

Future of Indian clinical trials: Moving forward from hyped potential to human protection

There are only two lasting bequests we can hope to give our children. One of these is roots; the other, wings - W. Hooding Carter II.

In 2005, when Schedule Y was amended, budding field of clinical trials started growing in India. The growth of this fledgling discipline required roots to stabilize and wings to fly.

The fundamental roots of clinical trials are ethical principles of ensuring protection of rights, safety, and well-being of clinical trial participants. These principles are enshrined in regulations and ethical guidelines. The wings are the knowledge and skills essential to conduct scientific, ethical, and quality clinical trials. The principal stakeholders – regulators, ethics committees (ECs), investigators, and sponsors – are responsible for nurturing this field by establishing strong roots and strengthening the wings. However, in the last 5 years, Indian media began highlighting safety issues and ethical deviations in clinical trials. The underlying factors were: (1) Sponsors' focus on potential for rapid recruitment of patients and cost savings; (2) the investigators' interest in commercial benefits^[1]; (3) inadequately functioning ECs^[2], and (4) lack of effective regulatory oversight. It became obvious that the roots were not stable and wings were not strong enough to support the growing field of clinical trials.

In 2013, in response to the supreme court directives, the regulatory authorities framed new regulations and guidelines for several critical processes – compensation, registration of ECs, and audio-visual (AV) recording of consent. These actions impacted the functioning of ECs, whose responsibility and workload increased enormously.^[2] The institutions and the investigators lost interest in the conduct of clinical trials as the increased burden of regulatory compliance activities far outweighed the perceived benefits of conducting clinical trials.^[1] The number of new trials plummeted as India lost its attractiveness as a cost-effective clinical destination for global sponsors. As the Indian clinical trial environment became unattractive, the regulators amended some of the stringent regulatory requirements in 2015. And now, there is optimism among the stakeholders about prospects of growth of clinical trials. However, as we look to the future of clinical trials in India, the question is: Have the regulatory actions post-2013 addressed the real issues of ensuring protection of rights, safety, and well-being clinical trial participants?

The new regulations provide compensation to the clinical trial participants, who suffer from serious adverse events (SAEs) – injury or death - related to clinical trial. In the absence of any standard assessment tool for establishing a relationship between SAE and clinical trial, the expert committee may be considered biased as it is dependent on SAE assessments reported by the sponsor and the investigator.^[3] There is thus a potential risk of depriving some clinical trial participants from their right to compensation. The compensation rule also ignores a category of SAE-important medical events - that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient, for example, convulsions that do not result in hospitalization.^[4] Clinical trial participants, who suffer from such important medical events, will not receive any compensation.

Since 2013, over 1000 ECs have been registered. However, there are still significant gaps in their functioning and standard operating procedures.^[2] It was expected that the Central Drugs Standard Control Organisation would inspect the registered ECs and ask them to correct deficiencies.^[5] However, in 2016, the ECs have been allowed to apply for reregistration, without any need for regulatory inspection. The United States Office for Human Research Protections found deficiencies in quorum requirement, approved informed consent (IC) documents, continuing review of research, and minutes of meetings in the evaluation of some Indian ECs.^[5]

AV recording of IC process provides documentation of the process, but can this ensure that the IC is truly voluntary from an illiterate and a poor patient. A study of quality of IC reported that the clinical trial participants from developing countries were less likely than those from developed countries to say that they could refuse to join or withdraw from a trial and were more likely to be concerned about the consequences of refusal or withdrawal.^[6]

Although the new regulations appear stringent, they fall short of ensuring protection of rights of clinical trial participants. The future of clinical trial depends on how the stakeholders strive to ensure protection of the rights of the trial participants. As there is no Indian guidance on what are Indian trial participants' rights, there is a need to develop a bill of rights for clinical trial participants.

The US National Institutes of Health The Clinical Center Patients' Bill of Rights,^[7] which aims to protect clinical research participants, includes right to (1) safe, considerate, and respectful care, (2) expect confidentiality of all communications and records, (3) know the physician responsible for coordinating care, (4) receive complete information about diagnosis, treatment, and prognosis from the physician, in terms that are easily understood by the patient or legally authorized representative, (5) receive information necessary to give IC before any procedure or treatment, including a description of the procedure or treatment, any potential risk or benefit, the probable duration of any incapacitation, and any alternative, (6) routine services when hospitalized in connection with research protocol, (7) know in advance what appointment times and physicians are available and where to go for continuity of care, (8) receive appropriate assessment of and treatment for medical conditions, (9) refuse to participate in research, (10) to be informed of the medical consequences of these actions, including possible dismissal from the study and discharge from the clinical center. If discharge would jeopardize patient's health, have the right to remain under care until discharge, or transfer is medically advisable, (11) to be transferred to another facility when the patient's participation in the Clinical Center study is terminated. This bill of rights can be adapted to Indian conditions and some special rights, for example, compensation for trial-related injury, special protection and care as vulnerable subjects, ancillary care, and posttrial access could be added. This bill of rights could serve as documentation of rights of the trial participants for accreditation process and along with other patient education material could also be used to create patient awareness about (a) clinical research process and its value in improving public health and drug development, (b) regulatory mechanisms for human subject protection, and (c) patients' rights when they participate in a clinical trial. There is an urgent need to create clinical research awareness programs for patients, patient groups, and society similar to patient education programs of the European Patients' Academy on Therapeutic Innovation - a consortium of patient organizations, academic institutions, and pharmaceutical companies.^[8]

The regulatory system should become proactive, state-of-the-art, unambiguous, and time bound. Some of the regulatory changes - AV consent, compensation guidelines, and registration of ECs - were discussed before 2010 but were not finalized and implemented in a planned manner. The current regulations need revision to accommodate 2016 amendments to the International Council on Harmonisation Good Clinical Practice (GCP) guidelines and the Indian Council of Medical Research Ethical Guidelines. Schedule Y includes requirements for clinical trials and marketing of drugs and covers in brief the responsibilities of the sponsor, investigator, functioning and responsibilities of EC, and IC process. In contrast, the US

Food and Drugs Administration (FDA) has comprehensive and in-depth regulations for Investigational New Drug (IND) application which describe application process, administrative actions, responsibilities of sponsors and investigators, IND safety reporting, Institutional Review Boards, and Protection of Human Subjects. In addition, FDA also provides guidance documents to explain the regulations and processes. As Indian regulations are not comprehensive and do not provide detailed guidance on protection of human subjects, ECs, IC process, and responsibilities of sponsors and investigators, the regulations are subject to diverse interpretations. Recently, the regulatory authorities delegated the responsibility of deciding about academic trials and number of trials per investigators to the ECs. However, the ECs are struggling with increased regulatory burden, and many are not adequately trained in ethical review. It is high time that regulatory authorities create comprehensive and contemporary regulations for clinical trials and guidelines which provide clear recommendations about the conduct of clinical trial in line with international regulations. In addition, it is of vital importance for regulators to conduct GCP inspections of investigator sites, ECs, and sponsors in a professional manner to monitor compliance with the regulations and GCP and to improve the quality of clinical trial conduct.

Post-2013, as the clinical trial environment became VUCA – volatile, unpredictable, complex, and ambiguous – and as clinical research professionals lost interest in the field, the training in knowledge and skills for clinical trial conduct has suffered. The accreditation standards can form the basis of mandatory centralized training and certification program for ECs. Unless the ECs are empowered by training to become independent and competent, they cannot fulfill their prime responsibility of ensuring human research protection.^[5]

Indian clinical trials cannot get recognition unless there is a culture of quality clinical research among physicians. A recent review of research publications between 2005 and 2014 reported that research output from Indian medical institutions was poor and 57.3% of the medical colleges did not have a single publication during this period.^[9] The physicians need to inculcate an attitude during the formative years and develop core capabilities for research^[10] - curiosity, observation, reasoning, and experimentation. The Academy of Physicians in Clinical Research recommends Clinical Investigator Competence certification programs for physicians to develop proficiency in (1) ethics and subject protections; (2) scientific concepts; (3) subject care; (4) operational excellence and regulatory compliance; and (5) leadership and business management.^[11] It is desirable to develop such certification programs for Indian clinical investigators. This would go a long way in improving research output and quality of clinical trial conduct.

The sponsors should be sensitive to local needs and support training and education of the clinical research professionals. They should be ready to invest in quality clinical trials, which have scientifically valid and ethically sound experimental design, and which ensure adequate protection of clinical trial participants' rights, safety, and well-being. ICH Integrated Addendum E6 (R2) recommends that the sponsor should implement quality management focusing on trial activities essential to ensuring human subject protection and the reliability of trial results. When noncompliance with regulations and GCP is detected, the sponsor should take prompt action to secure compliance. The sponsor should be ready to terminate investigator's/institution's participation in the trial, in case of serious and/or persistent noncompliance.

At present, the Indian environment is again becoming conducive to clinical trials. However, it is essential that all stakeholders work toward common goal of conducting quality trials which assure human subject protection while ensuring data integrity of the trial.

The future of clinical trials in India depends on how fast we move from reminiscing about hyped potential for clinical trials to investing in human protection!

Arun Bhatt

Consultant - Clinical Research and Development, Mumbai,
Maharashtra, India

Address for correspondence:

Dr. Arun Bhatt,
303/304, 3/C, Dheeraj Valley, Mohan Gokhale Road,
Goregaon (East), Mumbai - 400 063, Maharashtra, India.
E-mail: arun_dbhatt@hotmail.com

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