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Drug Discovery And Clinical Evaluation Of New Drug

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Abstract :-

Drug discovery and development is very difficult challenge for the pharmaceutical industries. It requires lengthy time period to discover and develop new drug. In this review article we are discussing about whole procedure involved in drug discovery that is paradigm for new drug discovery, innovative deficit, mainly focuses on actual process that is how target identification as well as validation is done, lead compounds identification and optimization this both processes are also comes under this lengthy and costly drug discovery procedure. Preclinical and clinical evaluation discovered drug that is newly developed drug is primarily done on some animal by following in vitro studies and then after completion its in vitro and animal studies it is almost ready for the further trails on human beings. Clinical trials involves some systematic phases, which evaluate the developed drug on the basis of safety and efficacy. If drug passed all the phases of clinical trail it ready to approved by food and drug administration (FDA) and then it is ready for deliver to the market.

Keywords :-

Drug discover, Food and Drug Administration, Target discovery, Target validation, Lead optimization, Pre-clinical studies, clinical trail.

Introduction :-

Before new drug becomes available for treatment of specific human disease, its benefits and harms are carefully studied, first in the laboratory and in animals and then in several types of clinical trials. In the most important of these trials so called “pivotal” clinical trials – efficacy and safety of the new drug and standard treatment are compared by giving groups of patients, the different treatments and measuring several predefined “outcomes”. These outcomes whether the new drug is more effective than the standard treatment and whether it has any other effects on the patient’s health and daily life. All this information is then submitted by the sponsor of the new drug to government body responsible for drug approval --- in the United States, this is the Food and Drug Administration (FDA). [2]

Drug is the process by which mew candidate medication are discovered. Historically, drug were discovered by identifying the active ingredient from traditional remedies or by the serendipitous discovery, as with penicillin. More

recently, chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that had a desirable therapeutic effect in a process known as classical pharmacology. After sequencing of the human genome allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets which are hypothesized to be disease-modifying in a process known as reverse pharmacology. Hits from this screen are then tested in cells and then in animals for efficacy. Modern Drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/ potency, metabolic stability (to increase half-life), and oral bioavailability. Once a compound that fulfils all of this requirements has been identified, the process of development can continue. If successful, clinical trails are developed.[1]

Need for the study :-

1. Unmet medical needs.
2. Downstream health cost.
3. Cost of therapy.
4. Costs to individual / Country.
5. Sustain individuals activity.
6. The overall aim of clinic evaluation is to access and analysed clinical data regarding the medical device to provide evidence for the products clinical safety and performance. [2]

The Drug Discovery Processes :-

The process of drug discovery involves following important steps:

1. Drug target identification
2. Target validation
3. Lead component identification
4. Lead optimization
5. Preclinical and clinical development

1. Drug target identification:-

The first step in the discovery in drug is identification of the Biological origin of disease, and the potentially targets for invention. Target identification starts with isolating the function of possible therapeutic target and its role in the disease. Identification of the target is followed by characterization of the molecular mechanism addressed by the target. An ideal target should be efficacious safe meet clinical and commercial requirements and be “druggable”. The technique used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines [6].

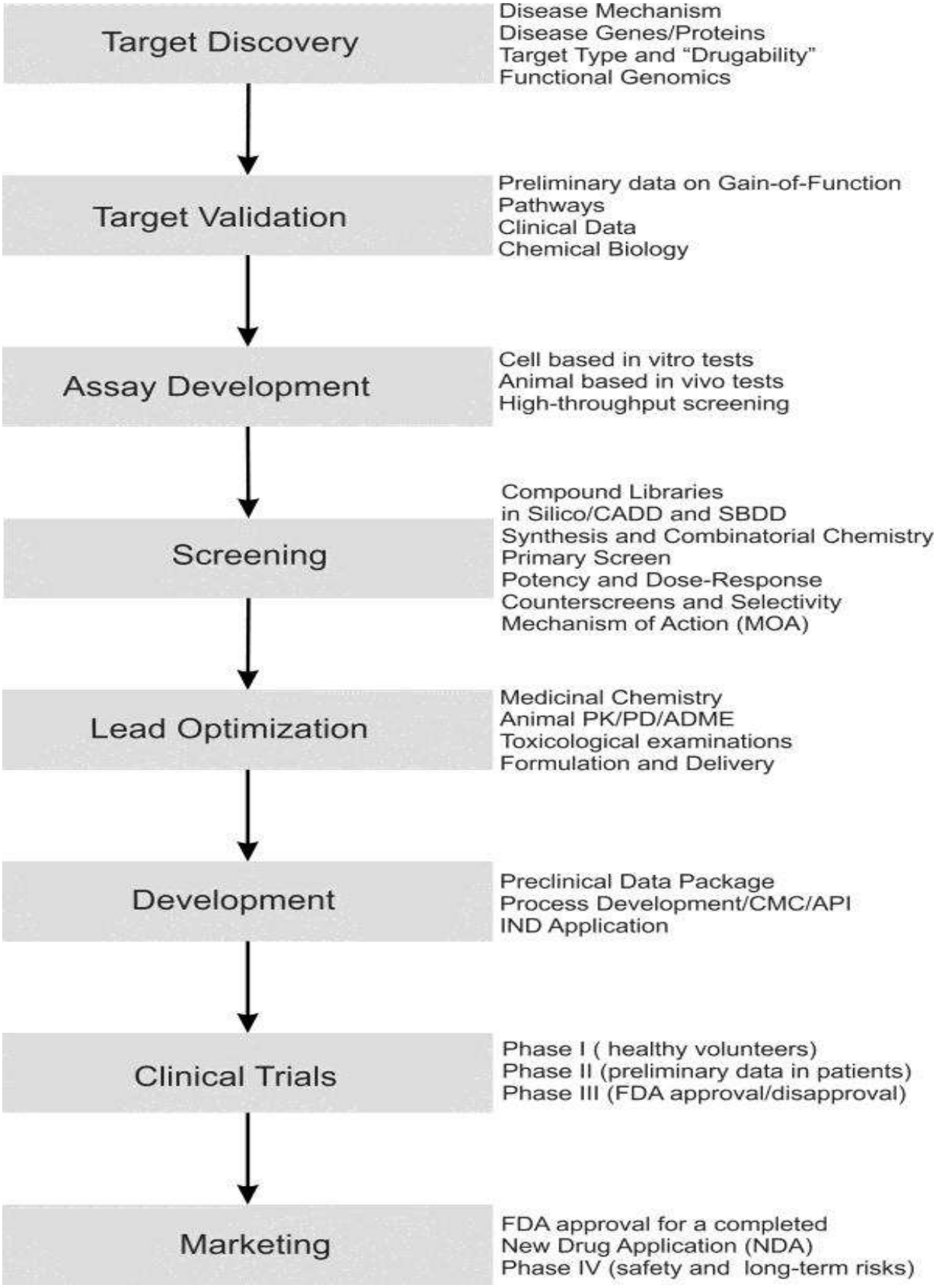

Figure: Flow chart for drug discovery and development

2. Target validation :-

Many drug fail during the various stages of clinical development either because they are not effective, or because they are toxic. This is often the consequence of a poor pre-clinical validation of the target: therefore, **target validation** (TV) is a crucial step on the path of drug discovery and development. The goal of target validation effort is to demonstrate that the biological target plays a critical role in the disease process, and that modulation of the target itself can exert a therapeutic effect in the absence of toxicity on normal cells and tissues [8].

Target validation involves demonstrating the relevance of the target protein in a disease process/ pathogenisity and ideally requires both gain loss of function studies. This is accomplished primarily with knock-out or knock-in animal models, antisense nucleic acid constructs, neutralizing antibodies[2].

3. Lead compounds identification :-

In this steps those compounds are identified which can interact with the target protein and can modulate its activity. Compounds are mainly identified by using random (screening) or rational(design) approaches [8]. Lead compounds are sometimes called developmental candidates. This is because the discovery and selection of lead compounds occurs prior to

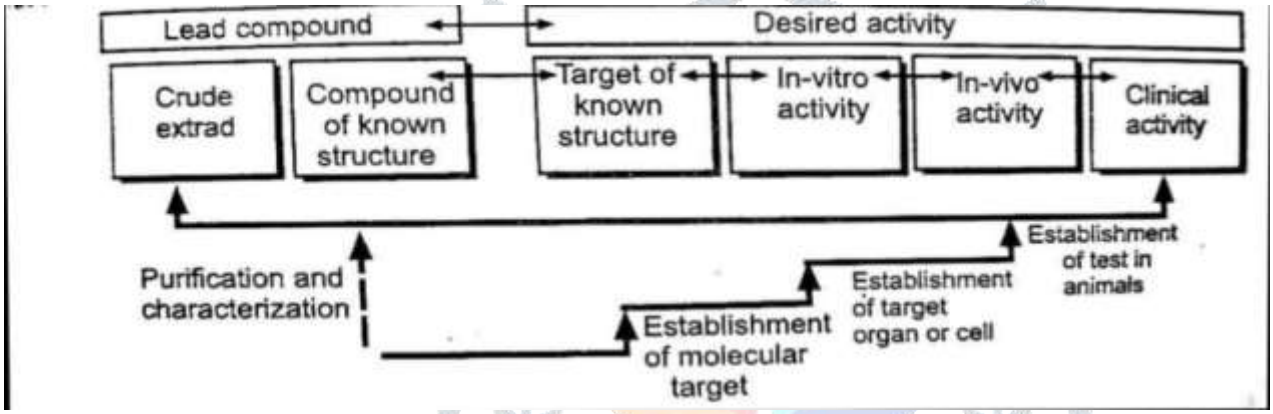

Figure: Lead Compound Identification

Lead compounds may be Identified by chance:

Example. Penicillin

Some drugs in the clinic have been found to have side effects. Structure of such drugs can be modified to reduce the primary indication and optimise side effects [2].

Identified from Natural sources:

Lead compound have been identified by isolation of active ingredients from natural products and use in remedies. The challenges facing conventional natural product drug discovery are many, and range from the basic problems of reliable access and supply, seasonal or environmental variations in the composition of living organisms and loss of source through extinction or leg-isolation, to the more practical concerns associated with the complexity of the mixtures after fractionation, the isolation of very small quantities of bioactive substance and challenging physicochemical properties such as solubility and stability [9].

For Example : Quinine for antimalarial, Colchicine for gout Morphine for pain relief [2].

Natural product screening:

Pharmacological screening of crude plant drugs and their extractives. The pharmacological screening of a single plant or drug sample can sometimes proceed using rather extemporaneous techniques, but this decision is accompanied by:

1. Some loss of efficiency coupled with an increase in relative ex-pense .
2. The inability to make interexperiment comparisons using previously obtained data for both known and test drugs.

3.Some real risk of missing unexpected, unique activities because of experimental bias [10].

80% of uses drugs exclusively from natural sources. 35% of drugs contain 'principles' of natural origin. Less than 5% of the 50000 higher plant species have undergone biological pharmacological screening. Each plant has potentially 10,000 different constituents [2].

Compound libraries (collection library) :-

A 'compound library' is a collection of a compounds. The variety (diversity) of compounds may be :

- Small and Very limited diversity (eg. Departmental library)
- Big but relatively limited diversity (eg. University academic library)
- Big and diverse (eg. City library)

The rapid, automated synthesis of molecular diversity to fuel high-throughput screening (HTS) for lead generation as well as the synthesis of directed libraries for subsequent lead optimization, has evolved into an effective strategy to accelerate drug discovery. Indeed, during the past decade, combinatorial chemistry has provided access to greatly expanded chemical collections of drug-like compounds through the development of practical solution phase and solid-phase methods, which proceed in high yields and product purities. Furthermore, both the high-throughput analysis and purification of compound libraries have been optimized in recent years to complement high-throughput organic synthesis and screening, routinely providing libraries of comparable quality to traditional medicinal chemistry collections. Newer advances in the field include libraries of natural product analogues with structural complexity as well as the utility of chemical libraries to define functional genomics and identify lead compounds in a single step. Clearly, in many organizations, combinatorial chemistry has fully integrated component of the drug-discovery process, striving to increase productivity with fewer resources[11].

How can we access new compounds as quickly as possible? Can combinatorial chemistry solve this problem?

Combinatorial chemistry:

The aim of combinatorial chemistry is generation of number of compounds very quickly. Combinatorial chemistry involves the generation of a large array of structurally diverse compounds, called chemical library, through systematic, repetitive and covalent linkage of various 'building blocks'. Once prepared, the compound in the chemical library can be screened, concurrently, for individual interactions with biological targets of interest. Positive compounds can then be identified, either directly (in position-position-addressable libraries) or via decoding (using genetic or chemical means) [12].

High-throughput screening :

High-throughput screening (HTS) is well established process in lead discovery for pharma and biotech companies and is now also being set up for basic and applied research in academia and some research hospitals [13]. Advances in molecular biology, human genetics and functional genomics continue to produce increasing numbers of molecular targets available for therapeutic intervention. This, coupled with major increases in compound collections produced by combinatorial technologies, has fuel an important need for improvements in high-throughput screening (HTS) capabilities. As a result, HTS technologies have undergone revolution in the latter half of the 1990s. Today, most pharmaceutical companies use HTS as the primary engine driving lead discovery [14].

Identification of pharmacophore :

The concept of pharmacophore is widely used in modern drug design and it is generally as the 3D arrangement of certain features in the ligand that are responsible for its activity against a particular protein target. The importance of pharmacophore stems from the fact that once it has been identified, it can be used to rationally design new ligands that

contain it and thus have a greater chance of producing the desired pharmacological effect. The pharmacophore can be relatively easily identified if the 3D structure is available for several ligands bound to the same binding site of the same protein by aligning the features of all the ligands and finding their largest common arrangement, referred to as the *common pharmacophore* (CP) [15].

Structure based drug design:

The process of structure-based drug design requires identification of a suitable protein target, determination of the structure of the target protein, implementation of an easy and reliable high-throughput screening assay, identification of a lead compound, development of Computer assisted method for estimating the affinity of new compound and access to a synthetic route to produced designed compounds [16].

Lead optimization / Drug development:

Lead optimization is the complex, non linear process of refining the chemical structure of the confirmed hit to improve its drug characteristic with the goal of producing a preclinical drug candidate. This stage frequently represents the bottleneck of the drug discovery program. The lead optimization process is highly interactive. Leads are assessed in pharmacological assays for their "druglikeness" typically one or more confirmed hits are evaluated in the secondary assays, and a set of related compounds called analogues, are synthesized and screen[17].

Preclinical studies :

Preclinical studies are performed in in vitro, in vivo, ex vivo and in silicon 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. human. 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 silicon models as per the needs of the focused indication and regulatory guidelines [18].

Steps involved in preclinical trail / studies:

1. Identify a drug target
2. Develop a bioassay
3. Screen the drug in the assay
4. Establish effective and toxic doses
5. File for approval as an Investigation New Drug (IND)

1. Identification of drug target :

Drug usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Scientists used variety of techniques to identify and isolate individual targets to learn more

about their functions and how they influence disease. Compounds are then identified that have various interactions that have various interactions with the drug targets that might be helpful in treatment of specific disease. [20]

2. **Develop a Bioassay:**

Bioassay is an assay involving a biological sample. Bioassay means concentration or potency of a substance by its effect on living cells or tissues. The effect of drug on biological sample typically is either graded or quantal. The quantal assay ideally provide yes or no answer and graded assay measure a property under multiple conditions.
They can be used to test :

- Drug / Target interaction – either presence or measure of kinetic property.
- Influence of a drug on target function – disruption of protein-protein interactions or enzyme kinetics.
- Physiological outcome of a drug on disease state.
  Graded assay can be adapted to give a quantal result through the use of defined thresholds. [20]

3. **Screen the drug in assay:**

This is the actual drug on the chosen bioassay. This will determine if the drug is SAFE and if it is EFFECTIVE in the bioassay (BEFORE it is ever tested on human). [2]

4. **Establish Effective and Toxic Doses**:

Most drugs have a toxic level or an amount at which the drug will become harmful instead of helpful. An effective dose(ED) in pharmacology is the dose or amount of drug that produces a therapeutic response or desired effect in some fraction of the subjects taking it. [2]

ED 50 and LD 50 :

The "median effective dose" is the dose that produces a quantal effect (all or nothing) in 50% of population that takes it (Median referring to the 50% population base). [2]

It is also sometimes abbreviated as the ED50, meaning "effective dose", for the 50% of people receiving the drug". The ED50 is commonly used as a measure of the reasonable expectancy of a drug effect, but does not necessarily represent the dose that a clinician might use. This depends on the need for the effects, and also the toxicity. The toxicity and even the lethality of a drug can quantified by the TD50 and LD50 respectively. Ideally, the effective dose would be substantially less than either the toxic or lethal dose for a drug to be therapeutic relevant. [2]

Toxicity is the degree to which a chemical substance can damage an organism, such as animal, bacterium or plant, as well as (cytotoxicity) or an organ such as the liver (hepatotoxicity). [2]

The lethal dose is an indication of lethal toxicity of a given substance. Because resistance varies from one individual to another, the "lethal dose" represents as dose (usually recorded as dose per kilogram of subject body weight) at which a given percentage of subjects will die. The lethal concentration is lethal dose measurements used for gases or particulates. The LD may be based on the standard person concept, the theoretical individual that has perfectly "normal" characteristics, and thus not apply to al sub-populations. [2]

5.Investigational New Drug (IND) approval process:

The United States of Food and Drug Administration's investigational New Drug (IND) program is the pharmaceutical company obtains permission to transport an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug had been approved. The FDA review the IND applications for safety to assure that research subject will not be subjected to unreasonable risk. If the application is cleared, the candidate drug usually enters a phase 1 clinical trail. [2]

Type of studies included in preclinical trials :

1. Screening test.
2. Tests on isolated organ, bacterial cultures.
3. Test on animal models of human disease.
4. General observational test.
5. Confirmatory tests and analogues activities.
6. Mechanism of action.
7. Systemic pharmacology.
8. Quantitative test.
9. Pharmacokinetics.
10. Toxicity study.

1.Screening test:

Its simple and rapidly performed initially screening test to determine the presence or absence of particular pharmacodynamics activity in the new drug.

Example: Determination of analgesic or pain relieving activity in the new drug . [2]

2.Tests on isolated organ :

These are few preliminary tests to determine specific activity in the new drug like anti-histaminic, anti-bacterial, anti-secretory, vasodilation healthy organs isolated from dead animals or bacterial cultures are used for these preliminary tests. [2]

3.Test on animal models:

Animal models like rat, pig, mouse, hamster and rabbit are used to determine actual effects of the drug in live organism. After successful results in initial stages, higher animal like cats, dogs, and monkeys are used for preclinical trails.

[2]

4.General observational test :

The drug idler the trail is injected in tripling doses to a small group of mice which are then observed for any hidden effects. [2]

5.Confirmatory tests and analogues activities :

Compounds which yields a desirable results are carried in the trail for more complex tests. Other activities like antipyretic and anti-inflammatory are further determined for an elaborate examination of the drug properties. [2]

6.Mechanism of action:

Experiments are conducted to determine the mechanism of action of drug.

Example: if the drug is anti- hypertensive drug, whether it is an alpha or beta blocker, ACE inhibitor or calcium channel blocker. [2]

7.Systemic pharmacology:

Besides determination of action of drug, it's effects on individual and major organ systems like nervous, cardiovascular, respiratory and renal are also examined. This can give a clue about any possible side effects of the drug on any major organ system.[2]

8.Quantitative test:

It includes examination of the dose-response relationship, maximal effects and comparative efficacy of new drug with the existing drug, thus establishing the market value of the drug. [2]

9.Pharmacokinetics:

It involves the study of the movement of the drug substance in the body of the living organisms which includes the processes of absorption, distribution, metabolism, localization in tissues and excretion from the body. They help to know the safe dose and preferred route of administration for the drug. [2]

10.Toxicity test:

Both short-term or acute and long-term or chronic toxicity testing are carried out to determine the toxic effects of the drug and mortality in animal models.

All these tests are carried out under a standard procedure of "Good Laboratory Practice" to safeguard the quality, integrity, and safety of the preclinical trials. [2]

Clinical trials :

The Clinical trail defines as any experiments on human being for the assessment of effectiveness of new drug or combinations of drugs, new approaches of surgery or radiography or technique to improve the diagnostic procedure of disease to improve the quality of life of patient. In clinical trail new drug is administered to patients for estimation of pharmacokinetics and pharmacodynamics, safety profile purpose. [2]

Types of clinical trail:

According to the objectives and way of organization, clinical trail can be categorized into treatment trail, prevention trail, observational trail, diagnostic and screening trail.

1. Treatment trial:

It is also called as interventional trails and intentions of treatments which are not yet approved.

For Example: The researchers or pharmaceutical company develop new drug and believe that the new drug would be effective in diabetic but is not tested on human being. So according to guidelines the new drug must be test on human subject in accordance with strict guidelines in order to insure the new drug is safe effective for the treatment of diabetic. [2]

2. Prevention trials :

In this trials, the tests are preformed to find the new way for the prevention of some medical condition. The prevention trail may also conduct to prevent the patient from recordings of specific medical condition. [2]

3. Observational trails :

In this trials, the study perform in large groups of people. In observational trail patients do not receive any kind of any treatment but the researchers may ask to provide the information regarding the health issue or ask for blood sample to investigate the disease conditions. [2]

4. Diagnostic and screening trials:

This trails are conducted by aiming to find new ways or technique to detect or diagnose the medical conditions. [2]

Clinical trials can also be classified according to the drug whether to be therapeutic or non therapeutic.

1. Therapeutic trails :

In therapeutic trail, given treatment believes to produce therapeutic effect which is likely beneficial to the patients in some way (at least those receiving the experimental drug - in the case of drug trail) [2]

2. Non therapeutic trials :

In this trials, treatment unlikely to produce direct beneficial effect but can provide knowledge or information which may contribute towards the development of new treatment or procedure in future or information irrespective of trails whether they are therapeutic or non therapeutic, it may described as randomised trials, blind trails, randomised blind trails, add on trials, open trails, placebo controlled trials. This term provide the information regarding the organization of clinical trail. Following are given brief description of terminologies used in clinical trail design. [2]

Phases of clinical trails :

Phase 0 clinical trail:

Phase 0 Implicates investigation first in human (FIH) tails are conducted according to FDA guidelines. Phase 0 trial besides termed as human micro dose studies, they have sings.[19]

Phase 1 clinical trail : safety and dosage

Phase 1 clinical trail are the first test of a drug with a lesser number of healthy humane sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific target without exerting pharmacological action. Pharmaceutical industries perform phase 0 studies to pick which of their drug applicant has the preeminent pharmacokinetic parameters in human. [19]

volunteers. In most cases, 20 to 80 healthy volunteer with a disease condition participate in phase 1. Patients are generally only used if the mechanism of action of a drug indicate that it will not be tolerated in healthy people. However, if a new drug is proposed for use in diabetes patients, researchers conduct phase 1 trails in patient with that type of diabetes. Phase 1 studies are closely monitored and collect information about pharmacodynamics in the human body.

Researchers adjust dosage regimen based on animal study data to find out what dose of drug can tolerate the body and what are it's acute side effects. As phase 1 trails continues, researchers find out research mechanism of action, the side effects accompanying with increase in dosage, information about effectiveness. This is imperative to design of phase 2 studies. Almost 70 % of drugs travel to the next phase. [19]

Figure : Phase Of Clinical Trails

Phase 2 clinical trail : Efficacy and side effects

Phase 2 trails are conducted on larger group of patient (few to hundred) and are aimed to evaluate the efficacy of the drug and to ensure phase 1 safety assessment. This trails aren't sufficient to confirm whether the drug will be therapeutic. Phase 2 studies provide with additional safety data to researchers. Researchers used this data to refine research question, develop research methods and design new phase 3 research protocols. Around 33% of drugs travel to next phase. Most prominently, phase 2 clinical trails and to found therapeutics doses for the large-scale phase 3 studies. [19]

Phase 3 clinical trail: Efficacy and adverse drug reaction monitoring

Researchers plan phase 3 clinical trails to prove whether a product deals an action benefits to a specific people or not. Some times known as "pivotal studies", this studies comprise 300 to 3000 volunteers. Phase 3 studies deliver most of the safety data. The previous study might not able to detect less side effect. But phase 3 studies are conducted on larger number of volunteers and longer in duration, the results are more probable to detect long term or uncommon side effects. Around 25 to 30 % drugs travel to the next phase of clinical research. If drug developer has data of its previous tests, preclinical and clinical trails that a drug is safe and effective for its intended use, then industry can file an application to market the medicine. The FDA review team comprehensively inspect all submitted data on the drug and makes a conclusion to approve or not to approve it. [19]

Phase 4 clinical trails: Post marketing drug safety monitoring

Phase 4 trails are conducted when drug or device has been approved by FDA. These trails are also recognised as post-marketing surveillance involving pharmacovigilance and continuing technical support after approval. There are numerous observational strategies and assessments patterns used in phase 4 trails to evaluate the efficacy, cost effectiveness and safety of involvement in real world settings. Phase 4 studies may be required by regulatory authorities (e.g. change in labelling, risk management/ minimize action plans) or may be undertaken by the sponsoring company for comparative purposes or other reasons. Therefore, true illustration of drug is safely essentially requires over months and even years that mark up a drug's lifespan in the market. FDA reviews reports of complications with prescription and OTC drugs, and decide to add precautions to the dosage or practise information as well as more serious adverse effects or drug reactions. [19]

Conclusion :

Drug Discovery and development are among most important translational science. Clinical trials are research studies that test how well new medical approaches work in people. Every clinical trail has a protocol or action plan, for conducting the trail. The describes what will be done in study, how it will be conducted. Each study answers scientific questions and tries to find better ways to prevent, screen, diagnose or treat disease. A key goal of drug discovery campaign is the recognition of new molecular entities that may be value in the treatment of diseases that qualify as presenting unmet medical needs. The plan of drug discovery describes, why each part of study is necessary. Clinical trials provide as essential link between scientific discovery and clinical practise.

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