

## ETHICS OF ETHICS COMMITTEES

# ICMR's Ethical guidelines for biomedical research on human participants: need for clarification

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### **Abstract**

The "Ethical guidelines for biomedical research on human participants" prepared by the Indian Council of Medical Research in 2006 came as a welcome step in the process of regulation of research on human subjects, since clear cut Indian guidelines were absent earlier. The guidelines have been accepted as the standard operating manual by Institutional Ethics Committees (IEC) in India. However, over a period of time, it has become obvious that the guidelines lack clarity in certain areas and require to be revised in the light of experiences of members in the IECs. Some of these problems with the ICMR guidelines have been highlighted in this paper to press for revision of the manual in the light of these experiences.

*Ethical guidelines for biomedical research on human participants* (1), published by the Indian Council of Medical Research, is the standard document adopted almost exclusively by ethics committees supervising research carried out on human participants in Indian medical institutions. As such, the guidelines have to be clear and comprehensive, and take into account the special situation prevailing in the country. At present, ethical issues in research in India do not get the attention they deserve, particularly outside major full-time research organisations. Utmost clarity is required to avoid difficulties in interpretation, or shades of opinion not intended by the ICMR. While serving as a member of the institutional ethics committee (IEC) in several institutions, I have noticed that there are several issues on which the guidelines are not clear enough, or appear misleading, or do not give adequate instructions, leaving scope for different interpretations depending on individual situations. This comment seeks to highlight such key issues. The figures in parentheses indicate the page numbers where the issues are discussed in the ICMR guidelines.

**1. Trials on as yet non-approved drugs (35):** The guidelines state "The proposed trial should be carried out, only after approval of the Drugs Controller General of India (DCGI), as is necessary under the Schedule Y of Drugs and Cosmetics Act, 1940. The investigator should also get the approval of Ethical Committee of the Institution before submitting the proposal to DCGI." This sequence is wrong and irrational as it expects the IEC to give approval, even if conditional, for

the trial of a drug which is yet to be approved by the DCGI for that indication. The DCGI certainly cannot expect an IEC to clear a drug for a trial even before it has been approved for that indication. This issue is especially difficult for the non-medical members of the committee to concur with, as they find the sequence irrational. The proper sequence would have been for the investigator to first submit the data to the DCGI for approval of the drug, and then present the project to the IEC once such approval has been obtained.

**2. Access to benefits of therapy (36):** The Helsinki Declaration of the World Medical Assembly, 2008(2), states that "at the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits." Likewise it is mentioned in the ICMR guidelines: "After the clinical trial is over, if indeed the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country and thereafter at a reduced rate for the participants whenever possible. A suitable *a priori* agreement should be reached on post-trial benefits." The guidelines themselves appear uncertain as they have made the clause conditional by stating that this should be done "whenever possible". Strong legislation is required for this purpose and it is not possible for any IEC to ensure that this happens. Many of these trials are multi-centric. In point of fact, since most patients enrolled in the trials are poor, they are not informed, or are ill informed, about this clause; and it does not form part of any informed consent document that this author has seen. Recently, there was an instance of a trial involving comparison of the conventional cheaper anti epilepsy drug and a newer, costlier alternative. The trial found that the latter was superior. However, for want of any agreement on this matter, the newer drug was withdrawn from the patients after the trial, since they could not afford to pay for it. There has to be a mandatory agreement signed by all participating centres to ensure that post-trial benefits are not denied to participants because they are unable to afford it.

- 3. Consent and assent for epidemiological studies on minors and school children (28,59):** On the issue of informed consent the guidelines say: "there is no alternative to obtaining individual's informed consent but what should be the content of the informed consent is also a crucial issue. In spite of obtaining informed individual consent, it is quite likely that the participants / patients may not be fully aware of their rights." The ICMR guidelines also say: "the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors from the age of seven years up to the age of 18 years." Several epidemiological projects are carried out on school children, from collecting simple anthropometric data to more complex studies such as those involving studying the effects of domestic violence on school performance. In almost all cases, these studies are done in government schools after obtaining consent from the department of education and the school principal. Although the subjects are minors, no consent is obtained from the parents or guardians of the children, and their own assent is never taken. The ICMR guidelines are totally silent on the rules to be observed while carrying out epidemiological studies on minors, particularly school children.
- 4. Role of control groups (3):** On page 3 of the ICMR guidelines it is mentioned with reference to the general principles involved in research that "such research is conducted under conditions that no person or persons become a mere means for the betterment of others and that human beings who are subject to any medical research or scientific experimentation are dealt with in a manner conducive and to and consistent with their dignity and well being ... " Such a recommendation in the absence of any clarification could be construed by the IEC to indicate that control groups who are on placebo or no other therapy are not permitted under any circumstance even if informed consent is obtained, since they do not benefit by such a study in their individual capacity. This has actually happened in some instances, in the authors' experience, when IECs have turned down proposals with a control group on the grounds that the control group does not benefit by participation in the study.
- 5. Scientific review before ethical review (11):** The guidelines say "The IEC should review every proposal on human participants before the research is initiated. It should ensure that scientific evaluation has been completed before ethical review is taken up." This procedure is seldom followed since many medical colleges; particularly those started recently, have not established a mechanism of scientific scrutiny of research proposals since such a process has not been mandated by the MCI. Hence the IEC has to function both as a scientific review committee as well as an IEC, whereas the investigators would like it to confine itself to the ethical issues involved, if any. An unscientific research proposal on human beings is *ipso facto* unethical as it violates scientific and ethical principles and is, therefore, well within the purview of the IEC. However, unless and until this is specifically mentioned in the guidelines it would be impossible for the IEC to function as a scientific review committee. Hence explicit directions are required in the ICMR guidelines to cover this contingency.
- 6. Research on archived specimens (12):** The guidelines permit an expedited review on "research involving clinical materials (data, documents, records or specimens) that have been collected for non-research (clinical) purposes." No further instructions are provided as to how this information is to be dealt with. Research on archived specimens opens a whole new can of worms. In many of the medical colleges, for want of sufficient prospective material, a large part of the research work for postgraduate dissertations is done on archived specimens. Previously reported slides or stored blocks are re-examined to determine disease patterns or to reclassify them in the light of advances in the field. The author has personally witnessed, as a member of an IEC, a review which has reclassified a number of earlier specimens, previously reported as benign as malignant, and vice versa. This review has been done without the approval of the patient from whom the specimen had been obtained. What would the ethical requirements be of this reclassification? Would one seek out and inform a patient that a diagnosis labelling him/ her as malignant in the past was wrong, and he had consequently received unnecessary therapy; or inform him / her that while he was told he had a benign disease it was in fact a malignancy which had earlier been missed and therefore, he had not received the appropriate therapy? The ethical dimensions are huge, and the guidelines are required to be much more explicit and comprehensive about the procedure for informed consent in such cases, and the procedures to be adopted when the earlier diagnosis is revised. Research on archived specimens carries with it not only ethical risks not easily understood by the investigators; but great legal risks to the institution for negligence and mismanagement.
- 7. Right to withdrawal (4, 22, 25):** The right of participants in research to decline to participate, or withdraw, or abstain from further participation, has been repeatedly emphasised by the ICMR guidelines. It has been clearly stated that the patients can "withdraw without penalty or loss of benefits which the participant would otherwise be entitled to." However, such a clause is meaningless if the contact involved between the subject and the investigator is a onetime affair – such as a single interview, or a single sample of blood or body fluids for investigations. Under such circumstances, what would the meaning be of the term "the right to abstain from further participation." Does it mean that the information provided by the subject cannot be used by the investigator; or that the sample of body fluid provided would have to be ignored? How does an IHEC ensure such an eventuality? What if the subject is part of an ongoing trial of a new medicine, such as the trial of a new epileptic drug mentioned earlier? Who would ensure that the subject is referred back for routine treatment and what would the investigator's responsibility be in case of adverse consequences of such an action?
- 8. Waiver of consent (23):** The ICMR guidelines mention that "voluntary informed consent ... "can be waived if it is justified that the research involves not more than minimal risk or when the participant and the researcher do not come into contact or when it is necessitated in emergency situations." The term "waiver of consent" needs further clarification in the guidelines as this provision is misused

even in situations where questionnaires are administered to subjects, merely because there is no invasive procedure, although the questionnaires may require highly personal data. The latter issue has already been covered in the paragraph on research on archived specimens. Here also the researcher and the subject do not come into contact. The adverse consequences of this type of research on patient welfare have been pointed out in the earlier paragraph. The guidelines say that such eventualities also include "Research on anonymised biological samples from deceased individuals, left over samples after clinical investigation, cell lines or cell free derivatives like viral isolates, DNA or RNA from recognized institutions or qualified investigators, samples or data from repositories or registries etc." It would be clear to all that such blanket permission can have serious repercussions, both medically and legally, in case the research uncovers an issue which can have adverse consequences on the subject, if alive, or on the family, in the case of an inheritable disease. Waiver of consent is a serious issue and should be given only in extreme cases after examining all aspects of the matter. The guidelines should make this clear.

#### **10. In-house monitoring and ongoing review process (18):**

The greatest problem with the working of the IEC in any institute is the lack of an ongoing monitoring process to ensure that the guidelines have been followed, that there is no deviation from the protocol, and that any adverse effects are reported. In actual practice, the IEC meets only once or twice a year, offers suggestions, and issues a letter of approval. It has no mechanism for monitoring, which is left to the individual institution. The guidelines must specifically state that an IEC should meet not less frequently than once in three months, and progress or deviation, if any, of every ongoing project should be circulated to the members, before the next meeting, to confirm that the process is the one which is approved.

**11. Funding of research:** It has been repeatedly noticed by several members of IECs in various medical colleges that there is no mechanism for the funding of research by the institute, and it is left to individuals to raise their own resources. This is quite normal if research is voluntary. However, if the process is compulsory as part of the curriculum, as in postgraduate dissertations, serious ethical issues are raised when the candidates raise the issue that they are forced to self fund projects as part of their dissertations. Can an ethics committee approve such coercive research work? The condition is similar to coercive research where students are compelled to serve as research subjects or control groups and do not have the option to refuse participation for fear of adverse consequences. The guidelines once again do not explicitly prohibit this.

**12. Trial on non-allopathic drugs and herbal remedies (51, 55):** These have become more numerous in recent times, particularly in medical colleges. The guidelines are quite clear on this issue: "when clinical trials of herbal drugs used in recognised Indian Systems of Medicine and Homeopathy are to be undertaken in Allopathic hospitals, association of physicians from the concerned system as co-investigators/ collaborators / members of the expert group is desirable

for designing and evaluating the study." Further, "However, it is essential that such clinical trials be carried out only when a competent Ayurveda, Siddha or Unani physician is a co-investigator in such a clinical trial." While appearing comprehensive, these lines leave some issues uncovered. Mere inclusion of a physician belonging to the correct alternative system does not ensure that patients' interests are protected. Who will take the responsibility in case of adverse reactions to these alternate system drugs? Will they be managed according to allopathic guidelines or will it be left to the concerned system to treat? This is important to know in advance, since treatment may be different according to different systems of medicine. Will there be provision for consultation from others belonging to that system in case of such emergency? Can the investigator escape responsibility by stating that the ayurvedic or unani or siddha physician is responsible? How will benefits of therapy be assessed since there is a vast difference in perception of improvement in different systems? How does one obtain informed consent for such a study? There are many other issues. It might be better that such research is restricted to a few national institutes which can offer the full range of facilities rather than be taken up in newly emerging medical colleges.

**13. Ethics of live operative workshops:** This issue has already been written about (3). Operative workshops call for a situation where a visiting surgeon performs a procedure, which may be major, on a patient whom s/he has not seen before, or perhaps not interacted with in any detail or any length of time before. It also involves circumstances where s/he has no responsibility for preoperative or postoperative care; this is left to the parent institution conducting the workshop. It is not clear how one would obtain proper informed consent in such situations. These workshops involve patients' safety and patients' rights. At present the situation is not monitored by any formal ethics committee. When such workshops are conducted by visiting surgeons from abroad, the situation is further vitiated by the fact that these surgeons are not licensed to practise in India unless they obtain special permission from the Medical Council of India. It is high time that these activities are regulated. The best form of regulating them is to bring them under the purview of the IEC which can be charged with monitoring the process.

#### **References**

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