Practical solutions to challenges in research ethics proceedings of Bangalore conference

On November 3rd and 4th, 2012, Manipal Hospital, Bangalore and Association for the Accreditation of Human Research Protection Programs (AAHRPP) co-hosted an invitation only regional conference titled “Practical Solutions to Challenges in Research Ethics.” This paper is a synthesis of the major themes of the conference. The authors discuss the current state of the clinical research in India today, need to focus on human research protection programs rather than Ethics Committees or institutional review boards, the factors that influence high-quality research and some practical solutions to improving the quality of research and the protection of research participants.

Key words: Ethics committees, quality improvement, research protections

INTRODUCTION

On November 3rd and 4th, 2012, Manipal Hospital, Bangalore and Association for the Accreditation of Human Research Protection Programs (AAHRPP) co-hosted an invitation only regional conference titled “Practical Solutions to Challenges in Research Ethics.” The impetus for this conference grow out of a desire to help other Indian hospitals that conduct clinical trials more fully develop high-quality research programs and provide the high standards of protection for human research participants. This paper is a synthesis of the major themes of the conference and lays out an agenda for improving participant protections in India. The themes of the conference were gleaned from the presentations given at the conference and the robust discussions that were a part of the conference; the presenters are recognized for their contribution in the acknowledgments.

From ethics committees (ECs) to Human Research Protection Programs (HRPPs)

For the past 50 years, sponsors, investigators, and institutions had looked to the EC as the primary, if not the sole, entity responsible for protecting individuals who participate in research (referred to in this paper as research participants). Early on, this view of ECs made sense because it was the only group of individuals within an institution that considered ethics issues associated with a particular research study and considered research in terms of what was in the best interests of research participants rather than investigators or the institution. However, in a series of evaluations of EC (also referred to institutional review boards or IRBs) conducted in the United States in the 1990s it became clear that EC were often isolated within their institutions, not respected, and generally viewed as a hindrance to the research process. In general, these perceptions could be explained by a lack
of resources provided to most EC. EC, though, were not and still in many instances are not performing as they were intended to do resulting in diminished protections for research participants.

Today, the research community recognizes that the responsibility to protect research participants is a shared responsibility of the institution, the EC, and investigators at the local level and more broadly, of sponsors and government agencies. The EC has the sole responsibility for determining that a proposed research study is ethically justifiable. The EC makes this judgment by determining, among other things that the risks are reasonable in relation to the anticipated benefits and there is a process in place to obtain voluntary consent from prospective participants. However, there are many other functions that are the responsibility of investigators or of the institution. For example, investigators must carry out the research according to the terms specified in the protocol. They must follow the inclusion and exclusion criteria for enrolling participants, administer procedures and intervention as specified in the protocol, and maintain confidentiality of identifiable data to name a few responsibilities. Ensuring that investigators and EC members are competent through education is an institutional responsibility as is negotiating clinical trials agreements, identify and eliminating financial conflict of interest, and quality improvement. This expansive thinking about the roles and responsibilities of the primary players in research is now referred to as a HRPP.\(^1,2\)

Objectives of a HRPP are more comprehensive than those of an EC. They include: Establish a formal process to monitor, evaluate, and continually improve the protection of human research participants, exercise oversight of research protection, education investigators and research staff about their ethical responsibility to protect the research participants, ensure the organization maintains the resources necessary to support the research infrastructure and intervene in research and respond directly to concerns of research participants, when appropriate.

**The current research environment in India**

Global trends in clinical research indicate that more and more clinical trials are being placed in Asia, primarily, and other emerging markets, secondarily. A vast, unwieldy population, a plethora of diseases, and rampant poverty was the picture India presented to the outside world until recently. Today, the fact that India has the largest pool of patients suffering from cancer, diabetes, and other maladies is leading the country to become the global hub of outsourcing of clinical trials.

Many pharmaceutical companies have set up clinical trial facilities in major Indian cities. The major advantages apart from India’s huge population of more than one billion and cost effectiveness is the availability of tertiary-care hospitals, high-end diagnostics, large pool of good clinical practice (GCP) trained investigators, and growth in the information technology sector. The largest pharmaceutical companies are also drawn to India because the country offers nearly 700,000 specialty hospital beds. According to a Confederation of Indian Industry study, clinical trials in India in 2002 generated $70 million in revenue will grow to $200 million by 2007 and anywhere between $500 million and $1 billion by 2010. \(^3\) India is continuing to gain importance as a destination for conducting clinical trials. The global clinical research outsourcing market was projected to reach US $23 billion by 2011, with India cornering 15% of the market by 2013. The rapid growth of clinical trials in India; however, has led to several challenges.

The lack of a robust regulatory structure for conducting research and protecting human research participants hinders the advancement of all research (clinical and non-clinical) in India. Currently, only the sponsors are monitoring or auditing their respective trials; however, there is an increasing need to perform a more detailed review and assessment of processes of the institution and the EC. Robust regulations and guidelines, rigorous training of investigators and research personnel, improvement of health-care and research infrastructure are required for good clinical research. India needs to look at research with a different perspective — a comprehensive objective approach — in order to protect the interests and safety of human research participants, and to see that the data generated are credible by strictly adhering to the protocol, having a robust consent process, and a thorough review process by the EC. On February 13, 2013, the Drugs Controller of India (DCGI) issued a circular stating that all ECs must be registered under DCGI with 45 days. \(^4\)

Other regulatory authorities, such as the US Food and Drug Administration (FDA), have found the following deficiencies in the conduct of clinical trials: Record-keeping deficiencies, either no or incomplete documentation, protocol deviations, deficiencies in handling and controlling test articles, and failure to report adverse events. In India, 43% of FDA inspections have results in a determination of voluntary action indicated. These actions resulted from inadequate or inaccurate records, inadequate accountability of test articles, failure to follow the protocol for the clinical trial, failure to notify the EC of changes to the protocol or submit progress reports, and failure to obtain or document consent from the research participants.\(^5\)
Factors that relate to research performance

Improved clinical trial performance and protection for research participants will result from better trial design and adherence and enhanced institutional support of conducting clinical trials through a HRPP. Quality research and sound ethics are intractably intertwined: Improvement in performance cannot occur without improvement in participant protection. Likewise, if one domain suffers, so does the other.

Whereas, many factors contribute to the success of a clinical trial in terms of producing high-quality data and protecting research participants, some are more likely more important. Excellent protocol design, stringent criteria for selecting investigative sites, well-trained investigators and staff, effective post-approval monitoring of trials, and strong EC are essential factors. At all levels — institutional or national — research is only as strong as the weakest link in this complex system. And, whether one is discussing improvement in data quality or participant protections, virtually the same factors are offered as the ones most important to the quality.

Research design

Although much attention is placed on obtaining voluntary, informed consent as the primary means to protection research participants, and consent processes will be discussed shortly, the expertise and experience of the EC, protocol compliance, and monitoring and reporting of safety are equally important. Participant protection begins with the design of the clinical trials, is followed by an expert review of the protocol (including the qualifications and experience of the investigative site) and determination that the clinical trial is ethically justified by the EC, and then followed by the voluntary informed consent of prospective participants. Consent of participants never makes a poorly designed trial or an inadequate EC review ethical. And, voluntary informed consent is only valid throughout the clinical trial if investigators conduct the trial according to the terms stipulated in the protocol. Post-approval monitoring of trials and quality improvement processes are vital to ensuring the ethical soundness of trials because they ensure that the protocol, which the EC and in which the participant agreed to enroll remains valid. This intertwined web of players and processes is supported through the HRPP locally at the investigative site and the government regulatory system nationally. As one can see, no player in research may focus exclusively on merely one role, but instead, must understand his or her role in the context of a complicated system, often referred to as the research enterprise.

Consent

Consent, more accurately, the consent document, receives far more attention than it deserves. First, the consent document should be merely a written description of what was discussed in the consent process and not the “consent process.” A consent document is not a consent process nor can it substitute for the required interaction between the investigator and the prospective participant where the investigator describes the trial, including, but not limited to, its purpose, risks, potential benefits, procedures, alternatives to enrolling in the trial, provisions to protect privacy and maintain confidentiality of data in which the prospective participant would be identifiable, the right to decide whether to participate and the right to withdraw at any time from the trial, and the availability of compensation should the participant suffer an injury related to the trial. Even for the most sophisticated person, absorbing and understanding the purpose and methods of a trial let alone the implications and consequences of participating in a trial can be daunting. Asking questions, discussing the trials, and having time to consider whether to participate are paramount to a good consent process. In countries, such as India, where there are many different languages spoken and understood and large numbers of individuals who are illiterate, obtaining voluntary informed consent poses many hurdles. This is evident in the current debates about clinical trials in India. The consequences of failing to obtain consent or not fully informing prospective participants can be dire, leading not only to allegations of unethical research, allegations of research misconduct, but also to harm of participants and widespread mistrust by the public. Witness the current environment in India today where a few highly visible cases of failure to obtain consent have negative colored the way all clinical trials and pharmaceutical sponsors are viewed.

Role of EC

The independent EC has the primary responsibility of ensuring that proposed research is ethically justifiable. Other partners or players share responsibility for protecting human research participants but only the EC is charged solely with this responsibility. Many documents in the form of laws, regulations, guidelines, and principles exist to regulate and guide EC in their review of proposed research.

At a minimum, by Indian law and guidance, ECs must determine that risk of harms are minimized by using the sound research design, risks are reasonable in relation to potential benefits, selection of participants is equitable, voluntary consent is obtained and documented, and privacy interests of participants are protected and confidentiality of identifiable data are maintained. ECs have other responsibilities such as ensuring compensation for research-related injury is available and in India, determining the amount of compensation. ECs pay special attention to vulnerability of prospective participants and ensure...
provisions are made in the research to reduce any coercion or undue influence on vulnerable participants.

Although many laws, regulations, guidelines, and principles direct the EC in the issues it must consider in order to approve, none inform the EC about how to review research. For example, one of the more important tasks of the EC is to conduct an analysis of the risks and potential benefits. Defining risk — magnitude and probability — of harm is difficult, especially for harms that do not involve medical procedures such as breaches in confidentiality or embarrassment of participants. Even among medical procedures, symptoms such as nausea or headache might be difficult to characterize in terms of magnitude; are they negligible, small or moderate. Equally difficult, is determining whether a study involves no greater than or greater than minimal risk because the benchmark for judging risk to be minimal is the risk associated with daily life, which varies by socio-economic status, health status, and geography.

The lack of specific guidance, though, is not necessarily disadvantageous to EC because well-informed ECs can exert flexibility in applying application laws, regulations, and guidelines as long as they able to interpret them appropriately. For EC members to work at their full potential, they need to receive education and training in ethical principles that govern research; applicable laws, regulations and guidelines; and methods to review research from a protectionist perspective. Otherwise, may err in not carrying out their responsibilities appropriately such as approving research without a thorough review, waiving consent or failing to document their discussions.

EC are most effective when they are competent to fulfill their responsibilities and work collaboratively with investigators. Recognizing their obligations as EC, they can still work with as opposed to against investigators. In highly effective HRPPs, the channels are communication between investigators and ECs are open; both work toward promoting research and protecting human research participants.

Compensation for research-related injury

Recently, India adopted a new law requiring that in the case of study-related injury the investigative site and sponsor will provide medical care and compensation for the injury. For harm or injury, compensation is paid when there is evidence of negligence on the part of the investigator and staff or the sponsor. The EC determines the amount of compensation. Although, the law is meant to have good intention, it is lacking in definition. EC are not composed by design to judge proof of injury and calculate compensation for research-related injury. The requisite skills and experience for these functions are not inherent in members of EC and should not be. Whereas, it is ethically appropriate to require that participants are compensated when they are harm, the implementation of this ethical standard should rest with those in a better position to determine when and in by what means compensation is appropriate.

However, the larger issue regarding compensation is that compensation is a last resort measure when things have gone wrong in a trial; things that most likely could have been prevented if the protocol were designed well, investigators followed the trial protocol, the EC conducted a thorough review and participants in the trial were appropriately informed about the trial.

Clinical trial agreements

Ensuring that certain protections for research participants are in place begins not only with the design of the trial, but also with the terms specified in the clinical trial agreement. While most view the clinical trial agreement as the vehicle for payment arrangements and ensuring the terms of the protocol are followed, they are useful in negotiating interests important to the institution, such as publication rights of the investigator, and to participants, such as compensation for research-related injury, indemnification and insurance; ensuring that data and safety monitoring results are shared with the local EC or institution; and requiring reporting of any unanticipated problems or non-compliance of the investigator to the EC or institution. Although, the concept of using the clinical trial agreement as a means to ensure the participant protections is new, pharmaceutical sponsors in the United States are familiar with these negotiations with institutions that have AAHRPP-accredited HRPPs.

Financial conflict of interest

Individual (investigators and staff) financial conflict of interest while new outside the United States is fast becoming an area of concern. Investigators and staff must not have financial interests that conflict with their interests to conduct research ethically and with integrity. Few countries outside the United States have laws requiring the management and elimination of financial interests that might impede research or jeopardize the protection of research participants. Most investigators participating in phase three trials overseen by the US FDA submit financial disclosure forms, but the financial conflict of interests regulations of the FDA do not require management or elimination of financial interests and therefore the financial disclosures are rarely reviewed. The International Committee on Harmonisation Good Clinical Practice (ICH-GCP) (E6) states that financial conflicts of interest should not exist but provides no guidance
on how to disclose or manage financial interests. The media on the other hand, and politicians in the United States and India have raised concerns about significant financial interests that are related to the clinical trial that is being carried out. Moving forward, institutions will need to develop strong and robust financial conflict of interest policies and procedures and take responsibility for ensuring their investigators and staff do not have financial conflicts when they conduct research studies.

Conflict of interest, whether financial or non-financial, is never allowed to exist for EC members. Members who have conflicts must not participate in the review of research in which they have a conflict and in fact, should left the room during the discussion and voting of the EC. That said many EC take for granted that their members are not conflicted. Strong ECs have and follow procedures to ensure members are not conflicted when they review research.

Role of the investigator and study staff
The list of responsibilities of the investigator and study staff in conducting research and protecting research participants is long. Beginning in investigator-initiated research with designing research to carrying out research (in industry-sponsored as well as investigator-initiated research) investigators and staff have many responsibilities, including recruitment, obtaining consent, performing the study methods and interventions, collecting data, and analyzing and reporting data and therefore, many opportunities for error. Occasionally, investigator error is significant: falsifying data or failing to inform participants and obtain their consent, but, most often, deficiencies relate to record-keeping or protocol deviations. In India, US FDA inspections show that most deficiencies leading to a voluntary action indicated are inadequate or inaccurate records, inadequate drug accountability, failure to follow the investigational plan, failure to notify the EC of changes or submit progress reports, and failure to obtain or document consent from participants.

Education and monitoring of investigators and staff are critical to ensuring high-quality research and protection for research participants. Education must be ongoing, required, and targeted to the audience. Investigator and staff education should include a wide range of topics from research design and research conduct to ethical responsibilities to documentation requirements.

Institutions play a key role by setting the standards within their institutions to which investigators and staff must adhere and holding them accountable through auditing and other forms of post-approval (of research by the EC) monitoring.

Importance of quality improvement
Rather than operating from a principle that one should perform at a minimum level in conducting research, organizations, investigators, ECs, and sponsors need to and are adopting a goal of quality — to be the best. It is the smart and right thing to have high-quality HRPPs. And to do so, means a change in focus to one on quality improvement. Organizations must examine themselves, looking inward and their strengths and areas for improvement. Starting with the organizational leaders and filtering throughout the organization, the “research bar” must be set high with policies, procedures, and practices that allow EC and investigators and staff to continually improve.

Practical solutions to improving protection of human research participants in India
India offers tremendous opportunity to sponsors of research — large urban populations, wide range of disease prevalence, well-trained investigators and staff, and a drug regulatory structure. Yet, recent publicity about research abuses undermines India’s strengths. To overcome negative perceptions and the problems that do exist, organizations, researchers, sponsors, and regulatory agencies should consider the following:

- Adopt and implement a law to protect human research participants.
- Promote and foster the concept of a HRPP at the local institution.
- Develop a mechanism to identify high-quality investigative sites.
- Develop or engage existing national associations to provide regular education for investigators, study staff, and EC members and staff.
- Develop education campaigns for patients and the public.

Although, these solutions are national in focus, with the exception of the first one, each can be implemented locally at the institutional level in some form, especially if sponsors were able to support some of the activities.

The responsibility to protect human research participants is shared. Institutions can adopt this framework for conceptualizing how to oversee research by developing HRPPs in which they clearly define the roles of the institutions, the EC, investigators and study staff, and other parties that are involved in protecting research participants. From this frame-work, institutions should evaluate their policies, procedures, and practices to ensure the basic infrastructure for overseeing research is in place, each party is knowledgeable about his or her role, and there open lines of communication among all the department and offices within the institution. Better
protections for participants and better compliance by investigators and staff begin with clear expectations set by the institution.

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