CHAPTER III
CLINICAL TRIALS
CHAPTER III

THE CLINICAL TRIALS

“Sure, science involves trial and error. Scientists refine theories each day. But as they do, they help us grasp more clearly the wonders of the World and of the Universe”.

Tony Snow

The history of drug discovery is often fascinating. Many of the drugs that are used today have been discovered by chance or by mere serendipity. India’s history of drug discovery and proficiency in medical research can be framed back to two ancient texts, Charaka Samhita (Text book of Medicine) and Sushruta Samhita (Text book of Surgery), compiled as early as 200 BC and 200 AD respectively. A lot has changed in the Clinical Trial Scenario since then.

Research is an important part of modern medicine and use of human beings as experimental subjects have a long history. Medicine has become increasingly sophisticated in the past 50 years and this increasingly scientific nature has heralded the widespread development of organized experimentation, generally by way of clinical trials. Clinical Trials are one of the most valuable sources of evidence about safety and efficacy of health interventions. It is only in the past few decades that the Clinical Trials has emerged as a preferred method in the evaluation of medical interventions. A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention. It helps to affirm whether the intervention has the postulated effect.

---

1 The word organized is important here as it is the preparation of, adherence to planned protocol that distinguishes true research from experimentation. S.A.M. McLean and J.K Mason, LEGAL AND ETHICAL ASPECTS OF HEALTH CARE, (1st edn., 2003), available at http://www.law.ed.ac.uk/people/ikenyonmason (Last visited on May 7, 2014)

2 A. Pandey, CLINICAL TRIALS REGISTRY – INDIA, National Institute of Medical Sciences, Indian Council of Medical Research, New Delhi.
3.1 HISTORY OF CLINICAL TRIALS

Probably the first record of a clinical trial is in the Bible, in the Book of Daniel\(^3\) versus twelve through fifteen. The King Nebuchadnezzar II, ordered that several youths be brought to his palace, to be fed & taught just like his own children. This included Daniel and he proposed that they should be allowed to eat ‘pulses’ and to drink water instead of wine and meat. It was found that those who consumed bread and water were better nourished than those fed on wine and meat.

The first clinical Trial of therapeutic intervention is attributed to Ambroise Parè (1510-1590). He used egg yolk and turpentine to heal a wound. It was he who identified that turpentine was more efficient at healing the wounds of soldiers, than the state of the art remedy, boiling oil.

In the 18th century, clinical trial began to be used routinely to test new medical treatments. The history of International Clinical Research dates back to 1747 with James Lind proving the effectiveness of lemon juice in preventing scurvy in a controlled comparative clinical trial. He, in his classical study on board the “Salisbury” evaluated six treatments ranging from vinegar to cider for Scurvy in 12 sailors in the British Navy. One of the 2 who were given oranges and lemons recovered quickly and were fit for duty in just 6 days. The second sailor was the best recovered of the others and was assigned the role of nurse for the remaining\(^4\). **International Clinical Trials Day** is thus celebrated every year on **21st May** in memory of James Lind.\(^5\)

Often, physicians would first test potential remedies on themselves or on relatives. In 1789, the English physician Edward Jenner developed smallpox

\(^3\) G.H. Mills and Mercs, *Comparing Emerging Ethical Issues And Legal Differences Impacting On European Clinical Trials*, available at http://www.powershow.com/view/1/50a58-ZDc1Z/Comparingemerging_ethical_issues_and_legal_differences_impacting_on European_clinical_trials_powerpoint_ppt_presentation (Last visited on December 12, 2014)


vaccine. He first tried inoculating his own son. His son caught smallpox but this did not stop Jenner from inoculating his neighbor’s child several months later. This time the child did not get the disease. The clinical trials become larger and more organized during the 19th century.

In Hungary, Ignaz Semmelweis (1818-1865) observed that the mortality rate of mothers from childbed fever was far lower among patients treated by midwives rather than doctors. By starting hand washing policy for doctors and medical students, he could dramatically reduce the death rate of new mothers. Further in a controlled trial using a chloride of lime solution, mortality rate fell to about 2%. This was almost same as the women delivered by midwives.

In France, Louis Pasteur (1822-1895) spent many years developing an antidote for rabies. He was aware of the ethical implications of his work. He tried out his medicine on nine years old boy, who had been bitten by a rabid dog, much after his two colleagues assured him that the child would certainly die without treatment. The boy survived to everyone’s astonishment.

Frederick Akbar Mahomed (1884) who worked at Guy’s Hospital in London, made substantial contributions to the process of clinical trial. He conducted detailed clinical studies and separated chronic nephritis with secondary hypertension from what we now term as essential hypertension. It was he who founded the ‘collective investigation record’ for the British Medical Association. This organization collected data from physicians practicing outside hospital setting and was the precursor of modern collaborative clinical trials.Dr. Carlos Finlay and Dr. Walter Reed conducted clinical trials to demonstrate the link between Aedes aegypti mosquito and yellow fever.

There has been enormous progress in medicine during the 19th century. Placebos⁶ were first used in the 1863. Randomization of clinical trials started

---

⁶ Placebo is a harmless substance given as medicine. In experimental research it is generally an inert substance, identical in appearance with the material being tested.
later in 1923. But, it was only in the past few decades that clinical trial has emerged as the preferred method in the evaluation of medical interventions.

Clinical trials hold enormous potential for benefiting the patients, improving therapeutic regimen and ensuring advancement in medical practice that is evidence based.⁷ Clinical trial 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 main stay for bringing newer or better drugs to market. Much of what is known today about any specific products and treatments has come from clinical trials that are designed to answer important scientific and healthcare questions.⁸

These trials are carried out with human volunteers to answer specific questions concerning the effectiveness of a drug, device, treatment or diagnostic method, are designed to advance scientific knowledge and promote discoveries to treat and cure illness and disease, increase longevity and quality of life for countless people⁹.

3.2 OVERVIEW OF CLINICAL TRIALS

Biomedical research can further be sub classified as basic/preclinical research and clinical research. Preclinical biomedical research is of paramount importance to expand the knowledge of basic biological mechanisms in the field of anatomy, biochemistry, microbiology, pharmacology etc. Preclinical research can contribute immensely in furtherance of discovery of new medical treatments.

Clinical research ranges from clinical laboratory or investigational studies to testing of new clinical procedures, new clinical diagnostic tools and new medicinal products in human beings. Clinical trials are the mandatory ‘bridge’ between pre-clinical discoveries of new medicinal products and their general

⁷ A. Pandey et al., Clinical Registration Gains Momentum In India, 130(1) INDIAN JOURNAL OF MEDICAL RESEARCH, 85-86, (July 2009).
⁸ WHO, Hand Book For Good Clinical Research Practice.
uses. It forms the basis for evidence based medicine. On an average, only one out of fourteen new drugs that enter clinical testing programs is eventually introduced for clinical use.\textsuperscript{10} If one examines the reasons for this high dropout rate, one would end up with the unforeseen side effects or insufficient treatment effects.

Thus the overall objective in conducting clinical trials on a medicinal product is to collect information about the safety and efficacy of the product in human participant i.e.; to take the test article from the pre clinical discovery and testing to usage. Thus these medicinal products are thoroughly evaluated for safe medical practice. Hence it provides an unbiased evaluation of the merits of using one or more treatment options for a given disease or condition of interest.

\textbf{3.3 DEFINITION – CLINICAL TRIAL}

A Clinical Trial is any investigation in human subjects intended to discover or verify the clinical pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.\textsuperscript{11,12}

A clinical trial is defined as a prospective study comparing the effect and value of an intervention against a control in human beings.\textsuperscript{13} A clinical trial is prospective in nature i.e., the participants are followed up, forward in time.

A clinical trial evaluates the effect of a new drug or device or procedure on human volunteers\textsuperscript{14}. These trials can be used to evaluate the safety of a new

\textsuperscript{11} EUROPEAN MEDICINES AGENCY - Note for Guidance on Good Clinical Practice.
\textsuperscript{12} Id.
\textsuperscript{13} L.M. Friedman et al ,supra note 4.
drug in healthy human volunteers or to access treatment benefits in patients with a specific disease.

In other words, clinical trial is an experiment in human beings to determine safety, efficacy and activity of a drug and intervention or a treatment for a given condition or disease.\textsuperscript{15} The primary aim of most clinical trial is to provide an unbiased evaluation of the merits of using one or more treatment options for a given disease or condition of interest.

Clinical Trials may be classified according to their purpose or by the way the researchers behave. Thus clinical trials wherein the investigators do not actively intervene the study but manage it only by observing the subjects and measuring their outcome is termed \textit{observational study}. In observational studies, the investigators only observe associations (correlations) between the treatments experienced by participants and their health status or disease.

Yet another type is termed \textit{interventional study}. Here, the investigator actively intervene the study by giving the research subject a particular medicine or intervention. This could be prophylactic, diagnostic or therapeutic agents, or devices, regimens, procedures etc. Hence they compare the treated subjects to subjects who receive no treatment or standard treatment. This further enables the researches to measure how the subject’s health changes. An ideal clinical trial is one that is randomized and double blinded.

The US National Institutes of Health (NIH) organizes trials into six different types by way of their purpose.\textsuperscript{16,17}

\textsuperscript{14}D.Wang and A.Bakhai, CLINICAL TRIALS: A PRACTICAL GUIDE TO DESIGN, ANALYSIS AND REPORTING, REMEDIICA, Medical Education and Publishing (1\textsuperscript{st} edn., 2006)
\textsuperscript{15} PWA Advisory Group, Clinical Trials, available at www.aids2006.org/PAG/material 10 (Last visited on September 9, 2014)
\textsuperscript{16}www.nihclinicaltrial.gov-glossary of clinical trial terms (Last visited on August 27, 2014)
\textsuperscript{17}www.eurodis.org, clinical trial glossary (Last visited on August 27, 2014)
(a) **Prevention Trials:**

Prevention Trials refers to trials to find 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 life style changes.

(b) **Screening Trials:**

Screening Trials refers to trials which test the best way to detect certain diseases or health conditions.

(c) **Diagnostic Trials:**

These trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.

(d) **Treatment Trials:**

Treatment Trials are trials that test new treatments, new combinations of drugs or new approaches to surgery or radiation therapy.

(e) **Quality of life Trials:**

This explores ways to improve comfort and the quality of life for individuals with a chronic illness.

(f) **Compassionate use Trials or Expanded Access:**

These provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy exists or a patient that has already attempted and faced all other standard treatments and whose health is so poor that he does not qualify for participation in randomized clinical trials. Usually, case by case approval must be granted by both United States Food and Drug Administration (USFDA) and the pharmaceuticals company for such exceptions.
3.4 PHASES OF CLINICAL TRIALS

Clinical trials involving new drugs are commonly classified into four phases. This trial phase classification proposed by International Council for Harmonization (ICH) in the ICH E8 Guide is based on the objective of the trials and not just a sequential numbers ranging from 1 to IV i.e., safety trials -/human clinical pharmacology trials, therapeutic exploratory trials, therapeutic confirmatory trials, therapeutic use post marketing surveillance trials\(^{18}\).

Phase 1 to IV classification is still the only one generally reorganized and adopted on a global basis. These four phases do not necessarily have to follow a sequence and they are not mandatory for inclusion in a medicinal product development plan. Also sometimes the phases of development provide an inadequate basis for the classification of clinical trials because one trial may combine several phases with different fundamental objectives. Thus, due to their multi objective characteristics, trials are often labeled not just as phase 1 but alternatively as early phase 1 (1A) or late phase 1 (1B) or phase 1/11 or phase 11/III. Human pharmacology study cannot always be restricted to phase 1 trials, it may be an objective even after the drug has reached the market. The same applies to exploratory and confirmatory trials.

The total number of trials, phase 1 to IV, per test article varies vastly from compound to compound. A realistic average estimate is 20 phase 1 trials, four phase II trials, three phase III trials and also two phase IV trials making a total of 29 individual trials for one test article. The average numbers of participants included in all trials for one and the same test article is 2000\(^{19}\).

Before pharmaceutical companies start clinical trials on a drug as medicinal product, they conduct extensive pre clinical studies. Pre clinical studies involve in vitro (test-tube) or in vivo (animal or cell culture) experiments using wide ranging

\(^{18}\) J.P.E.Karberg, supra note 21.

\(^{19}\) Glaxo SmithKline Clinical trial database, available at dij.sagepub.com/content/42/3/247.short (Last visited on December 12, 2014).
doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Absorption, distribution, metabolism and elimination are studied to determine plasma concentrations, biological half life and volume of distribution. Data from this phase of testing are collected to establish estimated dosages for human to determine a drug’s basic toxicity and to establish that there will not be unreasonable risk to humans in further testing. After meeting all these objectives, the agencies sponsoring the drug may apply for a ‘Notice of claimed Investigational exemption for a New Drug’, also known as Investigational New Drug (IND) form. This form registers the new drug and establishes intent to study the drug in clinical trials. Thus such tests assist the pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

3.4.1 Phase 0 Trials.

‘Phase 0’ is a recent designation for exploratory first in human trials conducted in accordance with the US FDA 2006 guidance on exploratory IND Studies. Phase 0 studies are also known as human micro dosing studies. These are designed to speed up the development of promising drugs by establishing very early, whether the drug or agent behaves in human subjects as was expected from pre-clinical studies.

Distinctive feature of phase 0 trials includes the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15). Preliminary data on pharmacokinetics (how the body process the drug) and pharmacodynamics (how the drug works in the body) is gathered. The scientific rationale for phase 0 trials is to find out whether a new drug is capable of modulating its intended target in humans, identifying its distribution in the body or describing the metabolism of a drug. This knowledge is often critical in drug development and may avoid larger Phase 1 and II trials for drugs shown to have unfavorable pharmacologic properties. Thus the concept of Phase 0 trials is an interim step between pre clinical researches and phase 1 studies.
A Phase 0 trial has no therapeutic intent; the objective is human pharmacology rather than identifying any toxic effects. Also, the results of phase 0 trials do not always predict the human pharmacology for the intended dosage. This may be the main reason why micro dosing has not become very popular.

Micro dosing is said to reduce overall drug development cost since the microgram amount of compounds required do not need to be scaled up to an expensive and time consuming manufacturing level. Also, fewer animal studies are needed to support micro dosing studies, compared to phase 1 trial. This attributes to ethical and financial advantages.

Phase 0 trials should be reviewed by experts in clinical pharmacology and toxicology. They should be conducted only at dedicated and experienced research units. These studies give no data on safety efficacy, since the dose is too low to cause any therapeutic effect. However, these studies are carried out to rank drug candidates, so that decision on which has the best pharmacokinetic parameter in human can be taken; which enables further development of the same. This enable go/no go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

The ICH, in June 2009 released a guideline - M3 (R2) - that has also been accepted by the European Union. It includes some guidance on micro dosing trials. This spells out that the aim of micro dosing is to collect human data early in development as well as information about the characteristics of the candidate compound. The dosage should have limited human exposure namely less than 150 mg/less than 1/100th of the pharmacological active dose.

**3.4.2 HUMAN PHARMACOLOGY / PHASE 1 CLINICAL TRIALS:**

These are initial studies to determine the metabolism and pharmacological action of drugs in humans, the side effects associated with increasing doses and to gain early evidence of effectiveness, may include healthy participants and/or patients. Phase 1 clinical trials test a new bio medical intervention in a small group of
people (eg: 20-80)\textsuperscript{20}. This represents the first stage of testing in human participants. The first step in developing a drug/biologic is to understand how well it can be tolerated in a small number of individuals. Certain Phase 1 trials are associated with high risk of harm, compared to others, especially those involving first to man trials and dose escalating trials.

Phase 1 trials are designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, pharmacodynamics of the drug. These trials also include dose ranging i.e in other words dose escalation, which enables to find the appropriate dose for the therapeutic use. The primary aim of Phase I trial is to determine how well the investigational drug can be tolerated in humans. & to find the maximum tolerated dose. The side effects in the participants cannot be known completely ahead of time, even though extensive studies in laboratory or animals have been carried out. Hence, phase 1 studies may involve significant risks.

Thus these trials are often conducted in inpatient clinics where the services of qualified staff are available round the clock, usually until several half lives of the drug have passed. The phase 1 trials may be Single Ascending Dose Studies (SAD), Multiple Ascending Dose studies (MAD) and food effects.

As is said earlier, one of the first steps in evaluating drugs is to estimate how large a dose can be given before unacceptable toxicity is experienced by the person. This dose is referred as Maximally Tolerated Dose (MTD).

Normally Phase I trials are carried out in healthy volunteers. However about 20% of all Phase I trials are conducted in patients. This may be in case of very toxic drugs, eg; anti cancer drugs. Most established phase 1 trial units do not experience Serious Adverse Events (SAEs) requiring intensive care\textsuperscript{21}.

\textsuperscript{20}Government Glossary of Clinical Trial Terms, supra note16.
\textsuperscript{21}SAE: serious adverse event (SAE) or serious adverse drug reaction (serious ADR): any untoward medical occurrence that at any dose (results in death, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization) results in persistent or significant disability/incapacity or is a congenital anomaly/birth.
The Association of the British Pharmaceutical Industry (ABPI) published a guide for phase 1 clinical trials in 2007\textsuperscript{22}. This includes detailed guidance on risk management of various trial aspects.

Further the European Medicine Agency (EMA) also has developed guidelines for phase 1 trials\textsuperscript{23}.

\textbf{3.4.3 THERAPEUTIC EXPLORATORY/PHASE II CLINICAL TRIALS:}

Once the MTD is established, the next goal is to establish / evaluate whether the drug has any biologic activity or effect or to estimate the rate of adverse events.

These are controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short term side effects and risks. The primary aim of Phase II trial is initial assessment of a drugs therapeutic effects and initial assessment of a drugs consequent adverse effects. Phase II clinical trials study the bio medical or behavioral intervention in a larger group of people (several hundred) across multiple study centers.\textsuperscript{24}

Phase II trials are begun only after Phase 1 trials have established a drugs basic safety and have identified preliminary drug toxicity. The aim is to assess the effectiveness of the drug in about 3 to 6 phase II trials in 200-600 participants. The primary aim is to explore the therapeutic efficacy in target patients. In addition, Phase II trials also aim to estimate the proper dosage for subsequent studies. These also serve as a basis for confirmatory trial design.

The Phase II studies may be further divided into Phase IIA and Phase II B trials. Phase II A is specifically designed to assess dosing requirement (how much drug should be given). Phase II B is specifically designed to study efficacy (how will the drug works at the prescribed dose(s). Combination of phase 1 and IV testing

\textsuperscript{22}www.abpi.org.uk/publications (Last visited on January 18, 2015)
\textsuperscript{23}EMA/CHMP/SWP/294648/2007.
\textsuperscript{24}Government Glossary of Clinical Trial Terms, supranote 16.
both efficacy and toxicity are also available. Phase II trials are typically conducted in a small, well defined group of participants, leading to a relatively homogeneous population\textsuperscript{25}. The most vulnerable aspect of Phase II, as well as Phase I study is the type of patients enrolled.

\textbf{3.4.4 THERAPEUTIC CONFIRMATORY/PHASE III CLINICAL TRIALS:}

Expanded, controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained and are intended to gather additional information to evaluate the overall benefit risk relationship of the drug and provide adequate basis for physician labeling. These studies investigate the efficacy of the biomedical or behavior intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects and to collect information that will allow the intervention to be used safely\textsuperscript{26}.

Phase III trials usually involve 500-3000 participants. However, prevention trials like vaccine clinical trials may require as many as 20,000 participants\textsuperscript{27}. The duration of this phase of trials may vary from a week to many years. Thus in other words, phase III studies are randomized, controlled, multicenter trials on large patient groups aimed at being the definitive assessment of how effective the drug is, in comparison with the current gold standard treatment. Since it involves larger groups for longer duration, Phase III trials are most expensive, time consuming and difficult trials to design and manage especially in therapies for chronic medical conditions.

The primary objective of a confirmatory Phase III trial is to demonstrate or confirm the therapeutic benefit of the drug. Thus it confirms the preliminary evidence collected during the exploratory phase of clinical testing i.e. that the

\textsuperscript{25}J.P.E.Karlb erg, supra note 10.
\textsuperscript{26}Government Glossary of Clinical Trial Terms, supra note 16.
\textsuperscript{27}J.P.E.Karlb erg, supra note 10.
drug is safe and effective for use in the specific indication and patient population. Hence these studies provide the basis for marketing approval. This is the key phase where the drug will either make or break its reputation with respect to safety and efficacy before marketing begins.

A positive study in phase III is often known as a “landmark study” for that drug through which it might gain a license to be prescribed for a specific disease. It is a very common practice to continue with Phase III trials while the regulatory submission is pending at the regulatory agency. This enables the sponsor for ‘label expansion’, to obtain additional safety data or to support marketing claims for the drug. At this stage, the study may be categorized as Phase III B study. Thus, it facilitate in meeting other aims of the study, i.e to find out the test article’s extended patient population, its use in different disease stages and in combination therapy with other drugs.

3.4.5 THERAPEUTIC USE/PHASE IV CLINICAL TRIALS:

These are post marketing studies to delineate additional information including the drugs risks, benefits and optimal use. These are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. Phase IV trials are also known as post marketing surveillance trial. These involve the safety surveillance (pharmacovigilence), ongoing technical support of a drug after it receives permission to be sold. These are crucial for gathering additional safety information from a larger group of patients in order to understand a long term safety of the drug and appreciate drug interactions.

Phase IV studies may be requested by regulatory authorities or may be undertaken by the sponsoring company for competitive or other reasons. The

---

28 To show that the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing.
30 Finding a new market for the drug or the drug may not have been tested for interactions with other drugs-new dosage regimens new routes of administration or on certain population groups
safety surveillance will help in detecting any rare or long term adverse effects over a much larger patient population and longer time period than was possible during preceding phases of clinical trial. The discovery of any harmful effects of any phase IV trials may result in withdrawal of the drug from the market or restricted usage of the same.\textsuperscript{31} Therapeutic use trials are not mandatory for approval. However, they are regarded as important for optimizing the usage of the drug.

“The greatest challenge to any thinker is stating the problem in a way that will allow a solution”.

(1872-1910) Bertrand Russell

This maxim holds as strongly for clinical trials as for any quest in life.

3.5 VACCINE CLINICAL TRIAL AND PHASES OF VACCINE TRIALS:

The guidelines for conduct of investigational vaccine clinical trial are similar to those governing a drug trial. But the phases of these trials differ from drug trials as given below.\textsuperscript{32}

**Phase I:** This refers to the first introduction of a vaccine in to a human population for determination of its safety and biological effects including immunogenicity. This phase includes study of dose and route of administration and should involve low risk patients. The class, subclass and the function of specific antibody response and the lag time for appearance and duration of adequate antibody titer is determined. Information about the cell mediated immunity, the cross reactive antibodies and/ or interaction with preexisting antibodies which might affect immune system is also obtained.\textsuperscript{33}

---

(eg) pregnant woman or additional patient population, new dosage regiments and new routes of administration.\textsuperscript{31} eg. Cerivastatin, Troglitazone, Rofecoxib etc were found to cause severe health risk to patients.\textsuperscript{32} INDIAN COUNCIL OF MEDICAL RESEARCH.Ethical Guidelines for Biomedical Research on Human participants.\textsuperscript{33} Id.
Phase II: This refers to the initial trials examining effectiveness (immunogenicity) and dose range in a limited number of volunteers forming the target groups, like children, adults or those at risk of exposure to pathogens. Pharmacokinetics and safety of vaccine is also studied. Early Phase II is usually an exploratory trial while late phase II is known as pivotal efficacy study. 34

Phase III: This focuses on the assessment of safety and effectiveness in the prevention of disease, involving controlled study on a large number of volunteers through multi centric studies. These studies determine the protection offered by the vaccine and provide pivotal data for licensure. Efficacy in vaccine trials means reduction in incidence of the disease after vaccination compared to the incidence that prevailed before vaccination. 35

Phase IV: These studies are done in the entire population or a subgroup to detect the rarer or unexpected events that may not be seen in smaller phase II/III studies. Post licensure studies of large populations, in a more heterogeneous group of people, over longer periods of time are necessary to provide ongoing assessment of vaccine safety and effectiveness.

Bridging studies in vaccine trials are conducted to support clinical comparability of efficacy, safety and immunogenicity of new formulation when there is change in vaccine composition with regard to adjuvant, preservative, or a change in manufacturing process, site or scale. These are performed either before or after post licensure. The rationale of bridging studies is to demonstrate product equivalency to that used in earlier pre clinical or clinical testing. 36

3.6 CLINICAL TRIAL SCENARIO IN INDIA

Clinical trials in developing countries are exploding. The clinical trial industry in India grew rapidly. India had become a preferred destination for global clinical trials. It was estimated that 20-30% of global clinical trial activities were being

34ICMR, supra note 32.
35ICMR supra note 32.
36Id.
conducted in developing countries. Today the globalization of clinical trial is accelerating, driven by scientific and economic needs to reach more patients. The 2002 Indian clinical trials market of $30-35 million was projected to grow 8-10 times by 2010 to $250-300 million. The total number of trials in India in 2005 was 101 which increased to 195 in 2009.

In a study by Confederation of Indian Industry (CII) shows that clinical trial in India in 2002 generated $70 million in revenue and it predicted that it would grow to $250 million by 2007 and anywhere between $500 million and $1 billion by 2010.

India’s pharmaceutical market is the second largest in Asia, growing by more than 9% annually. India was gearing up to attract more and more researchers from around the world to conduct their clinical studies in India. India was increasingly being recognized as a quality player and a preferred partner for global clinical trial and was being fast emerging as an attractive destination for outsourcing of clinical trials.

Internationally, India became a member of World Trade Organization (WTO) in 1995 and agreed to adhere to the product patent regime from 2005. As a result, the global pharmaceutical industry had rights to patent products as well as processes throughout the world, including India. Thus as a signatory of WTO agreements, India was looked upon as a favourable destination for conducting global clinical trial. India was making a name for itself in the International

41 Id.
43 Id.
Pharmaceutical arena as a preferred destination for leading global companies to conduct clinical trials.\(^{44}\)

The key enablers for the Indian clinical trial were many and varied. India thus became an attractive destination for outsourced, industry sponsored international clinical trials for various reasons.\(^{45,46}\) India clearly provided an advantage to the global drug development programs.

Analysts were predicting that total clinical research spending in India would increase by more than 30% annually. According to McKinsey report, the clinical trial industry in India touched 5000 crores in 2000 from a mere 100 crore.

### 3.7 THE ADVANTAGES OF CONDUCTING CLINICAL TRIALS IN INDIA:

The country was labeled as a “hub” for clinical trials. The advantages of conducting clinical trials in India were

(a) Wide population with wide range of races living in different climatic conditions, suffering from various diseases on the basis of socio economic and environmental changes. This huge, multiethnic and multiracial, genetically distinct patient population was surely an attraction for the global Pharma industry. This genetically diverse population of more than billion people who had not been exposed to any medication but have myriad diseases, ranging from tropical infections to degenerate disorders, attracted Pharma industry.

(b) Relatively low costs, availability of trained manpower and infrastructure were another added advantage. For instance, trials for a standard drug in the United States could cost up to $ 150 million, whereas a trial in India was conducted for nearly half that

---

44 MAJOR PLAYERS IN CLINICAL RESEARCH, supra note 42.
amount. The large pool of highly trained personal together with numerous world class medical facilities, well equipped IT industry which could be beneficial in the area of bio informatics to support a variety of drug discovery efforts, a favourable IPR environment and use of English as primary business and medical language were India’s assets. Data suggests that 50 to 60 percent cost saving was associated with conducting clinical trials in India, compared to the same clinical trial being conducted in developed countries. This was evident by a steadily increasing number of global clinical trials in India. Highly educated and English speaking researchers who were Good Clinical Practice (GCP) trained, availability of majority of medical records in English were other key strengths. Thus cheap Labour and low infra structure cost could reduce expenditure for clinical trials as much as sixty percent.

In developed countries, about US $ 800 million is the average cost of bringing a new molecule to the market, including the cost of possible failures. Within the pharma R&D value chain, failures occur at various stages and cumulative success rate of a given drug discovery program is about 1.5%. The probability of success increases to about 50 to 70 percent, once a molecule enters phase III clinical trials. By conducting R&D on new molecules up to phase II of clinical trials in India, the cost of innovation and development could be drastically reduced. This was one of the unique opportunities in India.

(c) Also there was a high enrolment rate, compared to that in the West, probably due to the treatment naïve population. They would not have been able to afford treatment, so they were ideal for testing new drugs. The rapid patient recruitment, compliance and better

48/Id.
retention attributed to significant reduction in clinical development process. Also this diminished the study timelines without reducing quality or increasing cost. This further lowered the cost of operations. This cost competitiveness further attracted the Pharma industry across the world to India, which was considered as a hot hub for clinical trial outsourcing.

(d) An increasingly accommodating and favorable regulatory environment and duty free import of drugs intended for use in trials, bio equivalence studies for export of data further accelerated the process. In India, since 2005, when IPR and schedule Y were amended, there had been a lot of buzz around clinical trial industry. The country had been labeled as a new "hub" for clinical trials.\(^{49}\) Government had taken initiatives like regulations in data protection and data exclusivity. Further, import duty on clinical trials was exempted.\(^ {50}\)

(e) High levels of ICH - GCP and US Food and Drug Administration standards compliance was another positive stroke in the effort. Since 2001, the Drugs Controller General of India (DCGI) had implemented conformity to ICH- GCP and Good laboratory Practice (GLP) guidelines. Hence generally most competent authorities including the US FDA found the standards of Indian clinical trials acceptable.\(^ {51} \quad 52 \quad 53 \quad 54 \)

\(^{49}\)Bhat, Supra Note 37


The benefits of clinical trials being conducted in India were:

1) Patients / Study Subjects who participate in clinical trials
   • Had access to the latest medication or treatment modalities
   • Got free medical care, which included cost of investigations and medicine
   • Entered into the trial voluntarily after signing an informed consent
   • Received more frequent and focused consultations leading to an improvement in the quality of health care.

2) Investigators who conducted clinical trials:
   • Got 1st hand experience with the most recent drugs
   • Got global recognition working on the same platform as other international experts on the project.
   • Got extensive training in the internationally accepted GCP & GLP guidelines.
   • Got an opportunity for publication.
   • Had access to the latest medicines for their patients.

3) Hospitals / Sites where the research was conducted:
   • Got infrastructural development
   • Got global recognition

3.8 CONCERNS EXPRESSED AGAINST CLINICAL TRIALS IN INDIA:

There is another side to this scenario. The use of Indians for the benefits of western world had extensively been criticized. Outsourcing clinical trials to India was considered “rash and risky”. Conclusion is drawn on the basis of concerns about timelines for regulatory approvals, deficiencies in the functioning of the ethics committees and an unethical approach to the recruitment of subjects in

\textsuperscript{55} Id.
Indian clinical trials.\textsuperscript{56} There had been growing concerns and fears that due to vested interests, negative trial results are often not brought out to the notice of general public and physicians. The Vioxx controversy\textsuperscript{57} and report of unethical clinical trials being conducted in India without proper clearance from relevant authorities or proper toxicity studies \textsuperscript{58} have brought to the forefront, the urgent need for registration of all clinical trials, including those conducted in India.

Whether the community be benefited post trial was another concern in HIV vaccine trials. This was a great concern hindering convincing of trial participants and local civic leaders. The community may never benefit from their contribution, if a product is eventually developed. Such was the case in the development of Hepatitis B vaccine. As journalist Michael Specter reports “Africans served as essential participants in trial for principal vaccine against Hepatitis B; yet when the vaccine finally arrived, they could not afford it”.\textsuperscript{59}

Other challenges expressed were lengthy approval timelines, lack of inspections by health authorities, manpower crunch and application backlog, and lack of communication as explained by Jayasheel in his article.\textsuperscript{60}

Despite all present pitfalls, India was certainly gearing up to attract more and more researchers from around the world to conduct their Clinical Trials studies in India. The need for clinical trials and making their results available publically was felt globally since long. Registration of clinical trials offered benefits like safeguarding the patient interests, ensuring greater transparency, accountability


\textsuperscript{59} The Quest for an HIV Vaccine: Logistical\& ethical consideration in HIV Vaccine Clinical Trial. \textit{available at} http://www.vaccineethics.org/issue_briefs/HIV_clinical_trials.php (Last visited on November 6, 2014).

\textsuperscript{60} B.G. Jayasheel, Carrying Out Clinical Trials in India, RAJ PHARMA, (June 2010) \textit{available at} http://wwwacunovalife.com/pdf/whitepapers/RAJ_pharga%20June%202010_jayasheel%20final.pdf, (Last visited on November 6, 2014).
and accessibility of clinical trials and raising the standard of research. A number of clinical trial registries were already in place, but mostly in developed countries and none were truly comprehensive. Many a times, due to vested interests, negative trials are often not brought to the notice of general public and physicians. With profit at the bottom line, exploiting opportunities rather than transparency or the protection of vulnerable populations appears to drive the industry.  

3.9 HOW PREPARED IS INDIA FOR GLOBAL CLINICAL TRIALS?

The regulatory affairs in India are still at its infancy. The DCGI is responsible for the regulatory approvals of clinical trials in India. The DCGI’s office depends on external experts and other government agencies for advice. The timelines for approval takes about 3 months in India as compared to US FDA approval taking an average of only 30 days. The potential for faster patient recruitment procedures in India makes up for the delay as patient recruitment procedures in US is time consuming. The 2005 amendment of Schedule Y of Drugs and Cosmetics Act is quite welcoming in this field as it allows parallel global trials. Earlier, foreign drug trials could be conducted only at one phase below the highest phase of testing abroad. Permission is now accorded for concomitant phase 2 and phase 3 trials.  

Though the DCGI gives approval for conducting clinical trials in India, there is no central monitoring mechanism to check whether the data is tampered at any point / or how the trial is conducted. However, the government has taken initiatives like regulations in data protection and data exclusivity. Also, import duty on clinical trials is exempted.

Further, DR CM Gulati is of the opinion that the DCGI office does not even read the protocols and accompanying documents. They were approving patently defective clinical trials, were approving trials with voluminous protocols in less

---

62 Schedule Y, Drugs and Cosmetics Act, 1940.
63 A. Bhatt, supra note 39.
than five working days which was humanly not possible. Also it was found that DCGI approved trials not having any provision for compensation in case of injury and no undertaking from sponsors were mandatory for approval of protocols. The regulatory bodies / ethical committees never asked for any conflict of interest information from the investigators. He even expressed concerns over the unsupervised, unethical and often illegal clinical trials leaving Indians crippled/dead. Further he is apprehensive about the regulatory capture.  

Another much neglected area is that of ethics in medical research. ICMR has given Policy Statement on Ethical Considerations involved in Research on Human Subjects in 1980 and revised these guidelines in 2000, 2006 as the Ethical Guidelines for Biomedical Research on Human Subjects. Due to further rapid developments in science and technology, it became necessary to update these guidelines to make adequate specific provision to meet ethical challenges posed by these advances. Necessitated by globalization leading to increasing research in the developing world, the international guidelines released in 2002 by the developed countries including the revised Council for International organizations of Medical Sciences (CIOMS) guidelines focused on observance of ethical norms. In India, the challenge faced is to apply universal ethical principles to biomedical research in the multicultural Indian society with a multiplicity of health care systems of considerably varying standards.  

The ICMR guidelines insist on the setting up of ethics committees at the institutional levels. The Institutional Ethics Committees (IEC’s) responsibility is to scrutinize and approve the clinical trial before the study begins and also to conduct periodic reviews of the progress of the trial.

The functioning of IEC is not satisfactory. Most research institutions in India either do not have IEC or there is inadequate representation in it by persons

---

64 C.M. Gulati, Needed : Closer Scrutiny Of Clinical Trials, INDIAN JOURNAL OF MEDICAL ETHICS, 1 (1), 2004
WHO has identified regulatory capture as a phenomenon in which the authority is seized by the interests it is supposed to regulate. ie; the regulators officially designated as public servants are in imminent danger of becoming servants of the industry.
65 Glaxo Smith kline, supra note 19.
other than those of the medical fraternity. Without a representation of persons from the non-scientific background, the opinion of the IEC is likely to be biased in favor of the study. The ICMR guidelines clearly specify the need for such personnel.

Further, though it is mandatory, the IECs do not hold regular meetings; do not have member representation according to the guidelines and lack Standard Operating Procedures (SOPs). But there are changes for the better. The IECs are audited by a Committee set up by ICMR known as Central Ethics Committee on Human Research (CECHR). In brief, India is already off the starting hurdles and gearing up for an inundation of clinical trials. The pharma industry is optimistic that the scenario will improve further. Dr Arun Bhatt, President, Clin inventive Research Pvt Ltd is of the opinion that the future of Indian clinical trials industry is likely to be shaped by local factors, eg; regulatory factors.  

Also, the way in which health research is required to be conducted has changed drastically due to the intervention of the Supreme Court of India in a PIL filed by Swasthik Adhikar Manch as also various amendments in Drugs and Cosmetic Act and Rules, which makes registration of Ethics Committee mandatory. The rule mandates the composition of ethics committee meetings to be held in connection with the clinical trial. The ICMR Guidelines for preparing the Standard Operating Procedure for Institutional Ethics Committee for Human Research lays down the meeting and quorum requirements, application procedures, documentation, review procedure; elements of review which will better equip the Institutional Ethics Committees to conduct the clinical trials with a view to safeguard the dignity, rights and safety of the research participants.  

The International AIDS Vaccine Initiative’s (IAVI) news letter dated 9 March 2015 has

highlighted India’s potential as a center of excellence in HIV vaccine research and development.  

3.10. SAFETY OF A SUBJECT IN CLINICAL TRIAL:

It is quite important to know who is responsible for safety of the subjects in a clinical trial. This responsibility is shared between the sponsor, the local site investigators, various IRBs that supervise the study and the regulatory body in that country. The sponsor is expected to inform the local site investigators about the product being tested at length including any existing safety concerns. The sponsor, or in larger trials, a Data Monitoring Committee is responsible for monitoring the results of the study, as the trial proceeds. Further, the sponsor is responsible for collecting any report of adverse event that has occurred during the course of the study and investigate whether the event is related to the trial or not. If the adverse event is due to the trial, the sponsor has the responsibility of informing the investigators. Along with the local site investigators, the sponsor has the duty to formulate site – specific informed consent.

A local site investigators primary duty is towards his patients. (Do no harm). He is additionally responsible for smooth conduct of the study according to the study protocol. He is responsible for ensuring that the subjects have fully understood the potential risks and benefits of participating in the study before they entered the trial.

The IRB (Institutional Review Board ) / ethics board approval is mandatory for a trial to commence. A “continuing review” report from the investigator further updates the IRB on the progress of the trial. Different countries have different regulatory apparatus and requirements which have to be met stringently.

3.11 GLOBAL NEED FOR REGISTRATION:

There was a felt need for registration of all clinical trials. In order to ensure transparency, accountability and to increase public trust in the conduct of clinical

research, all clinical trials should be registered at inception and all results made publicly available. Universal registration of clinical trial data would prevent the loss of valuable information from the tendency of selective reporting (avoid publication bias). Further, it prevents unnecessary duplication of trials while encouraging appropriate replication. It also serves as valuable sources of information for researchers as they initiate and design their studies. In addition, it helps the funding bodies for targeting their money where it is most needed. Thus in Nov 2004, at the Ministerial Summit on Health Research in Moscow of all stakeholders called for action to establish a platform linking a network of international clinical trials registers to ensure a single point of access and unique identifications of trials.

A one-stop search portal for searching registers worldwide, ie, International Clinical Trial Registry Platform (ICTRP) was set up with lead of WHO and consensus of 58th World Health Assembly(WHA) held on 25th May 2005. The ICTRP has recommended 20 key points as Trial Registration Data Set that need to be publicly declared before enrolment of the first patient. Concurrently, in a move towards making trial registration a more effective venture, in 2005, the International Committee of Medical Journal Editors (ICJME) implemented a policy that a scientific paper on clinical trial would only be published if the trial had been registered in a publically accessible registry.

In keeping with the global scenario and the need of the country, the National Institute of Medical Statistics, ICMR took up lead in India, with financial support from WHO in setting up the Clinical Trials Registry –India (CTRI). The CTRI, www.ctri.in was launched on 20th of July 2007, by DG, ICMR and is hosted at the National Institute of Medical Statistics, ICMR, and New Delhi. The CTRI is an online public record system for registration of all clinical trials being conducted in our country. This is a free searchable portal. Registration of trials is voluntary but some fields are mandatory for the registration to proceed. The primary purpose of this Registry is to make information regarding clinical trials being conducted in

---

70 WHA is the supreme decision making body of WHO which prepares policies and decisions.
India freely available to anyone who desires the information. Setting up the Clinical Trials Registry ensures that all clinical trials conducted in India are publically declared and identifiable. Registry establishes a public record system by registering all clinical trials. The registry also safeguards against “positive result bias” and “selective reporting” of research results to peer review publication. This further increases the awareness and accountability of all participants of clinical trials.

Ethics committees are also getting involved in the venture. For eg, Ethics committee of Christian Medical College (CMC) Vellore has made clinical trial registration a prerequisite for approval of clinical trial protocol. This is in one way ensuring that research in medical science keeps the interest of patient as its first priority.\textsuperscript{71}