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Review on Clinical trials

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Abstract:

Clinical trials are research studies conducted to evaluate the safety and effectiveness of new drugs. These trials are typically preceded by pre-clinical studies, which assess a drug's safety profile and potential side effects. While pre-clinical trials focus on the initial safety evaluation, clinical trials aim to determine whether a new treatment is more effective than existing therapies.

Clinical trials are carried out in several phases: Phase 0, Phase 1, Phase 2, Phase 3, and Phase 4. Phase 0 is designed to accelerate the drug approval process by providing preliminary data on how the drug behaves in the body. Phase 1 trials primarily focus on determining the appropriate dosage and identifying potential side effects. In Phase 2, researchers assess the drug's safety and effectiveness for a specific condition or disease. Phase 3 trials compare the new treatment to standard treatments, evaluating its overall safety and efficacy on a larger scale. Lastly, Phase 4 trials, conducted after the drug has been approved, aim to monitor its performance in real-world scenarios. These post-approval studies further assess the drug's long-term effects and ensure its continued safety and effectiveness for the approved indication.

Keywords

Clinical trials, History, Different phase of clinical trials, ICH-GCP guidlines.

Introduction:

Introduction:

When developing a new medicine, it is essential to evaluate its effectiveness and safety in humans. Clinical trials are research studies designed to test new medical treatments or innovative ways of using existing treatments. These trials aim to determine whether a treatment can improve the prevention, diagnosis, or management of diseases【1】. For a new drug, biological product, or medical device to advance, developers must ensure its safety, demonstrate its medical benefits in humans, and establish its suitability for mass production【2】.

Before entering clinical trials, new drugs must undergo preclinical studies. These studies involve *in vitro* experiments, such as laboratory tests outside the body, as well as trials on animal models. Researchers administer varying doses of the study drug to animal subjects or *in vitro* systems to gather initial data on efficacy, toxicity, and pharmacokinetics【1】. One challenge to the validity of clinical trials is observer bias, where expectations or hopes may influence the assessment of outcomes, potentially deviating from objective truth【3】.

Today, two internationally recognized guidelines govern the ethical conduct of human research in clinical trials. These are referred to as ethical codes rather than ethical guidelines, as a code of practice defines professional standards for behavior within a specific field. Over the past century, other human research codes have emerged, such as the Nuremberg Code, which arose after the Second World War【4】.

Overview of drug development

The process of drug development and approval has been regulated by the United States Food and Drug Administration (FDA) for many years. The primary focus of this process has traditionally been on ensuring safety, followed by evaluating the drug's efficacy. If a drug shows promise during preclinical studies, the sponsor or investigator submits an Investigational New Drug (IND) application. This application includes detailed information about the drug's preclinical data, investigator qualifications, and a request for exemption from federal laws that restrict interstate transportation of unapproved drugs. Upon IND approval, the drug undergoes clinical testing, progressing through Phase 1, Phase 2, and Phase 3 trials. These trials are designed to evaluate the drug's safety, efficacy, and suitability for the intended population. If the trials demonstrate that the drug is both safe and effective, the sponsor submits a New Drug Application (NDA) to the FDA. The NDA undergoes a thorough review to determine whether the therapeutic can proceed to Phase 4 trials. Phase 4 studies monitor the drug's long-term safety and effectiveness in real-world settings for the indicated population. To streamline the evaluation and approval process internationally, efforts have been made to harmonize regulatory requirements across the United States, Europe, and Japan. This collaboration is facilitated through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which promotes consistent standards for drug registration globally【5】.

History of Clinical Trials

The history of clinical research spans a long and remarkable journey, with its origins traced back to ancient times. The earliest recorded account of a clinical trial dates to approximately 500 B.C., as described in the Bible's *Book of Daniel*. In this narrative, a controlled comparison was made between a diet of vegetables and a diet of royal food to assess their health effects【6】【7】.

Pre-James Lind Era (562 B.C.–1537)

During this period, several key contributions laid the groundwork for clinical research. Avicenna, a renowned Persian physician, detailed principles for drug testing in his medical encyclopedia, *The Canon of Medicine* (1025 AD). He emphasized that treatments should be tested in their natural state on uncomplicated diseases【8】. The first accidental trial of a novel therapy occurred in 1537, when the surgeon Ambroise Paré tested a new wound treatment, marking a pivotal moment in the evolution of clinical trials【7】【9】.

The Arrival of Placebos (1800s)

It was not until the 19th century that the concept of a placebo—a substance with no therapeutic effect used as a control in clinical trials—emerged as a significant advancement in modern clinical research. The term "placebo" first appeared in medical literature during the early 1800s, signifying a major milestone in trial methodology【7】.

Clinical Trial Simulation

The phrase "clinical trial simulation" is believed to have been initially introduced as a reference to a game called "instant experience," highlighting early conceptual developments in trial modeling【10】.

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

In 1943, the Medical Research Council (MRC) in Britain conducted a pivotal clinical trial to evaluate the effectiveness of patulin, a compound extracted from *Penicillium patulinum*, as a treatment for the common cold. This trial was significant as it marked the first double-blind, controlled study conducted within the general population in modern times【11】.

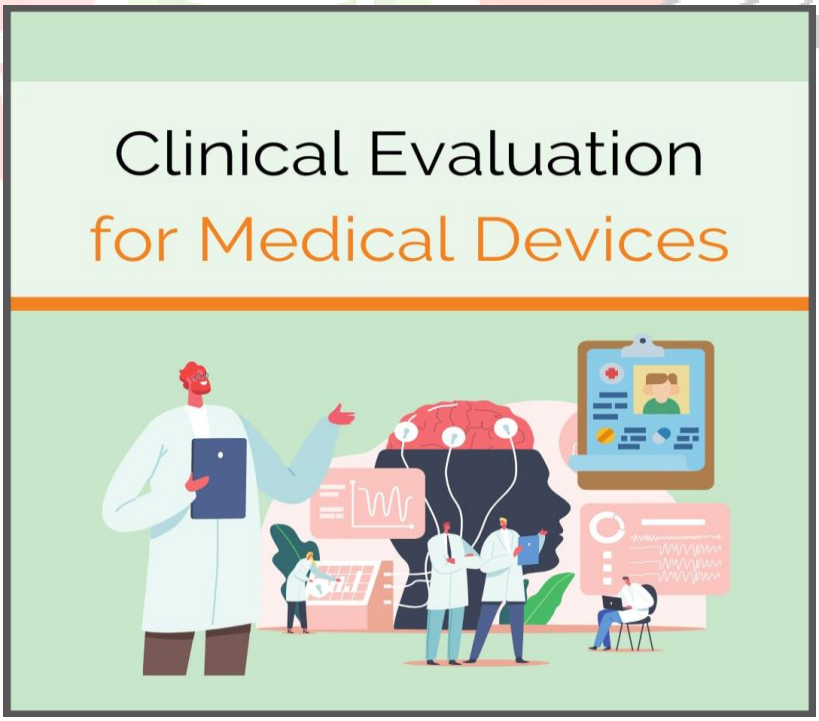
The concept of controlled treatment comparisons, however, dates back further. In the 17th century, John Woodall, an English military physician with the British East India Company, advocated for the use of citrus fruits to prevent and treat scurvy due to their antiscorbutic properties. Despite his recommendations, the widespread use of citrus for scurvy prevention only became standard practice much later【12】.

Evolution of clinical trials in india:

India has recently emerged as a prominent location for conducting clinical trials, thanks to its unique combination of medical expertise, diverse patient populations, and cost advantages. However, the nation's involvement in clinical research has a long and rich history.

India's ancient medical tradition, Ayurveda, offers a wealth of knowledge on diseases and remedies. The classic Ayurvedic texts provide detailed observations and guidance on treatments. While these insights were likely based on empirical evidence, they lack documentation of systematic clinical experimentation as understood today. Thus, India's documented history of clinical research primarily focuses on modern developments【13】.

In modern times, the Indian Council of Medical Research (ICMR) played a pivotal role in establishing ethical standards for clinical research. The Central Ethical Committee, chaired by Justice (Retired) M.N. Venkatachalam, held its inaugural meeting on September 10, 1996. Several subcommittees were formed to address ethical issues in specific areas such as clinical research on medical products, organ transplantation, and human genetics. In 2000, the ICMR released its ethical guidelines for biomedical research involving human participants, which were subsequently revised in 2006【14】.



Modern trials:

Austin Bradford Hill played a pivotal role in the advancement of modern clinical trial methodology. His contributions, along with the work of Sir Ronald A. Fisher, established the foundation for scientific rigor in experimental design.

Sir Ronald A. Fisher, while working at the Rothamsted Experimental Station in the 1920s, developed key principles of experimental design to ensure accuracy and reliability in research. These principles include:

1. Randomization: Fisher emphasized the importance of randomly assigning individuals to experimental groups. This approach helps minimize bias and ensures that the groups are comparable at the start of the trial【15】.
2. Replication: To reduce uncertainty, Fisher advocated for repeating measurements and replicating experiments. This practice helps identify sources of variation and strengthens the reliability of results【16】.
3. Blocking: Fisher proposed organizing experimental units into groups that are similar to each other. This reduces variability and improves the efficiency of evaluating the effects and potential interactions of multiple independent variables【17】.

These principles laid the groundwork for the structured and scientifically valid clinical trials conducted today, ensuring that modern trials are robust, reproducible, and capable of providing reliable evidence for medical advancements.

Types of clinical trials:

1. **Treatment trials:**

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

   2.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.

2. **Diagnostic trials :**

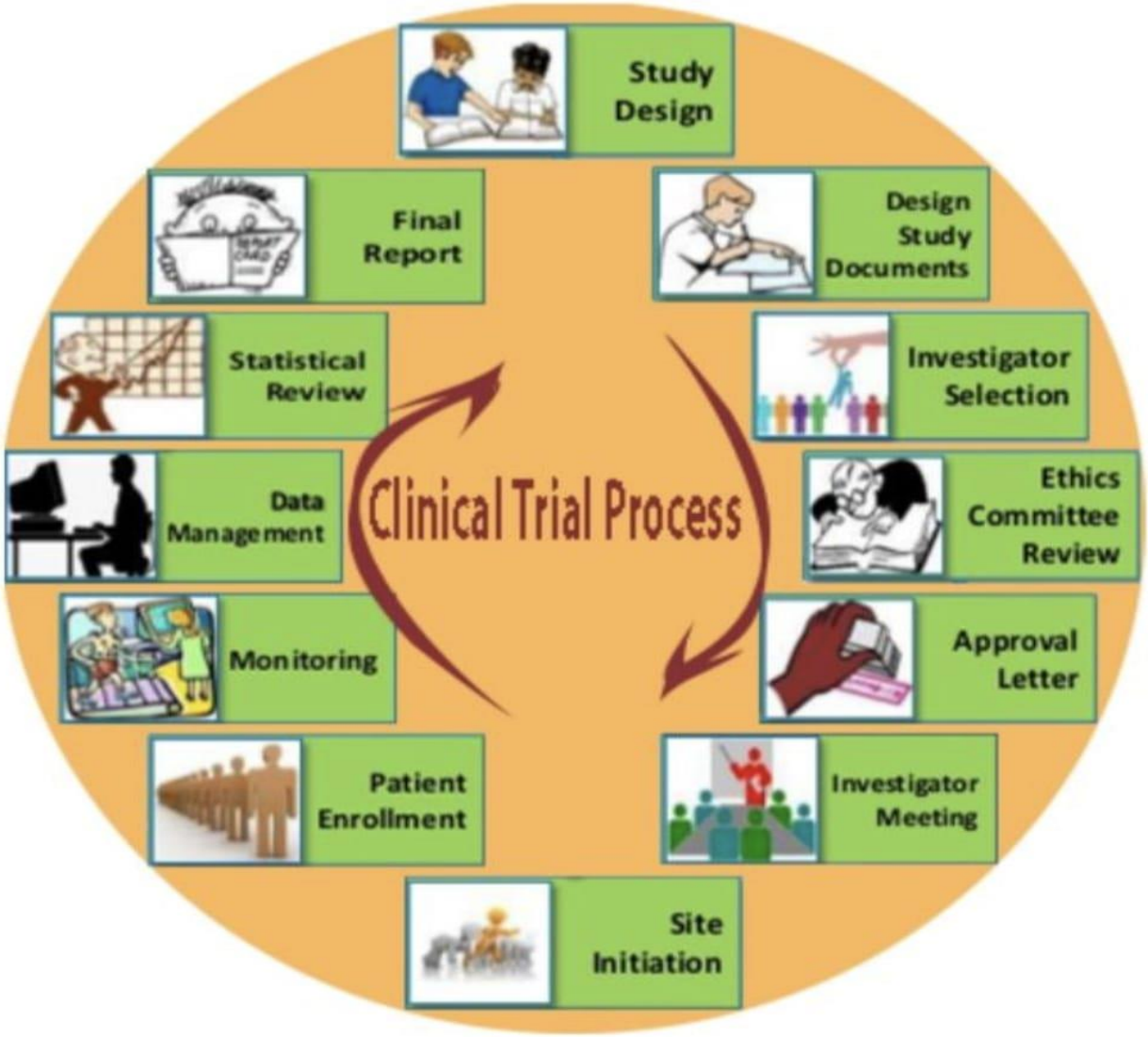
   Conducted to find better tests or procedure for diagnosis a particular disease or condition.

   4.Screening trials:

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

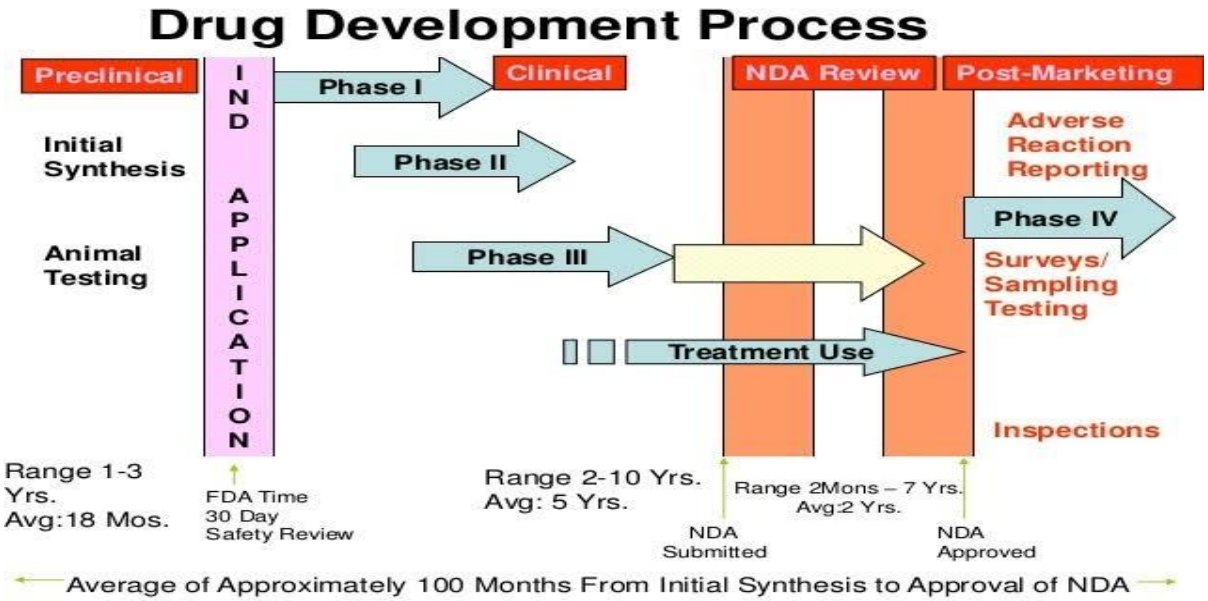
   5.Quality of life :

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



Phases of clinical trials:

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



Pre-Clinical study:

Pre-clinical investigations are essential preparatory steps before a drug can enter human trials. These studies typically involve animal testing and an analysis of the drug's production and purity. Animal studies aim to:
a) Evaluate the drug's safety at doses comparable to human exposure.
b) Study pharmacodynamics, which examines the mechanism of action and the relationship between drug concentrations and their effects.
c) Analyze pharmacokinetics, including how the drug is absorbed, distributed, metabolized, excreted, and its potential interactions with other drugs.

The results from these studies are critical for preparing the Investigational New Drug (IND) application, which is required to gain approval for testing the drug in human participants【19】.

Goals of Pre-Clinical Development

Pre-clinical development focuses on ensuring the safety and effectiveness of a drug before it enters clinical trials. During this stage, both *in vitro* (lab-based) and *in vivo* (animal-based) tests are conducted to assess toxicity, determine which organs might be affected, and identify long-term risks, such as carcinogenicity or reproductive toxicity.

If pre-clinical studies demonstrate that the drug is safe and effective, clinical trials begin. Clinical trials are defined as "scientifically controlled studies that evaluate the safety and effectiveness of therapeutic agents using willing human subjects."Possible outcomes of pre-clinical studies include:
a) The drug shows a significant therapeutic effect and outperforms existing treatments.
b) The drug performs similarly to existing treatments.
c) The drug demonstrates no significant difference compared to current treatments.
d) The drug is less effective than existing treatments【20–24】.

Challenges in Drug Development

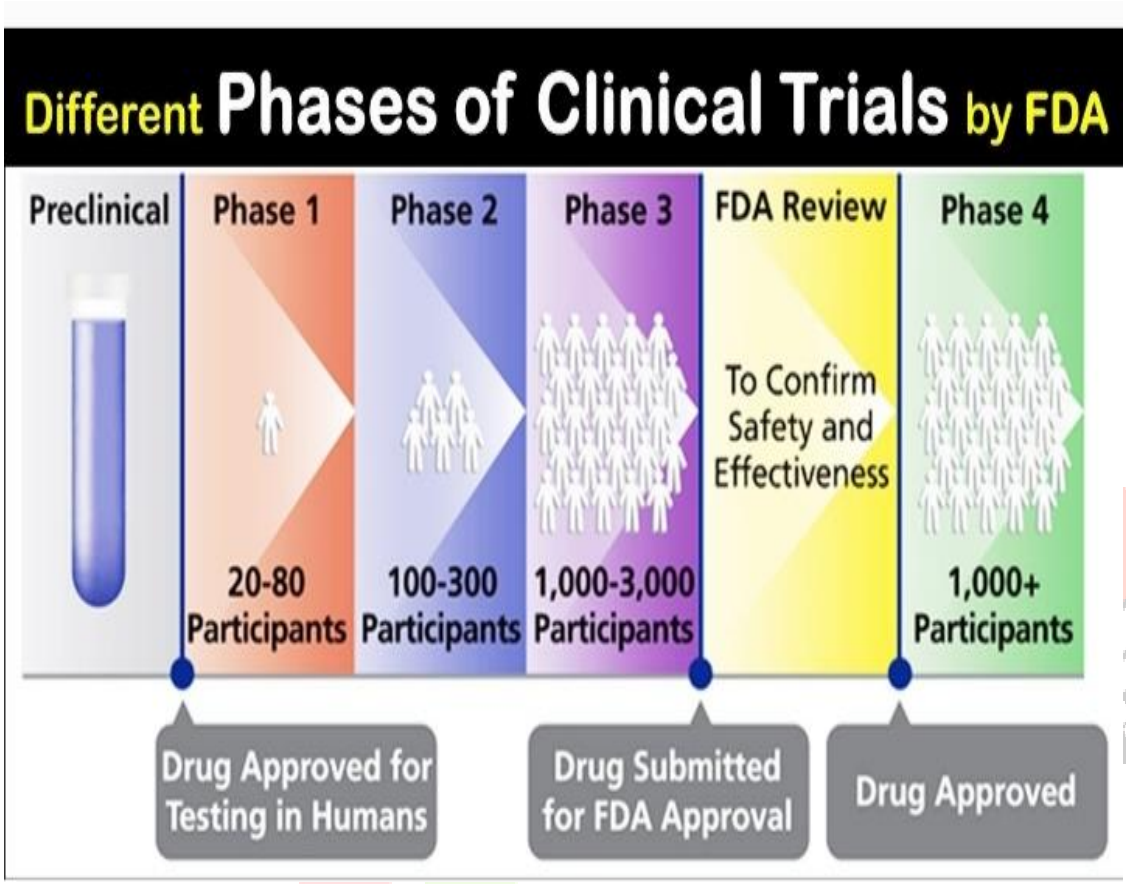
The process of developing a new drug is highly complex, requiring significant time and financial investment. Extensive evidence of the drug's potential effectiveness and safety is needed before clinical trials can begin【25】. Although animal studies are an integral part of this process, ethical considerations demand that researchers minimize animal suffering and explore alternative methods where possible【26】.

Despite these efforts, many drugs fail during development. For example, only 5% of drugs targeting conditions like stroke or septic shock make it to the market, despite substantial investments in pre-clinical studies and drug discovery. Similarly, the success rate for clinical cancer trials is estimated to be less than 5%【27】【28】.

Preclinical studies overall scenario:

Results of animal medicine experiments have immensely did not translate into human clinical trials that ar 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 ar 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].



Phase 0:

Selection of agents for phase 0 trials:

Phase 0 trials are the initial step in the drug development process, used to determine if a new drug candidate warrants further study. During this phase, specific criteria must be met to qualify a drug for testing:

1. **Pharmacodynamic Activity**: The drug must demonstrate a clear mechanism of action.
2. **Target or Biomarker Validation**: The drug must modulate a target or biomarker linked to a potential therapeutic effect.
3. **Broad Therapeutic Window**: The drug should have a wide range of safe and effective dosages.
4. **Non-Toxicity**: The drug should be non-toxic at the doses used in Phase 0 and must be tested on a limited number of volunteers (10-15).

These criteria are applied to suitable drug candidates, such as biomodulators and imaging probes. For example, PARP inhibitors like ABT-888, which meet these criteria, have been chosen for Phase 0 studies. On the other hand, drugs with a narrow therapeutic index or those targeting patients with specific biomarkers may not be suitable for Phase 0 trials【31】.

Phase 0 Study Characteristics:

- Phase 0 trials, also known as **"wildcat" Investigational New Drug (IND)** or **microdosing studies**, involve very limited human exposure and are conducted early in the drug development process.
- These trials are non-therapeutic and do not aim to treat or diagnose conditions. Instead, they focus on understanding the pharmacokinetics and pharmacodynamics of the drug.
- These early studies help determine whether the drug should proceed to more traditional Phase 1 trials, where dose escalation, safety, and tolerability are assessed【32【33】.

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 (microdose 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 invassive 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 cereful 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).

Phase-I clinical trials:

A section one run appraise the most effective thanks to administer a drug , it's 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 moniterd 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 accruement is that the primary goal of section one trial (39).

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) ar collected at numerous time points and analysed to grasp however the drug is processed inside the body .the dose is afterward escalated for furthe 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 markars . 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).

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 asses 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 plannaed 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 bais that one endpoint is of interest . A commanly used phase 2 design is based on the work of gehan ,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 exarcise tolerance [46,47], vaccines studies typically asses safety and immune response and may involve both treatment and control groups([48].

Phase 3 clinical trial:

Based on previous studies demonstrating beginning drug safety and potential effectiveness , a section three trial (conjointly refered to as a "Therapeutic confirming "."comparative effectiveness " or "pivotal trial".) could also be persued . 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 evant 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 monitered 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 phae a pair of knowledge , determination of toxicity ,design of studies with drug combination ,and cost of the trials [50].

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 recieve 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).

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 confidentially 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 absolve to finish AN experiment at any time.

10. The scientists guilty should be ready to finish AN experiment at any stage [53].

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 counselled on the correct use of the IMPs in addition to any 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 inject able IMPs, pharmacists will also ensure that they are prepared in accordance to the specifications stipulated in the trial, and that they are administered appropriately. Besides managing clinical trials, oncology pharmacists often run research projects that are aimed at improving outcomes in patients who receive medications, such as chemotherapy or other supportive drugs like anti-emetics, blood growth factor injections, etc. Drug Utilization Evaluations (DUEs) are 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. In addition, pharmacists also conduct observational surveys that are aimed at investigating patients' or physicians' perspectives and attitudes towards medications. 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. They are aimed at investigating patients' use of complementary and alternative medications and on patients' perspective on safe handling of oral anti-cancer drugs. Very often, pharmacy students who are adequately trained to conduct research are assigned to survey the patients. We would like to take this opportunity to thank all our patients who have consented to participate in the survey

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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