

Clinical trials

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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 testings, 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

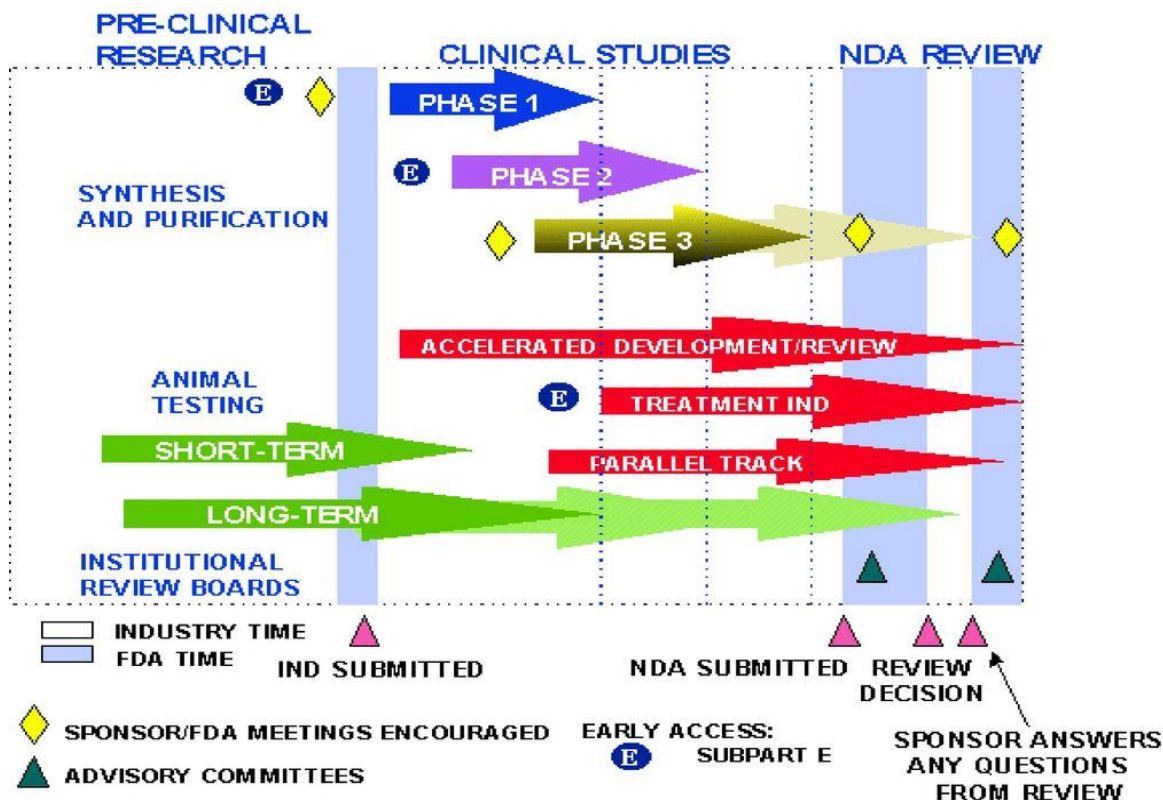
clinics send their opinion about the drug, regarding ADR, efficacy in phase IV.

Keywords: Clinical Trials, Preclinical Studies, Clinical studies, NDA.

I. 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. Clinical trials as the name suggests are set of experiments and observations done for clinical research. In human subjects. They are carried out in search of new treatments, interventions or tests as a means to prevent, detect, treat or manage various diseases or medical conditions. 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.[1]

Phases of clinical trial-



Before pharmaceutical companies start clinical trials on a Drug, they conduct extensive pre-clinical studies[1]

• **Preclinical studies-**

Before starting of clinical trials of a drug, the Pharmaceutical companies perform an preclinical Studies which consist of in vitro (animal), in

vivo (cell culture) experiments by using wide range of Doses study to obtain primary efficacy, toxicity and pharmacokinetic information. Such Experiments helps the pharmaceutical companies To decide whether the drug have scientific merit or Not. In addition, decision on whether it has been required for further development as and Investigational new drug. [2]

• **Phase 0**

Table 1. Clinical phase trials.

Phases	Dosing	Number of subjects	Main goal of clinical phase
Preclinical	Unrestricted	Not applicable	Testing in non-humans (efficacy, toxicities, pharmacokinetics)
0	Subtherapeutic	About 10	Pharmacokinetics and pharmacodynamics
IA/IB	Ascending doses	20 - 100	Dose-ranging
IIA/IIIB	Therapeutic dose	100 - 300	Drug efficacy
IIIA/IIIB	Therapeutic dose	1000 - 2000	Therapeutic effect
IV	Therapeutic dose	Anyone seeking treatment	Long-term effects
V	No dosing	All reported use	Research on data collected

Phase 0 has been regarded as is a recent Introduction for exploration of the trials. Initially, The human trails have been performed in Accordance with US Food and drug administration (FDA) 2006 Guidance On Exploratory Investigational new drug (IND) studies. Phase 0 Trails are also expressed as microdose studies, Which are designed with the motive of the Development of promising drug having the Specific characteristic's, which were expected from Preclinical studies^{11,13}. Moreover, the differential Features of Phase 0 consists of administering the Single sub therapeutic dose of the study drug to a Small number of patients or volunteers (10-150), In order to collect the preliminary data of drug on Pharmacokinetic and pharmacodynamic property Of drug. Surprisingly, Phase 0 studies do not Provide any specific data about the safety and Efficacy of the test drug. Furthermore, the drug Development companies have been noted to Perform Phase 0 studies for ranking the drug Candidate in order to decide the pharmacokinetic Parameters on humans for further development.^[2]

Phase I

This phase assess the safety of a Drug or device. This is initial phase of testing, Which may take about several months to complete. This phase usually includes a small number of Healthy volunteers (20 to 100). The purpose of Phase I trial is to determine the effect/ effects of The drug or device on humans including how it is Absorbed, metabolized, and excreted (ADME). This phase also investigates the dose related side effects. About 70% of experimental drugs pass This phase of testing.

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.^[4]

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 pre-Calculated 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).^[4]

2.MAD

Multiple Ascending Dose studies are conducted to better Understand the pharmacokinetics & pharmacodynamics of Multiple doses of the drug. ^[4]

Phase II

Phase I/II dose finding studies determine the foremost successful dose (MSD) which is that the dose which maximizes the merchandise of The probability of seeing no toxicity alongside the probability of seeing a therapeutic response. While a Phase I clinical study focuses on Determining the MTD, Phase II studies evaluate potential efficacy and characterizes treatment benefit for the disease in a convincing manner Participants in these trials have the disease or condition of clinical concern, e.g., hypertension, thus facilitating initial assessments of a Drug's safety and efficacy in the intended patient population. They are conducted by researchers trained in clinical trial methodology and Operational execution . ^[5]

The goals of phase II studies are:

To learn more about safety and side effects.

To provide data allowing selection of optimal doses for subsequent trials.

now within a short period of time whether the drug is likely to be effective . ^[5]

Phase III

Phase III clinical trials have been suggested to be Designed in order to analyze the efficacy of new Drug and its therapeutic effect in clinical Practices¹⁸. Phase III trials have been conducted Randomly on large number of patients (300-3000 Or more), having the target to achieve the definite Assessment of the new drug, by comparison with The standard drug

treatment. Also, due to their Longer duration and size, the Phase III trials have Been considered as the most expensive, time Consuming and difficult to design and run. In Phase III trials, the chronic diseases having a Period of evaluation related to the time period of The intervention can be used in practice¹⁸⁻¹⁹. In Common practice, some trials of Phase III are Continued until the regulatory submission is Pended at the appropriate regulatory agency. Once the drug satisfaction has been achieved after Phase III trials, the report is combined by having The comprehensive description of the methods And result of manufacturing technique, detail of Formulation and its half life. Moreover, the Collected information are submitted to the “regulatory submission” so that the hope Transpires to the sponsor in order to get the Approval of marketing the drug. Also, if any Adverse effects have been reported any where, the specific drug is recalled immediately from the Market. [2]

Phase IV

Phase 4 clinical trials collect results after a medication has been introduced into the general population to see how well it works on “real life patients” in order to determine the long-term benefits and risks. Most often, phase 4 studies are observational studies that collect data from real-life patients who are taking a medication as prescribed by their doctors. Phase 4 clinical studies are usually performed by the pharmaceutical or biotechnology companies that manufacture the study treatment. Sometimes, regulatory agencies like the FDA approve a treatment for marketing only if the effects of the treatment are further monitored in phase 4 trials. This may happen if previously untested groups of patients experience adverse reactions to the treatment. These findings are compared with all the results from the previous trial phases to make sure that the recently approved treatment is safe and effective. [6]

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. [4]

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

NDA (in the U.S.) and MAA (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. [1]

Types of clinical trials:

Treatment Trials-

Trials which involve test on new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

Screening Trials-

Trials which the best way to detect certain diseases or health conditions.

Prevention trials-

These are trials which intend to find better ways to prevent a disease in people who have never had the disease or to prevent a disease from returning. These approaches may include vaccines, minerals, vitamins, medicines.

Quality of life trials or supportive care trials

Trials that explore ways to improve comfort and the quality of life for individuals with chronic illness. [7]

Monitoring clinical trials-

According to ICH-GCP it is defined as an act of inspecting The clinical trial, it is the responsibility of the sponsor Assuring that trial is done according to protocol, GCP, SOP And regulatory requirements. The data that appears after Performing a clinical trial which ensures the rights, safety And well-being of the subjects is credible and accurate. Monitor responsibility is to assure whether the trial is

Conducted in accordance with Schedule Y, ICH GCP Guidelines, study protocol and any other guidelines / Regulations.[8]

Ethical consideration

Despite the first reported modern clinical trial described in James Lind's "A Treatise of the Scurvy" from 1753, it was not until the mid-20th century that ethical considerations in human research were addressed. In response to the criminal medical experimentation of human subjects by the Nazis during World War II, 10 basic principles of human research were formulated as the Nuremberg Code of 1949.2 This code was later extended globally as The Declaration of Helsinki and adopted by the World Medical Association in 1964.3 Notably, it advanced the ethical principle of "clinical equipoise," a phrase later coined in 1987 to describe the expert medical community's uncertainty regarding the comparative efficacy between treatments studied in a clinical trial.4 This ethical precept guides the clinical investigator in executing comparative trials without violating the Hippocratic Oath.[9]

Plans of clinical trial-

The clinical trial process involves protocol development, designing a case record/report form (CRF), and functioning of institutional review boards (IRBs). It also includes data management and the monitoring of clinical trial site activities. The CRF is the most Significant document in a clinical study. It contains the information collected by the investigator about each subject participating in a clinical study/trial. According to the International Council for Harmonisation (ICH), the CRF can be printed, optical, or an electronic document that is used to record the safety and efficacy of the pharmaceutical drug/product in the test subjects. This information is intended for the sponsor who initiates the clinical study. [10]

Plans may be open, blind and double blind

Open trial

In an open trial, the researcher knows the full details of The Treatment and so does the patient. These trials are open To Challenge for bias, and they do nothing to reduce the Placebo effect. However, sometimes they are unavoidable, As placebo treatments are not always possible (see Blinding). Usually this kind of study design is used in Bioequivalence Studies.

Blind trial

Single-blind study:-

In this study, patients do not know whether they are in the treatment group or the control group.

Double-blind study:-

In this study, neither the patients nor their doctors know which group they are in.

The purpose of blinded studies is to make sure the results are not biased by anyone's hopes for a certain treatment. Whichever group you are in, you will get the best care possible.[11]

Triple-blind trial

Some randomized controlled trials are considered triple blinded, although the meaning of this may vary according To the exact study design. The most common meaning is That the subject, researcher and person administering the Treatment (often a pharmacist) are blinded to what is being Given. Alternately, it may mean that the patient, researcher And statistician are blinded. The team monitoring the Response may be unaware of the intervention being given In the control and study groups. These additional Precautions are often in place with the more commonly Accepted term "double blind trials", and thus the term "triple-blinded" is infrequently used. However, it connotes An additional layer of security to prevent undue influence Of study results by anyone directly involved with the study. [1]

ICH GCP GUIDELINES

- Clinical trials should be conducted in accordance with the ethical principles that have their Origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP)And applicable regulatory requirement(s).
- Clinical trials should be designed and conducted in ways that ensure the rights, safety, and Well-being of participants.
- Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial Participation should be voluntary and based on a consent process that ensures participants Are well-informed.
- Clinical trials should be subject to objective review by an institutional review board (IRB)/independent ethics committee (IEC).
- 5- Clinical trials should be scientifically sound for their intended purpose, and based on robust And current scientific knowledge and approaches.
- Clinical trials should be designed and conducted by qualified individuals.
- Quality should be built into the scientific and operational design and conduct of clinical Trials.

- Clinical trial processes, measures, and approaches should be proportionate to the risks to Participants and to the reliability of trial results.
- Clinical trials should be described in a clear, concise, and operationally feasible protocol.
- Clinical trials should generate reliable results.
- Roles, tasks and responsibilities in clinical trials should be clear and documented Appropriately.
- Investigational products used in a clinical trial should be manufactured in accordance with Applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and Handled in accordance with the product specifications and the trial protocol.[12]

ROLE OF PHARMACISTS IN CLINICAL TRIALS

- Standardized safety practices for investigational drugs in clinical research protocols are limited and the vast majority of research pharmacists have concerns regarding its safety. Identified areas for medication safety risks include protocol complexity, medication ordering, and the processes for packaging, storage, and dispensing.
- investigational medications. Inclusion of a pharmacist creates multiple mechanisms to promote safety and improve the quality of clinical research. This is accomplished through collaborating in the development of a research protocol, reviewing as a member of an advisory committee, developing mechanisms that contribute to safety, and assuring compliance with local and national regulations and standards. Ultimately, the profession of pharmacy has foundational responsibility for assuring the safe and effective use of medications, including investigational drugs in clinical research. It is through multidisciplinary collaboration that a research study will attain the highest standards for safety and maximize the quality and effectiveness of the data obtained in the clinical trial.[14]
- Pharmacists traditionally have been involved in clinical trial research in a variety of Ways, from providing drug and record keeping for drug accountability to taking on the Roles from study coordinator to principal investigator.¹² Today, pharmacists are on the Forefront of patient care and do make a significant impact on the health status of patients' Directly through pharmaceutical care and indirectly by connecting patients to Pharmaceutical treatments through the practice of Evidence Based Medicine with existing Treatments or with participation in clinical trials. As medication experts,

pharmacists are Educated to develop the skills to solve medication related problems and improve patient Outcomes with their interventions. While not limited to clinical trial research, the basis of Evidence based guidelines are derived from clinical expertise and valid clinical Research.¹³ Evidenced based practice guidelines often recommend enrollment in a clinical Trial when other standard therapies fail and a treatment or cure is not possible.¹³ An Understanding of clinical trials and resources to learn about on-going clinical trial Research is essential for the pharmacist interested in collaborative efforts with the Patients, caregivers, and physicians to incorporate this value-added service to their Armamentarium of patient care services. [15]

- Clinical pharmacy is in growing stage in developing countries, especially in populated country like India wherein there is very limited number of hospitals that have clinical pharmacist in decision making to Patient. Diseases are increasing gradually putting the population at risk. In current situation in other developed Countries with good health care, clinical pharmacy plays contributing role in the improvements towards the Patient health. Professional authorities and organizations in developing countries should work together in Resolving the issues that hinder the standardization of clinical pharmacy practice in hospital. [16]

II. Conclusion

Clinical research and clinical trials are important from the public health perspective. Clinical research facilitates scientists, public health administrations, and people to increase their understanding and improve preparedness with reference to the diseases prevalent in different geographical regions of the world. Moreover, clinical research helps in mitigating health-related problems as evidenced by the current Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic and other emerging and re-emerging microbial infections. Clinical trials are crucial to the development of drugs, devices, and vaccines. Therefore, scientists are required to be up to date with the process and procedures of clinical research and trials as discussed comprehensively in this review.

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