International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 07 Issue: 05 | May - 2023 SJIF 2023: 8.176 ISSN: 2582-3930

Clinical Research

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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), medical procedures (e.g surgical procedures), and diagnostic tests. Clinical trials may also be conducted to study new combinations of treatments, or to compare 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).
This article will focus on clinical trials for new drugs or 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.*1

Preclinical Research :- Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity*2.
Preclinical studies are performed in in vitro, in vivo, ex vivo, and in silico models to obtain basic information about the safety and biological efficacy of a drug candidate before testing it in a final target population, i.e., humans. Preclinical studies or tests are mainly performed in compliance with GLP/GSP guidelines (good laboratory practice and good scientific practices) to ensure reliability and reproducibility of results. The FDA/EMA require supporting basic preclinical data to IND application especially on toxic effects, safety profile, pharmacokinetics, and pharmacodynamics. The data from preclinical trials must be accurate, reliable, and based on the best suitable and comparable model available to the target population. Typically, this means that the IND or drug product must undergo a series of robust tests and experiments using in vitro, in vivo, ex vivo, and in silico models as per the needs of the focused indication and regulatory guidelines*3.

Phase 0 :- Phase 0 of a clinical trial is done with a very small number of people, usually fewer than 15. Investigators use a very small dose of medication to make sure it isn't harmful to humans before they start using it in higher doses for later phases.

If the medication acts differently than expected, the investigators will likely to do some additional preclinical research before deciding whether to continue the trial*4.

- **Phase 1**:- The first few people in the study get a very low dose of the treatment and are watched very closely. If there are only minor side effects, the next few participants get a higher dose. This process

continues until doctors find a dose that's most likely to work while having an acceptable level of side effects.

- Phase I trials are also looking at what the drug does to the body and what the body does with the drug.
- Safety is the main concern. The research team keeps a close eye on the people and watches for any severe side effects. Because of the small numbers of people in phase I studies, rare side effects may not be seen until later phases of trials when more people receive the treatment.
- While some people may benefit from being on one, disease response is not the main purpose of a phase I trial,
- Placebos (inactive treatments) are not used in phase I trials.
- Phase I trials usually include a small number of people (up to a few dozen).
- Phase I trials most often include people with different types of cancer.
- These studies are usually done in major cancer centers.
- Phase I trials carry the most potential risk. But phase I studies do help some patients. For those with life-threatening illnesses, weighing the potential risks and benefits carefully is key. Sometimes people choose to join phase I trials when all other treatment options have already been tried*5.Their are different types in phase-1

  1] **SAD :-** A single ascending dose study (SAD study) is a type of Phase I trial. Single ascending dose studies are usually conducted in a small number of healthy volunteers (although some trials recruit patients). The aim is to find out the safe dose range, and to look for any side effects.

  2]**MAD**:- Subjects in a MAD study receive multiple doses of the study drug, whereas subjects in a SAD study receive only one dose of the study drug. SAD and MAD studies are both performed early in clinical development*6.

Phase2:- Phase II studies determine the effectiveness of an experimental drug on a particular disease or condition in approximately 100 to 300 volunteers. This phase may last from several months to two years.

A Phase II trial answers the question, "Does Drug X improve Disease Y?"

A secondary objective for a Phase II trial is to ascertain therapeutic dose level and dosing frequency. This answers the questions, "What quantity of Drug X works better on Disease Y, (1 mg, 2 mg or 3 mg)?" and "Does Drug X work better on Disease Y taken once or twice a day?"

Most Phase II studies are randomized, which means that subjects are assigned randomly (by chance not by choice) to receive either the experimental drug, a standard treatment or a placebo (harmless, inactive substance). Those who receive the standard treatment or placebo are called a control group.

Randomized Phase II studies are often double-blind, which means that both subject and physician don't know which treatment is being used. Blinding prevents any unscientific influence on the study results that could be caused by knowledge of the treatment. In a single-blind study, only the subject is unaware of the treatment used.

Since larger numbers of patients receive a treatment in Phase II studies than in phase I studies, there is a greater chance to observe and compile side effect information. Subjects in a Phase II trial may benefit from their participation if they receive an active treatment. Approximately 33 percent of experimental drugs which pass Phases I and II will go on to Phase III.

Phase3:- Phase III studies are conducted at multiple centers with several hundred to several thousand patients for whom the drug is intended. Massive testing of a drug provides continued generation of data on a drug's safety and efficacy. As in Phase II, most Phase III studies are randomized and blinded.

Phase III trials provide the bulk of information needed for the package insert and labeling of a medicine, after it has been FDA approved.

A drug in this phase can be studied for several years and may be one of 25-30 percent that pass Phases I, II and III. Once a Phase III study is completed, a pharmaceutical company can request FDA approval to market the drug. This is called a New Drug Application (NDA). The NDA contains all the scientific data that the company has gathered throughout the phases in all trials*7.

Phase4:- A type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market. These trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time*7.

Investigational new Drug (IND)Application :- Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:-

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:-

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:-

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

- Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk*2.

NEW DRUG APPLICATION (NDA) / MARKETING AUTHORIZATION APPLICATION (MAA):- An application made to a European regulatory authority for approval to market a medicine within the European Union (or Iceland, Liechtenstein or Norway).

An MAA includes comprehensive information about a drug to enable a regulatory authority to judge its quality, safety and efficacy*8

TYPES OF CINICAL TRIAL:- 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*9.

MONITORING CLINICAL TRIALS:- The purposes of trial monitoring are to verify that:-

1. The rights and well being 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/amendment(s), with GCP, and with the applicable regulatory requirement(s).

ETHICAL CONSIDERATION :-

An Independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non- medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by among other things, reviewing and approving /providing favorable opinion on, the trial protocol, the suitability of the investigators facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the independent Ethics Committee to act in agreement with GCP as described in this guideline.

COMPLIANCE WITH PROTOCOL:-

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies) and which were given approval/ favourable opinion by the IRB/IEC. The investigator/ institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement. The investigator should not implement in deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval / favorable opinion from the IRB / IES of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subject, or when the change(s) involves only logistical or administrative aspect of the trial (e.g. change in monitor (s), change of telephone no.(s). The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/ favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment(s) should be submitted.

1. To the IRB/IEC for review and approval/favorable opinion.

2. To the sponsor for agreement.

3. To the regulatory authority (IES).

PLANS OF CLINICAL TRIALS:-

Trials may be open, blind or double-blind. 1. 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

1. Blind trials

A. Single-blind trial:- In a single-blind trial, the researcher knows the details of the treatment but the patient does not. Because the patient does not know which treatment is being administered (the new treatment or another treatment) there might be no placebo effect. In practice, since the researcher knows, it is possible for him to treat the patient differently or to subconsciously hint to the patient important treatmentrelated details, thus influencing the outcome of the study.

B. Double-blind trial:- In a double-blind trial, one researcher allocates a series of numbers to 'new treatment' or 'old treatment'. The second researcher is told the numbers, but not what they have been allocated to. Since the second researcher does not know, he cannot possibly tell the patient, directly or otherwise, and cannot give in to patient pressure to give him the new treatment. In this system, there is also often a more realistic distribution of sexes and ages of patients. Therefore double-blind (or randomized) trials are preferred, as they tend to give the most accurate results.

C. Triple-blind trial:- Some randomized controlled trials are considered tripleblinded, 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*10

GCP - 13 Principles :-

- Ethics 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 GCP and the applicable regulatory requirement(s).

- Trial risk vs trial benefit 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.

- Trial participants The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

- Information on the Medicinal Product The available non-clinical and clinical information on an Investigational Product should be adequate to support the proposed clinical trial.

- Good quality trials Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

• Compliance with the study protocol A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

• Medical decisions 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.

• Trial staff Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

• Informed consent Freely given informed consent should be obtained from every subject prior to clinical trial participation. • Clinical trial data All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

• Confidentiality The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

• Good Manufacturing Practice Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

• Quality assurance Systems with procedures that assure the quality of every aspect of the trial should be implemente*11

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.

With ICH success, duplicative technical requirements for registering Pharmaceuticals would be eliminated, new drug approvals would occur more rapidly, patients' access to new medicines would be enhanced worldwide, the quality, safety, and efficacy of imported products would be improved, and there would be an increase in information transfer between participating countries.

The ICH's work toward uniform standards is focused on three general areas, quality, safety and efficacy. The quality topic includes stability, light stability, analytical validation, impurities, and biotechnology. The

safety topics include carcinogenicity, genotoxicity, toxicokinetics, reproduction toxicity and single and repeatdose toxicity.

The efficacy topics include population exposure, managing clinical trials, clinical study reports, dose response, ethic factors, good clinical practices, and geriatrics. For each topic, relevant regulations are identified, addressed and consensus guidelines developed.

The intension is that these guidelines will be incorporated in to domestic regulations. In the United states the resulting guidelines are published in the Federal Register as notices, with accompanying statements indicating that the guideline should be "Useful" or "considered" by applicants conducting required studies or submitting registration applications.

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 PLACEBO in Clinical Trail:- Placebo is a Latin term which means " I may please you." The placebo effect is an effect attributable to a medicament as a procedure, and is not due to any specific pharmacodynamic property of the substance for the condition being treated. Placebo effect may be defined as " how the patients perception of treatment influences his / her response." Placebos are used, During the clinical trial, to eliminate the possibility that the benefit of the drug is solely due to chance; and as therapeutic agents that work psychologically.

A placebo preparation is usually an inert substance like starch or lactose. However occasionally it may be a drug that is active but in a different situation. In fact, even when an active drug is used, its placebo effect often comforts the patient much before the drug is effective. It is well known that the patient as well as his relatives get some immediate relief as soon as the doctor's medicine is administered, irrespective of its drug content. This is because of their faith in the doctor that things will go well in his hands.

Placebos can often produce relief of subjective symptoms associated with psychological disturbances. This includes relief from anxiety, headache, pain, insomnia and breathlessness. Hence placebos are often employed in the treatment of certain diseases where the psychic element is suspected to be responsible for subjective symptoms. Objective responses such as increase or decrease in Europhiles and eosinophils may sometimes be seen with placebos. When administered for its therapeutic effects, the placebo preparation, must appear to be relevant to the illness, must be harmless, Should preferably conform to the patient's

expectations and To be effective, the 'potency ' of the preparation must be shown by some signs such as strong taste, a colorful capsule or a tablet of odd shape and sometimes even by obvious but harmless side effect like colored urine.

During clinical trials, placebos are used to eliminate the effect of bias of the physician and the patient, particularly in evaluating a new drug claimed to be effective in conditions like bronchial asthma, angina pectoris, pain and psychiatric disorders. In such cases the placebo should be indistinguishable from the active medicament in physical prosperities like color, smell, taste and form.

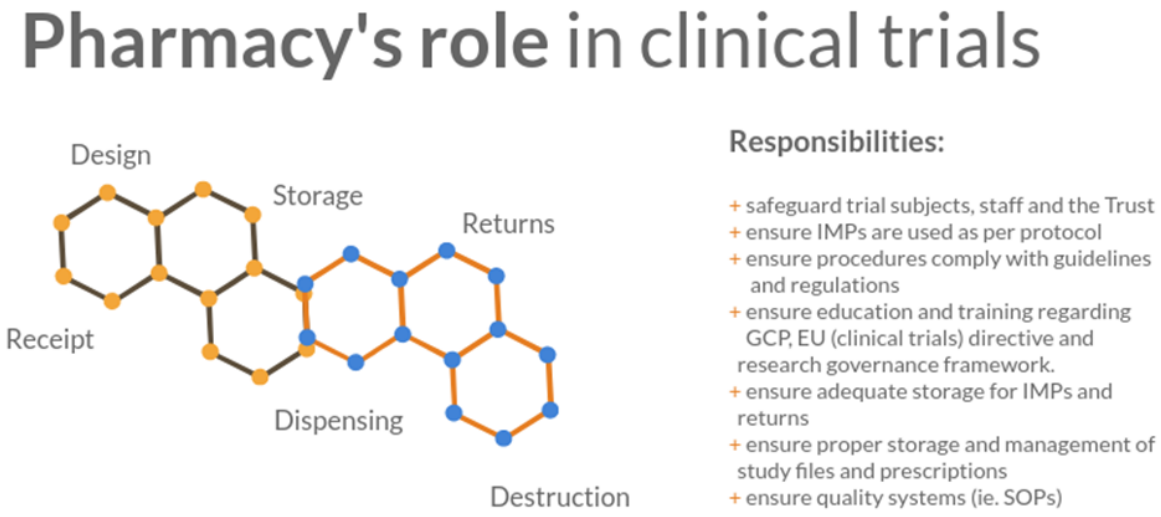
Placebo effect may be modified by:

1. Personality of the physician.

2. Personality of the patient.

3. Form of administration*13

Role of Pharmacist:-



- A pharmacist manages all aspects related to investigational study drug along with liaising with researchers to define and plan study design, identifying wide range of subject specific doses, dosage forms and training team members like clinical investigators and nurses in funding agencies and pharmaceutical companies*14

CONCLUSION:-

- A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial 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 and IV. These phases provide in detail explanation of pharmacokinetic, pharmacodynamic profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance

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