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Clinical Trials in India: A Scientific Approach for New Drug Development

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ABSTRACT

Clinical Research is an organized research and systematic study conducted on human beings to generate data for discovering or verifying the clinical, pharmacological or adverse effects with the objective of determining safety and efficacy of new drugs. Globally, Clinical research (CR) is becoming a thrust research area as it is essential for development of not only new drugs but also for new formulations, drug delivery systems, dosage regimen, surgical and diagnostic techniques, devices and therapies. India and other developing/under-developed countries have a plethora of poor and uneducated people, multinational companies are targetting these countries for conducting clinical trials of new drugs. Clinical trials in developing countries are exploding. It is estimated that 20-30% of global clinical trial activities are being conducted in developing countries.

Keywords: Clinical trial, New drug discovery, Regulatory requirements, Current and Future prospects

1. INTRODUCTION

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. Development of new drug involves two phases, namely drug discovery and drug development. The growth of an idea into a product may take over a decade of dedicated research by team of researchers including organic chemists, pharmacists, pharmacologists, toxicologists and clinicians. This is target oriented multistage ongoing process of clinical importance as each new discovery means relief to millions.

The first stage of drug discovery involves the identification of the target, drug designing and synthesis followed by its preliminary in-vitro screening. With the advent of high throughput screening technology, the number of New Chemical Entities (NCE) that are being generated has increased in leaps and bounds. NCE undergoes drug development that involves determination of its safety, efficacy, kinetics and developing formulation. There are two overlapping phases of drug development that can be differentiated, namely preclinical and clinical. Preclinical evaluation involves rigorous testing of efficacy and safety of new molecule by various in-vivo assays using animals. The necessary data for evaluation in humans is generated here and the test drug is now ready for its last and most crucial stage of evaluation, i.e., clinical evaluation. The clinicians in coordination with the pharmacists evaluate the efficacy and safety of the sample over four stages starting from healthy volunteers and moving on to small group of patients and special groups.

Phase one or clinical pharmacology forms the basis for clinical trial for any new drug and provides the link between preclinical and clinical research. Finally, the application for FDA review and approval may be applied and the approval sought [8]. Clinical trail are the mainstay for bringing new drugs to the market and constitute approximately 70% of the total time and money spent in drug discovery process. Typically it takes approximately 12 years and US$ 800 million (Rs 37,74,00,00,000) to bring one new drug from conception to market out of which 6-7 years are spent in various phases of clinical trials.

Clinical Research (CR) may be defined as an organized research and systematic study conducted on human beings to generate data for discovering or verifying the clinical, pharmacological (including Pharmacodynamic and pharmacokinetic) or adverse effects with the objective of determining safety and efficacy of new drugs.

Globally, CR is becoming a thrust research area as it is essential for development of not only new drugs but also for new formulations, drug delivery systems, dosage regimen, surgical and diagnostic techniques, devices and therapies. The Indian pharmaceutical industry is one of the fastest growing sectors of the Indian economy and has made rapid strides over the years. From being an important dependent industry in the 1950s, the industry has achieved self sufficiency and gained global recognition as a producer of low cost high quality bulk drugs and formulations. Number of factors favors the recognition of India as hub for CR due to which the multinational companies have identified it as their ideal destination. Firstly, there are numerous government funded medical and pharmaceutical institutions having state of the art facilities, which can serve as ideal centers for multi-centered clinical trials. Secondly, India can boast of a large well-trained and qualified manpower that is well versed in English as a means of communication. Most importantly, there is vast clinical material, which can be utilized. In terms of the cost efficiency, India works out to be a cheaper option as the cost to conduct a trial here is lower by 50 to 75% than that in either United States or European Union. R&D costs in India are much less than those in the developed world and it are possible to conduct both New Drug Discovery Research (NDDR) and Novel Drug Delivery System (NDDS) programs at competitive rates. Additionally, while clinical trials cost approximately $300 to 350 million abroad, they cost about Rs. 100 crore in India 6.

Advantage of Clinical trials in India

- Well-trained medical community to global standards.
- Wide spectrum of diseases, with low per capita drug expenditure.
- Huge patient base.
- Heterogeneous population base.
- High enrolment rates.
- Large and fast growing private healthcare sector.
- State-of-the-art hospital facilities.
- Government commitment to provide Intellectual Property Protection from January 2005 - transition already in progress.
- Proposed changes to regulatory policies to facilitate clinical research.
- Lower costs for clinical researchers, nurses, IT staff, along with reduction in patient-related costs.
- Diversity in India's gene pool.
- Difficulty in recruiting for trials globally. India has adequate patients and investigators.
- Overall lower costs for conduct of trials.
- Rapidly increasing awareness of ICH-GCP guidelines for conduct of clinical research.
- English as a primary language of education and communication.
- All investigators speak English and GCP trained investigators are increasing in number.
- Education level of the clinical researchers in India is quite high.
- Increasingly accommodating regulatory environment.
- The new IP regime as of 2005 provides a greater level of comfort level with doing clinical research in India.
- Communication and IT infrastructure and capabilities are at Western standards.
- Data generated in India is accepted by all major conferences and journals.
- Import duties on clinical material have been eliminated.

2. SCOPE OF CLINICAL RESEARCH IN INDIA

However, India is a land of diversity where alternative system of medicine like ayurveda, unani, siddha, homeopathy are practiced with equal fervor as allopathy. Thus, clinical studies for their evaluation can also be conducted with ease. Internationally, there has been recognition of the Indian advantage which is luring pharmaceutical companies to adopt collaborative outsourcing strategies so as to tap the potential to its fullest. Owing to these factors the India is globally attracting collaborative contract

proposal for conducting clinical trials and many have already come forward to set up their clinical research organizations (CRO'S).

Every new drug needs evidence from CR to supports its launch. Thus, whether it is a new chemical entity or an existing drug that is being marketed for new indication, clinical studies have to be conducted. Similarly launch of new formulations, drug delivery systems or even new fixed dose combination, requires clinical data before it can be marketed. Hence, it is obvious that the area of clinical research holds immense scope and promise for without the supporting data drug launches are not feasible. CR should not be merely viewed as a subsidiary to preclinical research. CR holds tremendous scope and opportunities not only for trained medical, pharmaceutical and paramedical professional but also for regulatory authorities, government and society at large. A mechanism of knowledge transfer can be worked out which would lead to a definite improvement in hospital infrastructure. It will make available the state of the art therapy for many deserving Indian patients who were hitherto deprived of such therapeutic advances [9].

Table 1: Figures in respect of revenue, human power and patient load for Clinical research in India

	2003	**2008**	**2010**
Value (Million USD)	50	200	1000
Revenue (Crore INR)	75	300	875
Full time staff requirement	800	4000	20,000
Site- Staff requirement	1500	6000	30,000
Patient load	10,000	50,000	300,000

3. JOB OPPORTUNITIES IN CLINICAL RESEARCH FOR PHARMA PROFESSIONALS

Clinical trials in developing countries are exploding. It is estimated that 20-30% of global clinical trial activities are being conducted in developing countries. The 2002 Indian clinical trials market of $30-35 million is projected to grow 8-10 times by 2010 to $ 250-300 million [3].

It is certain that in future as the number of clinical projects expands, there will be a demand for qualified personnel. Trained clinical research professionals are in great demand in India and abroad and will be for many years to come. There are more than 2, 50,000 positions vacant world wide, an unheard phenomenon in any industry. In India as per Mckinsey Report, 50,000 professionals will be needed by 2010.

Trained pharmacists and clinicians can fill this wide gap. They will be involved in the various aspects of clinical research starting from site-monitoring, site management, clinical data management, data analysis, report writing, report submission, presentation and publication. Pay scales in clinical research are considered amongst the industry's best. Salaries start at Rs. 2.4 lac p.a and go to over Rs. 15 lacs p.s. for professionals with less than 5 years experience [5].

Table 2: Figures with respect to India

Population	1 Billion plus
Crude birth rate	26 per 1000 population
Life expectancy	62 years
Population density	814 / Sq mile
Hospitals	15,000 plus
Doctors	500,000 plus
Nurses	737,000
Hospital beds	700,000 (85% urban)

Table 3: Clinical Trial capacity in India Vs United States – a comparison

	United States	**India**
Studies	4000	200
Investigators	40,000	<1000
Patients in Trials	800,000	<1000

4. REGULATORY REQUIREMENT FOR CONDUCTING CLINICAL RESEARCH IN INDIA

In 1988, the government made it mandatory for all new drug introductions as a regulatory requirement for getting NCE's approved Schedule Y stipulated that the first applicant for any new drug should generate data in local clinical trials conducted in approximately 100 patients at 4-5 centers. This schedule also indicates that permission for such clinical trials would be given for one phase behind the development status in the rest of world.

However, for a second and subsequent applicant for the same compound, no clinical trial would be required since they could show bio-equivalence to the first product approved and introduces their brand of the generic in the market. Due to the lack of protection, innovator companies have been losing money by virtue of not being able to introduce their new and cutting edge research in the Indian market due to the presence of generic brands of innovator compounds.

In the last few years, there has been increasing interest in the pharmaceutical industry in outsourcing drug discovery and clinical development programs to Asia, particularly India. Since clinical development accounts for about two-thirds of the total cost of developing a new drug, off-shoring clinical trials offers unique opportunities, especially in terms of access to study subjects, trained personnel, lower-cost infrastructure and labor pools. It has been widely recognized that India offers unique opportunities for conducting clinical trials due to a significant cost reduction and increased speed and productivity of all R&D phases required to bring a safe and effective drug to market. India has a large patient pool, well-trained and enthusiastic investigators, premier medical institutions, low per-patient trial cost and a highly favorable regulatory climate. It is estimated that as much as 20% of all global clinical trials might be conducted in India by 2010 [4].

However, emerging opportunities in India for clinical development are not without challenges especially in terms of quality control measures, availability of trained professional resources, regulatory timeline predictability and data protection.

In the last five years, India's business and regulatory climate has undergone dramatic change. In December 2004, Indian patent law was modified to harmonize it with international laws governing intellectual property protection. Regulatory processes are also being updated to harmonize with US and international standards, and plans are a foot to create a regulatory body in line with FDA, a central authority governing all drug development-related activities. Indian regulatory agencies are increasingly interacting with clinical development professionals to understand the caveats of old regulations and possible remedies. In addition to the primary concern about the safety of clinical trial subjects, Indian regulatory authorities need to address several other issues in developing regulatory guidelines, such as cultural differences, language considerations, investigator training, etc.

Various regulatory aspects related to drug import, manufacture, sale and advertising in India are covered under the Drugs & Cosmetics Act of 1940 and the ensuing Drugs & Cosmetics Rules of 1945, the Pharmacy Act of 1948 and the Drugs & Magic Remedies (Objectionable Advertisements) Act of 1954. Of these, the Drug & Cosmetic Act (Act) of 1940, which led to the Drugs & Cosmetics Rules (Rules) of 1945, is central legislation that regulates India's drug and cosmetic import, manufacture, distribution and sale. The Act's main objective is to ensure that available human drugs are safe and efficacious and conform to prescribed quality standards, and marketed cosmetics are safe for use.

Over the years, the Act has been amended several times to address public concerns. The Central Drugs Standard Control Organization (CDSCO), headed by the Drugs Controller General (India) (DCG (I)), discharges the functions allocated to the Central Government (similar to the US Federal Government) under the Act. CDSCO is attached to the office of the Director General of Health Services in the Federal Ministry of Health and Family Welfare. The DCG (I) has statutory authority under the Act with port offices, zonal offices and drug testing laboratories. The DCG (I)'s office is primarily responsible for:

- Approval of new drugs to be introduced in the country.
- Permission to conduct clinical trials.
- Registration and control of imported drug quality.
- Developing regulatory measures and amendments to acts and rules.
- • Establishing standards for drugs, cosmetics, diagnostics and devices and updating the Indian Pharmacopoeia.
- License approval as Central License Approving Authority for the manufacture of large volume parenterals, vaccines and biotechnology products and operating blood banks and also of such other drugs as may be notified by the federal government from time to time.
- Coordinating the activities of the States and advising them on matters relating to uniform administration of the Act and Rules in the country.

Clinical trials in India are regulated by Schedule Y of the Drug and Cosmetics Rules, 1945. The Rules were revised in 2005 and the current rules, the Drugs and Cosmetics (IInd Amendment) Rules, 2005, were released 20 January 2005. Under the updated Rules, the Schedule Y was extensively revised to bring the Indian regulations up to par with internationally accepted definitions and procedures.

Schedule Y defines the requirements and guidelines for import and/or manufacture of new drugs for sale or for clinical trials. These include details of the application process and components of the application for permission to conduct clinical trials, and the responsibilities of the sponsor, investigators, and the Independent Ethics Committee (IEC) [4,7].

5. CURRENT STATUS OF CLINICAL RESEARCH IN INDIA

Certainly over the past decade, there has been a perceptible change from skepticism to acceptance in how India is viewed for clinical trials; many consider it a core region for global plans (Figures 1 and 2). As a result, many global pharmaceutical players including Pfizer, Novartis, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Aventis, Novo Nordisk, Bristol-Myers Squibb, Roche, and Amgen have expanded their existing clinical research investment and infrastructure in India [9].

According to Asia times in 2002, outsourced clinical trial generated an estimated $ 70 million in revenues for Indian companies in this sector, and the number was predicted to grow to $200 million by 2007. There are predictions that the Indian clinical trials market will be valued between $500 million and $1 billion by 20101.

A decade ago, India had little in the way of clear cut regulatory guidelines for clinical trials, but it slowly progressed towards GCP clinical trial standards 3. Because of pressure from the industry and proactive initiatives of the regulators, the Central Ethics Committee on Human Research (CECHR) of the Indian Council of Medical Research (ICMR), New Delhi, issued Ethical Guidelines for biomedical research on human subjects in 2000. Subsequently in 2001, a central expert committee was set up by the Central Drugs Standard Control Organization (CDSCO) to develop Indian GCP guidelines in line with the latest WHO, ICH, FDA, and MHRA guidelines[7]. India currently participates in about 1 percent of worldwide biopharmaceutical clinical trials, involving 757 sites. But its average relative annual growth rate is nearly 20 percent [10].

6. FUTURE PROSPECTS OF INDIAN CLINICAL RESEARCH

Clinical data generated by Indian clinical sites have been used successfully for drug approval applications in the US, EU and other countries over the last decade. However, India's indigenous pharmaceutical industry still conducts only a small fraction of the total clinical trials in the country. Most clinical studies in India are for foreign sponsors. India is clearly on course to become a major center for clinical trials, and is routinely considered by international sponsors for their global trials. The country has a strong reputation for meeting global professional parameters, as demonstrated by the information technology and service industries. The involvement of regulatory agencies, such as the FDA, should be seen as a beneficial step to ensure that the clinical trials environment evolves in an appropriate fashion and that standards used to protect patients in other markets are also applied in India. Although companies face continuing pressure to reduce clinical development timelines and costs, it is important that these factors do not encourage staff to let standards slip in particular markets [2,11].

It is in the pharmaceutical industry's interest to fully engage with Indian patients in their work. Patient participation is essential if future drugs are to be developed successfully in India. If the public have confidence in the industry, then rapid patient recruitment will be enhanced.

Clinical trials in developing countries are exploding. It is estimated that 20-30% of global clinical trial activities are being conducted in developing countries. The 2002 Indian clinical trials market of $30-35 million is projected to grow 8-10 times by 2010 to $ 250-300 million. Forecasters say that, by 2011, India will be conducting more than 15 percent of total global clinical trials [3,9].

The World Health Organization (WHO) has played a catalytic role in pushing this process forward. WHO's involvement in clinical trial registration began in October 2003 with consultations with different stakeholders to identify a potential basis for collaboration to address complex issues related to trial registration and reporting [12].

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