



A REVIEW ARTICLE ON CLINICAL TRIALS

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Abstract: Clinical trials is a testing research of a new drug safety and efficacy. Pre-clinical studies starts before clinical trials. In pre-clinical trial may look at whether a drug is safe or the side effects it causes; later trials aim to test whether a new treatment is better than existing treatment.

Clinical trials study on different phases that are phase 0, 1,2,3,4. Main purpose of phase 0 to help speed up and streamline the drug approved the process. In phase 1 trials to find out about closes and side effects. A phase 2 clinical trial is to evaluate the effectiveness and safety of a new drug or drug combination for a particular indication. Then in phase 3 study that tests the safety and how well a new treatment works compared with a standard treatment. The main objective of phase 4 trials is to check the drug's performance in real life scenarios. The Phase 4 studies include all studies performed after drug approved and related to the approved indication.

Keywords: Clinical trials, Pre-clinical studies, Clinical studies, NDA, ICH-GCP guidelines.

I. INTRODUCTION:

Whenever we search out a new medicine then there is need of to check out that tests how well new medicines technique work in a human being. A clinical trial is a research study that test a new medical treatment or a new way of using an existing treatment 'to see if it we'll be a better way to prevent and screen for diagnose or treat disease [1]. Developers of a new drug, biological and medical devices must ensure product safety, demonstrate medical safety, and demonstrate medical benefits in human and mass produce the product [2].

For any new drug to enter in clinical trial, it must pass preclinical studies Pre-clinical studies including in vitro i.e. test tube or laboratory that is outside the body. Studies and trials on animal population .wide range of dosage of the study drug is given to animal subject or to an in vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information [1] One challenges to the validity of such trial is the tendency for assessment of outcomes to systemically deviate from truth because of predisposition in observers such as from hope or expectations [3].

Today, there are two internationally recognized human research guidelines that form the basis for the conduct of ethical clinical trial. We have chosen to use the term ethical codes rather than ethical guidelines. A code of practice defines professional rules according to which people in a particular profession are expected behave .other human research guidelines /codes of practice have emerged over the past century ,such as Nuremberg trial at the end of second world war[4].

1.1 OVERVIEW OF DRUG DEVELOPMENT:

The general road to drug development and approval has outlined and controlled by the USA food and drug administration (FDA) for many years. Safety has traditionally been its primary focus, followed by the efficaciousness if a drug seems promising in pre-clinical studies, a drug sponsor or sponsor investigator will submit Associate in nursing investigational new drug (IND) application. This careful proposal contains investigator qualifications and every one pre-clinical drug info and information and an invitation for exemption from the federal statutes that forbid interstate transport of unapproved, the drug is studied (phase one, phase 2, phase three trials) and if incontestable safe and efficacious within the meant population, the drug sponsor will then submit a brand new drug application (NDA) to the government agency. Once an intensive review by the government agency determines whether or not the therapeutic may be studied in part four trials, in which safety and effectiveness for the indicated population is monitored. To facilitate analysis and endorsement of foreign drug information. Efforts have been made of harmonize this approval method across the USA, Europe, and Japan through. The international conference on harmonization of technical necessities for registration of prescribed drugs for human use (ICH) [5].

1.2 HISTORY OF CLINICAL TRIALS:

The evolution of clinical research traverse a long and fascinating journey the the recorded history of clinical trials goes back to the biblical description in 500 B.C. [6]

562 B.C. 1537: pre-James Lind era :

The world's first clinical trials is recorded in the 'book of Daniel ' in the Bible [7].Avicenna (1025 AD) in his encyclopedic 'canon of medicine ' describes some interesting rules for the testing of drug [8]. He suggested that in the clinical trial a remedy should be used in it's natural state in disease without complication .the first clinical trial of a novel therapy was conducted accidentally by the famous surgeon ambrosia pare in 1537[7,9].

The term clinical trial simulation may have been first used to describe a game entitled "instant experience." [10].

1800: Arrival of placebo:

It took another century before the emergence of another important mile stone in the history of modern clinical trial; the placebo. The word first appeared in medical literature in the early 1800 [7].

1943: The first double blind controlled trial patulin for common cold:

The medical analysis council (MRC) Britain dole out an attempt 1943. To analyze patulin treatment for (an extract of genus *Penicillium patulinum*) the respiratory disorder. This was the primary run comparative trial with synchronal management within the general population in recent time [11].

John wood wall, an English military medico of country Malay Archipelago company, had suggested the consumption of citrus, (it has AN antiscorbutic effect) from the seventeenth century, but their use didn't become widespread [12].

Evolution of clinical trials in India:

India has recently been recognized as a horny country for clinical trials .but the country's journey in clinical analysis field includes a long history .India includes a wealthy heritage of ancient medicine-Ayurveda. The classic aurvedic texts contain elaborated observations on wellness and depth guidance on remedies. It's possible that these description square measure supported direct observation created by ancient piece of writing consultants. However, there's no recorded documentation within the ancient texts of any clinical experiments. Hence, one must fall back on current history of medical analysis in Asian nation.[13]

The central moral committee of ICMR on human analysis accepted below the billet of honorable justice (retired) M.N.venkatachalian control its 1st meeting on Sept ten, 1996. Many subcommittees were accepted to think about moral problems in specific areas e.g., medical specialty analysis; clinical analysis of product to be used on humans; organ transplantation; human biology, etc. The committee free moral tips for medical specialty analysis on human participants in 2000 that were revised I 2006 [14].

Modern trials:

Austin printer Hill was a crucial figure within the trendy development of clinical trials. Sir Ronald A. Fisher ,while operating for the Roth Amsted experimental station within the field of Agriculture , development his principles of experimental style within the Twenties as Associate in Nursing correct methodology for the correct style of experiments .Among his major concepts ,was the importance of organization -The random assignment of people to totally different teams for the experiment;[15] replication - to scale back uncertainty , activity ought to be perennial and experiments replicated to spot supply of variation ;[16] block - to rearrange experimental units into teams of units that square measure like one another ,and therefore reducing moot - economical at evaluating the consequences and doable interactions of many freelance issue [17].

1.3 TYPES OF CLINICAL TRIALS:**A) Treatment trials:**

Test experimental treatments, new combination of medication, or new approaches or radiation.

B) Prevention trials:

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

C) Diagnostic trials:

Conducted to find better tests or procedure for diagnosis a particular disease or condition.

D) Screening trials:

Test the simplest thanks to discover sure diseases or health conditions.

E) Quality of life:

Trials (or auxiliary care trials) explore ways in which to boost comfort and therefore the Quality of life for people with a chronic wellness [3].

2. PHASES OF CLINICAL TRIALS:

Before pharmaceutical industries start a clinical trials on a drug, they conduct extensive pre-clinical studies [18].

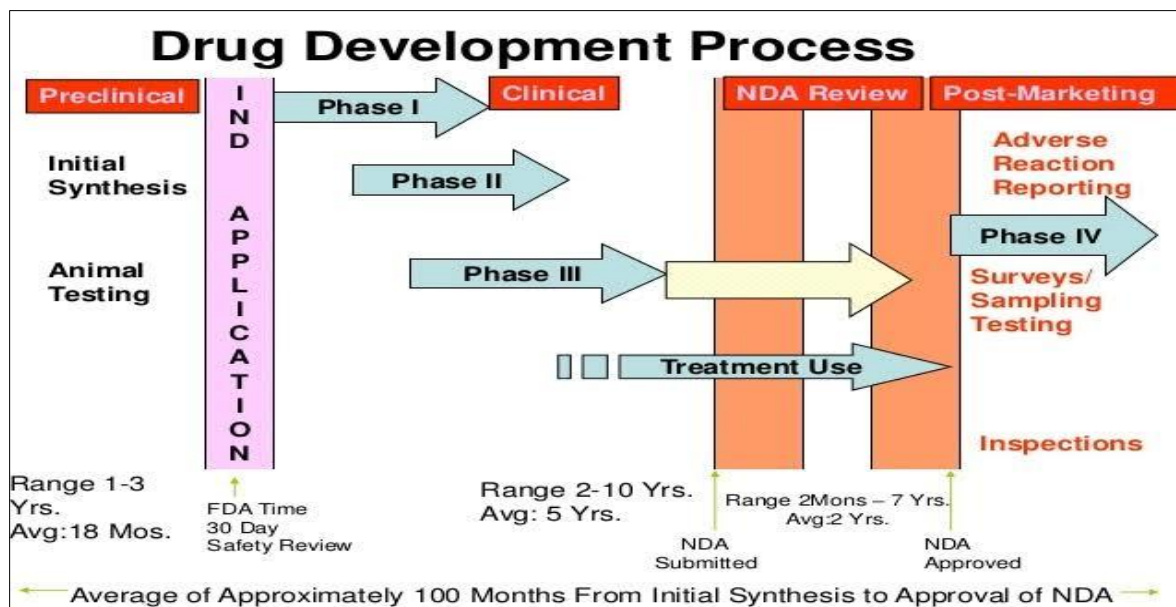


Figure 1: Drug development process

2.1. Pre-Clinical study:

Pre-clinical investigations embrace animal studies and analysis of drug production and purity. Animal studies explore :a)The drug's safety in doses similar to around human exposure) Pharmacodynamics (i.e. Mechanism of action ,and the relationship between drug levels and clinical response) ,and c) pharmacokinetic (I.e,drug absorption , distribution , metabolism, excretion ,and potential drug-drug interaction). This information should be submitted for IND approval if the drug is to be more studied in human subjects [19]. Preclinical development starts before clinical trials and also the main goal to work out safety and effectiveness of the intervention. Throughout diagnosing studies, in vitro and vivo testing is performed. Toxicity embrace studies of that organs arena targeted and long run cancer effects or effects on class copy. If diagnosing studies show that the medical aid is safe and effective , clinical trials ,defined as "Scientifically controlled studies of the security and effectiveness of therapeutic agent victimization willing human subjects," are started .the four attainable outcome are -a) the new treatment incorporates a giant helpful impact and is superior to straightforward treatment ;b)The new treatment is comparable to straightforward treatment .c) The new treatment is neither superior or neither inferior to straightforward treatment .d)A new treatment is a smaller amount effective than normal treatment [20- 24]. Complex method are concerned in developing a replacement drug alongside it is time and prices consumption. Before launching, it needs sort of proof to point out it potential activity [25]. In diagnosing studies, animal studies are excusable if f worn out the way to reduce pain in animal models and where applicable. Different methodology are explored and avoiding spare cruel nice to animals [26].

as an example, reports say that, concerning ninety five you look after medication that that enter clinical trials associated with stroke or septic shock don't get launched within the market although huge expenditure are handled the fundamental studies and drug discoveries [27] and equally, the average success rate in clinical cancer trials is a smaller amount than V-E Day when diagnosing estimation [28].

2.1.1. Preclinical studies overall scenario:

Results of animal medicine experiments have immensely did not translate into human clinical trials that are largely attributed as a result of variations within the underlying biology between humans and animals to short returning within the experimental style or to bias within the reportage of results from animal studies [29].

With relevance clinical studies, it depends on the study protocol that are designed when important data generated from presymptomatic studies .the application of this information to the human studies is of major concern whereby the overriding importance lies with the power to know the presymptomatic study results before inward at any conclusion [30].

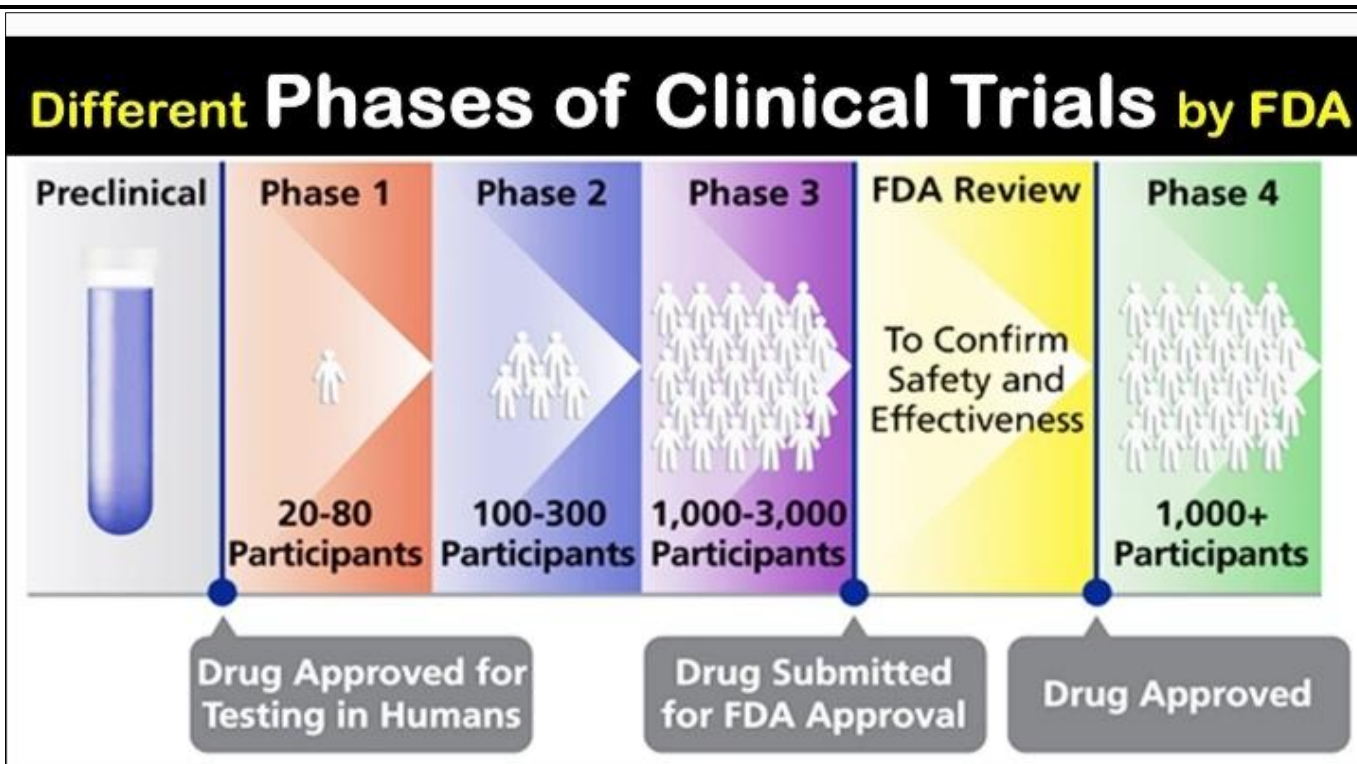


Figure 2: Different Phases of Clinical Trials by FDA

2.2. Phase 0:

2.2.1. Selection of agents for phase 0 trials:

Phase zero may be selected because the initiative of drug development method that determines whether or not the intent thought ought to run to the new chemical entity or not. Throughout drug development method, the ideal requirement for analysis of a brand new drug underneath section zero investigation may be classified as follows:

- 1) Pharmacodynamics activity of the drug.
- 2) Credentials of target or biomarker is (i.e. modulation of the target or biomarker in diagnosing studies is related to A growth effect).
- 3) Broad therapeutic window of drug candidate.
- 4) The hand-picked drug candidate ought to be non-toxic at dose level and will be exposed for period, That is, about a week on a restricted variety of volunteers (I.e., 10 to 15)

These ideal characteristics are applied to the suitable real medical aid, bio modulators and picture probes. The bio modulators embrace agent that interfere with DNA repair ,such as inhibitors of poly (Adp-ribose) enzyme (PARP).ABT-888Which is Associate in Nursing matter of the PARP met all the on top of criteria and was selected as a superb candidate for part zero studies . On the contrary ,if a cytotoxic agents bears a slender therapeutic index, or a targeted agent ,when it possess Associate in Nursing unidentifiable proportion of patients ,for instance thanks to certificated biomarkers absence ,it can't be used for the part zero investigation [31]. The part zero clinical trials have tremendous scope in close to future. It additionally known as wildcat investigational new drug (IND) OR "micro dosing methodology." the aim of this steerage the part wildcat IND study is meant to explain a test that;

Is conducted early in part one.

Involves terribly restricted human exposure and

Has no therapeutic or diagnostic intent (e.g., Screening studies, micro-dose studies)).

Such wildcat IND studies are conducted before the standard dose increase, safety, and tolerance studies that normal initiate a clinical drug development (32, 33).

2.2.2. Classification of phase 0 clinical trials:

The phase 0 clinical trials can be classified into three major types such as:

- 1) Determination of drug pharmacokinetic (micro dose trials).
- 2) Determination of pharmacological significant doses of drug.
- 3) Determination drug mechanism of action (34).

Successful modeling of phase 0 trial:

In addition to assay validation and optimization, successful modeling of clinical procedure (for tissue collection and handling) using preclinical models is also an important prerequisite for obtaining useful assay results and assuring the assay's clinical readiness. Importance of successful modeling with establishing optimal time window for drug administration and obtaining tissue samples is clearly evident from the past work (35, 36).

Ethical issues in conducting phase 0 trials:

Being non-therapeutic in nature, ethical concerns have been raised pertaining to conduct of phase 0 trials, including no direct benefits to patients, delayed participation in other trial and invasive biopsy procedures. Comprehensive analysis of ethical issues, however, did not disclose any issue making these trials inherently impossible (37), and these can be dealt with careful strategies focusing on informed consent process and study design. Patient should be carefully informed of no personal benefit and their understanding is required to be documented (38).

2.3. Phase-I clinical trials:

A section one run appraise the most effective thanks to administer a drug, its frequency and dose, the maximum tolerated dose (MTD), and facet effects. Tolerability, pharmacokinetic, and pharmacodynamics square measure evaluated. These studies verify, most importantly, if the treatment is safe trials typically embrace twenty to a hundred patients and Greek deity monitored by the clinical researchers. Doses square measure raised if there aren't any severe facet effects and patient square measure tested to work out if he or she is responding to the medical aid. These increase dose studies square measure accustomed verify the most effective and safest dose which will be administered and could be a fraction of the dose that caused damage throughout animal testing. Needless exposure of subjects to sub-therapeutic doses whereas maintaining safety and fast accrument is that the primary goal of section one trial (39).

2.3.1. Different kinds of phase 1 studies:

1. SAD:

(Single Ascending Dose Studies) little cluster of subjects receive one dose of the drug whereas they're ascertained and tested for a amount of your time. If tolerated, and the pharmacokinetic information is generally in line with foretold safe valves, the next cluster of subjects receive the next dose. This can be continued till pre-calculated pharmacokinetic safety level ar reached, or till the administered dose is related to unacceptable toxicity. The highest tolerated dose (MTD) is typically the dose below the one that turn out unacceptable toxicity. The MTD is additionally outlined because the dose that has a suitable variety of facet effects and is thus utilized in additional studies.

MAD:

(Multiple Ascending dose studies) follow the unhappy studies each temporary and in method, as these permit determination of MTDs with repeat dosing. MAD studies assess the pharmacokinetic and pharmacodynamics of multiple doses of the drug. Patient receive multiple low doses of the drug, whereas samples (Of blood and different fluids) are collected at numerous time points and analyzed to grasp however the drug is processed inside the body. the dose is afterward escalated for further teams, up to a planned level.

Food effect:

An investigation into any differences in absorption of the drug by the body, caused by eating before the is given. These student are often run as a crossover study, with volunteer being given two identical doses of the drug on different occasions; one while fasted, and one after being fed.

Outcome measures:

Another live of toxicity in section one trials involves finding the dose limiting toxicity (DLT) in healthy volunteers a DLT happens once a significant adverse event involving any reaction associated with the trial drug needs treatment and also the person should stop taking the new drug. different trial end that also are measured might embody the watching of drug uptake metabolism and excretion, body temp., pressure, drug plasma concentrations., And different biological and physiological markers. Several variable have to be compelled to be measured, to collect enough knowledge to work out whether or not the drug is safe enough and price work any (40-44).

2.4. Phase 2 clinical trials

Phase 1/2 dose finding studies determine the most successful dose (MSD) which is the dose which maximize the product of the probability of seeing no toxicity together with the probability of seeing a therapeutic response. While a phase 1 clinical study focuses on determining the MTD phase 2 studies evaluate potential efficacy and characterizes treatment benefit for the disease in a convincing manner. These studies are performed on larger groups (100 to 300 subjects) and are designed to assess how well the drug works and to continue safety assessments. Phase 2 may be divided into phase 2A which are pilot clinical trials to evaluate efficacy and safety in selected population with the disease or condition to be treated, diagnosed or prevented (dose-response, type of patient, frequencing of dosing, or other identifiers of safety and efficacy). And phase 2B which are the most rigorous trials designed to demonstrate efficacy. The development process usually fails during the phase 2 when the drug is discovered not to work as planned or to have toxic effects.

The phase 2 design depends on the quality and adequacy of phase 1 studies. Patients in phase 2 trials generally have more exclusion criteria than those in phase 3 trials. Single stage and multi stage phase 2 clinical trial design are often developed on the bias that one endpoint is of interest. A commonly used phase 2 design is based on the work of gain, a version of a two-stage design (45). Phase 2 trials typically employ one or occasionally a few dose levels. Larger cohorts of patient are exposed to the drug in order to observe one or more clinical endpoints in trials of heart failure., For example., Physiological parameters (e.g. ventricular remodeling) may be assed in addition to clinical measures such as exercise tolerance [46,47], vaccines studies typically asses safety and immune response and may involve both treatment and control groups[48].

2.5. Phase 3 clinical trial:

Based on previous studies demonstrating beginning drug safety and potential effectiveness, a section three trial (conjointly referred to as a "Therapeutic confirming", "Comparative effectiveness" or "pivotal trial".) Could also be perused. This stage of drug assessment is conducted in a very larger and sometimes additional various target population so as to demonstrate and/or make sure effectiveness and to spot and estimate the incidence of common adverse reactions. However, given that section three trial square measure sometimes no larger than three hundred to 3000 subject, they consequently have the applied math power to determine associate degree adverse event rate of no but one in one hundred person (supported Hanley's rule of three "[49]. Section e trial

square measure the complete scale analysis of treatment and square measure Designed to match effectiveness of the new treatment with the quality treatment. This can be the "pre-marketing phase" of run. Section three run is most costly and time overwhelming section. During this section one hundred to 3000 subjects square measure needed. Patient square measure monitored by the clinical investigator and private medical practitioner. section three clinical trials are the gold customary proof for the approval of latest medicine , issues related to drug development have embody restricted clinical edges in giant RCT's prediction of a victorious section three trial from phase a pair of knowledge , determination of toxicity ,design of studies with drug combination ,and cost of the trials [50].

2.6. Phase 4:

Phase four studies embody "all studies (Other than routine surveillance) performed once drug approval and associated with the approved indication (51). Part four trial is additionally called post promoting police investigation trial. Part four trials involve the security police investigation (pharmacovigilance) and current technical support of a drug once it receive permission to be sold-out . The security police investigation is intended to discover any rare or future adverse effects over a way larger patient population and longer fundamental quantity than was attainable throughout the part one to three clinical trials. Harmful effects discovered by part four trial might lead to a drug being now not sold-out, or restricted to sure uses (3).

3. ICH-GCP Guidelines: (INTERNATIONAL CONFERENCE ON HARMONIZATION -GOOD CLINICAL PRACTICE)

Good Clinical follow (GCP) is a global moral and scientific quality standards for the look, conduct, performance, monitoring, audition, recording, analyses, and coverage of clinical trials. GCP provides assurance that the info and rumored results area unit credible and correct, and that the rights, integrity and confidentiality of trial subjects area unit revered and guarded [52]

1. Participation in studies is voluntary and once the participant provides a consent.
2. The experiment ought to be helpful to group.
3. Human experiment ought to be supported results of previous animal experiments.
4. Physical and mental suffering to subjects ought to be avoided.
5. No experiment that will result in death or incapacity to subject ought to be undertaken.
6. The risk mustn't exceed the humanitarian importance of the matter to be solved.
7. Human subjects ought to be protected against even remote prospects of damage.
8. Solely qualified scientists ought to conduct medical analysis.
9. Human subjects ought to be absolute to finish AN experiment at any time.
10. The scientists guilty should be ready to finish AN experiment at any stage [53].

CONCLUSION:

Clinical trials of a new drug follow the guidelines of ICH-GCP which are performed on volunteers. New drug firstly goes under pre-clinical trial after that goes under clinical trial phases 1,2,3,4. These phases provide detail explanation about drug that is its pharmacodynamics and pharmacokinetic properties. Also provide its efficacy, safety and side effects.

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