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INTRODUCTION

The study of diseases and its prevention or treatment in human population is broadly divided into two parts :- Epidemiology and Clinical Trials. The systematic study of disease causes and origin of disease using observational data (the data collected from population not under controlled experimental setting) is done in Epidemiology. Ex .; Air pollution and respiratory illness, diet and heart disease. The study of the evaluation of intervention (treatment) on disease in a controlled experimental setting in done in clinical trials. Ex. Evaluating the effectiveness of new antifungal medication.

A clinical trial is an experiment which involves patients and is designed to elucidate the most appropriate treatment for future patients. It is an experiment testing medical treatment in human subjects. Clinical research involves systematic study of drugs, devices, vaccines, prevention or treatment of diseases. During the process of such study individuals are treated with an aim to develop an intervention for the patients of tomorrow.

The earliest evidence of clinical trial is a small experiment on 20th May 1747 in which James Lind evaluated six treatments in 12 patients of scurvy. Patients who were given lemons and oranges quickly recovered form signs and symptoms of scurvy and were fit for duty after six days. But the earliest
Experiments were arbitrary, non-systematic In 1926 R.A. Fisher introduced concept of randomization in agricultural experiments. In 1931 randomization was first time used by Amberson at al . Then onwards various techniques and principles were incorporated in the experiments
India has been a branded generic pharmaceutical market. The patent act was amended in 1970 to withdraw product patent. Clinical trials were not mandatory to obtain new drug approval. The first amendment to the drugs and cosmetics act was made in 1987 by schedule ‘ Y ’ .

THE NEED AND ETHICS OF CLINICAL TRIALS

OVERVIEW OF PHASES

The discovery of a new molecule and its development in to a new drug is complex, expensive and time consuming process. Thousands of chemical compounds are made and tested for desirable effect. After spending thousands of millions dollor, 8 to 10 years of time, only one in 10000 compounds can reach market. This includes laboratory and animal testing, then clinical trials using human subjects. The drug development industry has to be very careful as cost involved is high. James Lind is considered as the father of clinical trials. The focus on the concept of study design began in nineteenth century. Since 1945, ethical impact of clinical trials became important and strict regulations were imposed. Randomized controlled clinical trials became a definite tool to evaluate efficacy and safety of drugs.

The drug development procedure is same worldover. The following are three broad stages.

Discovery
Pre-clinical development
Clinical development

DISCOVERY

New drug discovery begins in the laboratory. Scientists work on molecules and screening is done on biological activities. They find a drugs which are associated with disease. Such drugs are called as targets.
Further studies are conducted to identify the most useful target. A molecule which having potential to treat disease is a lead molecule or lead target. The lead compounds are assessed to select compound with greatest potential and which would be developed in to safe and effective medicine.

PRE-CLINICAL DEVELOPMENT

IN this stage, an investigational drug is tested extensively in the laboratory under in vitro and in vivo conditions to ensure its safety in human beings. Toxicity studies in animals are conducted to identify potential risks to humans. The information about composition of drug, its safety, how drug will be formulated and manufactured , how drug will be administered to humans first time is obtained.

The results of these studies are included in the Investigational New Drug (IND) application to obtain permission from FDA / DCGI or the appropriate regulatory agency to begin clinical evaluation in humans. Regulatory agency review the submitted data and permits the organization to proceed to the next stage.

CLINICAL DEVELOPMENT

This stage starts only after permission from regulatory agency. This study can include evaluation of new doses form or new use of a drug already approved for marketing. In addition to permission from regulatory agency, an independent or institutional review board (IRB) or independent ethics committee must approve the study protocol as well as Informed Consent Document (ICD).
Clinical development is carried out in different phases, called as phase I, phase II, phase III. Each phase has different objectives. Increasing number of patients are enrolled in each successive phase.

Phase I Clinical studies :- This is the first study conducted in human beings and it takes about six to nine months. A small number of subjects, usually 20 to 100 healthy volunteers, is given the drug. This phase is designed to verify safety and tolerability of the drug in humans. We obtain the maximum dose that can be given before unacceptable toxicity is experienced by the subject. This is called Maximum Tolereted Dose (MTD). Dose response relation can be fitted to data and estimate of MTD and its S.E. can be obtained. Testing includes observation and careful documentation of pharmacodynamic and pharmacokinetic properties of the drug. Information about how drug acts in the body – how it is absorbed, distributed, metabolized and excreted is obtained.

Phase II Clinical studies :- Once the MTD is estimated, the further objective is to study effectiveness and estimate the rate of adverse events.
These studies have more statistical properties. This phase generally takes six months to three years. Testing is done on several hundred patients suffering from the disorder the drug is designed to treat. This phase establishes the minimum and maximum effective dose. Principle of randomization and double blinding are used in this phase. The patients are divited into groups, one receiving the drug under study and other gets placebo. Sometimes there is third group also receiving current standard treatment.

Phase III Clinical studies :-

PROTOCOL

It is a document that describes the objectives, design, methodology, statistical and organization of a trial. In short it is a reference document that describes why the trial is conducted, how it would be executed and what is to be done in any eventuality. A sensible thumb rule for protocol writing is to include the right amount of details necessary for the reader of each section to be able to understand exactly what is required to conduct the study.

Protocol covers the main decisions to be made along with scientific and practical considerations to be taken into account. The average clinical trial protocol may be 100-page text. It requires careful thought and structured plan to write a protocol.

The protocol users include all the staff as investigators, side coordinators, research nurses, pharmacists, dispensing staff, lab staff, staff involved in ECG, radiography, endoscopy, data managers, statisticians, report writers, auditors, ethics committee.

Along with information on medication protocol will also describe how the data collected in study will be analyzed. It will be relevant not only to the data managers and statisticians but also to ethics committee and regulatory authorities. The protocol will form part of the clinical research report (ICH 1995) and therefore it is important that the protocol writer should consider the requirements for this final report.

Writing protocol is time consuming but if good efforts are taken the result is a good sound document. Following are some questions that one should ask :

(i) Why protocol is needed ?
(ii) Where does the study fit into the clinical development plan for the product ?
(iii) Is the study required for a regulatory submission ?
(iv) What questions must the study be designed to answer ?

The protocol writer will also require input on the disease area in question, common treatments for the disease and the methods used to assess the disease in clinical trials. Once the required knowledge has been obtained then before starting to write, protocol writer should discuss the study design and possible subject number (sample size) with statistician. Writing the protocol will be futile exercise if it is subsequently discovered that the sample size is so large that study is not affordable within the budget provided.

Initial draft should be circulated for critical review and comments to all those who had provided inputs. The protocol will typically be refined through several drafts before it is finalized. Protocol writer shoud work in consultation with a small core team.

Writing a protocol is important task for trial is to take off with a good start.

CASE REPORT FORM(CRF)

It is a document for collecting and recording patient related information in a standardized and uniform manner. This is important for clinical research team because the analysis and reporting of trial outcome is largely based on the completeness and accuracy of data recorded from each patient recruited in the trial.

CRF enables to collect subject information enrolled in the study as per the protocol. The CRF cab be paper based or in the electronic format. The electronic format allows the direct entry into the database. DRF should be designed in a manner that helps the investigator, monitor and data manager to record and review patient's information which is vital for outcome of the trial.

A good CRF should have following characteristics :-

1. It should be clear, systematic and unambiguous.
2. It should provide comprehensive instructions to be followed by investigator to obtain complete information as per approved protocol and regularity requirements.
3. It should provide guidance on eligibility criterion for the patient to continue in the trial.
4. The design should minimize uncertainties and facilitate entry verification by monitor.
5. It should facilitate in designing and creating clean database requiring minimum query resolution between the investigator , monitor and data manager.
6. CRF should be reviewed by designer, quality assurance department, investigator, data manager and statistician.

All CRF must comply with ICH-GCP guidelines and fulfill regulatory requirements. CRF should be a part of protocol when finalized and submitted for approval. To prepare a CRF a committee of CRF designer, medical advisor , clinical monitor, data entry leader, data manager, statistician should be formed. If any changes are required to be done in final CRF, meeting of the committee should be called. The data collected through CRF should address two main issues, namely study hypothesis and drug safety. The identification code of every CRF and each page within CRF should be unique. The subjects should be identified by a code system to maintain confidentiality.

The layout for all CRF used in different trials of a particular day should be uniform. The investigator should be provided clear instructions for completion of CRF.
Among the challenges in the drug development process one of the key challenges faced is how to manage the large volume of critical data gathered. This problem can be overcome by electronic version of CRF. Due to advancement of information technology and the need for better data management, the present focus has been shifted to eCRF.

PLACEBO

A placebo is a medication with no active ingredients or a procedure without any medical benefit. A placebo is often used as a "control" in one group of people in order to study the effectiveness of an experimental drug or treatment in another group of people by comparing the results.

The biases may be avoided with proper blinding. However, blinding treatments takes a great deal of care and planning. If the treatment is in the form of pills, then the pills for the different treatments should be indistinguishable; i.e the same size, color, taste, texture.
If no treatment is to be used as the control group then we may consider using a placebo for patients randomized to the control group. A placebo is a pill or other form of treatment which is indistinguishable from the active treatment but contains no active substance. (sugar pill, saline,etc.) If you are comparing two active treatments each, say, with pills that cannot be made to be similar, then we may have to give each patient two pills; one active pill for one treatment and a placebo pill for the other treatment. (This can become overwhelming if we are comparing different combinations of drugs).
It has been well documented that there is a placebo effect. That is, there have been randomized studies conducted that gave some patients placebo and the other patients nothing with the placebo group responding significantly better. Consequently, in a randomized clinical trial which
compares a new drug to a placebo control, we are actually testing whether the active drug has effect equal to or greater than a placebo effect.

In the past, a placebo (the proverbial "sugar-pill") was sometimes given to individuals as a "harmless" way to make them feel better. A certain percentage of people (historically 30%) report feeling better after receiving a placebo based on the suggestion that it may help, something known as the "placebo effect." Considered unethical now for that use, placebos are frequently used in clinical trials to study the

effectiveness of new treatments and also control for the placebo effect, that is, eliminate the chance that any improvement seen is the result of suggestion rather than the treatment itself.

Regardless the accuracy of the claim, The power of suggestion needs to be considered when evaluating any experiment. This can be achieved by using placebo (or sham) in a comparative experiment. Hence use of placebo is important to make design valid.

BLINDING(MASKING)

The terms ‘ blind ’ refers to lack of knowledge of the identity of the trial treatment. Patients, investigators, data review committees, ancillary personnel, statisticians and monitors are the major individuals which are to be kept blind during the clinical trial. In clinical trials, if researcher knows which treatment is given to which subject, there is likelihood of the bias creeping in while assessing the response. Bias also can creep in when subject describes the response to investigator if participating subject knows the treatment given. For ex. If subject knows that he is given well established treatment, the subject may feel psychologically better. Blinding is a technique that that helps preventing biases of such type. Blinding is used to decrease the biases that occure in a clinical trial when patients are evaluated during treatment and to avoid a placebo effect that often occurs in open-label trials.

Following are the types of blindings.

1. Open Label Trial (Unblinded Trial) :- No blind is used. Both, investigator and patient know the identity of the medicine. Such trial is simpler to execute than other types. It is easier to design and carry out, also less expensive. The main disadvantage is the possibility of bias. These trials can be used in which ethical considerations do not permit blinding.

2. Single Blind Trial :- The trials in which only one party, either researcher or subject has information about the treatment are called single blind trials. These trials provides control on bias to some extent. It is simpler to carry out than double blind design. The knowledge of treatment may help the investigator to take proper care of health of the patient and arrive at better judgement.

3. Double Blind Trial :- The trials in which no party, neither researcher nor subject has information about the treatment are called single blind trials. These trials provides highest control on bias. Such trials are more complicated to initiate and conduct than open label and single blind trials.Such designs are considered to provide most reliable data.

   There are two methods of using double blind.

   Matching :- It two treatments are to be given in the form of tablets, then match both tablets in the terms of colour, shape, texture etc.

Double Dummy Technique :-If out of two treatments, suppose one is tablet (say A) and other is capsule (say B), then we give all subjects one table and one capsule. But subjects assigned to A will get real tablet containing A and one capsule (placebo) matching B. The subjects assigned to B will get real capsule B and one tablet (placebo) matching A. Hence all subjects are given one tablet and one capsule.

One must realize that although the principles of blinding are good, they are not feasible in some trials. For example, if we are comparing surgery versus chemotherapy in a cancer clinical trial, there is no way to blind these treatments.