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A REVIEW ARTICLE ON CURRENT RESEARCH AND REGULATORY STEPS FOR FURTHER DEVELOPMENT OF CLINICAL TRIALS IN INDIA

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Abstract:

The evolution of clinical research traverses a long and fascinating journey. The recorded history of clinical trials goes back to the biblical descriptions in 500 BC. The journey moves from dietary therapy – legumes and lemons – to drugs. After basic approach of clinical trial was described in 18th century, the efforts were made to refine the design and statistical aspects. Clinical trials hold enormous potential for benefiting patients, improving therapeutic regimens and ensuring advancement in medical practice that is evidence based. Unfortunately, the data and reports of various trials are often difficult to find and in some cases do not even exist as many trials abandoned or are not published due to "negative" or equivocal results. However, this tendency for availability of only selective information from the myriad clinical trials conducted is not commensurate with the practice of "evidence-based medicine". Today, world over, a need has been felt on the imperative for transparency, accountability and accessibility in order to re-establish public trust in clinical trial data. And this would be feasible only if all clinical trials conducted are registered in a centralized clinical trials registry. Registration of trials will ensure transparency, accountability and accessibility of clinical trials.

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INTRODUCTION:

1800: Arrival of Placeboic Remedy

It took another century before the emergence of another important mile stone in the history of modern clinical trial: the placebo. The word placebo first appeared in medical literature in the early 1800s.(1) Hooper's Medical Dictionary of 1811 defined it as “an epithet given to any medicine more to please than benefit the patient.” However, it was only in 1863 that United States physician Austin Flint planned the first clinical study comparing a dummy remedy to an active treatment. He treated 13 patients suffering from rheumatism with an herbal extract which was advised instead of an established remedy. In 1886, Flint described the study in his book A Treatise on the Principles and Practice of Medicine. “This was given regularly, and became well known in my wards as the ‘placeboic remedy’ for rheumatism. The favorable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients. (2)”

1943: The First Double Blind Controlled Trial - Patulin for Common Cold

The Medical Research Council (MRC) UK carried out a trial in 1943-4 to investigate patulin treatment for (an extract of Penicillium patulinum) the common cold. This was the first double blind comparative trial with concurrent controls in the general population in recent times. It was one of the last trial with non-randomized or quasirandomized allocation of subjects.(3) The MRC Patulin Clinical Trials Committee (1943) was chaired by Sir Harold Himsworth, and its statisticians were M Greenwood and W J Martin. This nationwide study enrolled over a thousand British office and factory workers suffering from colds. This was quite a challenging endeavor in wartime, The study was rigorously controlled by keeping the physician and the patient blinded to the treatment. The treatment allocation was done using an alternation procedure. A nurse allocated the treatment in strict rotation in a separate room. The nurse filed the record counterfoil separately, and detached the code label for the appropriate bottle before asking the patient to visit the doctor.(3) The statisticians considered this an effective random concurrent allocation. However, the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin.

Evolution of Ethical and Regulatory Framework

The ethical framework for human subject protection has its origins in the ancient Hippocratic Oath, which specified a prime duty of a physician – to avoid harming the patient. However, this oath was not much respected in human experimentation and most advances in protection for human subjects have been a response to human abuses e.g. World War II experiments. The first International Guidance on the ethics of medical research involving subjects – the Nuremberg Code was formulated in 1947.(4) Although informed consent for participation in research was described in 1900, the Nuremberg Code highlighted the essentiality of voluntariness of this consent.9 In 1948, Universal Declaration of Human Rights (adopted by the General Assembly of the United Nations) expressed concern about rights of human beings being subjected to involuntary maltreatment.(5) The brush with thalidomide tragedy helped the U.S. pass the 1962 Kefauver-Harris amendments, which strengthened federal oversight of drug testing and included a requirement for informed consent.10 In 1964 at Helsinki, the World Medical Association articulated general principles and specific guidelines on use of human subjects in medical research, known as the Helsinki Declaration. The Helsinki Declaration has been undergoing changes every few years the last one being in 2008. However, the use of placebo and post-trial access continue to be debatable issues.

CLINICAL TRIALS

These are experiments or observations done in clinical research. Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on safety and efficacy.(6) They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial – their approval does not mean that the therapy is 'safe' or effective, only that the trial may be conducted.

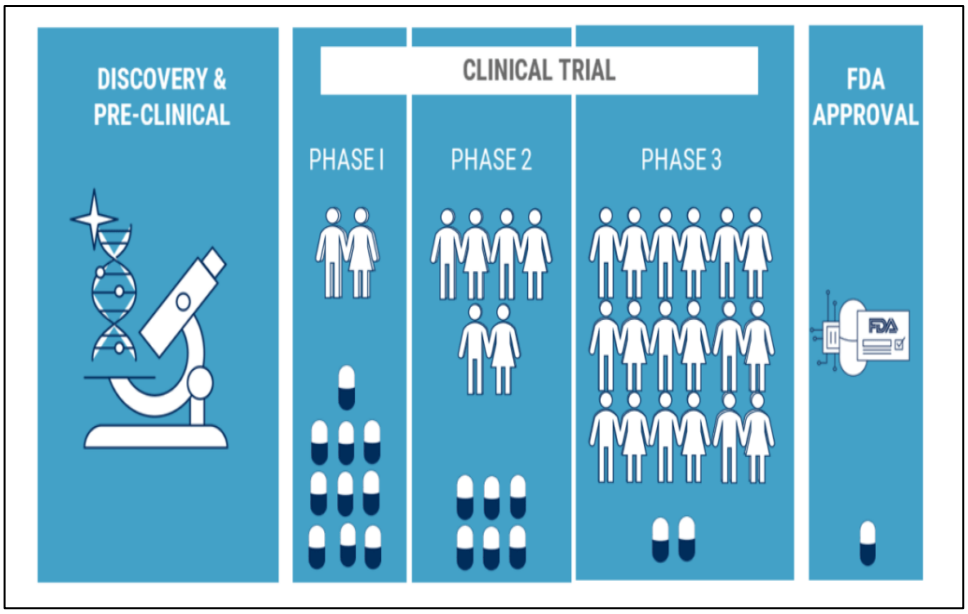


Figure:1- CLINICAL TRIAL

CLINICAL RESEARCH AND CLINICAL TRIALS FACTS [7]

● "Clinical" as a term refers to the medical care of real patients.

● Clinical trials are a form of medical research that follow a defined protocol that has been carefully developed to answer a specific patient care question.

● Clinical trials are in use to test cancer therapies, treatments for cardiovascular disease, the safety and efficacy of new drugs, and a number of other conditions.

● Clinical trials may investigate the effectiveness of new drug treatments, new combinations of drugs, surgical procedures, or behavioral and lifestyle modifications.

● Clinical trials are broken down into phases, with each phase having a different purpose within the trial.

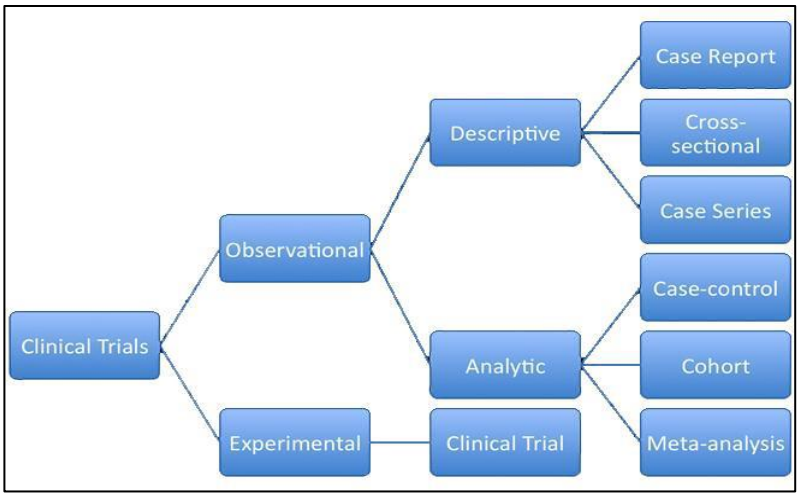
● An Institutional Review Board (IRB) consisting of physicians, statisticians, researchers, patient advocates, and others must preapprove every clinical trial in the U.S. This ensures that the trial is ethical and protects patients' rights, and is appropriate to answer the question asked from a scientific and statistical viewpoint.

● Every clinical trial follows a protocol that describes what types of people may participate in the trial; outlines the exact schedule of tests, procedures, medications, and/or dosages involved in the trial; and specifies the length of the study.

● Each trial has specific inclusion and exclusion criteria to determine the exact patient populations that may participate. Inclusion criteria may be based on age, gender, underlying disease, health history, or other factors.

● Double-blinded trials offer the advantage of allowing the treating health-care team and the patient to make unbiased observations about patient progress and the effectiveness of the treatment being evaluated.

● Clinical trials may be sponsored and funded by government agencies, institutions, hospitals, physicians, pharmaceutical or biotechnology companies, advocacy groups, or other organizations.



GLOBAL AND INDIAN SCENARIO [8]

Pharmaceutical companies difficult to recruit enough patients to test the drugs in their laboratories because more than 4000 patients are required for the Food and Drug Administration to approve an experimental drug for marketing but fewer than 5% of patients in the United States are willing to participate in clinical trials. 86% of all US clinical studies are delayed on average 366 days because they fail to recruit the required number of patients results, every day a product is delayed in getting to market, one million dollars a day are lost in revenue. Permission is given to researchers to reimburse subjects for their time, inconvenience and expenses incurred in connection with research by The Council for International Organization of Medical Services (CIOMS). In Western countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, has become increasingly difficult to test drugs and all of which make the recruitment of research subjects slow and expensive. Due to the shortage of investigators, Clinical research is also losing its popularity in the US. The major challenge of large number of quality professionals in medical and clinical research can only be met by cooperative and collaborative efforts between industry, academia and government. Besides the manpower efforts, the training activity will need financial support for example the industry $300 million spends on training In the US9. The Chinese government has improved the environment and infrastructure for clinical trials by implementing a series of important legislative measures that's why China is transforming into an attractive location for clinical trials. The system of intellectual property (IP) rights has improved, After China joined the World Trade Organization (WTO) but at present the challenges China is facing are slow regulatory process, lack of qualified central laboratory and difficulties in sample export. Permission is required from China Human Genome Resource Administrative office for whole blood or tissue sample, and special permit from MOH is required for plasma or serum sample.

METHODOLOGY [9]

New Drug

I. A drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licencing Authority with respect to its claims; or

II. A drug approved by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

III. A fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or

IV. A modified or sustained release form of a drug or novel drug delivery system of any

drug approved by the Central Licencing Authority; or

V. A vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;

VI. Explanation: The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licencing Authority; and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs;

THE NATIONAL REGULATORY BODY [10,11]

The Drugs Controller General of India (DCGI) is an official of the CDSCO who is the final regulatory authority for the approval of clinical trials in the country. His ambit, in addition, also extends to inspections of trial sites, inspections of sponsors of clinical research and manufacturing facilities in the country, oversight of the Central Drugs Testing Laboratory (Mumbai) and the Regional Drugs Testing Laboratory as also heading the Indian Pharmacopeia Commission among various other roles, responsibilities and functions.

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND MANUFACTURE OF NEW DRUGS [12]

1. Application for permission
2. Approval for clinical trial
3. Responsibilities of Sponsor
4. Responsibilities of the Investigator(s)
5. Informed Consent
6. Responsibilities of the Ethics Committee
7. Human Pharmacology (Phase I)
8. Therapeutic exploratory trials (Phase II)
9. Therapeutic confirmatory trials (Phase III)
10. Post Marketing Trials (Phase IV)

OPPORTUNITIES FOR CLINICAL TRIALS IN INDIA [13]

1. High patient enrolment rate
2. Spectrum of diseases
3. Human resources and technical skills
4. Regulatory compliance
5. ICH-GCP Compliance
6. Cost advantage
7. Reliable data quality
8. Clinical data management
9. Infrastructure
10. Economic environment
11. Manufacturing
12. Speed
13. Favorable environment
14. Higher growth in Asia pacific
15. Alliances
16. Established pharma companies

CONCLUSION:

In drug development, two partly over lapping hases can be differentiated, namely the preclinical and clinical phase. During the first part of drug development necessary requirements for first use in man are met by performing preclinical pharmacological, toxicological, and pharmacokinetic investigations in the animal and in in-vitro testing.[14] These investigations are playing a central part for the benefit/risk evaluation of new drugs. Only if the risks connected to the clinical study are medically justifiable in relation to the likely therapeutic benefit of the compound, the clinical trial may basically take place under consideration of the legal requirements of the country in which the study is carried out. In drug research, clinical pharmacology is the connecting link between preclinical and clinical research. Clinical pharmacology produces the necessary basis for the clinical trial of a new substance in the patient with the target indication. After a first clinical-pharmacological profile of the new substance has been established during phase I on the basis of which a decision for the continuation of the clinical trial and the probable effective dose range and dosing interval is made, the aim of phase II-IV is to answer the important questions of the therapeutic efficacy and tolerability in a large number of patients with the target indication. Only with a very careful drug investigation during phase I-IV it is really possible to register the

therapeutic risk and benefit of a new drug and to control resulting serious problems.[15]

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