Are institutional review boards prepared for active continuing review?

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Abstract

Continuing review is an important responsibility of Institutional Review Boards (IRBs). Though being mentioned by many of the national and international guidelines, it is carried out routinely only in UK. The reasons may be inadequate training, overworked IRBs, less enthusiasm among the IRB members, cost bearing, etc. So, the oversight mechanism at the local site, which is the responsibility of IRB is not fulfilled. Are there any solutions to overcome these difficulties? The IRBs should have a Standard operating procedure for continuing review, members can be regularly trained, institutions can create their own internal Data and Safety Monitoring Boards who will only monitor studies where monitoring systems are non-existing and there can be budget allocated at the start of the study by the sponsor or the institution. In this way, we can try to safeguard the rights and well-being of the study participants.

Key words: Continuing review, ethics, institutional review boards, monitoring, site visit

INTRODUCTION

Clinical research is an ever expanding field. More than 1,800 trials are registered in the Clinical Trials Registry of India.[1] As the field of clinical research expands the issues such as protocol deviation, discrepancies in the informed consent process etc., come to the fore-front, endangering the rights, safety, and well-being of the subjects. Various regulatory bodies such as European Medicine Agency,[2] International Conference on Harmonization-Good Clinical Practice (GCP)[3] and Indian Council of Medical Research (ICMR)[4] guidelines suggest that Institutional Review Boards (IRBs) should conduct continuing review of each on-going trial at intervals appropriate to the degree of risk to human subjects. However, few, if any, IRBs comply with the same.[5]

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IRBs in the UK carry out regular site monitoring through questionnaires and/or by a visit to pharmaceutical industry-sponsored trials.[6] However, India lacks mechanisms, manpower and resources for the same, resulting in dependence on only passive monitoring.[7] Higher number of investigator-initiated studies in India puts an emphasis on the greater need for continued monitoring by IRBs.[8] Furthermore, according to our institutional experience, for investigator initiated and government sponsored studies, once the IRB gives its approval there is no monitoring carried out. Except in situations, where the institutions have their own monitoring boards that monitor all

investigator-initiated studies, which is a rarity in India. Whereas, pharmaceutical sponsored studies have inherent Data and Safety Monitoring Boards (DSMB) for all studies that monitor each study and report to the concerned IRBs. The IRB of King Edward Memorial (KEM) hospital, Mumbai, India conducted seven site visits to monitor protocol adherence and informed consent process and found major aberrations in informed consent issues (6/7), protocol deviations (5/7) among others.[9]

Gogtay *et al.*, studied the warning letters issued by United States Food and Drug Administration (US-FDA) to investigators and IRBs, in which 15 out of 32 were due to issues related to informed consent processes and 2 out of 15 for inadequate or lack of monitoring systems.[10]

TYPES OF MONITORING

Passive versus active

Continuing review by IRB can be passive or active. Active monitoring means monitoring studies by visiting study site by IRB members while passive monitoring is a review of documents submitted by an investigator in the form of periodical updates on the study. Most commonly IRBs do only passive monitoring, which includes reviewing data such as serious adverse event (SAE) reports, reviews of protocol violations, progress reports, protocol amendments etc., at pre-specified regular intervals according to the guidelines.[9] However, "active monitoring" should also be conducted, which includes the creation of safety monitoring committee, random audit of the consent process, site visits etc.[11] ICMR 2006 guidelines recommend site visits by IRB as one of mechanisms to monitor the on-going studies.[4] IRB of Seth G.S. Medical College and KEM Hospital does passive monitoring by following their standard operating procedure (SOPs) for continuing review of study protocols,[12] review of study completion reports,[13] and review of SAEs reports and unexpected adverse events.[14]

Routine versus for cause

Routine

For routine monitoring, Tata Memorial Centre, Mumbai in its SOP15/V1 states that "sites will be identified for routine monitoring at the time of approval of the project by the full board which will be recorded in the minutes."[15]

For cause

Increased protocol violations, many studies going on simultaneously, higher than expected enrollment rate, significant SAE reports, complaints from study participants, non-compliance, reports of inadequate infrastructure at study sites, and incidences of missing documents may prompt IRBs to conduct a site visit and continuing review.[15,16]

IRBs tend to be more rigorous about monitoring those clinical trials involving path breaking research who might have greater media coverage. This might not only be attributable to increased risks to the participants, but also a higher sense of responsibility on the part of the IRBs, which might in turn be due to feeling of exposure of the IRBs itself. For example, University of Utah, appointed a patient of artificial heart implantation as a non-voting member of the IRB, to ascertain that the protocol review procedures were followed to the word. Another example that can be cited here, is the case of xenotransplantation at Loma Linda Medical Center where an IRB member monitored the consent process being administered.[17] Intensive monitoring is essential in trials that involve a higher unconfirmed risk, aggressive intervention and highly susceptible participants.[18]

Current scenario

A 4 year review of Canadian Research Ethics Boards published by the National Council on Ethics in Human Research in 1995 revealed that only 53% IRBs had a requirement of submitting an annual report from investigators, which is the bare minimum for continuing review and only 18% stated that they performed on-going review of research.[11] A similar study conducted in Scotland bared the facts that 56% of the studied IRBs never conducted monitoring of research while progress reports were never requested by 44% of them.[19] Data obtained by a review of Australian committees showed that only 44% undertook the on-going review of which in almost all (99%) cases involved only annual review.[20] The aforementioned examples highlight the fact, that monitoring of research is the exception not the rule. A study published by Gogtay *et al.*, reported that 40 warning letters issued by the US-FDA to IRBs between January 2005 and December 2010 showed the following major reasons: 93.8% highlighted that IRBs failed to follow SOPs and maintain documentation, 59.4% had inappropriate membership and quorum problems, 46.9% pointed toward informed consent issues, 21.9% failed to follow regulatory requirements etc.[10] Furthermore, a report by McCusker *et al.*, conducted at St. Mary's hospital, Montreal showed that there were incidences of wrong consent forms being used, discrepancies in fulfilling the inclusion criteria, incidences of unsigned and undated consent forms were observed along-with missing signatures of investigators and witnesses. Incidences of patients signing Informed Consent Documents (ICDs) in the language that they do not understand and participants having very little understanding of the risks associated with the study participation were also noted.[21] Hence, for the

ethical conduct of clinical research, continuing review by IRBs is imperative.

Differences between monitoring by IRB and by DSMB

DSMBs review data from on-going clinical trials and advise the sponsor on the safety of trial participants, continuing validity, and scientific value of the trial; while IRBs are accountable for assessing a trial to verify whether the risks to trial participants are curtailed. As compared to IRBs, DSMBs, by and large, have greater access to trial data, such as interim efficacy and safety out-comes. DSMBs are liable to monitor the study until the intended completion of follow-up, regardless of the treatment period as in certain studies trends in survival or other severe results may not manifest until follow-up. On the other hand, IRBs continue reviewing a trial only until its completion at the site. DSMBs review the study quality and definitive capability to concentrate on the scientific questions of interest along with effectiveness and safety measures. Study data such as recruitment rate, non-compliance reports, protocol violations, drop-outs, comprehensiveness of data, difference between site monitoring reports, and centralized review, baseline characteristics of study arms are also evaluated by DSMBs. However, IRBs are more concerned with the ethical aspect of the trial and continuing review conducted by them focuses on whether the risk has substantially changed in lieu of new safety data that becomes available or due to suspected mismanagement of the trial. Conflict of interest might arise since DSMB is appointed by the sponsor.

Similarly, one major problem faced by the IRBs is to find suitable and trained site monitors. According to our institutional experience IRB members monitoring the site are mainly faculty of the institute and by that extension, peers of those whose site will be monitored. This might induce professional rivalry or engender enmity amongst them. The monitors of pharmaceutical sponsored studies are usually trained by their Medical affairs teams. On similar lines IRBs in India should create monitoring bodies that are trained by IRB members and training should be customized as per every protocol.

Furthermore, the monitoring by sponsor appointed DSMB is pre-decided and is mentioned in the protocol submitted to the IRB. However, the monitoring conducted by IRBs is not pre-decided and is carried out when there are increased incidences of violations from the study site or can be routinely performed.

Objectives of continuing review by IRB

- Ascertaining the ethical conduct of clinical research.
- Reviewing study protocol, relevant background information, ICDs, proposed plans for informing participants about the trial, and any other procedures associated with the trial.[22] Ensuring safety and wellbeing of the study participants.
- Quality assurance and continued education of research staff.[21]
- Ensuring data integrity.[20]

Requirements

Fulfilling the aforementioned objectives might further burden the already overworked IRBs in the form of additional manpower, training, and financial resources.

Action plan

To fulfill the aforementioned requirements, IRBs and regulatory bodies from different parts of the world have come-up with innovative plans.

Research, which may involve more than minimal harm to the participants such as possible serious adverse drug reactions, serious morbidity and mortality, the IRB, in the non-existence of a special committee might appoint one to monitor data, and safety.[15,20] In 1998, a Tri-Council Policy Statement issued by three research funding bodies of Canadian government, suggested that every institution conducting funded research should have its own monitoring programs. Apart from annual submission to the IRB, there should be an official review and arbitrary inspection of the informed consent process, assessment of adverse events reports, setting up of safety monitoring committees, intermittent review of study documents by a third party and uninformed evaluation of patients' charts.[21] One can cite the example of internal DSMB appointed by TATA Memorial Hospital Human Ethics Committee for conducting monitoring activities on behalf of the IRB.[15]

Furthermore in view of the lack of additional manpower, certain ethics committees have come up with novel strategies for continuing review. This is exemplified by a Scottish program, in which the IRB sent a questionnaire to around 300 investigators of ongoing projects. 10% of the projects were followed-up by two board members, who reviewed their responses, assessed them further with a detailed questionnaire, inspected consent forms and case record forms. They concluded that following such a strategy would require an average of 6 person/h, at a cost of £120.[11] This process of continuing review though adds value to the conduct of clinical research, who should bear the cost of this process is a topic of heated debate. Weijer points out potential sources of such funding. Some IRBs in Canada charge $1000 or more from pharmaceutical companies to review a protocol. This will not only take care of the direct costs of continuing review, but also allow the IRBs to increase staff and computerize their

systems, thereby increasing the efficiency of review.[11] As per McCusker *et al.*, expenses related to monitoring of non-funded projects might have to be borne by the institution.[21] Since, the types of protocols received and the available infrastructure of each IRB vary, there should be customized SOPs for continuing review.

One of ways for continuing review is monitoring of the consent process. According to the Guidelines on Research Involving Human Subjects, Canada, there are two means of doing this. One can inspect the way, in which the consent is administered to the study participants or can enquire with the subjects after the consent process to know how much they have understood.[11]

Apart from the usual practice of participants' family member giving consent on behalf of the participant for his/her involvement in the study, there are instances when IRB has hired an advocate for the study participants who would be in attendance when the consent is being administered. McGrath and Briscoe also cite an example where a research center had employed a permanent advocate for this purpose.[11] For monitoring data integrity, IRBs usually review the audit documents of monitoring committees employed by the pharmaceutical companies for sponsored research. However, the biggest concern for IRBs is the investigator initiated research, which is not scrutinized by external agencies, like data safety monitoring boards as in pharmaceutical-sponsored trials. To circumvent this problem, institution may set up an internal program for intermittent inspection of data.[11] Taking this into consideration the IRB of Seth G.S. Medical College and KEM Hospital undertakes internal monitoring by following their SOP.[16]

Furthermore, Pilon states that annual reports from investigators to ethics boards do little to protect research participants there should be collaboration between IRBs and investigators where they classify protocols according to the risk involved and build up new systems to monitor high-risk research protocols.[18] There are a number of ways, which might help the IRB classify the studies on the basis of risk involved so as to decide different planes of monitoring. Levine recommends categorizing risks as social, economic, physical, and psychosocial. Furthermore, benefits can be sorted as direct health benefits, psychosocial, and kinship. This structure might help IRBs choose studies, which should be monitored.[18]

The following actions were taken by KEM Hospital IRB in view of the violations found by its site monitoring committee. In case of protocol deviations and non-filing of progress reports, the IRB asked for explanations and the investigators were cautioned to avoid recurrence of the same. Furthermore, further enrollment was constrained and sponsors were asked to submit reports to the IRB. There were instances when the investigator was unaware of protocol and informed consent process. In such situations continued GCP training of the investigators was suggested.[9]

CONCLUSION

In summary, though certain disagreements over the role of continuing review such as those that may affect the trust element between IRBs and investigators exist among researchers and IRBs finding continuing monitoring unjustifiably costly; continuing monitoring and timely project reviews by IRBs ascertains the ethical conduct of research. Continuing review by IRBs should be recognized as means of quality assurance and not as moral policing, thereby achieving the definitive goal of educating researchers and safe-guarding the safety and well-being of the participants.

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