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Review Article

PHASES OF CLINICAL TRIALS: A REVIEW

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ABSTRACT

According to WHO, the clinical trial is any research study that prospectively assigns human to one or more health-related interventions to evaluate the effects on health outcomes. The reliance on clinical trial methodology in order to generate scientific data on the value of therapies working with all chronic diseases has been adopted worldwide. The clinical trials can be divided in various phases which five phases, i.e. 0, I, II, III and IV trials. The present review aims to discuss about the various phases of clinical trials, the characterization of which has arisen from drug trials.

Keywords: Clinical trials, Phases.

INTRODUCTION

Clinical trails may be defined as the process designed to determine the safety and efficacy of a particular drug or device on humans[1-2]**.** According to WHO, the clinical trial is any research study that prospectively assigns human to one or more health-related interventions to evaluate the effects on health outcomes[3]. Generally, clinical trials have been performed when the satisfactory information regarding the quality of non clinical safety are available which have been approved by the governed authority of drug or device[4]. Initially, the trials have been known to depend upon the product quality in conjunction with the various stages involved in the development of product. Initially, the investigators select the volunteers or patients into small quantities and conduct the clinical trials[4-6]. Once, the positive data have been collected regarding safety and efficacy, the patient number is increased. Moreover, the clinical trials have been performed in several countries. In addition, clinical trials include new drugs that can be classified into four phases. Each of the phases is treated as a separate clinical trail for the approval of drugs. Usually, clinical trials can be divided into five phases, i.e. 0, I, II, III and IV[7-8]. Phase 0 trials have been designated to the pharmacodynamic and pharmacokinetic studies; Phase I includes screening and safety; whereas Phase II involves the establishing of testing protocol; with Phase III as the final testing; and Phase IV as the post approval studies[4-6]. In addition, the phases of clinical trials are the processes in which the scientist performs their tests with healthy mediation in an attempt to find sufficient proof for processes which were useful as a medical treatment. In case of pharmaceuticals study, the phases started from designing of drugs, and discovery that further go on animal testing and finally to the human volunteers[9-10]. This review article highlights about the various phases of clinical trials.

VARIOUS PHASES OF CLINICAL TRIALS

Usually, clinical trials can be divided into five phases, i.e. 0, I, II, III, IV, and V trials based upon specific conditions and requirements (Table 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 an investigational new drug[11-12].

Phase 0

Phase 0 has been regarded as is a recent introduction for exploration of the trials. Initilally, 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 characterstics, 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[12].

Phase I

The third phase of successful clinical trials is referred to as Phase I trials that accounts for the first step for volunteer testing. In this trial, a small number of volunteers (20-100) are selected for the study. Generally, this phase has been conducted in order to analyze the safety, tolerance, pharmacodynamic and pharmacokinetic properties of a drug. These trials are often performed in clinical centres where the subjects are kept under observations by full–time staff[14-15]. Also, the clinics of such clinical trials have been often run by the private contract research organizations (CRO) who perform these trials on the behalf of researcher or pharmaceutical companies. The Phase I trials consists of the normal ranging of dose and are also called as dose magnifying studies, so that the safest and best dose can be determined[15]. Generally, in Phase I trials, the healthy volunteers have been selected. These studies are performed under controlled conditions or clinics called CPUS (central pharmacological units) where the volunteers receive 24 hours of medical attention facility and observation by full time clinical staff. Further, the Phase 1 trials have been categorized in types which include single ascending dose (SAD) trials, and multiple ascending dose (MAD) trials[11-15]. In SAD, a small number of volunteers administered with a single dose of the drug are selected and are observed for a particular dose. Further, if none of the adverse effects have been noted alongwith production of safe pharmacokinetics data, then the dose of the drug is increased which is administered to a new group of participants[4]. If the drug shows unacceptable toxicity or adverse effect in participants, an addition in the participants number occurs. In addition, if any untolerable toxicity is observed, then the increased dose is terminated, and the earlier dose is declared as the maximum tolerated dose (MTD). Such designs consider MTD when one-third of the volunteers experience unacceptable toxicity[11]. In MAD, the studies are performed in order to understand the pharmacokinetic and pharmacodynamic property of multiple dose of the test drug. Generally, in this study, a group of patients have been administerd the multiple low doses of the drug, while samples are collected at various time intervals and analyzed in order to collect information regarding the processing of drug inside the body. Later on, the dose of the test drug is increased for further groups upto a certain level in such studies[11-15].

Phase II

As it has already been reported that in Phase I trials, the dose calculation of the test drug has already been done. The next aim is to analyze whether the drug have the biological and therapeutic level or not[4-5]. In Phase II trials, the studies have been conducted in vast groups (100-300) and are designed to analyze working of drug alongwith Phase 1 assesment of safety in the larger participants. Genetic testing is very much common if there is enough proof of variation in metabolic rate. The Phase II trials have been divided into two groups which include Phase IIa clinical trials that rare designed to analyze the dosing requirement, and Phase IIb trials which have been designed to analyze the drug efficacy. Moreover, there have been some trials which are performed in the combined form for both efficacy and toxicity. Phase II trials are performed at special clinical centers like that of universities and hospitals)[16-17]. A vast range of the toxicity can be detected in the Phase II, which have the highest range of failures. The contention is supported by

the fact that only 25% of the inventive drugs moves to the phase II trials.

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 practices[18]. 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 evalution related to the time period of the intervention can be used in practice[18-19]. 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[20-21].

Phase IV

Phase IV, also referred to as "Post marketing surveillance" (pharmacovigilance), includes the technical support of the drug after the selling permission of the drug is achieved[4-5]. The Phase IV studies can be performed with the help of regulatory authority or by sponsoring company for finding a new market of the drug. Such trails have been designed to find out if any long term adverse effect over a much large population of patients for a longer period of time, that were not possible during Phase II and phase III trials, has been noted. However, the whole process of the drug from the lab to this point takes about 12-18 years approximately[21].

Phase V

Phase V, a new term used in the literature, is also termed as "translational research" to refer the effectiveness and community based research studies. It is used to find the interrogation of a new clinical treatment into a large number of public health practices. Generally, the Phase V trials have been considered as the "field research" and it is particularly designed to test generalization of the mechanism to a large sample[22-23].

Table 1: Phases of Clinical Trials

Phases	Primary goal	Dose	Monitering of patients	Number of participants	Notes
Preclinical	Nonhuman efficacy, toxicity and pharmacokinetic information	Unrestricted	Researcher	Invitro, invivo animal	
Phase 0	Pharmacokinetic and pharmacodynamic	Very small sub therapeutic	Clinical researcher	10 people	Often skip from this Phase
Phase I	Testing of drugs on healthy volunteers for dose ranging	Often sub therapeutic but with ascending dose	Clinical researcher	20-100 people	Determines that whether the drug is safe and efficient
Phase II	Testing of drugs on patients to asses efficacy and safety	Therapeutic dose	Clinical researcher	100-300 people	Determines whether the drug can have an efficacy
Phase III	Testing of drug on patient to asses efficacy and safety	Therapeutic dose	Clinical researcher and personal physician	1000-2000 people	Determines therapeutic effect of drug
Phase IV	Post marketing survillence-watching drug use in public	Therapeutic dose	Personal physician	Any one seeking treatment for their physician	Watch drug long term effect
Phase V	Translational research	No dosing	None	All report used	Research on data collected

CONCLUSION

Clinical trials involving new drugs have been commonly classified into four phases, with each phase of drug approval process treated as a separate clinical trial. The drug-development normally proceeds through various phases over many years. However, much has been investigated about the requirements and agreements of various phases of clinical trails but further studies are in demand in order to completely explore the basic conditions and parameters to be adopted for the successive completion of clinical trials.

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