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Phases of clinical trials: a review

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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 trails 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 pharmacokinetic, safety, gross effects are studied on human volunteers, by clinical pharmacologists. If the drug passes the test, it enters phase II testing, 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, IND, ICH Guidelines.

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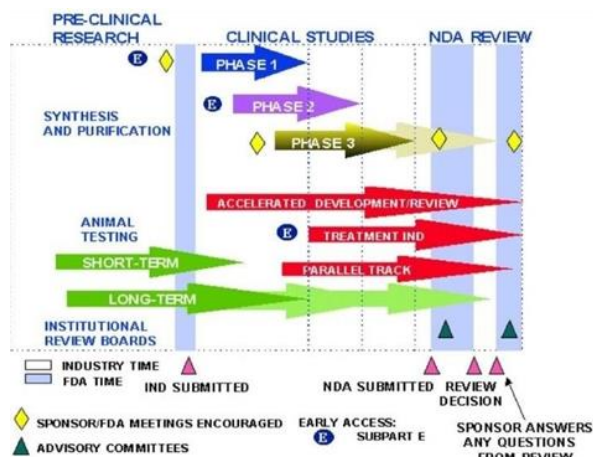
Introduction

Clinical Trials are research studies that are conducted in people (healthy participants or patients with a specific health issue) in order to study and test new medical treatments, such as drugs vaccines, medical devices (e.g. Spinal cord stimulators procedures), medical procedures (e.g. surgical procedures), and diagnostic tests clinical trials may also be conducted to study new combinations of treatments, or to study an already available treatment for a new use (e.g. to trial a drug currently used for depression in patients with chronic pain) [1]. This article will focus on clinical trials for new drugs are medical devices. It will provide an overview of the research that comes before clinical

Trials, the stages/ phases of clinical trials, the regulatory, ethical and safety requirements, who is involved in conducting a clinical trial, what is involved, and what happens after a trial is complete [2].

In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients or to no interventions [3].

Phases of Clinical Trials



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

Pre-Clinical Studies

Pre-Clinical studies involve in vitro (i.e. test tube or laboratory) studies and trials on animal populations. Wide ranging dosages of the study drug are given to the animal subjects or to an in vitro- substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further testing [4].

Phase O

Study of new drug in micro doses to derive PK information in human before under taking phase I studies is called PHASE O.

Micro Dose: less than 1/100 of the dose of a test substance calculated to produce pharmacological effect with a max dose less than 100 micro grams.

Objective

To obtain preliminary pharmacokinetic data.

Pre-Clinical Data

Sub-acute toxicity study in one/species by two routes of administration.

Phase O is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory.

Investigational new Drug (IND) studies phase O trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. Distinctive features of phase O trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10-15) to gather preliminary data on the agent's pharmacokinetics (how the body

processes the drug) and pharmacodynamics (how the drug works in the body) [5].

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety, (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed.

Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have

End-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer center. 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 [5].

There are different kinds of phase I trials

1. Sad

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effect, 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).

2. Mad

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug [6].

Phase II

Once the initial safety of the study drug has been confirmed in phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how the drug works will, as well as to continue Phase I safety assessment in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given). Whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed doses). Some trials combine Phase I and phase II, and test both efficacy and toxicity [7].

Phase III

Phase III studies are randomized controlled multicenter trials on large patient groups (300-3000 or more depending upon the disease/medical condition studied) and are aimed at being the definite assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. It is common practice that certain phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies (FDA (USA), TGA (Australia), EMA (European Union), etc. Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market [8].

Phase IV

Phase IV is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long term adverse effects over a much larger patient population and longer time period than was possible during the phase I-III clinical trials. Harmful effects discovered by phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lip bay), in troglitazone (Rezulin) and rofecoxib (Vioxx) [9].

Investigational New Drug (IND)

INDs (in the U.S), CTXs (in the U.K.) and CTAs (in Australia) are examples of 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 [10].

New Drug Application (NDA)

NDAs (in the U.S), and MAAs (in the U.K), are examples of applications to market a new drug. Such application documents 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 in other countries. The application must present sustainable evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed recommended or

suggested in the labeling, obtaining approval to market a new drug frequently takes between six months and two years [10].

TYPES OF CLINICAL TRIALS:

They are five types

1. Treatment trials

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

2. Prevention trials

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

3. Diagnostic trials

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

4. Screening trials

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

5. Quality of Life

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness [11].

Monitoring Clinical Trials

The purposes of trial monitoring are to verify that:

1. The rights and wellbeing of human subjects are protected.
2. The reported trial data are protected.
3. The conduct of the trial is in compliance with the currently approved protocol/ amendments, with GCP, and with the applicable regulatory requirements.

ICH GCP Guidelines

The principles of ICH GCP

1. Clinical trial should be conducted in accordance with the ethical principles that have their origin in the declaration of Helsinki, and that are consistent with GCP and the applicable regulatory authorities.
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and wellbeing of the trial subjects are the most important considerations and should prevail over

proposed clinical trial.

4. The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) independent ethics committee (IEC) approval opinion.
7. The medical care given to and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician, or when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by an education, training, and experience to perform his or her respective tasks.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement.
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approval protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implanted [12].

International Conference on Harmonization Guidelines

In recognition of the international market place for pharmaceutical and in an effort to achieve global efficiency for both regulatory agencies and the pharmaceutical industry, the FDA, counterpart agencies of the European union and Japan and geographic representatives of the pharmaceutical

industry formed a tripartite organization in 1991 to discuss, identify, and address relevant regulatory issues. This organization, named the international conference on harmonization of pharmaceuticals for Human Use (ICH) has worked toward harmonizing, or bringing together, regulatory requirements with the long-range goal of establishing a uniform set of standards for drug registration within these geographic areas.

Examples of specific ICH developed guidelines

1. Stability testing of new drug substances and products
2. Validation of analytical procedures for Pharmaceuticals
3. Impurities in new drug substances and products
4. General consideration for clinical trial [12].

Role of Pharmacists in Clinical Trials

Pharmacists have an active role to play in research and clinical trials first of all, we provide the necessary facilities required for proper storage of the investigational medicinal products (IMPs), either in the fridge or at controlled room temperature, regular temperature monitoring is ensured and recorded. It is also the pharmacist's duty to ensure there is constant supply of IMPs, at all times, and that they are dispensed to patients accordingly. Patients are counseled on the correct use of the IMPs in addition to written information that is provided, such as, informed Consent Form or the patient Information Leaflet. IMPs returns from patients are counted and documented to determine compliance to the treatment. For injectable IMPs, pharmacists will also ensure that they are prepared in accordance to the specifications stipulated in the trial, and that they are administered appropriately. Drug Utilization Evaluation (DUEs) is research projects that are commonly conducted by pharmacists. These projects aim to facilitate rational use of drugs within our patients. Essentially, providing insights on how drugs are used in patients and observing prescribing patterns by our physicians. DUEs are sometimes considered as drug audits because pharmacists are ensuring the use of medication is appropriate. Results obtained from surveys are used to improve the services that we provide to our patients. Currently, NCC's oncology pharmacy is conducting two surveys. We would like to take this opportunity to

thank all our patients who have consented to participate in the survey [13].

Conclusion

A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trials are conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III, IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamics profile and side effect which may be harmful or beneficial, adverse effect and Post marketing surveillance.

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