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Ethical Guidelines for Clinical Trials and Research in India

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Executive Summary

This discussion document proposes a modified set of 8 ethical principles and a guidance questionnaire that researchers and ethics committees can refer to, to ensure that the research is within the ethical boundaries.

ICMR's ethical guidelines of 2017 need to be revised, with more focus on the fundamental ethical principles that govern the moral decisions and on ethical dilemmas that arise while conducting clinical trials/biomedical and health research.

This document recommends revising the section on categorisation of risk to reflect the fact that the definition of risk may differ from one study to another. Additionally, various aspects of ethical principles should be explained with relevant examples for the researchers to understand the ethical dilemmas in research.

Introduction

Ethics are values and principles that serve as a guide for people to decide what is morally good or bad for individuals and the society. Ethics form one of the most important aspects of research, in general and clinical trials, in particular. They guide the moral compass of researchers, ensuring the protection of both the dignity and rights of the participants and the integrity and effectiveness of the research study.

A strong moral compass in research is vital for protecting the well-being of participants. The history of research, however, has been chequered. During the 1900s, human beings were subjected to scientific experiments, over large swathes of time, without any ethical protocols. The significance of ethics came to a tipping point in 1947, when the Nuremberg Code was formulated, in response to the torturous human experiments conducted by the doctors of Nazi regime. Since then, the Nuremberg Code has majorly influenced the approach, countries have taken to formulate their ethical guidelines for research.[1]

Following Nuremberg Code, many international guidelines and declarations were passed to encourage better ethical compliance in research. UNESCO's Universal Declaration on Bioethics and Human Rights, 2005 rightly states that the research cannot be solely rooted in scientific practices; psychosocial and cultural factors also need to be taken into account.[2] These factors often come to the fore, in the form of ethical dilemmas and hence, guidelines are essential to ensure that research studies are respectful of human rights.

Guidelines perform two functions – first, they establish ethical boundaries for conducting research and second, provide guidance to the researchers to design studies within those boundaries. The US commissioned the Belmont Report in 1979 on identifying and solving ethical dilemmas. This report states the principles and guidelines which act as a framework for the researchers to resolve ethical issues.[3] The European Union uses the 'Ethics for researchers' framework which associates the fundamental human rights with the ethics of research.[4]

In India, until March 2019, the Schedule Y of Drugs and Cosmetics Rules, 1945 regulated clinical trials. However, the rules were barely sufficient to ensure that clinical trials remained within ethical boundaries. They briefly touched upon the aspects of informed consent and the responsibilities of ethics committees.[5] In 2000, the Indian Council of Medical Research released the Ethical Guidelines for Biomedical Research on Human Subjects, which were then revised to Ethical Guidelines for Biomedical Research on

Human Participants, in 2006.[6] These versions did not cover public health and socio behavioural research and their ethical aspects. They also did not address the special considerations of vulnerable populations in research and clinical trials.

According to an investigation carried out by the Independent, a news agency from the UK, since 2005, India had become a destination for Western pharmaceutical companies, for conducting clinical trials.[7] The reason for this was the amendment of rules on clinical trials of new drugs which unreasonably favoured the interests of private sector.[8] As a result, there were many instances where clinical trials were conducted beyond the bounds of ethics. In 2010-2011, survivors of Bhopal gas tragedy were included in at least eleven trials at Bhopal Memorial Hospital and Research Centre, by making them sign "informed" consent forms without explaining what the trials were about. There were 10 deaths during the trials which were reported several months later. Moreover, some of the members of the ethics committee were the ones conducting those trials, indicating a serious conflict of interest.[9] In another instance, in Andhra Pradesh and Gujarat, hundreds of minor tribal girls were included in a Human Papilloma Virus vaccine trial, on the basis of an illegal consent given by their hostel warden. Meanwhile, their legal guardians – whose consent is mandatory - were unaware of their participation in the study and were informed only after a few participants died. [10] The sheer disregard for informed consent is of concern, especially for vulnerable populations, as it reflects the disrespect for the personal agency of the individuals.

In 2017, covering the unaddressed areas such as public health and social sciences, the ICMR came up with National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. The ethical guidelines of 2017 are applicable to all biomedical and health research, including clinical trials. They aim to adhere to international standards while still maintaining the sensitivity to Indian "cultural, social and natural environment".[11]

In 2019, the Central Drug Standard Control Organisation (CDSCO) released the New Drugs and Clinical Trials Rules (NDCTR) which makes it mandatory for research not including clinical trials to be governed by the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. The rules also make it mandatory for Ethics Committees for clinical trials to have at least 50% of non-affiliated members and for them to undergo training from time to time.[12] The increased focus on the ethics aspect of research and clinical trials is definitely a welcome move. However, the way ethical guidelines are formulated is not sufficient to ensure that ethics are truly understood by the researchers and the scientific community involved. There are some issues with NDCTR 2019 too, such as the lack of appeal mechanisms for participants, which needs to be addressed.

The ethical guidelines by ICMR are too procedural, at best. They focus a lot more on what the Ethics Committees need to do, instead of tackling how to analyse the ethical aspects of the study. The guidelines need to be revised, so that it will be easier to distinguish normative ethics from procedural ethics, which are the fundamental principles and values that govern the moral decisions.[13] For instance, all types of research included in the guidelines state that ECs should get a subject expert, review all the study procedures, conduct benefit-risk assessment and so on. However, the ethical issues that are mentioned along with it do not go into details of what the conflicting sides could be. Thus, it takes the focus away from the normative ethics.

Furthermore, the COVID-19 crisis has highlighted the need for an effective regulatory environment to conduct research and clinical trials, in order to expedite a solution for the disease. Public health emergencies, particularly those inflicted by a novel disease, are challenging because of the urgency to find a medical solution for an unknown pathogen. Such emergencies present the scientific community and the governments, with the conundrum of how to speed up the scientific processes to ready drugs and vaccines, while balancing ethical safeguards.

The current guidelines address ethical concerns of health emergencies, especially when it comes to vulnerable populations. However, how effective their implementation is something that remains to be seen. There has already been a violation of Monitored Emergency Use of Unregistered and Experimental Interventions (MEURI) section of the ethical guidelines of 2017, when the hospital staff were told to take Hydroxychloroquine without getting their informed consent, based on the ICMR's advisory.[14]

This document proposes a guiding questionnaire to analyse ethical boundaries of research studies and recommends that the guidelines be amended to link the ethical principles and ethical issues, so that they are better understood by the researchers.

Ethical guidelines around the world

in this section we look at ethical guidelines of other countries, to provide a context while analysing India's ethical guidelines.

1. **United States of America** – In 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created to design basic principles that would direct the conduct of research and guidelines to ensure the principles were followed. Following this, the Belmont Report was released in 1979. Its objective is to "provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects".[15] The report states three basic ethical principles – respect for persons, beneficence, and justice. It elaborates how these three principles should be applied while getting informed consent, assessing risks and benefits, and selecting subjects for the study. While doing so, it provides examples of ethical conundrums that one might face, which makes it easier to understand the principles and their application. [16]

2. **European Union** – Its 'Ethics for researchers' document talks about ethical issues such as data protection and privacy, informed consent, research involving developing countries etc. It links the rights laid out in the European Charter of Fundamental Rights such as right to integrity of the person, respect for private and family life, protection of personal data, and freedom of arts and sciences with research ethics. While explaining the ethical issues, it provides a separate link for procedural ethics relevant, for further reading. For example, it talks about the ethical dilemmas of research on human embryos and foetuses and provides the link for technical aspects such as donation, procurement, storage of samples as a further reading.[17]

3. **Canada** – The ethical guidelines are stated in 'Ethical Conduct for Research Involving Humans' include both procedural and normative ethics. The guidelines state the core principles, similar to that of the USA. They describe different types of research and the ethical issues specific to them.[18] It also addresses the role of Research Ethics Board and their governance.

National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017

Following the Nuremberg Code of 1947, the World Medical Association adopted the Declaration of Helsinki in 1964. It is "a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects".[19] In India, the ICMR released the first ever official document on ethics in research, known as the Policy Statement on Ethical Considerations Involved in Research on Human Subjects, in 1980. Following that, ethical guidelines were released in 2000 and revised in 2006. Meanwhile, in 2005, the UNESCO came up with the Universal Declaration on Bioethics and Human Rights, in response to the rapid developments in science and technology and the subsequent growing need for a global response to the ethical issues.[20] The Declaration of Helsinki was amended several times since its adoption, the latest being in 2013. Considering these international developments and the emerging concerns with regards to ethics in research, the ICMR revised its guidelines in 2017, renaming it as *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants*.

The 2017 guidelines has detailed sections added on informed consent, public health research, social and behavioural sciences research, research during humanitarian emergencies and disasters, responsible code of conduct, and vulnerability. It has expanded the four basic ethical principles of respect for persons, beneficence, non-maleficence, and justice into 12 general principles. The principles section duly highlights the need to review the essentiality of including humans in the research, unbiased selection of participants to distribute the benefits and burdens evenly and having institutional mechanisms to facilitate transparency and accountability. For the research to be ethical in the context of Indian society, there is principle for social responsibility which implies for the researcher to be culturally and socially sensitive while designing the study. The principle of environmental protection implores the researchers to be respectful of the environment and not damage it for the sake of the research.

The guidelines emphasize the importance of informed consent in research. The decision to be a part of the research study or to withdraw solely lies on the participants or their legal guardians. The guidelines clearly list out all the important components of informed consent, responsibility of researchers in that context, and the special situations. The

guidelines also talk about inclusion of vulnerable populations in research and recognizes the special considerations needed to protect those populations. They address the issue of conflict of interest as well and direct the institutions to have mechanisms to identify and address the same.

ISSUES WITH THE GUIDELINES

1. **Lack of distinction between procedural and normative ethics** - It is difficult to distinguish normative ethics from procedural ethics in the guidelines. While the guidelines do talk about the principles to be followed, they focus a lot more on what Ethics Committees need to do. The guidelines have sections for various kinds of research (public health, stem cell, biobanking etc.) and all of those sections describe the functions of ECs, while not really addressing the ethical concerns. There is no guiding questionnaire to help the ECs and researchers to navigate through the ethical issues.

   The application of ethical principles should be explained with examples. The Belmont Report , while it talks about what the principle 'Justice' entails, provides an example of including vulnerable populations in the study. In 1940s, the US Public Health Service had included rural black men in a syphilis study, under the pretext of providing them free medical treatment. Even when penicillin was approved to be the treatment for syphilis, the participants were not offered it.[21] The principle of justice entails that whenever research funded by government leads to the development of therapeutic treatments, the advantages of it should be provided to everyone irrespective of who can afford it and it should not unfairly involve individuals who are unlikely to be the beneficiaries of the subsequent applications of the research.[22]

2. **Ethical concerns of some types of research not mentioned** - This is in continuation of the first concern. There are many sections in the guidelines which do not have a clear mention of ethical concerns.

   a) **Clinical trials with stem cells**

      The guidelines talk about the kind of research that is allowed and prohibited within the areas of Stem Cell research, without addressing the ethical concerns associated with them, in detail.

      While human Embryonic Stem Cell (hESC) research is allowed, there are some fundamental ethical questions which arise because embryos are destroyed while conducting the research.[23] There have been unending debates over when life exactly starts – embryo stage or foetus stage. If research is to be

conducted should only spare embryos be used from IVF treatments/abortions or should they be produced especially for the purpose of research?[24]

Ethical conundrums in hESC research are often associated with opposition to abortion. On one hand, there are people who believe that human life starts at the foetal stage rather than during fertilization and on other hand, there are those who believe that "embryo is a person with the same moral status as an adult or a live-born child".[25] Although abortion is legal in India, there are diverse cultural and religious beliefs regarding abortion. The answers to questions discussed in this section cannot be fixed and will vary depending on one's beliefs and the circumstances. Hence, it is necessary that instead of a one-size-fits-all guideline, a guiding assessment is created that allows researchers to establish ethical boundaries based on the study and the participants.

b) Surgical interventions

ICMR allows the use of sham surgery in surgical research only when three conditions are met – there must be a clear justification for the use of sham surgery, no serious harm is caused, and the participant must receive appropriate intervention at the end of the trial. The guidelines mention that sham surgery should not be conducted unless it is absolutely necessary, due to the "inherent ethical issues". However, it does not talk about what those ethical issues are.

Sham surgeries are placebo/control surgeries, which are "characterised by a physical change of bodily tissue through manual or robotic operation and thereby inherently imply physical harm and/or risks".[26] Considering the principles of beneficence and nonmaleficence, it means that surgeons should not perform invasive procedures on patients except for the purpose of curing a medical condition.[27] In sham surgery, there is a high probability of therapeutical misconception. It occurs when the participant does not completely comprehend the study design implications and fails to distinguish clinical research from therapeutic procedures.[28] In the case of a sham surgery, the participant may mistake the placebo surgery for individualised treatment.[29]

c) Monitored Emergency Use of Unregistered and Experimental Interventions

Under the Humanitarian Emergencies and Disaster section, the guidelines approve MEURI with certain precautions, but they do not explain what the particular ethical concerns could be or even what it entails. There are diseases for which cure has not been found yet, the latest example being COVID-19. Under normal circumstances, potential interventions go through clinical trials to establish their safety and efficacy in humans. However, during emergencies

there may not be enough time for clinical trials to happen. Experimental interventions may be approved when no proven effective treatment exists.[30] This implies the use of off-label drugs, wherein drugs are used for medical conditions, that they are otherwise not approved to treat.[31] Considering the conditions under which off-label drugs are used, some ethical issues are bound to exist.

There is a probability of manufacturers using this as an opportunity to market these drugs which may result in haphazard and unregulated use of off-label drugs. The decision to use off-label drugs depends entirely on the doctor's discretion, so there are chances of patients not being informed properly.[32] The guidelines do make it clear that informed consent is a must and fair distribution of drugs should be ensured. However, in spite of the guidelines being in place, the approval of usage of hydroxychloroquine as a prophylactic for COVID-19, by ICMR, was not regulated and it resulted in a serious diversion from ethical practices (see the case study below). This is of concern, because of the kind of the precedent that India's apex research body set during a public health emergency.

3. **Categorisation of risks** – One of the main principles of research, including clinical trials is beneficence, which implies not doing any harm and maximising the benefits and minimising the risks for the participants.[33] The ICMR guidelines have categorised the risk into four levels, defining what constitutes each category, as seen in the figure below.

Type of risk	Definition/description
Less than minimal risk	Probability of harm or discomfort anticipated in the research is nil or not expected. For example, research on anonymous or non-identified data/samples, data available in the public domain, meta-analysis, etc.
Minimal risk	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of an average healthy individual or general population or during the performance of routine tests where occurrence of serious harm or an adverse event (AE) is unlikely. Examples include research involving routine questioning or history taking, observing, physical examination, chest X-ray, obtaining body fluids without invasive intervention, such as hair, saliva or urine samples, etc.
Minor increase over minimal risk or Low risk	Increment in probability of harm or discomfort is only a little more than the minimal risk threshold. This may present in situations such as routine research on children and adolescents; research on persons incapable of giving consent; delaying or withholding a proven intervention or standard of care in a control or placebo group during randomized trials; use of minimally invasive procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress, such as drawing a small sample of blood for testing; trying a new diagnostic technique in pregnant and breastfeeding women, etc. Such research should have a social value. Use of personal identifiable data in research also imposes indirect risks. Social risks, psychological harm and discomfort may also fall in this category.
More than minimal risk or High risk	Probability of harm or discomfort anticipated in the research is invasive and greater than minimal risk. Examples include research involving any interventional study using a drug, device or invasive procedure such as lumbar puncture, lung or liver biopsy, endoscopic procedure, intravenous sedation for diagnostic procedures, etc.

Fig 1: Categories of risk as presented in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017

This categorisation can be problematic because it can be interpreted in many ways. The definition of minimal risk states that "discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities". Firstly, it is not clear what discomfort actually is, because discomfort perceived by one person might not be a discomfort for another person. Secondly, routine life will differ from person to person. To generalise a definition like this will leave room for confusion. While providing examples of types of research that involve high/low risk is helpful, it does not say what that risk is.

The Belmont Report states that assessment of risks should be as explicit as possible and vague terms like "small risk" or "more than minimal risk" should be avoided.[34] While there is no obvious fixed formula to calculate risks involved in research, it should be ensured that the determination of risks is informed by the existing data, their probability of occurring, and their short and long term consequences.[35]

4. **Inclusion of aspects not relevant to ethics -** The ethical guidelines include technical aspects too, which are not relevant to the rest of the document. For example, the Human Genetics Testing and Research section talks about aspects such as storage and transport of genetic samples , quality standards of laboratories, intellectual property rights related to gene patenting. Synthetic Biology under Clinical Trials of Drugs and other Interventions section addresses safe handling of products. While these aspects are important and need to be done following correct procedures, they are not a substitution for the core issues of the ethical design of the study. These aspects should, instead, be included in the respective technical guidelines for these topics.

Considering the above issues and the lack of a framework that enables the analysis of ethical aspects of any research study, this document presents a framework that can be used by the researchers and the ethics committees for the analysis.

Ethical guidance questionnaire

The ethical guidelines need a assistive set of broad questions which can guide researchers to make a call on whether the study design is within the ethical boundaries. The current guidelines have 12 principles. This document proposes 8 ethical principles, which retains most of the existing principles and clubs the remaining ones, to present a succinct and clear idea of what those principles entail.

Table 1: Proposed principles

Existing principles	Proposed principles	Description
Essentiality	Essentiality	The essentiality of a study and of human participants in that study needs to be established. Before beginning a study, questions like is the problem important enough to fix and is there any evidence of previous studies that points to a need for this study must be asked. Factors like feasibility, and value for money also need to be considered.[36] The use of human participants in any kind of research has to be on an essential basis, only after ruling out all the existing options. This has to come with the acceptance of the fact certain studies might have to be forsaken.[37]
Voluntariness	Autonomy	The principle of voluntariness refers to the right of the participant to agree whether to participate or not, or to withdraw from the research study. The proposed principle of autonomy is essentially the same, however, the word 'autonomy' entails the agency of the participants which enables them to practice voluntariness. The informed consent is an important instrument which strengthens the autonomy of the participants to make decisions.
Non-exploitation	Non-exploitation	It refers to the non-discriminatory selection of participants, so that the burdens and

		benefits of the study are fairly distributed. Special attention needs to be given to vulnerable populations (for e.g. - the elderly, sex workers, people with HIV) so that they are not exploited, due to their limited autonomy.
Social responsibility	Social responsibility	Care needs to be taken that the research does not disturb the social harmony.
Ensuring privacy and confidentiality	Ensuring privacy and confidentiality	It refers to the participants' right to privacy, wherein their private data has to be kept confidential. While data sharing is essential for extending the benefits of the research, it has to be ensured that all identifiable data is protected.
Risk minimisation	Minimisation of risk and maximisation of benefits	The original document presents risk minimisation and maximisation of benefit as two separate principles, however, it is better to see those in tandem. The basic principle of beneficence applies to this, which implies not just protecting the participants from the harm but also securing their well-being. It is essential for researchers to decide when the benefits justify the risks involved or when the benefits should be forsaken because of the risks.[38]
Maximisation of benefit		
Professional competence	Transparency and accountability	These four principles have been clubbed into one, because transparency and accountability imply the rest three as well. This principle refers to the availability of mechanisms that ensure studies are conducted and approved by professionally competent researchers and ethics committees, respectively. There are institutional arrangements to hold everyone involved in conducting the research accountable, in cases of misconduct or malpractices.
Institutional arrangements		
Transparency and accountability		
Totality of responsibility		
Environmental protection	Environmental protection	Any kind of research needs to respect the environment and its biodiversity.

A set of questions will help in realising if the principles are being followed or not. These are the questions that the researchers (R) can ask themselves while designing and conducting the study and the ethics committees (EC) need to consider while approving the studies. This is not an exhaustive list and the questions may be modified/added depending on the type of research that is being conducted.

Table II: Ethical guidance questionnaire

Principles	Questions to be asked
Essentiality	Are human trials absolutely necessary for the study? Are all existing alternatives ruled out? (EC, R)
Autonomy	Is the study explained in a comprehensive and clear manner (in the vernacular language if required) so that the participants can decide whether to volunteer or not? Is it certain that the participant has understood all the aspects, before signing the informed consent form? (R)
	Has care been taken that the participant's autonomy is not compromised and that they have not "volunteered" under coercion or undue influence? (R)
	For vulnerable populations who cannot exercise autonomy, are appropriate guardians identified for obtaining informed consent? (e.g. children, mentally disabled) (EC)
	Are the participants regularly updated about the progress of the study so that they have the agency to withdraw, if they are not comfortable with the way the research is progressing? (R)
Non-exploitation	Are the participants selected on a fair basis using appropriate statistical methods, without any personal bias? (This is to ensure that vulnerable populations are not included in risky research and the rich and powerful are not prioritised for potentially beneficial research) (EC, R)
	Are the rights and dignity of participants protected irrespective of their gender, class, and religion? (EC, R)
	Will the benefits of this study, to larger populations, come at the cost of the participants? (EC, R)
	Are mechanisms for grievance redressal in place, for participants to voice their concerns about the conduct of the researcher or the study? (EC)

Social responsibility	Is the research study designed keeping in mind the social norms and values of that particular population/area? (EC, R)
	Are there feedback mechanisms in place to assess the social impact of the research outcomes? (R)
Ensuring privacy and confidentiality	Are technical frameworks and security measures in place, at institutional level, to protect the personal data of participants? (EC)
	Is the participant made aware that he/she has all the control over the information that may be disclosed, collected, and stored? (R)
	Is extra care taken to protect sensitive information, which if disclosed might lead to stigmatization or discrimination? (e.g. HIV patients, sex workers etc.) (EC, R)
	Are the circumstances under which private information might need to be revealed, explained to the participants? (e.g. legal issues, criminal cases etc.) (R)
Minimization of risk and maximization of benefit	What are the risks involved in the study? Are those risks analysed in terms of "nature, probability and magnitude" as much as possible?[39] (EC, R)
	Are the risks clearly communicated to the participants? (R)
	Is a conscious effort taken to minimise those risks and is there a mechanism to account for that? (EC)
	Will the results of the study lead to benefits for the larger society? If yes, are there mechanisms for information sharing to maximise those benefits? (EC, R)
Transparency and accountability	Will the results of the research be shared with the participants and be made available on public platforms? (EC, R)
	Are the conflicts of interest disclosed and resolved? (EC, R)
	Are there independent mechanisms to hold all those involved in conducting the study accountable? (EC, R)
Environmental protection	Will the research result in irreversible damage to the environment? (EC, R)
	Are all relevant rules and regulations complied with, to protect the environment and its resources? (EC)

Case study: Use of Hydroxy chloroquine as a prophylactic for COVID-19

Hydroxychloroquine is a drug commonly used to treat malaria and auto-immune diseases like Lupus. The drug is contraindicated in persons with known case of retinopathy, pre-existing cardiomyopathy, and hypersensitivity to HCQ.[40] This means the drug has to be prescribed only after knowing the medical history of the consumer.

On 22 March 2020, the ICMR released an advisory which approved the use of HCQ as a prophylactic for healthcare workers and persons directly in contact with COVID-19 patients. However, at that point of time, no study had proved the safety and efficacy of HCQ in a prophylactic or a curative capacity.[41] Following the advisory, many hospitals directed their staff to take HCQ, without informing them about its potential side effects or even the fact that it is an experimental drug. The advisory mentioned nothing about informed consent. When Mumbai's Government hospital ran out of HCQ supply, the staff got anxious as they thought they would be left out from being protected against COVID-19. Some of them even went to pharmacies to buy HCQ on their own.[42]

When the member secretary of ICMR's bioethics unit was contacted for this matter, the reply was that ICMR's ethical guidelines of 2017 were not applicable to the prophylactic use of HCQ. However, many bioethics experts have disagreed and argued that the ethical guidelines are meant exactly for situations like this and the ICMR is violating its own guidelines.[43] The NDCTR 2019 clearly makes it mandatory for biomedical and health research to follow the 2017 ethical guidelines, which includes a section on MEURI too. This violation of ethics by India's apex research body is disturbing, as populations during any kind of emergencies (health, natural disaster etc.) are vulnerable and it is the responsibility of researchers to be as protective of the population as they can be. The ICMR and the hospitals thereby, clearly ignored the principles of voluntariness, risk minimisation, non-exploitation, and transparency and accountability as stated in the guidelines.

The ICMR before releasing the advisory and the doctors before directing their staff to take HCQ should have considered the following questions, in order to address the ethical concerns of experimental use of HCQ and prevent the violation of ethical principles.

Table III: application of ethical principles to Hydroxychloroquine case study

Principles	Questions that should have been asked (by ICMR/doctors)	Answers
Essentiality	Is including humans absolutely needed for the study? Are all existing alternatives checked? (ICMR)	At that point of time, clinical trials on HCQ in other countries such as France and China had not produced favourable results for HCQ. Despite that ICMR decided to approve it under MEURI.
Autonomy	Is the experimental use of HCQ for COVID-19 explained in a comprehensive and clear manner so that the hospital staff can decide whether to take the drug or not? Has the staff signed the informed consent form after understanding all the aspects of MEURI? (Doctors)	This would have ensured that the doctors had explained to the staff that HCQ is not an approved drug and that it is being used on an experimental basis. This would have allowed the hospital staff to make informed decision whether to take HCQ or not.
	Has care been taken that the participant's autonomy is not compromised and that they have not "volunteered" under coercion or undue influence? (ICMR, Doctors)	The doctors never questioned the advisory and with the staff trusting the hospital doctors, they did not question the doctor's advice either. An external agency could have ensured that the staff was volunteering only after having all the information, which would leave no room for personal bias.
	Are the participants regularly updated about the effectiveness of HCQ as a prophylactic? (ICMR, Doctors)	The aggregate results of effectiveness of HCQ as a prophylactic would have been communicated to the staff who had taken HCQ.
Non-exploitation	Are the participants selected on a fair basis, without any personal bias and not because	Considering the 'assumed' benefits of HCQ, the ICMR would have ensured that the

	they are easily available for the study? (ICMR, Doctors)	doctors are not administering HCQ to their immediate family or top authorities of the hospital, but are fairly distributing it among the hospital staff.
	Will the benefits of this study, to larger populations, come at the cost of the participants? (ICMR)	Considering HCQ's potential side-effects and contraindications, ICMR would have come up with the risk assessment for participants and ensured that the benefits and burdens are equally distributed.
	Are mechanisms for grievance redressal in place, for participants to voice their concerns about the conduct of the researcher or the study? (ICMR)	The ICMR should have ensured that there is a platform designated for grievance redressal so that the hospital staff could have registered complaints in case of malpractices and raise any other issues.
Minimization of risk and maximization of benefit	What are the risks involved in the study? Are those risks analysed in terms of "nature, probability and magnitude" as much as possible?[44] (ICMR)	The ICMR would have made a risk profile of HCQ which would include the kind of risks (side-effects, contraindications) it could lead to, the probability of them occurring and the consequences (short and long term).
	Are the side-effects and contraindications of HCQ clearly communicated to the participants? (Doctors)	While getting the informed consent from the staff, the doctors would have explained the side-effects and contraindications of HCQ in a way that would be easy to understand.
	Are medical histories taken into account to minimise the risks	The doctors would have made sure to take medical histories of the staff before administering

	and is there a mechanism to document that? (Doctors)	them with HCQ. There would have been a documentation system in place which would serve as a point of reference in case of any adverse events.
	Will the results of the study lead to benefits for the larger society? If yes, are there mechanisms for information sharing to maximise those benefits? (ICMR)	The ICMR, through the benefit-risk assessment would have estimated the level of benefits to the larger society. It would have come up with platforms for information exchange.
Transparency and accountability	Will the results of effectiveness of HCQ as a prophylactic be shared with the participants and be made available on public platforms? (ICMR)	The ICMR and the doctors would have shared the results of effectiveness of HCQ with the staff who took it and with the general population.
	Are there mechanisms at national level (independent from ICMR) to hold all those involved in conducting the study accountable? (ICMR)	The ICMR should ensure that there is an independent body which will evaluate the proceedings of the study from an unbiased point of view.

Had the ethical guidelines proposed in this document been adhered to, prior to releasing the advisory, it would have led to more ethical regard of the persons supposed to take HCQ. It would have also reflected ICMR's consideration of dignity of hospital staff, even under public health emergency situation.

Conclusion

The 2017 ethical guidelines need to be revised to serve their purpose. The mix of procedural and normative ethics without clear distinction can take away the focus from the latter. It needs to be stressed that while procedural ethics are to be followed as they are, the ethical principles will not always have answers ready for researchers. They need to be used as a framework for making tough decisions in times of ethical dilemmas.

Various aspects of ethical values and principles should be explained with relevant examples of ethical conundrums which will make it easier to understand. The categorisation of risks needs to be presented in an improved way. The definition for levels of risk may change from study to study and hence, analysing the risk as explicitly as possible should be encouraged.

The ethical principles should serve as a framework to guide the judgment of the researcher. A clear link between the ethical principles and ethical issues needs to be established. The principles and ethical issues cannot be seen separately. Instead, which principle is applied to what issue needs to be made clear so that the importance of ethical principles is reinforced.

The primary aim of the guidelines should be to ensure welfare and safety of participants with whom researchers work. The revision of ICMR's ethical guidelines along with that of New Drugs and Clinical Trials Rules, 2019 is needed. This will help in compliance of research with ethical principles. The implementation of the guidelines and the rules need to be strengthened at administrative and institutional levels in order to have better social outcomes of the research.

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