

Clinical Trials in India

Dilemmas for Developing Countries

Clinical research is an indispensable part of the drug discovery process to ensure the safety and efficacy of any new drug. In today's global scientific era, clinical trials are the mainstay for bringing newer and better drugs to market. Although a set of robust guidelines is available to govern the conduct of clinical trials in any country, the conduct of clinical research is also looked upon as an area of humanitarian concern.

Various articles published recently in the professional and popular press enumerate the opportunities and challenges of conducting global clinical trials in India. However, the majority have been from the perspective of authors who have never conducted clinical trials in India themselves. In contrast, this article conveys the perspective of someone who has worked as a principal investigator for various global clinical trials in medical oncology.

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Country Background

A nation with more than 1 billion people, India has the second largest population in the world. Having gained its independence from British rule in 1947, its prime minister is the head of government and its president is the head of state.

Internationally, India became a member of the World Trade Organization (WTO) in 1995 and agreed to adhere to the product patent regime by 2005. As a result, the global pharmaceutical industry has the rights to patent products as well as processes throughout the world, including India. This has led to a significant growth of the pharmaceutical industry, both domestically in India and globally, including increased stakes of multinational companies in Indian operations.

As a signatory to the WTO agreements, India is looked upon as a favorable destination for conducting global clinical trials. India clearly provides an opportunity in terms of availability of large patient populations, highly educated talent, a wide spectrum of disease, lower costs of operations, and a favorable economic and intellectual property environment.

The overall time and cost advantage in bringing a drug to market by leveraging India's resources could be as high as US \$200 million, hence the steadily increasing number of global studies in India over the past two years. Major pharmaceutical companies estimate the total market for conducting clinical trials either directly or through contract research organizations (CROs) in India through 2010 at US \$2 billion. CROs themselves are fast gaining importance because of their global presence, specialized local expertise, and competitive

pricing strategies. And a significant number of new CROs have set up operations in India over the past two years.

However, some key barriers stand in the way of opportunities, including patients' rights and safety, regulatory framework, infrastructure, organization of ethics committees, data quality, lack of training curricula focusing on clinical research, and other factors. Most of these barriers are common to all developing countries and need to be addressed in a similar way.¹

Because the clinical investigator plays a major role in the ethical conduct of any clinical trial, its successful outcome depends on how the investigator(s) has assumed overall responsibility. Most of the barriers mentioned above can be easily addressed if a clinical investigator is committed to the ethical conduct of trials. A segment of ideologues in India believe that clinical trials conduct poses a serious threat to society because of issues related to patient rights and safety, regulatory compliance, unethical trials, infrastructure and training issues, and exorbitant drug pricing. These threats are perceptions, not reality.

Patients' Rights and Safety

In today's scientific era, research is taking major strides in multiple areas to develop new and better drugs to cure ailments that are difficult to treat. In a majority of cases, these drugs are aimed at providing answers to unmet medical needs. However, the drug development process requires 10 to 12 years on average to reach the marketing approval stage.

Participation in clinical trials provides an opportunity to experience the benefits of these new drugs. So a critically ill patient who participates in a clinical trial, and who may not be alive after eight to 10 years when the drug would be made available in the market, has access to what may provide either longer term health benefits or an improved quality of life. By carefully evaluating the eligibility criteria, a clinical investigator can offer new hope to patients across a wide range of therapeutic areas.

Participation in clinical trials also provides research professionals opportunities to offer the best care to patients. A well-designed and executed study has built-in provisions to ensure patient rights and safety. In fact, a patient may be far safer in a clinical trial than in routine medical care because careful observations are made on safety (toxicity) and efficacy.

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In addition, clinical trials move in phases, that is, Phase II trials are initiated only if the Phase I results are promising. Similarly, Phase III trials are conducted only if the drug has shown required safety and efficacy in early phase trials. Hence, a patient is at minimized risk during later phases of clinical trials. In contrast, historical events like the sulfanilamide² and thalidomide³ disasters could have been avoided with appropriate clinical trials. This phase process is particularly important in developing countries if carefully understood and explained to potential subjects.

Regulatory Framework

Multinational pharmaceutical companies and CROs are able to conduct good quality clinical trials in India despite infrastructural challenges at the regulatory department level. They can do so because of required professional

training and the professionals' willingness to comply with regulations and applicable standards in a spirit that protects the rights and safety of trial subjects. In India, no less than in the rest of the world, it is the responsibility of individual stakeholders (sponsors, CROs, investigators) to observe self-discipline while conducting clinical trials, especially when there are more than 20,000 big and small companies and a mere handful of regulatory professionals.

The belief that compliance with Good Clinical Practices (GCP) and applicable regulatory guidelines requires the presence of a robust regulatory inspection system is erroneous. Rather, what may be required is a change of mindset from one of "situational ethics" (that is, compliance with medical ethics in clinical trials only) to one of "holistic ethics" (that is, compliance with medical ethics in clinical trials as well as routine medical care). No regulatory authority can ensure 100% GCP compliance unless the individual stakeholders are willing to comply with the applicable regulations.

Conduct of Illegal/Unethical Trials

Scientific misconduct is a global phenomenon linked to human behavior rather than to an individual country. For instance, the U.S. Food and Drug Administration (FDA) website lists the details of clinical investigators who have been "disqualified" or "restricted" from doing research on grounds of scientific misconduct.^{4,5} Details of warning letters issued to various stakeholders (clinical investigator, ERB/IRB, sponsor, CRO, etc.) can also be obtained from the same website. However, FDA has not banned clinical trials based on these grounds, these individuals, or individual organizations. Rather, FDA has increased its surveillance over clinical research programs. In like manner, the Indian regulatory authority is also in the process of setting up surveillance teams for ensuring ethical conduct of clinical trials.

Companies acting ethically set globally consistent standards and conduct trials only in the countries where GCP compli-

ance is assured. Indian investigators have demonstrated their compliance by virtue of participation in more than 60 global trials so far. Moreover, a majority of those trials were FDA or European registration trials, requiring strict compliance with GCP and regulatory guidelines. The data have been accepted by foreign regulatory authorities and published in international scientific journals of repute.

Infrastructure

Participation in global clinical trials requires an upgrade in existing infrastructure and facilities at a majority of Indian hospitals in terms of functioning of ERB/IRB, calibration and quality control of diagnostic equipments, maintenance of patient medical records, handling of investigational product, and other critical areas.

There have been instances of sponsors providing highly expensive diagnostic instruments to trial sites in order to achieve consistency in trial data globally. All the trials include investigator grants and funding that is generally utilized to upgrade the infrastructure and education facilities at a site. The Institutional Ethics Committees at a majority of Indian hospitals are gaining competence in evaluating the trial proposals from scientific and ethical standpoints. This, in turn, is strengthening the healthcare system of the country while bolstering the ability of institutions to conduct research. In short, clinical research offers value and value-added infrastructural incentives to the country.

Training

Lack of technical knowhow on drug development and the habit of “copying” (mostly producing generic drugs) are the major hurdles for indigenous drug research. Participation in global trials provides learning opportunities to Indian doctors and scientists, which in turn can be utilized to find the answers for the diseases that are endemic to the country, such as kala-azar, leprosy, trachoma, and tuberculosis. The medical

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research intellectual base of the country has been suboptimally utilized so far due to the absence of basic research facilities and knowhow.

Participation of Indian investigators in global trials and subsequent publication/presentation motivate them to develop research protocols for domestic healthcare issues. This, in turn, is nurturing a culture of medical research that can match international standards.

Pricing

Less than 10% by value of drugs used in India are of the premium category; the other 90% are established off-patent drugs (drugs for which multiple generic versions are available). Even for premium category drugs, the pricing is generally moderated by three important factors:

- the purchasing power of the customers;
- the existence of unpatented drugs and cheaper substitutes; and
- the Drug Price Control Order, which regulates the pricing of essential life-saving drugs in India.

Even today, people who can afford the premium category drugs are getting them imported from the West or are traveling to other countries to get better medical care. The availability of such drugs in India is going to reduce the overall healthcare cost.

Conclusion

Although it typically takes 10 to 12 years and millions of dollars to bring one new drug to market, the success rate is small.

In the developing world, no company or institute wants to, or can, invest such time and resources for a marginal improvement in responses over existing therapies. Fortunately, in a majority of cases, clinical trials can provide answers regarding the use or not of a therapeutic agent that can benefit millions of patients worldwide. Being the second most populated country in the world, India can contribute significantly to global drug development programs.

The foundation of knowledge-based industries in India was laid down by the information technology industry, and there is no reason why clinical research cannot follow in those footsteps. Indian investigators and clinical research professionals have already demonstrated their medical and scientific skills by participating in multiple global clinical trials. It is time now to move forward to capitalize on the opportunity.

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