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Clinical Trials: It's Growth & Opportunities

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ABSTRACT

A clinical trial is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are fastest and safest way to find treatment that work in people and way to improve health. Investigational trials determine whether experimental treatment or new ways of using known therapies are safe and effective under controlled environment. Observational trials address health issues in large groups of people or population in natural settings. Clinical trials aim to measure therapeutic effectiveness and constitute an important and highly specialized form of biological assay. In phase I pharmacokinetics, safety, gross effects are studied on human volunteers, by clinical pharmacologists. If the drug passes the test, it enters phase II testing's, where pharmacokinetics, safety, therapeutic efficiency are studied on selected patients by clinical pharmacologist, if passes hundreds of selected patients are now studied, primarily for safety and therapeutic effectiveness by clinical investigators in phase III. If this is passed the drug is now approved and marketed. Even after marketing, physicians from various hospitals and clinics send their opinion about the drug, regarding ADR, efficacy in phase IV.

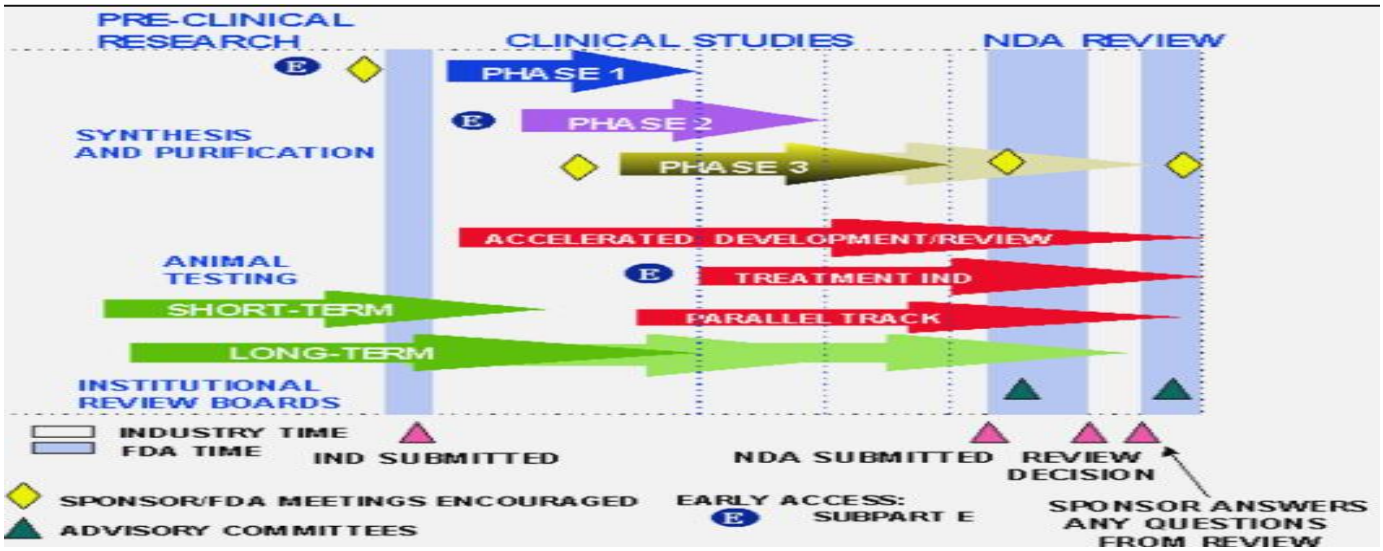
Keywords: Clinical Trials, Preclinical Studies, Clinical studies, NDA, Global and indian scenario,Opportunities ,Role of pharmacist in clinical trials

INTRODUCTION

A clinical trial is a research study that tests a new medical treatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease[1]. For any new drug to enter in clinical trial, it must pass preclinical studies. Preclinical studies involve in vitro (i.e. test-tube or Laboratory) studies and trials on animal populations. Wide range of dosages of the study drug is given to animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information[2], A clinical trial is an organized research study designed to investigate new methods of preventing, detecting, diagnosing, or treating an illness or disease and attempt to improve a patient's quality of life[3]. The first clinical trial of a novel therapy conducted by Renaissance surgeon Ambroise Pare in 1537; used a concoction of turpentine, rose oil and egg yolk to prevent the infection of battlefield wounds. The first known controlled clinical trial was carried out by James Lind; documented citrus fruits in the diet could prevent scurvy. Placebos were first used in 1863, and the idea of randomization was introduced in 1923. In 1948 by the Medical Research Council, the first trial using properly randomized treatment and control groups was carried out, and involved the use of streptomycin to treat pulmonary tuberculosis. Since 1945, the ethical impact of clinical trials has bec-

ome increasingly important, resulting in strict regulation of medical experiments on human subjects[4]

PHASES OF CLINICAL TRIAL



Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies[5]

- **Phase 0**

Phase 0 is a recent designation for exploratory, first-inhuman trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

- **Phase I**

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay ranges from a small amount of money for a short period of residence, to a larger amount of up to approx £4000 depending on length of participation. There are different kinds of Phase I trials:

1. SAD

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the

drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until precalculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up at which point the drug is said to have reached the Maximum tolerated dose (MTD).

2. MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug.

- **Phase II**

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given), whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)). Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

- **Phase III**

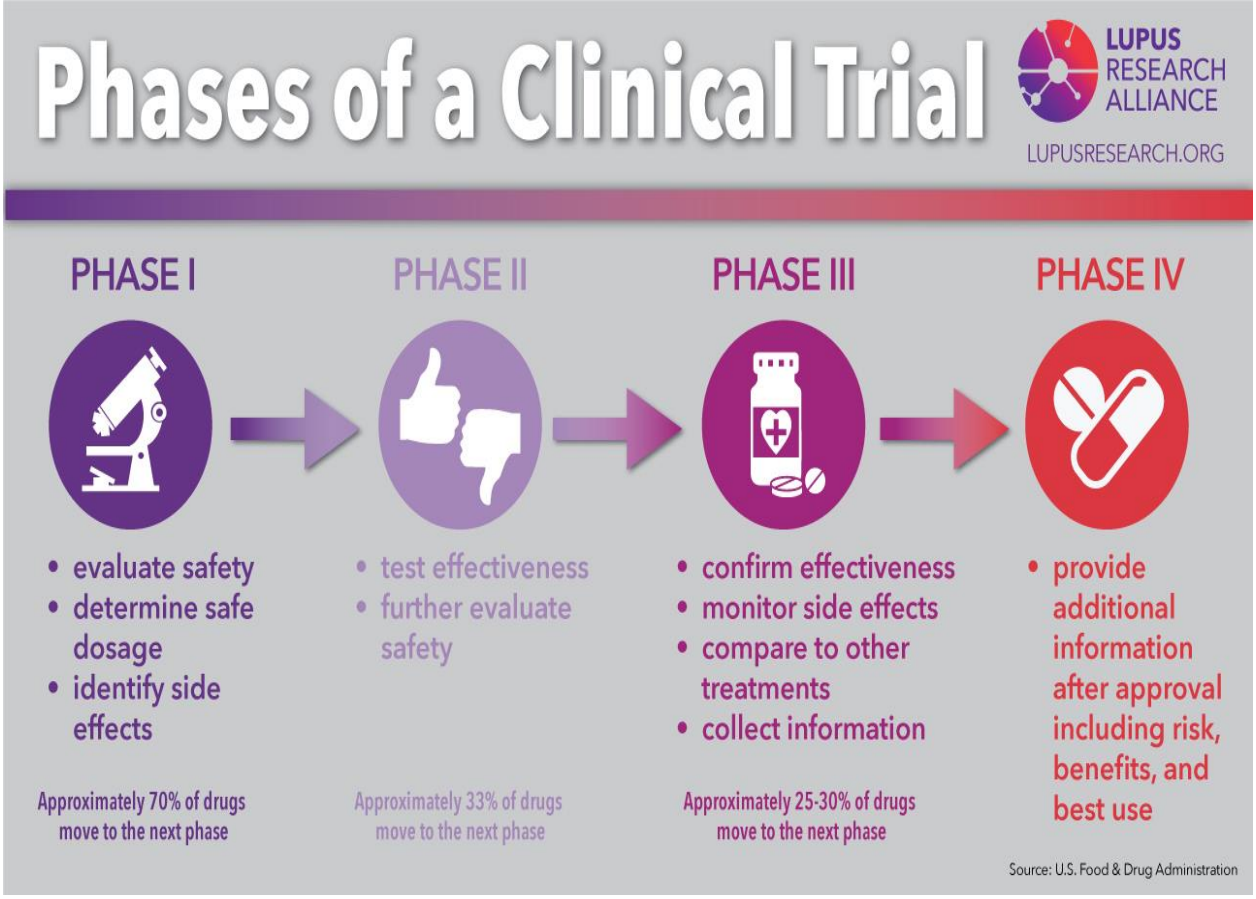
Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-conditions. It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies (FDA (USA), TGA (Australia), EMEA (European Union), etc.). Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authoritiesin different countries. Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market.

While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

- **Phase IV**

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time

period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no long sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx) .



TYPES OF CINICAL TRIAL

1. **Treatment trials**

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

2. **Prevention trials**

Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

3. **Diagnostic trials**

Conducted to find better tests or procedures for diagnosing a particular disease or condition.

4. **Screening trials**

Test the best way to detect certain diseases or health conditions.

5. **Quality of Life Trials (or Supportive Care trials)**

explore ways to improve comfort and the quality of life for individuals with a chronic illness[2] .

Trial Design

1. **Adaptive clinical trial:** - purpose of an adaptive trial is quickly identifying drugs that have a therapeutic effect done by adjusting dosing levels. This trial evaluates a medical device or treatment

by observing participant outcomes on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations. Modifications parameters include dosage, drug undergoing trial, patient selection criteria, sample size and mix.

2. **Randomized trial:** - Purpose of Randomized trial is to reduce bias for testing new drug treatment. In this trial, each study subject is randomly assigned to receive either the study treatment or a placebo. Group receiving placebo is control group Randomized trial are used to check effectiveness and efficacy of drug.
3. **Blind trial:** - In blind trials, the subjects involved in the study do not know which study treatment they receive and for what purpose. In double blind trials, subjects and investigator / doctor do not know which medication is given. Neither the patients nor the researchers

INVESTIGATIONAL NEW DRUG (IND) / CLINICAL TRIAL EXCEPTION (CTX) / CLINICAL TRIAL AUTHORIZATION (CTA) APPLICATION

INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed. In addition to obtaining permission from appropriate regulatory authorities, an Institutional or Independent Review Board (IRB) OR Ethical Advisory Board must approve the protocol for testing as well as the informed consent documents that volunteers sign prior to participating in a clinical study. An IRB is an independent committee of physicians, community advocates and others that ensures a clinical trial is ethical and the rights of study participants are protected.

NEW DRUG APPLICATION (NDA) / MARKETING AUTHORIZATION APPLICATION (MAA)

NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such application document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities ion other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes between six months and two years.[10]

THE RISKS OF PARTICIPATING IN CLINICAL TRIALS[15]

1. There may be unpleasant side effects or outcomes, may last only a short time, or they may affect
2. You for the rest of your life.
3. decide to participate is because you hope to try a treatment that is not yet publicly available, you usually have, at best, a 50% chance of receiving that treatment.
4. The treatment being studied may have no positive effect, either because you aren't really receiving the treatment being studied and the treatment isn't appropriate to help you.
5. The long time and attention required of participants involved. It may require hours of testing, miles of travel, hospital stays or complicated dosing.
6. New doesn't always mean better.

7. Clinical research creates employment for site personnel, study monitors, and ancillary services, with an economic impact on the whole community.
8. The drugs and protocols offered during clinical trials are often provided at no cost to participants. Patients who have trouble affording the drugs or treatment they need may consider enrolling in a clinical trial in order to access the protocols that may help them.
9. Some patients have no alternatives for treatment and permanent debilitation or deaths are imminent. In such cases, participation in a clinical trial may give them hope or possibilities that do not exist otherwise.
10. Many drugs, devices and therapies have previously been tested on white men, and found safe and useful. Fewer trials have been designed and run for women, minorities, or children. Participation in a trial that broadens the use of a good drug for one of these lesstested groups is useful to humanity.

PRESENT STATUS OF CLINICAL TRIALS

Today, India has the largest pool of patients suffering from cancer, diabetes and other maladies: the global hub of outsourcing of clinical trials. A non-profit organization, Clinical Data Interchange Standards Consortium (CDISC), USA, committed to the development of clinical research organizations' standards the world over, looking at setting up in India. In India, contract research was valued at $100–120 million and growing at a rate of 20–25% each year in 2005.

(1) Status of CROs and multinationals in India[12]

In India, Around 25 contract research Organisations(CROs) and almost all multinational pharmaceuticals companies(like Pfizer, Eli Lilly, GlaxoSmithKline, SanofiAventis and Roche have already started Phase-I and II trials in India.) have started full-fledged clinical trials, since last 3 years. Many independent CROs (Mumbaibased CRO, Metropolis Health Services,) conduct clinical trials in various therapeutic segments (like antiinflammatory, allergic disorders, cardiovascular, central nervous system and oncology) and offer a spectrum of clinical development services (Table-1). The Gujarat government is also taking steps to promote clinical trials in the state. At the Vibrant Gujarat Investor's meet last December, it proposed to invest Rs 30 crore in setting up an animal testing lab for toxicology. The state has also proposed to set up a USFDA approved kilo quantity manufacturing plant at an investment of Rs 20 crore for manufacturing chemical solutions for clinical trials.

(2) Training programme in clinical trials[12]

At present there are mainly three institutes offering courses related to clinical research and data management (Table-2).

(3) Survey by doctor NDTV[19]

Recently Doctor NDTV conducted a survey on whether the government of India should have made it easier for foreign pharmaceutical companies to conduct trials of new drugs in India (Table-3)

Table 1: Clinical Development Services

S.no.	CONTRACT RESEARCH ORGANISATIONS (CROS)	FUNCTIONS
1	Ahmadabad-based CRO, Synchron Research	Rapid pharmacokinetic (PK) analysis, qualitative and quantitative medical imaging, silico drug metabolism studies and conducted over 200 bioavailability studies.

2	Bangalore-based Lotus Labs	Completed more than 450 bio-studies and conducting several phase III trials.
3	Mumbai-based ClinInvest Research	Focuses on all phases of clinical trials mainly in the areas of oncology, neuropsychiatry
4	Clingene International, a Biocon subsidiary	Concentrates on bio-analytical, bio-statistical and data management services to its clients.
5	Quintiles Spectral (India), subsidiary of Quintiles Transnational	Conducts studies in oncology, psychiatry, neurology and anti-infective. The company has conducted over 90 clinical studies on 13,000 patientsv
6	Pharma giant Pfizer	Conduct clinical trials on 300 patients for a new malaria drug that combines chloroquine and azithromycin, an antibiotic. It is also carrying out clinical trials for drugs to treat osteoporosis, breast cancer and schizophrenia. Pfizer is conducting around 20 clinical trials. It has independently conducted more than 40 good clinical practices (GCP) workshops and has trained more than 2000 investigators.
7	Eli Lilly	Has over 17 large and small clinical research projects running in 40 hospitals across India. The company has already held clinical trials involving more than 600 patients for human insulin and insulin lispro. It is also conducting trials on oncology besides developing a new molecule for lung cancer.
8	Glaxo- SmithKline (GSK) Plc	Has started seven simultaneous clinical trials of its vaccine and pharma molecules
9	Aventis Company sources	It will conduct clinical trials in the Cardiovascular, Diabetes and oncology segments and is presently setting up trial infrastructure in India
10	Roche, the Swiss pharma major	Has set up clinical trial sites in India as part of its global trials of a new drug for a particular variant of lung and blood cancer
11	State pharma industry, Gujarat,	Offers expertise in conducting phase I to phase IV trials in bio-equivalence and bioavailability studies and data management for almost all therapeutic drugs.

Table 2: Institutes offering courses related to clinical research and data management

S.no.	INSTITUTES	PROPERTIES
1	Academia of Clinical Excellence	ACE was set up in October 2002 at the Bombay College of Pharmacy through the initiative and financial contribution of Pfizer India Ltd. The

	(ACE)	academy was opened up for industry collaboration and Suven Life Sciences Ltd. of Hyderabad has become a partner of ACE by making a financial contribution. The academy is conceived, as a one-stop-shop for all training needs of all clinical research professionals in the country
2	Institute of Clinical Research India (ICRI)	The ICRI commenced its operation in 2004 with its campuses located at Dehradun in Uttaranchal and in Mumbai.
3	**Bioinformatics Institute of India (BII)**	**Bioinformatics Institute of India (BII) has been set up at Noida for the promotion, growth and prosperity of Bioinformatics and related sciences in India and abroad. The academic programs the institute offers in pharmacology include pharma regulatory affairs, pharma business management, pharmaco-informatics, drug designing and patenting, contract research and clinical trials etc.**

Table 3: Percentage Thinking of People about conduct of Clinical Trial

PERCENTAGE	THINKING OF PEOPLE
87%	Compensation should be provided to people who suffered adverse effects during these trials.
65%	Drugs relevant to Indian diseases would be studied
49%	It would be unethical to conduct such trials here.
65%	These trials could not be conducted without giving incentives to doctors and patients. It was generally felt that these trials would help improve the healthcare facilities in this country.

OPPORTUNITIES FOR CLINICAL TRIALS IN INDIA

1. High patient enrolment rate

India has a huge population base of more than 1 billion, Who are genetically, culturally and socio-economically diverse. Indians represent about 15% of the global population. The patient enrolment rate 0.3 patients per month in US as against 3 patients in India and it has a vast pool of heterogeneous population and treatment native patients with a high incidence of diseases common to both the developed and developing world, as a result, recruitment of patients is generally five to ten times faster in India than it is in the United States[11,20]

2. Spectrum of diseases

It is home to a wide variety of diseases ranging From tropical infections to degenerative diseases (according to IGATE Clinical Research International, India has 40 million asthmatic patients, 34 million diabetic patients, 8–10 million people HIV positive, 8 million epileptic patients, and 3 million cancer patients, So India offers the opportunity to pharma companies to develop drugs for a wide spectrum of diseases, including multidrug-resistant pneumonia, hepatitis B, diabetes, and cancers. Table-4 and Table-5 shows the number of clinical trials in the various fields due to a spectrum of diseases and the status of trial in India in different field respectively[21].

Table 4: The numbers of trials going on in the various fields are as follows

CATEGORIES	NUMBER OF TRIALS (Data till January 2010)
NERVOUS	212
BLOOD DISEASE	208
RESPIRATORY	159
DIGESTIVE SYSTEM	141
IMMUNE	125
HEART DISEASE	121
ONCOLOGY	80
ENT	64
DIABETIC	58
BEHAVIORS AND MENTA	40
URINARY TRACT DISEASE	27
VIRAL DISEASE	20
TOTAL	1255

Table 5: The status of trial in India in different field

CATEGORIES	NUMBER OF TRIALS)
COMPLETED	441
COMPLETED (HAS RESULTS)	11
NOT YET RECRUITING	37
RECRUITING	438
ACTIVE, NOT RECRUITING	231
TERMINATED	71
ENROLLING BY INVITATION	15
SUSPENDED	8
WITHDRAWN	3

3. Human resources and technical skills

Clinical trial execution is a labour-intensive and processdriven activity and English-speaking, motivated work forces are well suited to meet the needs of the clinical development sector. In India, the huge and skilled manpower available could revolutionize the clinical trial field. India has 3–4 million scientists, 500 investigators, 572,000 doctors, 43,322 hospitals and dispensaries and about 8.7 lakh beds including both private and public. Many of these scientists are English-speaking and have an excellent technical skill[16,22]

4. Regulatory compliance

In India, responsible for regulatory approvals of clinical trials is Drugs Controller General of India (DCGI) and for advice The DCGI's office depends on external experts and other government agencies. For the export of blood samples to foreign central laboratories, additional permissions are required. All this usually takes about 3 months in India. To scrutinize and approve the clinical trial before the study begins and also to conduct periodic reviews of the progress of the trial, IEC's is mainly responsible for

additional approval. Bioequivalence studies can be approved by the local ethics committee in India for more than 4 years do not need to go to the DCGI. In January 2005, India adopted a new rule that will allow pharmaceutical companies to begin phase II and Phase III trials concurrently with trials of the same phase conducted abroad, thereby reducing clinical development time. The reporting of adverse events from clinical trials has become clearer and unambiguous after the latest amendment (20th January 2005) to the Schedule Y of Drugs and Cosmetic Act 1945 and the implementation of the GATT has opened a new opportunities for India to concentrate on the clinical trial market. India has implemented product patents since 2005, which will encourage multinational companies to import technology into India to develop new products. These developments will open up increased opportunities for the clinical trials of biotech, medicinal, and indigenous like Ayurvedic products. India represents an embracing international IP protection legislation, with important consequences to both its local industry as well as its positioning in the global pharmaceutical industry. This legislation enabled the growth of a domestic generic pharmaceutical industry. India is committed to recognize and enforce product patents in all fields of technology including pharmaceuticals after signatory to the WTO Trade Related Intellectual Property Rights (TRIPS) agreement in 1995 [23,24,16]

5. ICH-GCP Compliance

The Drug Control General India (DCGI) has implemented conformity to ICH (High level of International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use) GCP (Good Clinical Practice)/ GLP (good laboratory practice) guidelines. Generally, most competent authorities (CAs), including the FDA (US Food and Drug Administration), will find the standards of Indian clinical trials acceptable[24] .

6. Cost advantage

The amount of analytical work completed in India, most sponsors will enjoy a 30–50% cost advantage over a similar trial in the US or Europe, depending on the number of patients and investigators. Investigator and site fees are approximately one-half of those in the United States. Further costs to the sponsor for providing trial-related medication, investigations, and hospitalization could be as low as 30% of those in America. Because of the concentration of sites in the major cities and comparatively less costly fares and tariffs that's why Domestic travel costs for monitoring sites are lower and Support services such as printing, translation, and local courier fees are also less expensive. A 2004 study by Rabo India Finance found that in India, phase I trials cost less than half of similar trials in the United States; Phase II and III trials cost less than 60% of their American equivalents[24,14,11].

7. Reliable data quality

Indian research/data generation capabilities are of international standards and Indian data is accepted by all major medical conferences and journals because of its reliable data quality that's why Clinical trial data has been accepted by international regulatory authorities for pivotal studies. Generally, sponsors have been satisfied with the quality of clinical data provided by clinical trial sites in India in spite of the relatively nascent clinical development environments[21,14] .

8. Clinical data management

Access to a large resource pool with IT and business process skills in a low-cost labour environment provide the basis for cost-effective data management services by large numbers of IT-literate biomedical graduates. India ideally positioned for the widespread adoption of EDC technologies to prevalent high-speed Internet connectivity and absence of the biases stemming from the use of legacy systems[14].

9. Infrastructure

At present, India can offer a considerably good and suitable infrastructure for conducting clinical trials. For example, a specialty oncology centre (Tata Memorial Hospital in Mumbai) is very well suited to participate in global clinical development. The centre is equipped with state-of-the-art facilities, including spiral CT scanner, gamma cameras, linear accelerator, and bone marrow transplant facilities. Each year 25,000 cancer patients visit this hospital, 1000 patients attend out-patient clinics every day, 441 inpatient beds, 10,000 major operations are performed and about 5000 radiotherapy and chemotherapy treatments are delivered each year. A Clinical Research Secretariat, Scientific Review Committee, and Ethics Committee have been established to coordinate the ever increasing interest to international and domestic sponsors[14] .

10. Economic environment

The present day economic environment in India is quite favourable for foreign direct investments (over US$2 billion a year). According to the recent reports, clinical research outsourcing is, perhaps, seeing the fastest growth for example, Pfizer had announced a doubling of its R&D spend in India, bringing the cumulative investment on clinical research in India to around $13 million and Novartis, Astra Zeneca, Eli Lilly and GSK, were also committed to making India a destination for their clinical research activities. India 20-fold increased the bio statistical and clinical trial logistics services[25]

11. Manufacturing

According to Kotak Securities, as far as manufacturing was concerned, things looked pretty good for India. The country ranked second only to the US in terms of the annual number of global Drug Master Filings (DMFs)[25] .

12. Speed

For almost all drug companies, speed is of essence. To develop a new drug, it takes 10-15 Years and the 20-yearclock on a drug patent starts ticking when a new compound is discovered. The faster a drug is developed, the longer its patent protects it. Conducting Phase III trials can save companies between two and five years in getting their drugs to market in India.

13. Favorable environment

India offers to the established pharma and biotech industries. These include contract research, R&D alliances, clinical trials, R&D for neglected diseases, inlicensing of preclinical as well as early clinical drug candidates, IT applications and data management and herbal heritage and solve the serious problems are Increasing the expenditure on drug development, lengthening time lines for clinical trials, patent regime, changing regulations in pharmaceutical research for development of new drugs.

14. Higher growth in Asia pacific

Pharmaceutical R&D expenditure in Asia is growing faster than in US and Europe. The Importance of Asia-Pacific market is growing, as pharmaceutical and biotechnology companies continue to explore new geographic opportunities to expand their pipelines of products and create business efficiencies. According to the various estimates, the global contract research market is estimated at US$10 billion in 2004 and about 40 to 50% in 2010

15. Alliances

India established its strength in developing, manufacturing and marketing generic products for global market. This success is attributed primarily to its strength in the process chemistry, formulation development and manufacturing areas. A number of contract research organisations, pharma companies from developed countries forging R&D alliances with Indian companies because they offer quality and

cost-effective services in medicinal chemistry, formulation development, and toxicology areas. These alliances are giving preclinical candidates or clinical candidates with proof of concept in humans.

16. Established pharma companies

Indian companies have already proven its capabilities in discovering and developing drug candidate molecules and they are highly capable in research and development particularly in drug discovery. There are opportunities to apply modern science to elucidate molecular mechanism of action and to identify active ingredients of those medicines; their molecular mechanism of action and identity of active ingredient(s) may not be known of traditional medicines. The process of reverse pharmacology can be applied to discover new drug candidate molecules from these traditional medicines. To elucidate molecular mechanism of action and to identify active ingredients of these medicines, to apply modern science. Table-6 shows Key pharma companies in clinical Research in India[26] .

Table 6: Key pharma companies in clinical Research in India

S.No	. NAME OF COMPANY	LOCATION IN INDIA
1.	Abbott	Mumbai
2.	Altana (Zydus	Mumbai
3.	Astra Zeneca Foundation	Bangalore
4.	Astra Zeneca Pharma India Ltd	Bangalore
5.	Aventis Pasteu	Delhi
6.	Bayer	Mumbai
7.	BD Biosciences	Delhi
8.	Bharat Biotech	Hyderabad
9.	Bharat Serum	Mumbai
10.	Biocon	Bangalore
11.	BMS	Mumbai
12.	Boston Scientific	Delhi
13.	Cadila Pharmaceuticals	Ahmadabad
14.	Chiron	Mumbai
15.	Cipla	Mumbai
16.	Cordi Baxter	Delhi
17.	Eisai Pharmaceuticals	Mumbai
18.	Eli Lilly	Delhi
19.	Emcure	Pune
20.	Fulford India	Mumbai
21.	GE	Delhi
22.	Glenmark Pharmaceuticals Ltd.	Mumbai
23.	Himalaya Drugs	Bangalore
24.	Hospira	Delhi
25.	Ranbaxy Research Laboratories	Delhi
26.	Indus Bio therapeutics	Ahmadabad
27.	Intas Pharmaceuticals Ltd	Ahmadabad

28.	IPCA	Mumbai
29.	LG Life Sciences	Delhi
30.	Lundbeck	Bangalore
31.	Lupin Ltd	Pune
32.	Maceuticals Ltd	Mumbai
33.	Merck	Delhi
34.	Novartis International Clinical Development Center	Mumbai
35.	Novartis Pharma	Mumbai
36.	Nicholas Piramal	Mumbai
37.	Novo Nordisk	Bangalore
38.	Nsenn Cilag	Mumbai
39.	Panacea Biotech	Delhi
40.	Pfizer Biometrics	Mumbai
41.	Pfizer Ltd	Mumbai
42.	**Ranbaxy Research Laboratories**	**Gurgaon**
43.	Roche	Mumbai
44.	Sandoz	Mumbai
45.	Sanofi Aventis Syntho Lab	Mumbai
46.	Serum Institute of India	Pune
47.	Shantha Biotechnics Pvt. Ltd.	Hyderabad
48.	Shreya Biotech	Pune
49.	Sun Pharm	Mumbai
50.	Torrent Pharmaceutical Ltd	Gandhi nagar
51.	Torrent	Ahmadabad
52.	USV Ltd	Mumbai
53.	Wockhardt	Mumbai
54.	Wyeth	Mumbai
55.	Zydus Cadilla	Ahmadabad

ISSUES AND CHALLENGES AND ITS SOLUTIONS WHEN CONDUCTING CLINICAL TRIALS IN INDIA / OPERATIONAL DEFICIENCIES

The increase in clinical trials is fuelled by the recent push for global commerce. Regulatory uncertainties about involvement of multiple agencies for approval of biotech products, for processing import/export licenses, time to approval and several other factors are hurdles in planning a clinical trial. A large majority of potential investigators lack knowledge of regulations, ethics and GCP, and skills for clinical trial management, lack of uniformity the quality of global trials and academic clinical research, inadequate permanent research staff and lack of adequate infrastructure for communication, drug/sample storage, archival. Perhaps the most important challenge is that of designing elegant clinical trials that will test concepts rather than simply compare products. Some of the major operational deficiencies are as follow

1. **Training for clinical trials**

In India, There is a shortage of trained manpower because in Most medical schools lack a formal course in training for clinical research, and investigators have relied on mentors to learn how to conduct clinical trials. India has only about 500 – 1000 investigators as compared to United States that has 50,000 investigators. With the projections made for the industry in 2010, India would need about six times its present number of investigators.

2. **Government policies and weak patent law**

Regulatory approvals in India can take three months or more, compared to 30 days in the US. In India, opportunities will become limited unless there is a very strong patent law and mechanism to enforce it. Drafting patent laws with the help of industry experts and its implementation is highly essential.

3. **Bureaucratic hurdle**

Inadequate funding and training of regulatory personnel, that's why the time for getting approvals still extremely slow in India. Severely understaffed and lacks the expertise in the office of the Drug Controller General of India (DCGI), to evaluate protocols. As a result, persistent follow-up, including personal visits to the DCGI, is required in order to push an application for a trial forward and DCGI routinely approves poorly designed trials. After approvals are granted, DCGI lacks an enforcement mechanism to ensure compliance with its guidelines. Some Indian drug companies have conducted trials that would not have been approved in the U.S. because Ethics committees are few in number and relatively inexperienced. To solve above problems, the industry could attempt to working closely with the regulator's office for organizing workshops and seminars that highlight the importance of restructuring the regulatory activities for clinical trials. Provide a fast track approval program to initiate clinical programs in India by the respective regulators, starting from registration, to ethical committee approvals to importing supplies .

4. **Lack of ICH-GCP compliant sites**

ICH-GCP norms are one of the main challenges the industry is facing to attract large number of international clinical trials into India. Non-availability of sufficient number of hospital sites meeting ICH-GCP norms for example Among some 14,000 general hospitals, no more than 150 have the adequate infrastructure to conduct trials, and there are fewer than a dozen pathology laboratories that meet the criteria for compliance with good laboratory practice

5. **Declining research productivity**

The research productivity is continuously declining, when discovery cost of a new molecular entity has increased, for example In year 2005, only 28 new active substances were launched globally

6. **Lack of data protection**

Regarding data protection, since the data become valuable from the viewpoint of the originator and need to be protected as mandated in TRIPS when they are collected through various phases of clinical evaluation. India should allow at least 5 years data protection from the date of marketing approval .

7. **Mushrooming of non-accredited CROS**

A number of new CROs are mushrooming without adequate quality accreditation. An accident from such poor quality CRO's could bring a bad name for the whole industry. The Government should stop non-accredited CROs from functioning .

8. **Lack of awareness and education amongst patients**

One main challenge related to patient compliance is education. Care must be taken to ensure that they are well educated and compliance issues are well understood because as many patients in the trial

scenario are from rural and semi-urban areas. To avoid these problems, Efforts are needed to create a more widespread awareness of clinical research amongst the general public, patients and medical community to build confidence[27] .

9. IP Protection

International companies seek to resolve protection of intellectual property rights in accordance with international law in India. They want that the Indian legal system and Government will fulfil its promise under the TRIPS agreement to protect intellectual property. The Government and scientific research councils to ensure that India will respect and uphold intellectual property rights in accordance with international standards .

10. Ethical Issues

The ethics in clinical trial conduct in a country with little commercial value for the trial sponsor. India an unattractive market for expensive drugs due to Low health insurance coverage, limited consumer purchasing power and controlled drug-pricing make. India will be unable to access the product on successful completion of the trial because institutional review boards have not yet formulated standard operating procedures and lack the expertise with which to evaluate protocols. To solve these problems can easily stray into making paternalistic decisions that do not respect the ability of competent people in the developing world to make decisions themselves[16].

CONCLUSION

In India, in spite of all the present pitfalls, the country is certainly gearing up to attract more and more researchers from around the world to conduct their clinical trial studies. Laws are being amended to facilitate the entry of global clinical trials and the regulatory system is being polished. The current situation improves by massive and concerted efforts are on to train research professionals and increase the Base of investigators and supporting staff. India is already off the starting blocks and gearing up for an inundation of clinical research trials and this will ensure the timely conduct and completion of the clinical trials and at the same time generate high quality data for international submission. India is poised to offer the global pharmaceutical industry high quality and costeffective contract services(a proven track record for some of these services and an enthusiasm to expand into services at the higher end of the value chain.) to support drug discovery, clinical trial conduct, data managementand manufacturing. An increasing number of international pharmaceutical companies will seek to establish outsourcing arrangements in variety of forms after uphold international intellectual property laws with high ethical standards. The primary driver for outsourcing will change from cost saving to the quest for high quality and speed as the sector matures. India’s more ambitious pharmaceutical companies to fulfill their aspirations of becoming players in global pharmaceutical industry through a thriving contract Skills developed by Indian workforce.A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial are conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III and IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamic profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.

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