Ethics committees walking the high tension wire: can revised national ethical guideline support them to stay in balance?

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Abstract

In this commentary, I discuss four sections of the 2017 national ethical guidelines for biomedical and health Research involving human participants: the statement of general principles, general ethical issues, ethical review procedure, and biological materials, biobanking and datasets. I compare the sections of general principles; general ethical issues and ethical review procedure to the same sections from earlier ICMR guidelines published in 2006 and elaborate on the strengths and few areas for improvement in the revised guideline. The guideline review demonstrates that huge responsibility of ensuring safety of human participants of research is bestowed on the fair, transparent and independently functioning ethics committee but being member of such a committee seems as challenging as walking on a tight rope especially if the guideline does not get the statutory status or if it just remains a morally binding document to research stakeholders.

In 2017, Indian Council of Medical Research published revised national ethics guideline for biomedical and health research involving human participants. The revision process spanned over a period of three years (2015-2017) and involved inputs and contributions from more than 100 scholars representing central ethics committee on human research, various subcommittees, advisory groups, invited experts and members of national and regional consultations(1). In this commentary I will focus on four sections of the revised guideline: the statement of general principles, general ethical issues, ethical review procedure, and biological materials, biobanking and datasets. I will compare the sections of general principles, general ethical issues and ethical review procedure to the same sections from earlier ICMR guidelines published in 2006(2), describe how critique on earlier version has been addressed in 2017 guidelines(3) and elaborate on the strengths and few areas for further improvement.

*General comment on ICMR ethics guideline 2017*

The first striking change in the revised guideline is the breadth of its scope; reflecting rapid changes taking place in the field of biomedical research and incorporating evolving interdisciplinary research methods and fields such as public health research, social and behavioral sciences research in health, biobanking and research during humanitarian emergencies and disasters. Though some inputs on these topics were already evident in 2006 guidelines, the revised guideline provides detailed guidance. The term health research is added in the title of the revised guideline to already existing term biomedical research. Social and behavioral sciences make significant contribution in understanding individual, cultural and community level factors that influence and alter human health and wellbeing.

In addition, novel research methods and approaches are convergent with information technology, facilitated by internet and go beyond traditional clinical research paradigm (4-6). The risks ~~involved~~ to human participants in such research projects are beyond physical harms and risks of a medical intervention such as obtaining blood or tissue sample and yet important from psycho-social aspects of harm, stigma and burden. It also makes us think about threats to voluntary participation in research and ~~making~~ informed decisions when individual level data is collected outside research contexts ~~such as~~ through activity-tracking devises and arm bands but the data is used for research purpose without obtaining informed consent from each user(7, 8). Similarly challenges created by large scale storages of human biological material and individual and community level health data especially in the day and age of ‘big data’ need to be addressed(9-11). Though it is impossible to include everything in one national guideline, these developments in science and society in general need careful assessment and ethical analysis.

One such evolving field is the research and health data exchange facilitated by the internet. Many mobile devises and gadgets are capturing valuable information about the ordinary individuals in their everyday life, either through the information they share through social media, or simply by tracking their movement, daily activity, life style choices such as food they consume. Seemingly not so sensitive personal data collected in this way and stored in data storage clouds covering large population and over prolonged period of time is a valuable resource for understanding human behavior and choices that clearly influences health(10). Internet based research is becoming a valuable tool in many disciplines such as medicine, genetics, social sciences, behavioral economics and psychology. It is important to keep a critical eye on ways in which such research while valuable could still harm individuals and communities if not monitored and regulated. Unlike most forms of traditional research, in internet based research, the research participants do not come in direct contact with the researchers, informed consent is often limited to initial agreement a user makes while accepting an app or devise without reading in detail the fine print of terms and conditions of data handling and usage(12). The individuals knowingly or unknowingly contributing to research in this manner are also prone to being harmed as was recently seen from the research on emotional manipulation done through Facebook(13, 14).

*Statement of general principles*

The 2017 ICMR guideline opens with the statement of general principles which states that four universal ethics principles of autonomy, beneficence, non-maleficence and justice are expanded into 12 principles which should be followed by all stakeholders engaged in biomedical and health research. The first noticeable difference in description of these principles as compared to 2006 guideline is the readability and brevity of their explanation. All principles are easy to understand and a few of them indicate the key stakeholder responsible for safeguarding the principle. For example whether a particular research proposal is investigating a valuable and meaningful research question is to be assessed by the ethics committee. On a close reading, one realizes that different research stakeholders have different degree of direct control and influence over application of a particular principle as well certain level of responsibility in research implementation. There could be situations where stakeholders have a conflicting interest in application of a particular principle. Who should then assess such conflicts and take a decision? Whose assessment should carry more weight? For example the principle of institutional arrangement states that the institutions hosting research should have appropriate governance and infrastructure to facilitate planned research. An institution must be able to assess its capacity and infrastructure in neutral way and may have to decline possibility to conduct research if necessary facility is not available. But that could mean loss of external (national, international, public, industry sponsored) funding as well as academic and research reputation. Ethics committee of such an institution realizes that the sufficient infrastructure is not available; raising this concern could mean challenging their home institution which might not always be easy or even appreciated. Though it is not clearly defined who the research stakeholders are, one can see that ethics committees have significant responsibility to ensure implementation of these principles. It is questionable though whether they have enough authority or power to influence other stakeholders. Principle of totality of responsibility states that ‘the professional, social and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly’. If the guideline does not get the statutory status, in what ways can it be binding to the stakeholders? Are we referring to moral or professional binding alone? Furthermore what is the direct and indirect binding to the guideline? Some elaboration on these two points will be useful for the end-users of the guideline as well as for the ethics committees who are often bestowed with the responsibility of implementing these ethical principles.

Other research stakeholders who are only indirectly (if at all) referred to in the description of these principles are the patients and the general public. Patients and human research participants appear to be the passive entities whose interests should be safeguarded by all other stakeholders especially the ethics committees. Can we envision an active role for patients and for that matter even the general public to shape and influence research agenda and funding, to be involved in research design, implementation, data analysis and dissemination? Lived experience of the patients in regards to their illness is a valuable input in the translational research loop from ‘the bedside to bench’ which can guide not only pertinent research questions but also contribute to patient driven research. Similarly we must create scope for the general public to engage in the research enterprise to ensure fair utilization of public funding for research and trust of the society in science(15). It might be worthwhile to reflect more on the role and potential contribution of patients and the general public as an important research stakeholders rather than just being the participants of research endeavor. Last point to consider under the principle of transparency and accountability is the duration for which research data and record should be retained for possible external audit. The duration may vary depending on the institution or the requirements of the funding agency. It is not clear from the current guideline whether the minimum duration for which data should be preserved will be defined in the standard operating procedure of the institution or at some national or regional level. Modern research often involves different national, international, public and private partners. It will be beneficial to have some standard time frame which is the minimum duration applicable to all research activities irrespective of the sponsor involved.

*General ethical issues*

The section on general ethical issues is detailed, easy to read, elaborates on important ethical issues such as informed consent, payment for research participation, post research access and benefit sharing and provides a table for risk categories. The opening paragraph of the section ends stating that ‘the ethics committees are responsible for ensuring that research is conducted in accordance with the aforementioned principles’. The table below displays key ethical issues described in this section and the responsible stakeholder when specified.

|  |  |
| --- | --- |
| **Ethical aspect** | **Responsible stakeholder** |
| Benefit-risk assessment | Researcher, sponsor and **ethics committee** |
| Informed consent process | **Researcher**, ethics committee |
| Privacy and confidentiality | **Researcher/research team**, organization |
| Distributive justice | Not clearly described except when it has potential commercial value, it should be discussed a priori by all stakeholders and reviewed by the ethics committee |
| Payment for participation | **Ethics committee** and researcher |
| Compensation for research related harm | **Researchers,** research organizations, sponsors, ethics committees |
| Ancillary care | Not clearly described, provision of care by the research team and to be reviewed by the ethics committee |
| Conflict of interest | **Researcher, research institution, ethics committee, sponsor** |
| Selection of vulnerable groups and special populations as research participants | **Researchers and ethics committees** |
| Community engagement | Not clearly defined, researcher, research institution |
| Post research access and benefit sharing | **Researcher**, ethics committee, **sponsor** |

The ethics committees clearly play a significant role in ensuring all the ethical issues described in this section. However one cannot help but wonder, whether the ethics committees have adequate number of trained members, infrastructure, time, financial means and resource to undertake initial and continued ethics review during research implementation and if they have necessary power to influence the behavior of researchers and the interest of research organizations and sponsors. Referring again to the statutory status of such guidelines, ethics committee might be limited in their scope and authority. If we look at the division of labor in clinical research enterprise from the perspective of different stakeholders as proposed by Anderson et al (16), we realize that the role, direct accountability and the responsibility of each of these stakeholders towards human participants varies a great deal and has potential to create conflicting interest.

Let us take a look at reporting, assessment and calculation of compensation for research related harm. The researcher is responsible for reporting all serious adverse events. Unless reported by the researcher, the ethics committees will not be able to assess its relatedness to the research. Reporting a SAE means additional paperwork and potential reprimand from the research organization or the sponsor as it could involve compensation if linked to the research. The guideline states that the medical management should be free if the harm is related to research which means significant financial costs to the institution and sponsor. In an ideal situation, irrespective of these financial and reputational consequences, researchers should report each SAE in a timely manner, the ethics committees should evaluate their relatedness without being influenced by the institution they are based at, propose compensation and ensure that the institution and the sponsor not only pay such compensation but also provide needed medical care to the participant involved.

Can ethics committees fully ensure that each SAE is reported? What means do they have to monitor the research and confirm that no SAEs went unreported? How could they maintain their neutrality while assessing the relatedness of SAE to research? What role the mutual trust has when we expect all stakeholders involved in research to take their duty seriously especially when the ethical guidelines remain just a morally binding document? Though all of us would like to believe that stakeholders always act in the best interest of the patients and meticulously fulfill their responsibility, it might be quite challenging to ensure this in reality. One way to strengthen implementation of such guidelines in practice is to back it up with ongoing research, retrospectively and prospectively analyzing trial related records, monitoring reports, ethics review and reporting and analysis of SAEs. Such research should not be seen as additional burden on already overworked researchers and ethics committee members but as a valuable tool highlighting areas of research implementation that need rigorous monitoring as well as training of researchers and ethics committee members.

Before moving to the next section, I would like to elaborate on one more point related to ancillary care described in this section. The guideline states that the participant may be offered free medical care for non-research related conditions or incidental findings if these occur during the course of participation in the research as long as it doesn’t amount to undue inducement. First thing I notice here is the use of the verb ‘may’, so it is not required but is left to the assessment of researchers and research institution. It is not clear what non-research related conditions or accidental findings occurring during the research participation could be. Occurring could be seen as new cases or it could mean that a particular condition might have been present for a long time or since recent past but was only diagnosed during the research participation as will be the case of incidental findings. Consider a research participant who is diagnosed to have a chronic health condition such as diabetes mellitus or hypertension during initial assessment for trial participation. Being hypertensive or diabetic is not an exclusion criteria and the participant fulfills all other inclusion criteria and hence is enrolled in the trial. Treating hypertension or diabetes is not very expensive but does that mean the particular research institution may provide free medical care for this non-research related condition and if so for how long? What if a patient is diagnosed with a cancer or other serious incidental findings management of which requires significant treatment costs? In this situation, could one argue that informing the participant about the finding and giving them a reference note for further management and treatment of the diagnosed condition is sufficient?

*Ethical review procedure*

The section on ethical review procedure elaborates in great detail various aspects of composition and function of ethics committees both institutional and independent. This description is definitely useful for researchers as well as institutions and ethics committees themselves. Below I highlight a few points that could provide additional guidance and information. From the point 4.1.2, one can conclude that each ethics committee is responsible for preparing, regularly updating and making the SOPs available for all its committee members. The ethics committees can refer to ICMR and CDSCO guidelines for preparing SOPs. The annexure one of the national ethical guideline lists a number of SOPs that ethics committees should have. So it seems that all ethics committees across the country should have their own SOPs but could there not be discrepancies and differences in SOPs from different ethics committees and how could it affect the review and monitoring of multicenter trials?

Point 4.2.5 recommends that the ethics committees should have access to all research records including source documents and research participants. What does it mean in reality, especially access to research participants? Is this more of a procedure for monitoring the ongoing research or for investigating reports of SAEs or other protocol violations. Most important point to consider here is whether ethics committees have enough human resource, time and authority to undertake such thorough monitoring of research. The guideline briefly refers to fee structure for ethics review. Should this be also defined at the level of each ethics committee or will it be standardized across the country?

Point 4.7.14 states that the ‘me too’ research should be discouraged. This is important recommendation however ethics committees also need to keep in mind the difference between me too research and research replication undertaken with the same research question and same patient population. Such replication studies are valuable to ensure reproducibility of research findings and should not be discouraged unless there are other valid reasons. The same point also notes that the submission of same research to different funding agencies should not be accepted. Thinking through the procedure of grant applications to funding agencies, ethics committees have limited role. Not all funding agencies ask for ethics committee approval at the time of grant submission. Ethics committees are likely to find out that the same research proposal was submitted to different funding agencies only when the study is submitted for ethics review at the onset of research. At that point in time, what could ethics committees do when the funding has already been released at least partially? Should ethics committees investigate all the grant applications made to different funding agencies and relatedness of the proposal? If it is clear that indeed the same proposal was submitted to more than one funding agency, should they be required to inform all the concerned funding agencies directly or encourage the study investigators to do so? In academic research context where obtaining research funding is highly competitive, such situations can indeed become extremely complicated and uncomfortable to deal with. Ethics committees would need further guidance and authority to challenge the researchers on their grant applications and to inform the funding agencies of such situations when warranted.

The revised guideline of 2017 briefly discusses protocol violations (point 4.11.6) and states that the high number of protocol violations could justify ‘for cause’ monitoring of ongoing research (Box 4.6) by the ethics committee. The researchers are responsible for reporting protocol violations but unless they do so, the ethics committees have limited ability to pick up protocol violations especially if they cannot routinely monitor all the ongoing research in their institution. For industry sponsored research, where the sponsor conducts rigorous monitoring, it could provide another source of reporting protocol violations but that would mean any monitoring agency such as the clinical research organizations or the sponsors themselves must be made to report all protocol violations. It might be worthwhile to discuss and reflect on how this could be realized in research practice and what kind of support the ethics committees would need to monitor and assess all protocol violations.

Finally, the text box 4.6 mentions high recruitment rates as a justification for ‘for cause’ monitoring of ongoing research. Here the main concern from the ethical point of view is undue inducement of the study participants. In addition, the ethics committees might also need to flag and monitor studies with slow or low recruitment, not so much from the participant safety point of view but to ensure fair utilization of research resource and to prevent consequent early discontinuation of clinical trials due to inadequate recruitment(15, 17).

*Biological material, biobanking and datasets*

The section on biological material, biobanking and datasets is comprehensive and consistent in its structure and scope with other international guidelines issued by the World Medical Association (18) and the Council of Europe(19). It defines biological materials and biobank and describes the diversity in size of biobanks, and the samples and data they store, which helps readers to get oriented with the theme. The section also outlines differences and nuances in anaonymized, identifiable, and nonidentifiable data with elaboration of coding, its reversibility and linkage to the sample stored, and its implications for the privacy and confidentiality of the donor. The section offers rich input on return of results to individuals or groups whose samples are stored in biobank and different possibilities of informed consents in relation to use of stored biological samples and data for future research including elements of a multi-layer consent. I will discuss two aspects of biobanks in further detail, the first being the regulation of commercial purposes of biobanks and profits made thereby and second is the ownership of biological material. I will end this analysis with further discussion on biobanks in India storing reproductive tissues and their regulation.

ICMR National Ethical guideline 2017 covers biobanks with potential commercial purposes as well as for profit entities such as pharmaceutical and biotechnology based industry. It is not clear whether publically funded biobank affiliated with universities and research centers could share their stored samples and data with for profit organizations and if there are commercial gains from such an action how those profits will be shared. Point 11.4.1 states that the participant owns the biological sample or data collected from him or her and can hence withdraw usage of their sample and data unless specified in the informed consent. It further states that the biobanks and institutions are custodians or trustees of the samples and data and the researchers have no claim for either ownership or custodianship. To elaborate on the conflicts involved in this scenario, I am going to use the example of HeLa cells. I am aware of the fact that story of HeLa cells has number of ethical breaches from informed consent to ultimate commercialization and profits of billions of dollars made around the world(20). But this example provides us with an excellent opportunity to reflect on ethical issues of ownership of stored biological material, their commercial application and the benefit sharing with the donor or the community they belong to.

Biological material stored in this case was the surgical specimen of cancerous lesion on the cervix of Henrietta Lacks removed during hysterectomy. According to ICMR guidelines, the patient from whom the sample and the data are collected owns the data and the sample which implies that H. Lacks owned the specimen of her uterus and her medical data. The hospital pathology lab and the university hospital where she was operated will be considered the custodians of her sample and the health data. Her physicians can claim neither ownership nor custodianship of the sample. The cell lines produced from the cancer lesions on her uterus lead to development of HeLa cell line which not only revolutionized the medical research and biotechnology industry but also led to significant financial gains for the researchers and the industry where as the Henrietta Lacks died poor and her family never received any direct or indirect benefits. The three considerations detailed in box 11.5 of ICMR revised ethics guideline regarding benefit sharing were not fulfilled in case of Henrietta Lacks. It is interesting to note that the third consideration for benefit sharing recommends that as much as possible the benefit to the donor should be indirect or in kind even though the commercial entities may benefit from direct or financial benefits. I wonder why this should be the case especially given that a number of individuals are storing their samples especially in private stem cell repositories for future personal use. Unlike in the case of research participation, the users of private stem cell repositories store their samples for future personal use and not in the hope of direct financial benefit if it leads to successful commercial application. Even though the case of Henrietta Lacks is a rather extreme example, it helps us think proactively about the ways to minimize occurrence of such tragic case again in the future. Storage of sources of stem cells such as umbilical cord blood and more recently menstrual blood with potential for therapeutic benefits and commercial gains must carefully consider various ethical issues related to ownership, informed consent and benefit sharing in case of commercial application (21, 22)and national ethics guidelines should provide further guidance in this regard.

Unlike the guidelines issued by the council of Europe which excludes embryonic/ foetal tissues or materials collected and stored in context of assisted reproductive technology (ART), the ICMR guideline appears to include biological material kept for ART such as oocytes, sperm, semen and embryos. Storage of reproductive substances in commercial biobanks either for ART or for safeguarding health of individuals through storage of stem cells raises different ethical concerns as compared to other biological material and data used in research. We must also keep in mind that spare human germ cells, embryos or sources of stem cells can be donated for research or destroyed depending on national regulation at the end of time period stipulated in contract with the commercial biobank or when individuals fail to pay the annual fees for storing samples. Considering all these peculiarities related to storage of reproductive substances in commercial biobanks, it might be useful to have further guidance on these topics with reference to the relevant sections of ICMR National Guidelines for Stem Cell Research 2017 instead of clumping storage of reproductive substances with all other biological materials in this ethical guideline for biomedical and health research.

*Conclusion and way ahead*

The 2017 National Ethics Guideline for Biomedical and Health Research involving Human Participants is a great effort to ensure and encourage ethically and scientifically sound research which not only investigates relevant and socially valuable research questions but also provides detailed description of role and responsibility of all stakeholders involved in research. The guidelines are comprehensive and make significant attempts to keep up with evolving scientific progress and ethical issues unfolding thereby. However, I cannot fully comprehend the tasks bestowed upon ethics committees and wonder if they have necessary training, strength, time, resource and authority to fulfill the role expected from them in a timely and comprehensive way. The ethics committees have a very sensitive position in the research process. They are affiliated to the research institutions; need to work closely with the researchers and at the same time should be seen as partners in research undertaking regular monitoring and providing constructive feedback and recommendations that would not block ongoing research but will ensure safety of human participants and ethical conduct of research. This is no simple task and it is very easy to be perceived as a fault finding entity or the body entrusted with policing research. This guideline clearly demonstrates that huge responsibility is bestowed on the fair, transparent and independently functioning ethics committee but being member of such a committee seems as challenging as walking on a tight rope especially if the guideline does not get the statutory status or if it just remains a morally binding document to research stakeholders. The fate of the guidelines in this regard will become clear in the future. If we really want to build a strong country wide network of ethics committees as equal partners of biomedical and health research, we must be committed to provide necessary financial resource and some degree of authority to establish, train and strengthen the institutional capacities for thorough ethics review and monitoring. Finally one cannot reiterate enough the importance of undertaking research on experience and constraints of ethics committees, challenges they face in fulfilling their role as the revised guidelines come into force. Without these two efforts, we only risk further alienating ethics committees by adding more responsibility on their shoulder but not providing them with means and resources to function in an independent manner.

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