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Institutional review boards: Challenges and opportunities

Abstract

Institutional Review Boards (IRBs) are an important link in subject protection program, and their function defines ethical credentials of research. Of late there has been a furore in the country over the number of deaths in clinical research, and allegations of unethical research. Clinical trials have been discussed in medical and lay press and even in the parliament, these discussions called for strengthening the subject protection program. The Central Drug Standards and Control Organization (CDSCO), amended the Schedule Y, by issuing three amendments to introduce new compensation rules and registration of IRBs functioning in the country. IRBs in India face a variety of challenges, and need support from the regulators or independent experts. This is also an opportunity to revamp the subject protection program and strengthen the IRB functioning. An independent advisory body comprising of experts who have hands on experience in administering IRBs, is essential to provide support to IRBs in the country. This body should be independent of regulatory influence and work with IRBs to strengthen them.

Key words: Challenges, clinical research, ethics, guidelines, Institutional Review Boards

INTRODUCTION

The requirement of a review of research prior to sanction of grant was first communicated in a memorandum issued by the Research Grants Division of United States Public Health Service (USPHS) on February 8, 1966.[1] It stated that:

"No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates."

This committee later christened as the Institutional Review Board (IRB) or Ethics Committees (ECs) was recommended by the Food and Drug Administration in the US, since 1971. Approval by an IRB was essential for studies if institutionalized subjects were used for research or the institution had an IRB.[2] After the expose of the Tuskegee Syphilis Study the National Research Act was signed in 1974, and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) was created. The mandate of the Commission was to make recommendations for the protection of vulnerable population. The Commission's report (Belmont Report) was published in 1979 and it reaffirmed the need for IRBs.

Around the same time the World Medical Association amended its Declaration of Helsinki (DOH) at Tokyo in 1975 enlarging the declaration to almost double the original size and incorporating review by an IRB before a study could proceed[3] In India the Indian Council of Medical Research (ICMR) issued the guidelines for the formation and working of ECs.[4]

Today, there are a large number of ECs operating in India, as of 16th August 2013, 565 IRBs have been registered. The three amendments (GSR 53 (E) of 30.01.2013,

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GSR 63 (E) of 01.02.2013 and GSR 72 (E) of 08.02.2013) have detailed rules for compensation of injuries, IRB review and IRB registration, respectively. It is too early to see an effect of these regulations, yet the number of trials being done in the country has dropped in the last 2 years and a number of studies have been withdrawn from the country.

IRBs are bodies with high power and responsibility. They stand as a bridge between the researcher and the ethical guidelines of the country.[5] However, a lot of questions are being asked about the competence of IRBs in India. These questions center on the composition of the IRBs, the competence and training of their members, their independence, and their overall approach towards protection of human subjects. A number of studies have doubted the competence of IRB[6] and a full session was devoted to this problem at a recent conference in Gurgaon.

As stated, the Central Drug Standards and Control Organization (CDSCO) has granted registration to 565 IRBs in the country, this means that at least on paper these IRBs are compliant to the norms. Beyond that, not much can be said in the absence of detailed studies on the IRB functioning. There is no doubt that there are IRBs that are very competent, but there are many which are not. A number of IRBs were found to be deviating from the norms in 2011[7] and 2 years later the situation is not significantly better.

Challenges

IRBs face numerous challenges, in establishment, composition, and their working. Some of these challenges are due to conflict of guidelines, some inherent to guidelines, and other reasons. There is need to study the problems of IRBs in depth to assess their needs, and provide the support, if subject protection is to become stronger and effective. Unless this is done, the future of clinical research will remain uncertain the advantages that the country offers come to naught.

Structure and composition of IRBs

The IRBs are set up by the institution involved in clinical research; the institute is likely to choose members who are known to the institute with some selection bias in the IRB. During selection of members, institute heads need to be clear about the qualifications of members required to constitute a compliant IRB. When individuals who have little previous experience in ethical review are selected, they would need to be trained. Presently, there are hardly any organizations that can be called upon to train the members on their roles and responsibilities. Workshops on research ethics are held by some organizations, but there is no official recognition of these organizations for conducting training. Additionally, these training sessions are more of a business activity rather than a service, and not available when needed.

Institute heads need to appreciate that the CDSCO requirements differ from the international guidelines and that these requirements are not flexible. IRBs in India must have at least seven members in place of five members required in the International Conference on Harmonization (ICH) region. The institute should also provide for members who may remain absent, to prevent falling short of quorum. Thus, the optimal strength of an IRB can be anywhere between 10 and 12.

Indian requirements specify that the Chairman must not be from the institute. It is clear that a regular employee of the institute cannot become the Chairman, but whether a consultant could play this role is not clear. Since consultants are not on the pay roll of the institute, they are very often the choice for the post of the Chairman, but the CDSCO has refused registration to at least one IRB on this ground. The CDSCO would do well to clarify this in a guidance document.

The chosen IRB members need to be trained viz-a-viz ethical codes (both international and local) and their roles and responsibilities as members. Due to differences in training, there is wide disparity among IRBs, and this may come in the way of their functioning.[8] IRB training must include local regulations and some countries have developed their own modules for ethics education.[9] The National Institutes of Health (NIH) office of extramural research has an online training module available at http://phrp.nihtraining.com, which is very suitable for IRBs operating in the US. There is need to develop a national training program for Indian IRBs, this will go a long way to ensure that IRB members across the country have a uniform training.

European experience shows that IRBs across a region need not be standardized, pluralism of IRB function exists across Europe despite the European Commission (EC) Directive 2001/20/EC.[10] There are major differences in the composition of IRBs across Europe. Yet a standardized training of IRB members is recommended by the majority of European countries. In India, there is standardization of the composition of IRBs and qualifications of their members, thanks to Schedule Y, and a standardized training module is more likely to succeed here.

There is need for clarification on the qualifications of IRB members. The qualifications of a basic medical scientist are intriguing. Schedule Y specifies that the basic medical scientist should preferably be a pharmacologist. On the basis of queries received from the CDSCO it appears that

the pharmacologist should hold an Bachelor of Medicine and Bachelor of Surgery (MBBS) with a postgraduation in Pharmacology and not M. Pharm, Ph. D., or an M.Sc., Ph. D. Such emphasis on qualifications seems out of place in a world where cross-functional expertise is the order of the day.

The definition of a layman is also disturbing. The Oxford and Cambridge Dictionaries define a layman as a "person without professional or specialized knowledge in a particular subject", or nonscientist by education. This means a chartered accountant or an architect could serve as a lay person.

The role of the lay person on the IRB is to view the research from a nonscientific point of view and opine whether the informed consent form is in a language that is comprehensible to a lay person. It may therefore be essential to have a person with nonscientific bent of mind, though he or she could be an expert in a different field.[11]

The precise description of what the regulators mean is very essential, the author is aware of two IRBs whose registration is held up for these reasons. For doing so there is no need of an amendment to the Schedule Y, which is a cumbersome process. A simple guidance document from the regulator would suffice. The United States Food and Drug Administration (US FDA) issues guidance documents on numerous issues, and there is no reason why our regulator cannot.

Adherence to specific policies

Every IRB must have its policies that are spelt out clearly in their standard operating procedures (SOPs). While applying for registration, these have been sent to CDSCO, it is only hoped that the SOPs have been scrutinized for correctness. Since many IRBs have no expertise in preparing SOPs, these may need improvement. In any case the SOPs of an IRB must cover the following, among other aspects:

- Appointment of members for the IRB (including qualifications and term)
- Roles of individual members
- Source of proposals that will be reviewed (only those from the parent institute or otherwise)
- Method for initial review, continuing reviews, and amendments
- Method of approval or rejection
- Conflict of interest.

SOPs lead to consistency of processes, and if followed assiduously, they ensure that deviation from norms will be minimal. The Indian regulator could issue a guidance document on each of these issues, which reflects the thinking of the current regulators. This guidance may change at times; it is not a 'gospel truth' that is immutable. Guidance documents do not require parliamentary clearance as do amendments and will help IRBs keep in sync with the current thinking of the regulators.

Completeness of its ethical review process (including challenges related to conduct of meeting)

It is the responsibility of the Chairman to ensure that the IRB focuses on relevant issues and the ethical review is complete. In the absence of adequate training the members tend to deviate from the norms neglecting some very important issues. In addition to the mandated issues, those that must be reviewed include the following:

- Inclusion/exclusion criteria
- Use of placebo
- Post trial access to investigational product (IP)
- Use of legally authorized representative (LAR)/witness
- Compensation in case of injury
- Continuing review
- Documentation and archiving.

Inclusion/exclusion criteria

This section of the protocol decides the type of subjects that will be recruited for the study. Whether the study includes vulnerable subjects or not becomes clear from these criteria. Guidelines describe different classes of vulnerable subjects; however the personal judgment of the investigator to use about every subject's vulnerability is the key to ethical research. In cases where the investigator feels that the subject lacks the power of self-determination, such a subject may be excluded. Vulnerability of some subjects such as women is very situational and dependent on the society they live in. These factors should be considered, while recruiting the subjects. Ethical codes merely define the bar below which and IRB or investigator should operate, there is no rule preventing anyone from being more ethical than required.

Use of placebo

The use of placebos (and denial of treatment) is a very controversial issue. In India the DOH is the guiding principle for research (in addition to the ICMR Guidelines).[12] The DOH categorically does away with the use of the placebo except under two situations,[13] while the ICMR guidelines are not very clear on this issue. Many trials originating from the US (which does not follow the current version of the DOH) have a placebo arm; placebos and ethical research are not considered mutually exclusive.[14] The IRB must carefully consider the implications of having a placebo in trials at an Indian site.

The use of placebo could put the subject at high risk. Should one of the subjects on the placebo arm, suffer an attack, in the US 911 would be dialed and the subject

would be in the hands of the doctors within the next hour, if not sooner. IRBs in India need to consider the outcome, should a patient in India suffer similarly. The ground reality of reaching the health provider very fast needs careful consideration before approving a placebo controlled trial.

Post trial access to IP

The DOH lays much emphasis on post-trial access to trial drugs stating.

"The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits." The ICMR guidelines make a vague recommendation that post trial access should be provided whenever possible, and states that in student's projects this may not be possible. It is doubtful if many of the 596 IRBs registered in the country have paid attention to this clause.

Supplying the IP in the post-trial period is fraught with difficulties. Firstly, the IP would be used outside the trial, without the safeguards the trial provides. In case a serious adverse event (SAE) occurs, the subject would have to consult the original principal investigator (PI), since another physician may not have the knowledge about the IP to handle the SAE. Also sponsors do not make additional IP available to the PI, hence the IRB must look into this more carefully.

Use of LAR/witness

Though there has been a lot of debate on who may be considered the LAR, a precise definition of LAR is lacking. The GCP requires that "the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law". In a country where there is a multiplicity of laws, one does not know which law is the applicable one. Indian regulators need to clarify this in a guidance document.

The Indian Good Clinical Practice (GCP) speaks of the use of impartial witness while taking consents of vulnerable subjects (CDSCO GCP 2.4.3.1.2). The impartial witness is defined as:

"An impartial independent witness who will not be influenced in any way by those who are involved in the Clinical Trial, who assists at the informed consent process and documents the freely given oral consent by signing and dating the written confirmation of this consent".

Impartial here means that a person who will not take either the investigator's side or the subject's side; neutral person.

However, the Belmont report states that "the third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest",[15] calling for judgment of the investigator rather than the relation of the potential LAR to the subject. A clarification on this issue is urgently needed.

Conflict of interest

Commercial IRBs raise the possibility of financial conflict of interest; such IRBs abound in the US.[16] India is largely spared of this problem. Yet conflict of interest among IRB members remains to be checked. In the US, as many as 36% of IRB members were found to have had some relation with the pharmaceutical industry,[17] the figure for India is not known. The CDSCO's GCP requires an IRB member to withdraw from the Independent Ethics Committee (IEC) when making a decision where there is a conflict of interest (CDSCO GCP 2.4.2.6.2). Most people understand what conflict of interest means, but would find it difficult to decide the level at which the conflict interferes with a fair decision. There are two main areas of uncertainty relation and financial investment.

Relation

There is clearly a conflict of interest when a member's near relative (spouse) is the partner/shareholder in the sponsor's business. Yet if the spouse were to be an employee at a lower cadre in the sponsor's business, would that be a conflict of interest? Alternately if a more distant relative of the member is a partner/shareholder in the sponsor's business, would the member be considered to have a conflict of interest?

Investment

There is a clear conflict of interest when an IRB member holds significant stock in the sponsor's company. Today a large number of people invest in mutual funds, who invest the money in shares. Few people would be aware as to how much of their money is invested in which company at any given time. The CDSCO's GCP does not define a conflict of interest, in hard terms and it is difficult for a member to know whether there exists a conflict or not.

Compensation

Medical or surgical management of injuries during clinical research and compensation to subjects are vexing issues before IRBs. Any discussion on the challenges facing the IRBs will be incomplete if the recent compensation rules were not to be discussed. However, a lot has already been said about these rules.[18-20] Further discussion on this is deferred since the Drug Technical Advisory Board has already considered issues raised by the industry and others, and have made recommendations to the government to revisit the compensation rules.[21]

Whether the rules of compensation are fair or not is to be discussed at a different level. When an IRB meeting is

in progress, the role of the members is to calculate and recommend compensation, without going into the merits or demerits of the rules. The government has provided a formula of calculating compensation and that needs to be followed. The formula is quite simple and its use does not really constitute a hurdle in the IRBs activity.

However, a large number of situations have cropped up in the last 6 months, where IRB members are in a real confusion as to whether medical management or compensation needs to be granted or not. There is no mechanism by which an IRB member or the entire IRB could approach an expert body to ask for advice. Approaching the regulator does not help, since in our experience, the regulators rarely reply a question and in time.

Continuing review

Continuing review is an IRB's most basic but neglected activity.[22] This activity should take up the maximum amount of an IRB's meeting time, and in the era of multicentric trials, this does not increase subject safety.[23] Amendments to trial documents are reviewed by the IRB as and when they are made and SAE reviewed when they occur. Hence, at IRB meetings the members need to review the patient recruitment status and little more. This activity should be led by an SOP, which would standardize the attention paid to every trial in progress.

Documentation and archiving

With increasing space crunch in cities, archiving is bound to take a hit. Electronic formats are being used at all stages of clinical trial activities and are controlled by 21 Code of Federal Regulation part 11 (21CFR11). There is need for national guidelines on electronic archiving, since sooner or later this is going to be the norm.

Additional issues

In the list of IRBs registered by the CDSCO, one finds mostly IRBs. IECs have been registered only for reviewing bioavailablity/bioequivalance (BA/BE) studies. Does this mean that IECs will no longer be allowed to review clinical research projects? Does it also mean that IEC which are not institutional will no longer have a role?

Additionally, a number of medical schools and hospitals are conducting nontherapeutic research. In this type of research, there is no sponsor behind the study. In such studies compensation is going to be a problematic issue and a decision needs to be taken about these studies. Whether they review clinical trials or research projects done as a part fulfillment of Doctor of Medicine (MD) or Diplomate in National Board (DNB) studies, IRBs must function on similar lines.

CONCLUSIONS

While hanging up her boots, the Secretary Department of Health and Human Services (DHHS) wrote that she was worried about the fairness with which research was reviewed in the US. She announced that the NIH and FDA would take up the responsibility of training investigators, IRB members, and IRB staff in bioethics.[24] Similar initiatives were taken in Germany by private hospital based groups and they have been responsible for setting up IECs throughout the country.[25] It would lighten the burden on our regulators if we could take this responsibility ourselves and not cast it on them.

The Indian Society of Clinical Research (ISCR) represents organizations and people who have the largest stake in clinical research in India. It would therefore be appropriate if ISCR takes the lead in setting up a Forum of ECs to undertake this activity. This forum could be formed by getting as many Indian IRBs as possible of ECs together, working in a democratic fashion. The Forum should lay down the requirements for training of IRB members; and also create a core team of trainers to actually deliver the training modules. Additionally, this Forum should accept the following responsibilities:

- Lay down guidelines for self-regulation for IRBs
- Customize training requirements for individual IRBs
- Provide training to IRB members
- Provide support and advice in interpretation of regulations and guidelines
- Interact with regulators and other authorities on the issue of regulations
- Interact with the lay press to provide assurance that clinical research is ethical.

The IRBs are one of the most important mechanisms for protecting subjects. All efforts must be made to ensure that IRBs across the country are competent. There is urgent need for oversight of IRB functions and the regulators needs to have a division which will have oversight over IRB functions, monitoring them regularly, auditing them sometimes, and help to protect human subjects. To support the regulator, there should be national or regional ethics forums which will work with the IRBs so that subjects are protected better and clinical research gains ground.

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