Indian clinical trials: Paradigm shift from speed to quality?

"CLINICAL TRIALS: GOOD, FAST, CHEAP; CHOOSE ANY TWO"

Over the last decade, Indian has become an important country for clinical trials of international pharma companies. Since 2004, the number of new trials has increased at 31% Compound Annual Growth Rate (CAGR).[1] The clinical trials market has grown at 30%, which is almost double the global average.[1] Bolstered by the promise of fast and cheap trials, India has become one of the most attractive strategic imperatives for global clinical trials. However, globally, there has been a concern about ethical and scientific implications of globalization of clinical trials to developing countries.[2] These concerns have also been reflected in Indian media stories, questioning India's quest for attracting global clinical trials. It is time to reflect on the QUEST – Quality, Ethics, Speed, and Trust.

Good Clinical Practice (GCP), the international standard of quality, rests on assuring protection of rights, safety, and well-being of trial participants and ensuring that data and reported results are credible and accurate. Compliance to GCP standard can be evaluated by audits and regulatory inspection. Over the last several years, routine Food and Drugs Administration (FDA) inspection findings have been Voluntary Action Indicated (VAI) 59%, No Action Indicated (NAI) 40%, and Official Action Indicated (OAI) 1%.[3] In India, out of 22 site inspections for global trials, 11 (50%) were NAI and 11 (50%) were VAI. The quality of local trials conducted in India is difficult to judge as there are hardly any regulatory inspections of the local trials.

The common inspection findings at the Indian clinical trial sites have been in the area of data credibility – inadequate and inaccurate records and failure to follow investigational plan. However, at one site, there was a finding of failure to notify Institutional Review Board (IRB) of changes and failure to submit progress reports, which could impact protection of subjects. As the number of FDA inspections in India increases, deficiencies in the other areas of subject protection – consent, IRB approval, reporting of adverse drug reactions – are likely to surface.

The ethical dimension of Indian clinical trials has been the focus of most media stories. Deaths in clinical trials, commercialization of clinical research, exploitation of subjects, consent deviations, fraud, regulatory laxity, compensation for patients, and ethics committee (EC) functioning form the theme for alarming headlines. Although these reports might appear biased, they also bring focus on lack of awareness of ethical conduct in clinical trials. For example, in the cervical vaccine project, the government officer suggested that the warden of hostel could authorize the trial in girls without parental permission.[4] Another story exposed how the so-called "independent" ECs function.[5] After any such major press report, the government holds an enquiry or Drugs Controller General India (DCGI) office conducts an inspection. However, there is a lack of transparency in sharing the findings in public domain and a reluctance to act against those who are responsible. This fosters a perception that there is a lack of ethical and regulatory oversight on Indian clinical trials and creates a climate of mistrust amongst the clinical trial participants.

It would be worth reflecting on why there are deviations in ethical quality standards. One possible reason could be stress on recruitment speed of Indian trials. In a comparison of a sample of Indian sites and global sites, the number of patients per active sites was much higher compared to USA and UK.[1] However, in our study of recruitment performance of Indian sites, we found large variations in recruitment rates between the sites.[6] Based on marketing applications approved by US FDA in 2008, Indian sites recruited an average of eight patients per site.[7] In contrast, the average number of subjects per site was 13 for China and 16 for Brazil. Although the data supporting the claim that Indian sites can recruit rapidly are anecdotal, this puts pressure on the Indian sites to speed up the subject enrollment process and leads to a

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situation where ethics and quality may suffer. Regulatory delays in clinical trial approval process will put additional pressure on the sponsor and the investigator to speed up recruitment of subjects. As we do not have a large number of GCP trained investigators, most sites are busy with several clinical trials simultaneously. This reduces the time available for the investigator to supervise the site team, to communicate with the subjects, to review ethical aspects, and to go through the study documentation. Even for the clinical research associate (CRA), who gets 1–2 days to monitor a fast recruiting site, source data verification of completed case record forms (CRF) and review of trial master file consume bulk of the time, leaving little time to focus on ethical aspects. The ECs of many well-known institutions are loaded with review of multiple projects in meetings lasting a few hours. The attention of EC members gets divided between scientific aspects, ethical issues, and legal concerns – indemnity/insurance. No wonder the ECs miss out on in-depth analysis of risk:benefit of the study and protection of rights, safety, and well-being of subjects.

Training gaps in ethical issues is another major reason for ethical quality issues. The topics on ethics – codes, guidelines, consent, EC responsibilities – are usually covered in basic GCP training. However, when the clinical trial begins, the focus of training during the investigator meeting and site initiation is on protocol, CRF completion, source data, safety reporting, recruitment strategy, etc. The ethical aspects are limited to a documentation of informed consent. There is hardly any discussion on ethical issues/challenges in conducting the trial project in Indian population.

Essential training for ECs includes basic training – ethical codes, GCP regulations, clinical research, and risk:benefit analysis, EC responsibilities, and EC review process – and specific training – vulnerable population, conflict of interest, placebo-controlled trials, etc. A recent survey of EC approval letters found deficiencies in composition, quorum, and review of insurance and clinical trial agreement, revealing gaps in education and training of EC members.[8] Although most Indian ECs have received some training in basic aspects, there are lacunae in awareness of ethical guidelines and changing regulations, competency of assessing risk:benefit of investigational products and study procedures in subjects who are economically disadvantaged or illiterate, and review of safety information.

Trust is the most important factor for subjects who participate in clinical trials. According to a meta-analysis of clinical trials conducted in Indian patients, 7% of patients mentioned trust in the physicians as one of the favorable factors for participation in clinical trials.[9] In contrast, 26% of patients reported mistrust of trial organizations as a barrier to trial participation. Dr Getz, after a review of public opinion polls, has commented: "Although the public holds positive attitudes about the general importance of clinical research, the same cannot be said for public trust in the professionals who oversee, manage and support research. Distrust in clinical research professionals and those organizations responsible for ensuring patient safety, has increased dramatically."[10] There is an urgent need to rebuild trust and confidence amongst clinical trial participants. This would require strengthening ethical and regulatory oversight and developing accreditation process for all stakeholders.

The ECs should improve their procedures and practices to fulfill their prime responsibility of safeguarding the rights, safety, and well-being of all trial subjects. International Conference on Harmonisation (ICH) GCP recommends that EC should pay special attention to trials that may include vulnerable subjects.[11] As the definition of vulnerable subject includes unemployed or impoverished persons, most Indian subjects are considered vulnerable. Another important function of EC is continuing review of the trial conduct. Indian GCP recommends, "The Ethics Committees are not only entrusted with the initial view of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the ethics of the approved programs till the same are completed."[12] The EC should make it a practice to monitor consent by having one of its members observing and verifying the adequacy of consent process. Video recording of consent process of each subject would be helpful in this process. During the continuing review, the EC should focus on protocol deviations, safety reports, and progress reports, and seek additional information from the investigator.

The regulatory oversight requires regular and frequent inspections of the investigator sites, ECs, sponsors, and contract research organizations (CROs). The inspections should be followed by actions in case of major or critical findings. The findings should be available on CDSCO website to create awareness amongst all stakeholders about the common deficiencies in clinical trial conduct.

The EC and regulatory actions will be useful in the short term. Nevertheless, there is a need for a long-term approach – accreditation – to improve the quality of ethical conduct in clinical trials. It would be desirable to create a National Accreditation Board for Human Research Subject Protection (NABHRSP), which can provide accreditation to investigator sites, research institutions, sponsors, and CROs. The modus operandi of NABHRSP could be along the lines of Association for Accreditation of Human Research Participant Protection (AAHRPP). This

organization assesses the standards for the organization, EC, and researcher and his/her staff, with a focus on how they meet the primary goal of protection of the rights and welfare of research participants.[13] For ECs, the approach would be similar to Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) recognition instituted by Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP).[14] The SIDCER has five standards: 1) structure and composition of EC; 2) adherence to specific policies; 3) completeness of its review process; 3) after review process; and 5) documentation and archiving. FERCAP issues a certificate of recognition to EC/IRB that meets the five criteria standards.[14] Korea has 21 and China has 10 FERCAP recognized ECs, whilst India has just 2 recognized ECs.[14]

For far too long, speed and cost have been the focus of clinical trials, now it is high time to take steps to make quality the heart of Indian clinical research. Major reforms in the regulatory and ethical supervision and mandatory accreditation of all stakeholders – investigator sites, ECs, research institutions, sponsors, and CROs – are vital to rebuild the credibility of clinical research and to foster India's image as an ethical clinical trial destination.

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