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# VARIOUS METHODOLOGY USED IN CLINICAL TRIALS: AN OVERVIEW

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## ABSTRACT

Clinical trials are also called as pharmacological trials because they are specially designed to establish the safety, therapeutic action, tolerability, and pharmacodynamic characterstics. There are various phases in which the clinical trials is carried out. A clinical trial is a method which involves the testing of a new medicine to evaluate whether it is safe and effective. From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion. Less than 12% of the candidate medicines that make it into Phase 1 clinical trials will be approved by the FDA.

**Keywords -** Clinical research methods, Clinical trial methods, Statistics in clinical research.

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## INTRODUCTION

Clinical research is a branch of medical science dealing with any research or study in living humans. 'Clinical trials' is, the term interchangeably used with the terms 'clinical research' or 'clinical study'. Clinical trials are conducted to collect data regarding the safety and efficacy of new drug and device development. There are several steps and stages of approval in the clinical trials process before a drug or device can be sold in the consumer market, if ever. Drug and device testing begins with extensive laboratory research which can involve years of experiments in animals and human cells. If the initial laboratory research is successful, researches send the data to the Food and Drug Administration (FDA) for approval to continue research and testing in humans. Once approved, human testing of experimental drugs and devices can begin and is typically conducted although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined and designed protocol. Clinical trial is defined as "a systematic study of new drug(s) in human subject(s) to generate data for discovering and/ or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/ or adverse effects with the objective of determining safety and/ or efficacy of the new drug".[1]

**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. [2]

**HOW TO CONDUCT CLINICAL TRIALS:**

Depending upon the objective, clinical trial is conducted either on healthy volunteers or on volunteer patients. Healthy volunteers are generally included in such trial that determines pharmacokinetics, tolerability, safety and even efficacy of certain types of drugs (e.g. hypoglycemic, hypnotic, diuretic etc.). Otherwise, for majority of drugs (e.g. antiepileptic, antipsychotic, anti-inflammatory, antitubercular etc.), efficacy can only be assessed in patients.[2]



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The research entailing the use of human participants is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research. In other words, when a new drug is with clear significant benefit at human side, human as participants for trial experimentation becomes justified.

International Conference on Harmonization has provided a guideline on Good Clinical Practice (ICH GCP) as an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

World Health Organization Guidelines for good clinical practice for trials on pharmaceutical products also describe provisions and prerequisites for a clinical trial, protocol and protection of trial subjects, responsibilities of the investigator, responsibilities of the sponsor, responsibilities of the monitor, monitoring of safety, record-keeping and handling of data, statistics and calculations, handling of and accountability for pharmaceutical products.
Several issues and principles have been discussed in various guidelines on conducting clinical trial (especially drug trial) which must be addressed while conducting a trial.[3]

**These include the following:**
1) Ethical justification and scientific validity of biomedical research involving humans
2) Ethics review board
3) Informed consent process
4) Choice of control in clinical trials
5) Research involving special group of research participants. [4]

**PHASES OF CLINICAL TRIALS**
Clinical trial of a drug is conducted through various phases. The number of phases as trial varies from literature to literature and from author to author. Most literatures describe a clinical trial/ testing of a new molecule to comprise of four phases. [5]

**Phase 0:**
Phase 0 trials are the first clinical trials done among people. They aim to learn how a drug is processed in the body and how it affects the body. In these trials, a very small dose of a drug is given to about 10 to 15 people.

**Phase I:**
Phase I trials aim to find the best dose of a new drug with the fewest side effects. The drug will be tested in a small group of 15 to 30 patients. Doctors start by giving very low doses of the drug to a few patients. Higher doses are given to other patients until side effects become too severe or the desired effect is seen. The drug may help patients, but Phase I trials are to test a drug's safety. If a drug is found to be safe enough, it can be tested in a phase II clinical trial.

**Phase II:**
Phase II trials further assess safety as well as if a drug works. The drug is often tested among patients with a specific type of cancer. Phase II trials are done in larger groups of patients compared to Phase I trials. Often, new combinations of drugs are tested. Patients are closely watched to see if the drug works. However, the new drug is rarely compared to the current (standard-of-care) drug that is used. If a drug is found to work, it can be tested in a phase III clinical trial.

**Phase III:**
Phase III trials compare a new drug to the standard-of-care drug. These trials assess the side effects of each drug and which drug works better. Phase III trials enroll 100 or more patients.
Often, these trials are randomized. This means that patients are put into a treatment group, called trial arms, by chance. Randomization is needed to make sure that the people in all trial arms are alike. This lets scientists know that the results of the clinical trial are due to the treatment and not differences between the groups. A computer program is often used to randomly assign people to the trial arms.
There can be more than two treatment groups in phase III trials. The control group gets the standard-of-care treatment. The other groups get a new treatment. Neither you nor your doctor can choose your group. You will also not know which group you're in until the trial is over.
Every patient in a phase III study is watched closely. The study will be stopped early if the side effects of the new drug are too severe or if one group has much better results. Phase III clinical trials are often needed before the FDA will approve the use of a new drug for the general public.

**Phase IV:**
Phase IV trials test new drugs approved by the FDA. The drug is tested in several hundreds or thousands of patients. This allows for better research on short-lived and long-lasting side effects and safety. For instance, some rare side effects may only be found in large groups of people. Doctors can also learn more about how well the drug works and if it's helpful when used with other treatments. [6]

**Clinical research can be based on any of the following four concepts:**
1) Treatment of a disease
2) Diagnosis of a disease or disorder or dysfunction
3) Systematic review of several clinical studies
4) Prognosis of a particular disease. [7]

**CLINICAL STUDIES**
**Descriptive studies**
Descriptive studies report unusual or new events such as the occurrence of sudden infant death syndrome (SIDS) in several siblings within a single family, prevalence of albinism in a single family etc. The researcher simply records the observations and co-relates the events observed with possible reason. These are neither randomized nor pre-designed researches. They may be presented as case reports whereby certain individual patients with distinguished clinical characteristics are included in the study. All the baseline characteristics are recorded and the individual patient is treated as unique case with control over all the variables. The patient is


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observed and evaluated for the possible outcome. The results are compared with baseline values or are expressed as success or failure of the treatment given. If the treatment succeeded, a hypothesis is generated for an expanded and more rigorous study to find the relationship between the treatment and the outcome observed. In caseseries, observations are documented at regular intervals from patients exposed to a particular drug or a group of drugs. They may also cover prior histories of patients with the same outcome, to find a possible cause-effect relationship if exists. These are useful in predicting the incidence of an adverse event of newly-marketed drug when reports on such events are limited.[8]

**Explanatory studies / Observation studies**

In an observational study, the subject to be observed chooses whether or not to take the drug or to have the surgery being studied. Errors that are likely to occur include the differences in profile of the subjects since variables such as age, family history of disease, cause and severity of disease etc. may not be defined. For example, two patients have left ventricular (LV) dysfunction, in one it is because of ischemic heart disease (IHD) and in another it is because of severe mitral valve stenosis. Thus, the therapy of both the diseases differs due to different oetioes and hence both the patients can not be compared in one study. Another example is of two patients suffering from headache, one because of migraine and the other because of common cold. These two patients can not be compared for the analgesic activity of one drug since the cause and the severity of headache and hence the analgesic activity of the drug would vary greatly. Observational studies can never be blinded. Hence, biases from patients, observer and experimenter may result into systematic and random errors.[9]

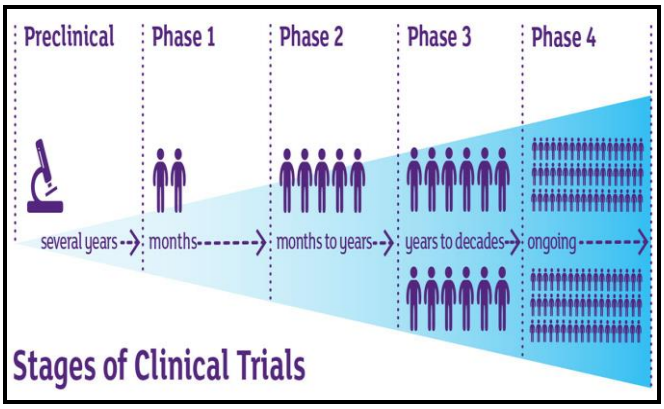


**Figure 1: Various stages of clinical trials [10]**

**Aggregate observation studies**

Pandemic and epidemic studies on communicable diseases and their treatments are generally carried out as aggregate observation studies e.g. occurrence and effective treatment of malaria and its relapse in particular geographical area.

**INDIVIDUAL OBSERVATION STUDIES**

In individual observational study, the patients/ subjects are individually observed and they are assembled in groups on the basis of outcome or exposure or both. Depending upon the basis of the grouping, the individual observational study is sub-classified as 1) Case-control; 2) Cohort and 3) Cross sectional. [11]

1) **Case-control study**

Case-control study involves assembling of subjects in groups on the basis of the outcome found in those subjects. It compares the subjects with outcome in question (the group behaves as a case group) with the subjects without the outcome (the group acts as a control) e.g. occurrence or nonoccurrence of myocardial infarction (MI) in patients with hypertension (HT). It generally follows the retrospective design and evaluates how the exposure is related to the well defined outcome using control group. However, grouping on the basis of outcome incorporates subjects with variety of distinguished characteristics. It is quick and inexpensive. Further, patients with rare outcome can be assembled in a group to study oetioes, pathophysioes and prognosis of a disease. Results are generally expressed in terms of odds ratio (OR) and risk ratio/ relative risk (RR). Although multiple exposure variables can be correlated with outcome, it does not allow the correlation of temporal sequence of cause and effect with the final outcome. [12]

2) **Cohort**

It includes groups assembled on the basis of exposure. Here the exposure is well-defined but the outcome is variable. Thus, it allows study of one exposure with many more outcomes. Cohort study can be retrospective wherein the groups are defined in past or it can be prospective wherein the groups are defined in present. The retrospective cohort correlates the exposure occurred in past with the outcome resulted just in recent past. Here the patients have been followed forward and hence it associates the exposure with some temporal outcomes though not all. If the patients have been treated with different treatments to control out come related variables, it limits the correlation between exposure and one outcome only. Like case-control study, it is also quick and inexpensive. If carried out on the basis of well-defined, - controlled exposure and followed with control over variables, retrospective cohort study suffices the requirements of prospective study with additional advantage of less time and money consumption. In prospective cohort study, the groups are observed for outcomes at particular, pre-decided time intervals. Thus, it finds firmly whether a particular exposure or sign or symptom is related with the outcomes. If the outcome is rare, the study requires inclusion of large number of patients and longer follow-up. Thus, it is expensive in terms of time and money. If the patients are not randomized and blinded, the outcomes may be influenced by bias and confounding.

3) **Cross-sectional**

Cross-sectional study assesses both the exposure and outcome concurrently. Generally it is survey- or review based. Cross-sectional study is, therefore, good for prevalence research. However, it is not suitable for causal outcome assessment.[13]

**EXPERIMENTAL STUDIES**

**Non-randomized studies** - Patients are selected on the basis of selection criteria. They are not randomized to the particular treatment(s) and are given a treatment depending upon course of disease. Generally, phase IV of



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clinical trial follows this way. Further, in many experimental studies in humans, randomization is not possible. Many of the surgical experiments have evolved with specific indication and application. They have a focused patient group and therefore, randomization is not possible or is unethical. For example, patients with both the kidneys failed require undergoing kidney transplantation. Although, dialysis is an available option it is not comparable with renal transplantation and hence patients can not be randomized to such options. [14]

**Randomized controlled trials**

In the studies which are randomized, controlled clinical trials (RCTs), human subjects (either healthy volunteers or patients) do not choose the therapy being studied or compared. Experimental clinical studies are generally RCTs. Randomized controlled trials are, as the name indicates, based on randomization. When a new drug successfully passes the pre-clinical studies, it is challenged to clinical experiments that follow random assignment of subjects to two or more groups one of which behaves as control group and therefore, such clinical experiments are called RCTs. [11]

**THE SEVERAL COMPONENTS TO BE CONSIDERED INCLUDE**

1) Study design;
2) Patient population;
3) Control group;
4) Randomization;
5) Blinding or non-blinding/ open-labelling;
6) Treatment considerations and
7) Outcome measures. [15]

**1) Study design**

The common study designs employed in RCTs include parallel group design, matched pairs and cross-over designs.

In parallel group design, the patients are enrolled, followed and observed for outcomes on parallel basis. Parallel group design requires large number of patients. In matched pairs, patients are matched for different variables and those matching the required variables are then randomized to various treatment groups. This type of study design overcomes the influence of variables on outcomes, although it is difficult to follow. Cross-over design is particularly used when the effect of a drug is reversible and transient. In crossover design, the patients are given more than one treatment but in sequence i.e. one after another when the effect of previous treatment is washed out. Cross-over design, thus, requires less number of patients.

**2) Patient population**

As a common and required method, the RCTs are carried out on specific subject population selected on the basis of "selection criteria" which are derived in line with various fixed, independent and dependent variables. This is to overcome the misleading by variables. For example, if effects of angiotensin-converting enzyme inhibitor (ACEI) on cardiac function are to be studied in patients with LV systolic dysfunction, variables like family history of cardiac disease, presence of other cardiac diseases such as heart block or valve failure etc. should be avoided as patients with these variables are different from those not having the variables.

**3) Control group**

Randomized controlled trial also includes control group (either placebo control or active control) to show the control and effect over dependent variables and to obtain clear effects of drug under consideration. Control group can be placebo control, no-treatment control, historical control or active control. The placebo means dummy to the drug under evaluation with regard to organoleptic properties but lacking any pharmacological actions. Thus, it is to overcome the psychological impact of drug administration manifested by an individual on disease progression. It allows the investigator to determine the true efficacy of the treatment being researched for a particular condition. Some studies also include no-treatment control or historical control as types of controls. In no-treatment control group, the patients do not receive the placebo even. Therefore, they know that they do not receive any treatment and hence, individual bias due to psychic factors affects the study outcomes. In other words, it is least preferred type of control. Historical control is the control group of previous study that was a different with respect to treatment group. Here control group of one study is utilized for another study and both the studies differ with regard to treatment only. This is done for studies not allowing placebo control or no-treatment control and involving high mortality disease even after availability of effective treatment e.g. studies on treatment for cancer and human immunedeficiency virus (HIV) infection. [16]

Inclusion of placebo in drug research and sham surgery has 6 been debated. Moreover, when an effective established treatment is available, use of such placebo control group is unethical. For examples, a drug is to be assessed for its effects on cardiac function in patients with LV systolic dysfunction, as per American College of Cardiology/ American Heart Association (ACC/ AHA) guidelines all the patients would be necessarily receiving ACEI, if not contraindicated. Therefore, in this type of study all the patients receive the recommended drug which has already proved its beneficial effect on cardiac function. Thus, one can not have a placebo control group but will have an active control receiving the best current therapy. It provides information about relative efficacy of the investigational drug over existing one. In the present example, the patients would be randomly assigned to a group receiving ACEI or to a group receiving ACEI in addition to the drug being evaluated- the former behaving as an active control and the later as a treatment group. [16]

**4) Randomization**

Randomization is an optimal method of distributing the variables between the treatment and control groups. Therefore, the bias of selecting specific treatment does not occur. Random assignment of subjects to various groups provides equal distribution of all variables in all the groups and does not let them influence the final outcomes. Randomization techniques mainly used in RCTs are simple randomization, cluster randomization and stratified randomization. In simple randomization, patients matching the selection criteria are randomized to various treatment groups. In cluster randomization various groups of patients matching the criteria are randomized to treatment under investigation. This kind of trial is especially used to find the geographical, genetic



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variations. In stratified randomization technique, subjects are classified in groups i.e. strata and then within a group they are randomized to various treatment groups. In RCTs, three main methods of randomization include 1) Tables of random numbers; 2) Mathematical algorithms for pseudorandom number generators and 3) Physical randomization devices such as coins, cards or sophisticated devices such as Electronic Random Number Indicator Equipment (ERNIE). [17]

**5) Blinding**

To avoid bias, trial is carried out in blind fashion. Blinding means "concealing or masking of the patients-assignment to a study group (control or treatment) from those participating in the study i.e. patients, observer and experimenter". RCTs can be blinded or non-blinded. The non-blinded experiment is also called open-label study. In this type of study all three- the patient, the physician or the observer and the experimenter or the researcher, are aware of the treatment used. In many instances it is unethical to hide the treatment module from the patients especially those suffering from life-threatening disease such as cancer, AIDS, end-stage HF etc. Additionally, open-label study permits the patients to buy brand of the drug of his choice independently. However, it has the biggest disadvantage of introducing bias from any of the three components of the RCTs.

Blinding is carried out at the beginning of study. The blind RCT can be single-, double- or triple- blind. In a single-blind experiment, the participants either the patient or the healthy volunteer does not know whether he receives the test intervention or placebo. In double-blind trial, neither the patient/ subject nor the experimenter knows who belongs to the control group and who belongs to test group but the observer knows. In triple-blind RCT, none of the three components of study knows name or nature of the treatment given. Therefore, the triple-blind RCT is totally devoid of any kind of biases and allows the outcomes to be free from any such influence. In double- and triple-blind experiment the keys identifying the patients/ human subjects and the group they belonged to are preserved by a separate another party and given to the researcher only at the end of the study.

Randomized controlled trial can also be conducted as PROBE. PROBE is an acronymus of Prospective, Randomized, Open-label, Blinded-End point as used earlier by Neutel and Smith (2003). This type of trial is easier to carry out than a double-blinded placebo controlled design (DBPC) because it does not require the "matched placebo group" and the "open-label" allows the enrolled patients to receive a marketed preparation of the drug. However, the PROBE studies have only the end-point blinded i.e. observer is unaware of the treatment being studied while investigator and patients are aware of it. Therefore, the investigator or the patient bias may be introduced and thus, the results obtained are less reliable than those with double- or triple-blind study. [18]

**6) Treatment considerations** -

While conducting RCTs, the treatment (either being studied or behaving as active-control) must be considered with regard to its dosages, dosing frequency and other concurrent medication. A drug is generally available in various dosage forms viz. tablet, capsule or injectable etc. and it varies in strength. Moreover, depending upon the dosage form, the route of administration differs and hence, the amount of administration and dosing frequency also. Whenever dose and frequency need to be changed, it is done gradually and stepwise. If two drugs are to be administered one of which is likely to interfere with the other either pharmacokinetically or pharmacodynamically, the dosage must be reconsidered to overcome the influence of such interference on study outcomes. Patient compliance is another important part of the treatment consideration. A treatment should not be non-compliant as the patient avoids or less prefers to take such medication resulting in erroneously less efficacious outcomes than those obtained with the other treatment group.

**7) Outcome measures**

The objective of the study determines the outcomes of interest to be measured. These measures are nothing but the points of checking and recording to accomplish the comparison. In experiments the outcomes are measured in terms of efficacy end-points i.e. primary end-points and surrogate end-points which are also called secondary end-points. For examples, in an experiment evaluating an antihypertensive agent, the clinical end-point of real interest is whether the treatment under investigation can reduce cardiovascular events; a surrogate is the ability of the treatment to reduce blood pressure. The primary end-points of the study are the main measures to support or refute the hypothesis of the study. For example, when diuretics are used for treating hypertension, serum glucose level measurement can also be added though serum electrolytes are usually measured as main secondary endpoint. Although various measures are determined as primary and secondary end-points, quality of life is now-a-days becoming main primary end-point. [19]

## STATISTICS IN CLINICAL RESEARCH

Statistics play a crucial role in concluding a clinical research. It is applied in clinical research to analyze data and to infer the results obtained. It is important to obtain a statistically significant difference between two or more groups being compared in a clinical research, in order to make the outcomes acceptable. Statistics is also required at the beginning of the trial to calculate the sample size required to reach a statistical significance in the findings.

### 'P' value and level of significance

In a clinical research, a null hypothesis is stated and tested by finding the difference between/ among the results of groups involved in the research. The difference in the results obtained between/ among various groups should be of statistical significance in order to reject the null hypothesis and thus, to accept the alternative hypothesis i.e. "treatment being study as effective one". In many instances, clinical research finds the difference in the results of clinical significance but fails to attain a statistical significance and therefore, the null hypothesis is accepted. Rejection or acceptance of a null hypothesis is based on 'P' value. 'P' value is defined as "the smallest level of significance of the difference in the results that would reject the null hypothesis". It tells how likely it is that the difference between/ among groups occurred by chance rather than because of an effect of treatment.[20]



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**Types of errors and power of study**

The 'P' value is based on two types of errors that one may encounter during experiment. These two errors are designated as type I error and type II error. The former is also called alpha (α) error and the later beta (β) error. A type I error occurs if a difference is found between A and B when none actually exists. Thus, α error indicates the chances of detecting a difference which does not actually exist i.e. the chances of having False Positive Difference. A type II error occurs if no difference is found though A and B do actually differ. Thus, β error indicates the chances of not detecting a difference which actually exists i.e. the chances of having False Negative Difference. Alpha error indicates the level of significance of the result difference among various treatment groups. The level of significance is usually set at the traditional value of 5%. Beta error gives an idea about power (1-β) of a clinical study. Beta error is often chosen to be between 5 and 20%. Power is the ability of a statistical test to show significance if a specified difference truly exists. It is essential to minimize these errors at pre-decided levels or below to draw a conclusion in a clinical study. Furthermore, results of a statistical analysis are found conclusive only when the sample size is sufficiently large. However, because of time and cost factors, it may not be possible to enroll large sample size in a study. In that case, finding power of the study may disclose and support the inability of a test not to reach a statistically significant difference between the groups, even when the clinical difference is significant. [21]

**Confidence interval**

The confidence interval (CI) gives a range. It gives a measure of reproducibility of the results within the obtained range. Expression of 'P' value along with CI is clinically more useful and acceptable by many researchers. Generally, it is kept at level of 95%. A 95% CI indicates that if the study is repeated 100 times, the study results would fall within this interval 95 times.

For example, if improvement in LV ejection fraction (LVEF) after revascularization in 95 patients is 6% on an average when compared with baseline with a 95% CI of 4.5 to 9% for the difference, it is concluded that the revascularization has the specificity of producing improvement in LVEF by 4.5 to 9% if this revascularization is performed in such 100 patient populations i.e. if it is repeated 100 times. [22]

**Odds ratio and relative risk**

Odds ratio (OR) and relative risk (RR) both are measures of the size of an association between an exposure and a disease or death. For example, association between smoking or HT and development of IHD; use of a medication and occurrence of a side effect; exposure to MI over global LV ischemia and mortality etc. are expressed in terms of OR or RR.

Observational studies usually report their results as OR or RR, although experiments also include these types of measurements as safety and efficacy end-point. A RR of 1.0 indicates that the exposure does not change the risk of disease.

A RR of 1.9 indicates that patients with the exposure are 1.9 times more likely to develop the disease or have a 90 percent higher risk of disease. For example, if the RR of hyperlipidemia is 1.4 for development of IHD indicates that patients with hyperlipidemia are 1.4 times more likely to develop IHD than those without hyperlipidemia or they have a 40% higher risk of developing IHD.

Odds ratio is a way to estimate relative risks in case-control studies, when the RR cannot be calculated specifically. [23]

**DATA ANALYSIS:**

The test to be applied depends on the type of data and their distribution in the study. At large, the data are categorized as parametric or nonparametric. However, in clinical study, the data collected for analysis can alternatively be classified in four classes [24]

1) Continuous e.g. blood pressure, blood sugar

2) Discrete, associated with numbers and ordered e.g. number of anginal episodes per week, number of MI attack in past etc.

3) Attributes: categorical, ordered e.g. degree of overweight, intensity of pain

4) Attributes: categorical, not ordered e.g. male or female, patients with diabetes mellitus or not.

Data can also be typified alternatively as categorical or numerical. The categorical data can be nominal or ordinal in nature. Nominal data are expressed as proportion e.g. sex - male or female proportion in occurrence of a disease. Ordinal data are expressed as scores and ranks e.g. pain, categorized as mild, moderate and severe and can be scored as 1, 2 and 3 respectively. The numerical data are observed in form of interval measurements either continuous (e.g. blood sugar level, blood urea level) or discrete (e.g. number of patients admitted to a hospital, heart rate etc.). [25]

**STATUS OF CLINICAL RESEARCH IN INDIA:**

Clinical research in form of trial is conducted not only as unicenter but also as muticenter at various clinical research centers spread over various countries including India. In India, for international collaborative study, details about foreign collaborators and documents for review of Health Ministry's Screening Committee (HMSC) or appropriate Committees under other agencies/authority like Drug Controller General of India (DCGI) are implemented and followed in line with the guidelines by Indian Council of Medical Research. The centers participating in the trial are taken care by clinical research organizations (CROs), which play a distinguished role of central facilities. With advancement and development of various guidelines to implement in such trials, more than 20 CROs have come up with many known to conduct trials at international level. Though developing at full swing, further expansion of field to include research on biologics and devices is needed. [26]

**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



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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. [27-29]

## CONCLUSION:

Clinical trials provide knowledge of the benefits, possible adverse effects and uses of new medicine. With the help of clinical trials we can evaluate whether the medicine is safe and effective, although clinical trials reduce the chance of developing the disease. Clinical trials determine what does and what doesn't work in humans that cannot be learned in the laboratory or in animals.

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