherein some of the drugs may be tried based on anecdotal evidence or their use in other viral diseases. Moreover, the dosage required may be higher than that supported by animal studies. It is incumbent on the ECs to be aware of such possible scenarios and review such proposals judiciously. In Covid-19 related research, there is very little scholarship available to guide the ECs, and it continues to change from day-to-day. Hence, the ECs may need the help of subject experts to aid them in decision-making.

Covid-19 is an evolving disease, with varying manifestations and rapid progression. Considering this, trials involving a particular phase of the disease may need to be completed in a very short time. This requires good laboratory support with rapid turnaround time. If ECs are aware of these requirements, they can ensure that the research site is supported by accredited laboratories with required facilities, which, in turn,

Table 1:
Comparison between the ICMR-Covid-19 EC guidelines and the ICMR 2017 guidelines

S. No.	Ethics themes and sub-themes	Covid-19 EC guidelines	ICMR 2017 guidelines	Analytical remarks
1	Payment for participation/ inducement	No payment beyond routine clinical care and reimbursement of reasonable amount to cover incidental expenses (Sec 2.4)	Addressed in section 2.5	Subtitle is contradictory to the explanation. Section talks about participant paying for routine care.
2	Compensation for research-related harm	Entitlement to free healthcare and referrals in case of direct physical, psychological, legal, social, or economic harms and compensation in case of serious adverse events (SAEs); timeline of SAE reporting (Sec 2.5)	Similar to section 2.6; assistance (financial and otherwise) in case of direct physical, psychological, legal, social, or economic harms	Direct physical and mental harm require healthcare and referral. Other research related harm will require different mode of redressal
3	Post research access and benefit sharing	Communication of results and sharing of benefits with communities/participants (Sec 2.8)	Addressed in section 2.11	No additional information is given.
4	Storage of biological material/ datasets	Safeguards for storage of infectious samples and clarity on custodianship of samples (2.9)	Addressed in section 11.2	Anonymous and irreversible anonymisation may not be feasible in a highly infectious disease scenario where contact tracing and identification of hotspots are conducted.
5	Public health and socio-behavioral research	Issues like inequitable participant selection, use of alternate modalities of data collection, confidentiality, and privacy, risk to dignity and increased vulnerability, validity of data, all of which are unique to Covid-19 have been mentioned (2.11)	Not addressed	This section would have benefited with a more structured and elaborate presentation.
6	Biosafety in laboratories and hospitals	Biosafety levels in research, the need for additional safeguards in handling specimens, precautions to be followed in dealing with patients, the importance of regular active screening of the hospital staff, and the possible role of telemedicine in the current scenario (Sec2.13)	Not addressed	This is an entirely new section, if presented in a structured format would have added value to the guidelines.
7	Categories of research	Three categories of research: New Covid-19 related research, Ongoing non-Covid research, New non-Covid research, prioritisation of review, needful amendments in ongoing research (3.1.1)	Not addressed	This is an appropriate inclusion.
8	Registration of EC	ECs should be registered with both the Department of Health Research (DHR) and the Central Drugs Standard Control Organisation (CDSCO) (3.2.2)	Registration with appropriate relevant authority addressed in section 4.15.2	This is an appropriate requirement. ECs reviewing clinical trials should be registered with the Central Licensing Authority (CLA).
9	Considerations during review	Highlights the need to consider oral consent, electronic method of documenting consent, oversight via phone, enquiry and identification of adverse events and serious adverse events, the importance of notifying the ECs if the principal investigator (PI) is indisposed and has had to delegate parts of her/his duties temporarily to the co-investigator/others (3.4.8)	Addressed requirment for electronic/oral consent	The possibility of change in PI if indisposed on account of the highly infectious nature of COVID-19 and action to be taken has been appropriately highlighted.
10	Privacy and Confidentiality	Risk of breach of privacy and confidentiality through the need to provide information to health authorities during an emergency (3.4.9)	Addressed partly in sections 12.4	This is a new addition
11	Review of multicenter research	Suggested for the COVID-19 situation – common review by one main designated EC with provision of strict monitoring by local ECs (3.5)	Addressed in section 4.10.2	This was applicable earlier to low or minimal risk research. This provision has been added now for COVID-19 research.
12	Decision regarding ongoing studies	Measures suggested to minimise risk to participants in ongoing studies in view of the physical distancing and the travel restrictions imposed, such as extension of study duration, temporary halt, postponement, inactivation of non -initiated sites, phone/ video visits. (3.7)	Not addressed	These changes are appropriate. The importance of re-consent in view of changed parameters of the study has been highlighted.
13	Review of non -COVID research	Steps to minimize risk to participants, researchers, and EC members to be suggested/ implemented to enable continuation of non COVID -19 research (3.8)	Not addressed	This is an appropriate addition.

Table 1: continued
Comparison between the ICMR-Covid-19 EC guidelines and the ICMR 2017 guidelines

S. No.	Ethics themes and sub-themes	Covid-19 EC guidelines	ICMR 2017 guidelines	Analytical remarks
14	Therapeutic misconception	Therapeutic misconception	Addressed in sections 6.10.1 and 7.1.6	Impaired cognition due to severe illness may result in therapeutic misconception. Impaired decisional capacity is likely to affect voluntariness.
15	Surrogate consent	Impartial literate witness for illiterate participant (4.1.3)	Addressed in section 12.2.6	Logistics of the same in quarantine /isolation needs to be addressed
16	Broad consent with opt out option	For residual clinical samples (4.1.4)	Addressed in section 8.4.3	Opt out option should be included in the participant information sheet . Tiered consent could be considered.
17	Electronic informed consent	Use of technology for interactive formats for informed consent and use of digital signature. Audio/ video recording (4.2)	Addressed in section 5.5	Privacy and confidentiality issues need to be addressed.
18	Waiver of consent	Anonymised samples (4.3)	Addressed in section 5.7	Irreversible anonymisation may not be feasible in a COVID-19 pandemic.
19	Safety of healthcare workers	Includes prioritisation of research, biosafety precautions, and training (5.3)	Not addressed	This is appropriate but needs more detailed elaboration on various aspects and how it will affect COVID-19 research.
20	Psychological needs and mental health	Requires empathy, respect, emotional and psychosocial support to affected persons and families, in quarantine or isolation (5.4)	Not addressed	This is appropriate and required; trained counsellors should be made available, or it could lead to undue dependence on the researcher for all psychological needs.

will prevent wastage of human resources and time. Covid-19 related trials also require other high-level technology and infrastructure support, which may not be available in public hospitals or, if available, may be limited on account of the high cost and patient volume. However, restricting research requiring sophisticated equipment or expensive tests to private hospitals only will result in a non-equitable selection of participants and therefore violate the principle of justice. ECs may need to keep this mind. Further, as Covid-19 is a new disease, sample size in a trial may need to change for adequate power of the study, and ECs need to be cognisant of this fact.

The current gold standard in trials is the randomised controlled trial. However, considering the central principle of *primum non nocere* and the fact that Covid-19 is a new, high-risk disease, randomisation, blinding, and placebo should not be insisted upon, and in many circumstances, it may be unethical to use these. In the current scenario, alternative study designs may need to be adopted. Further, the informed consent process in Covid-19 related research is fraught with issues. Considering that Covid-19 is a highly infectious condition, requiring the researcher to wear personal protective equipment with the participants possibly being very ill, communication between the two will likely be affected; efforts should be made to keep communication simple and comprehensive for an autonomous and voluntary consent. Further, in situations requiring surrogate consent, ECs must consider the possibility and suitability of digital/ telephonic consent and video conference call between the researcher, participant/legally authorised representative (LAR), and witness, wherein the informed consent process can be carried out without increasing the risk of transmission of infection. In such situations, documentation of consent may not be possible on account of possibility of transmission of the infection; therefore, a record of the conference proceedings may be saved as a proof of verbal consent.

Physical site monitoring and review of hard copies of documents is not advisable during the Covid-19 pandemic. For trials in the current situation, it may be necessary to adopt alternative measures, such as review of scanned documents during the trial. Site monitoring may also be performed through video surveillance. These measures should be laid out in the protocol and reviewed by the ECs.

Conclusion

The ICMR-Covid-19 EC guidelines are an important and welcome addition to the existing national guidelines for ethics review committees reviewing biomedical and health research with human participants. These are certainly timely and much needed. However, the urgency to develop guidelines during such pandemics also shrinks opportunities to engage with the wider peer community, leading to minor or major substantive gaps in these documents. Our critical analysis has identified and discussed such gaps in these new guidelines. The most critical issue that has been missed in drafting these guidelines

is the fact that the dimensions of risk in research have changed. The risks associated with routine activities are different and the concept of minimal risk is no longer applicable to routine day-to-day activities; this changes the entire risk–benefit paradigm. Addressing this effectively would warrant further engagement with the peer community. This would enable revisions to the guidelines to ensure their comprehensiveness in terms of capturing the research ethics issues that are unique to research undertaken during Covid-19 and those that may be manifested differently during such pandemics. It would benefit if it is treated as a "living document" for the coming few weeks, while it seeks comments and inputs from the peer community. The document should then be revised for use alongside other key international ethics guidelines developed for the purpose of responding to ethics issues in research studies during such pandemics.

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