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Challenges in reviewing and approving clinical trials by ethics committee

Abstract

Institutional Ethics Committee (IEC) plays an important role in protecting the rights, safety, and well-being of participants in biomedical research. Guidelines from the Indian Council of Medical Research (ICMR) has stated that all research involving human participants should obtain the institutional ethics committee permission. In spite of these guidelines, significant challenges persist in reviewing and approving clinical trials. This narrative review analyses the key challenges related to submission of documents for protocol review and institutional ethics committee experiences at Seth GS Medical College and KEM Hospital, Mumbai. The main challenges identified are maintaining appropriate IEC composition and training, managing the therapeutic misconception among research participants, the informed consent documentation process, standard of care, and risk-benefit assessments. Overlapping regulatory requirements and multiplicity of guidelines, such as those from ICMR, ICH-GCP, NDCTR 2019, and funding agency guidelines, add to the operational burden. Additionally, the difficulties arising from post-trial access guidance may lead to inducement of participants, so IEC must critically review the protocol before conducting the study. This helps to maintain the autonomy and integrity of the participants. Research undertaken should be as per the country requirement or else multinationals can burden the Indian patients without any benefit. IEC has the responsibility to review not only the scientific rationale but also the ethical rationale from time to time to ensure the safety

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of the participants in the trial and credibility of the data generated. Strengthening IEC functioning in India requires standardized operating procedures, adequate infrastructure, continuous training, and regulatory coordination. Although the review process is of high standard, the process has become more robust and stronger after achieving the SIDCER recognition and NABH accreditation.
Keywords: Ethics committee, clinical trials, regulatory guidelines, biomedical research.

Introduction

According to Ethical Guidelines for Biomedical research on human participants, 2017(Indian Council of Medical Research, 2017), all proposals on biomedical research involving human participants should be cleared by an appropriately constituted Institutional Ethics Committee to safeguard the welfare and rights of the participants. At the Institutional Ethics Committee of Seth GS Medical College and KEM Hospital, a meeting is held every month to review protocols, and scientific and ethics related queries are sent to the investigator. Investigators are required to respond within 180 days, after which final approval may be granted. A research study from Spain has shown that two third of protocol submitted to IEC required some sort of amendment (Martín-Arribas et al., 2012). The study conducted in India by Kuyare etal has found that as many as 1676 queries were raised for the 219 studies in the period of January 2006 and December 2011 (Kuyare et al., 2014).

The Institutional Ethics Committee (IEC) of the KEM Hospital was established in 1986 and is one of the first few ethics Committees to have been established in India. Since then, the IEC has evaluated both the scientific and ethical aspects of research studies, as the institution does not have a separate scientific review board. Its working was based on the "Policy Statement on Ethical Considerations involved in Research in Human Subjects" released by the Indian Council for Medical research (ICMR) in 1980 (Indian Council of Medical Research, 2017) and continued to work on these guidelines till 2000. However, a systematic working of the IEC occurred only after the committee was reformulated in 2000, to meet the

requirements of, ICH-GCP guidelines (1996) (International Conference on Harmonisation, 1996) and "Ethical guidelines for biomedical research on human subjects" -2000 (Indian Council of Medical Research, 2000).

The new IEC conducted a GCP training workshop for the IEC members in April 2000 and laid down standard operating procedures (SOPs) related to its functioning for the first time in May 2000. In 2004, a sample of Informed Consent Document was included in the SOPs to guide investigators. After the revision of Schedule Y in January 2005 (Ministry of Health and Family Welfare, 2005), the SOPs were further revised to include elements of review for the IEC members. A revision of the ICMR's guidelines in 2006 necessitated further amendments to the SOPs and the IEC started reviewing clinical trial agreements, insurance and subject compensation details. To further strengthen the quality of ethics review, strategic initiative for developing committees for ethical review (SIDCER) recognition was sought and obtained by Institution in 2010 (Forum for Ethical Review Committees in the Asian and Western Pacific Region [FERCAP], 2010).

Over the last 25 years, there were revisions in guidelines which may have led to changes in the performance of the IECs with respect to the number and type of queries raised during review of projects and the IEC has witnessed changes in the type of research studies which are undertaken by investigators and pharmaceutical industries. It was therefore felt that a review article on challenges faced by ethics committee while reviewing and approving the studies needs to be elaborated, and it would be worthwhile to share these with the scientific community.

Institutional ethics committee works on the objective of safeguarding the rights, safety, and well-being of the research participants
Challenges faced:

Constitution, roles, and responsibilities. It needs to be constituted as per the law of the land, presently in India it is the New

Drugs and Clinical Trials Rules, 2019 (NDCTR 2019) (Central Drugs Standard Control Organization, 2019).

The institutional Ethics committee needs to be registered with DHR while reviewing academic studies or registered with CDSCO if reviewing regulatory studies or accreditation which is voluntary. The registration lapse should not happen, so timely re-registration also needs to be done. IEC members need to be trained and should know the guidelines and regulations. Equal number of internal and external members to remove bias and facilitate independent decision making. Timelines need to be followed for initial review of protocol and post approval review – of protocol, Serious Adverse Event, Protocol Deviations and final reporting. Approval letter for the study or disapproval letter and interim data, as decided by the regulators need to be submitted to The Drug Controller General of India (DCGI). Registration and SAE reporting from institutional ethics committee need to be uploaded on Sugam portal.

Therapeutic misconception. In 1982 Paul Appelbaum, Loren Roth, and Charles Lidz coined the term "therapeutic misconception" which means that participating in research is the same as receiving individualised treatment from a physician. Here, participants fail to appreciate that the aim of research is to obtain scientific knowledge and any benefit to the patient is a by-product of that knowledge. It is more commonly observed in early-phase clinical trials, particularly Phase I oncology studies, where terminally ill participants have exhausted of standard treatments and when the scientific investigator is the treating physician for the patient. It is found to be 68.4% in Phase I Oncology trials and is associated with lower education (P = .008) and family income (P = .001), but not associated with the vulnerability of having hardly any treatment options. So, the consent forms must explicitly state the design and goals of the trial, as well as the potential benefits and risks (Pentz et al., 2012).

Therapeutic Misestimation is incorrectly estimating the chance of a research trial benefit as >20% or underestimating risk as 0% and is found to be 94% in_Phase I Oncology trials.

A CRO-conducted survey of the informed consent process in clinical trials in India provides some interesting information on the patient recruitment procedure and the quality of informed consent in clinical trials in India. 525 patients from 40 sites had been interviewed. When they asked about the reason for participation, seventy-six per cent of patients said the trial's principal investigator was their primary physician. A further 21 per cent said they were referred by their primary care physician (Srinivasan & Nikarge, 2009). During the informed consent process, understanding needs to be checked by the investigator before the patient participates in the study. The language, along with the mandatory elements as per ICMR guidelines 2017 and the technicality has to be well reviewed by the IEC.

Informed consent documentation. Voluntary written informed consent should be obtained in an informed consent document (ICD) from each participant to protect each individual's freedom of choice. It is a continuous process involving three main components: It involves providing relevant information to potential participants, ensuring their comprehension and competence, and confirming the voluntariness of participation. The 10 elements of an ICD need to be included, the number of pages (reams of material), technical terms must "Inform without overwhelming". IEC has to review the back-translations and translation certifications also. IEC can demand for site specific changes. Waiver of consent needs to be approved by IEC if the research involves not more than minimal risk or when participant and the researcher do not come into contact or in emergency situations. The IEC reviews who should give (and sign) consent. If the patient is Illiterate, then impartial witness signature is a must and if a minor, then legally acceptable representative (LAR), signature is taken. For assent your ICD language should be of that pediatric age because they should understand, comprehend and later participate in the study. In HIV studies how will be the confidentiality be maintained and who will be the impartial witness needs to be ascertained (Indian Council of Medical Research, 2018).

Standard of care. What should be provided to participants in a control group in clinical trials of an experimental drug? This remains a major dilemma, and the COVID-19 pandemic further complicated the issue. So, should it be universal *vs*. local standard of care, and will it lead to inducement? And what is the impact of variable standards on clinical outcomes? What should we provide research participants who become ill with a disease other than that being studied- so ancillary Care can it be provided? What should be provided to participants in prevention studies who acquire the "target disease" during the trial? This area is many times very grey and the scientific members need to review the protocol and should be well versed with the disease specific guidelines (Indian Council of Medical Research, 2017).

Risk benefit assessment. Risk at large is defined as a multidimensional concept: involves both probability and magnitude of harms and benefit, on the other hand is defined as the magnitude of a positive outcome without reference to its probability (Weijer, n.d.). Risk benefit assessment as per the International Council for Harmonisation's Good Clinical Practice guideline (ICH -GCP) (International Council for Harmonisation, 2025) needs to be undertaken by all the stakeholders (researchers, ECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized and appropriate care and compensation is given if any harm occurs and it has its impact from the start to the end of the study. Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results. It should be managed prospectively (Indian Council of Medical Research, 2017).

As per ICMR guidelines, the type of IEC review is based on risk involved in the research; so accordingly, the study can undergo exempt from review, expedited review or full board review. The IEC should assess the inherent benefits and risks, ensure a favourable balance of benefits and risks, evaluate plans for minimizing the risk and discomfort and decide on the merit of the research before

approving it. The IEC should also assess any altered risks in the study at the time of continuing review. In phase I - normal volunteer study, are the therapeutic procedures justified by their potential to benefit the subject and Non-therapeutic (Phase 1 and 2) procedures justified by their potential to generate knowledge.

What happens after the trial is over? This is very important aspect to be considered when there are no treatment available for the disease studied, will this treatment be made available for reasonable time. NDCTR 2019 have thrown some light on this aspect. IEC and regulators have to be very clear when the post-trial access be provided, will it lead to inducement? Will the drug be registered in India? (Central Drugs Standard Control Organization, 2019). Post-trial access depends on the availability of treatment to patient and community to effective medicine. Practicalities of the provision of interventions and where responsibility should lie must be addressed at the beginning of the study. It is essential to address issues at planning stage through discussions between range of stakeholders: sponsors, researchers, health authorities and governments. Who should fund the post-trial access many times it very difficult to balance between idealistic and realistic goals. In sponsor study, it is very clear that the pharmaceutical industry will sponsor, but in academic study when the investigator is wearing the hat of sponsor cum investigator the things are not very clear. Can we consider increasing the number of healthcare givers or development of expertise of local scientists or improving health infrastructure also as post-trial access. There is no clarity how long this access needs to be provided.

Multiplicity of guidelines and regulators. While reviewing the protocol, the scientific members should be aware of all the regulatory guidelines, funding agency guidelines [e.g. The National Institutes of Health (NIH); Wellcome Trust, United States Agency for International Development (USAID)], Guidelines for specific diseases, Institutional Guidelines, and Recommendations from advisory bodies along with ICH GCP, ICMR 2017 Guidelines and NDCTR 2019

guidelines. If the IEC is not experienced, untrained and unaware of the guidelines, the studies can be approved without any significant review or comments which can be detrimental for the research scenario.

Ethical review. Effective Institutional Ethics Committees are those whose functioning are as per Standard Operating Procedure (SOPs) (Seth GS Medical College and KEM Hospital, Mumbai, 2024) guidelines, and they maintain minutes with robust archival. They should have resources, adequate man power, office and need members with appropriate qualifications, experience, training and independent in decision making with no conflict of Interest. They should have adequate time to review and monitor studies. They should be willing to attend ongoing training in ethics, GCP and NDCTR 2019 guidelines. They should be consistent in review and follow timelines. Each member should play his role and responsibility: eg, Lawyer, Lay person, Social scientist, Chair, Secretary adequately. Initial review and continued review also need to done for each study till its completion. Site Visits, consent documentation, serious adverse event (SAE) management, protocol deviations also need to be vigilantly reviewed and decisions taken by the IEC. They should maintain quality of functioning by registering the IEC to Department of health research (DHR) or The Central Drugs Standard Control Organisation (CDSCO) / undertake national or international Accreditation.

In general IEC queries are classified into those related either to scientific or ethical issues. Ethics related queries were further categorized into those related to the protocol or informed consent document (ICD).

Scientific queries are related to rationale of the study, selection criteria, study procedure, inclusion exclusion criteria and statistical analysis. Ethics related queries in protocol are mainly categorized in to placebo justification/ study design, withdrawal criteria and rescue medication and procedure. Ethics related queries in ICD are regarding aims and methods of research, risk or discomfort to the participants, free treatment or compensation for study related injuries and improper translation of ICD.

IEC role is challenging when they check the suitability of the investigator for which they need to understand their qualifications, experience, availability of support staff, facilities, and emergency services to manage participants. How many studies Principal Investigator is involved in and if involved in multiple studies, how much time dedicated for research. IEC has to assess the voluntariness of participation of participants. Would there be an inducement: specially in Oncology, Cardiology trials if access to health care is given. What are the retention activities proposed in the study, will payments to participants lead to inducement? (compensation, payment, reimbursement) – IEC has to decide payment to participation as there are no guidelines (Marathe et al., 2018).

Elements that can be challenging is checking the rationale of study in which many times there is no therapeutic equipoise, identifying risks: physical/ psychosocial (discrimination, stigmatisation, breach of confidentiality) and providing ways to overcome/handle them and vulnerable subjects inclusion and its special protections.

Only sponsors have policies regarding compensation of participants. Compensation limited to management of adverse events that occurred during a trial: issue of compensation for lost wages/ death/ permanent disability not addressed in academic trials. Many a times participants had to pay and would be reimbursed later the amount of compensation. Role of legal person is very crucial in such situations.

There are special concerns where guidelines are not very clear such as in Devices, Drug eluting stents, surfactant, formulations, AI based or in emergency research study where IEC has to take decisions based on the experience or expert opinion or common sense.

Is research 'responsive' to the health needs of the population?

Steps need to be taken before the research is initiated to ensure that successful products are made available to the population at the conclusion of the research? If not, the population in wealthier countries who will be able to afford the products benefits, and the drug companies will realize a profit. The developing countries only participate in such research which is not as per their need, so

chances of exploitation are there. IEC has to critically review such protocols and place comments or reject such studies.

Conclusion

Although the review process of our IEC was of high standard, a further strengthening of the ethics review process was observed after Strategic Initiatives for Capacity in Ethical. Review (SIDCER) recognition of the Institution and National Accreditation Board for Hospitals and Healthcare Providers (NABH)) accreditation.

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