INTRODUCTION

Definition given by WHO

A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health – related interventions to evaluate the effects on health outcomes.

Clinical trials are also known as therapeutic trials, which involve subjects with disease and are placed in different treatment groups. It is considered a gold standard approach for epidemiological research.

While designing a clinical trial, it is important to select the population that is best representative of the general population. Therefore, the results obtained from the study can be generalized to the population from which the sample population was selected. It is also as important to select appropriate endpoints while designing a trial.

HISTORY

The world's first clinical trial is recorded in the "Book of Daniel" in The Bible.This experiment resembling a clinical trial was not conducted by a medical, but by King Nebuchadnezzar a resourceful military leader.

The 1st clinical trial was conducted by physician James Lind in 1747-

He included diet with acidic food at crew members of ship affected with scurvy. Crew divided in 6 groups including control group.

In 1863 – physician Austin Flint gave patients a fake remedy, for rheumatism later known as placebo effects.

1964- After World War II, the research community saw a need for ethical codes. The declaration of Helsinki created by the World Medical Association offered guidelines to physicians who used human subject.

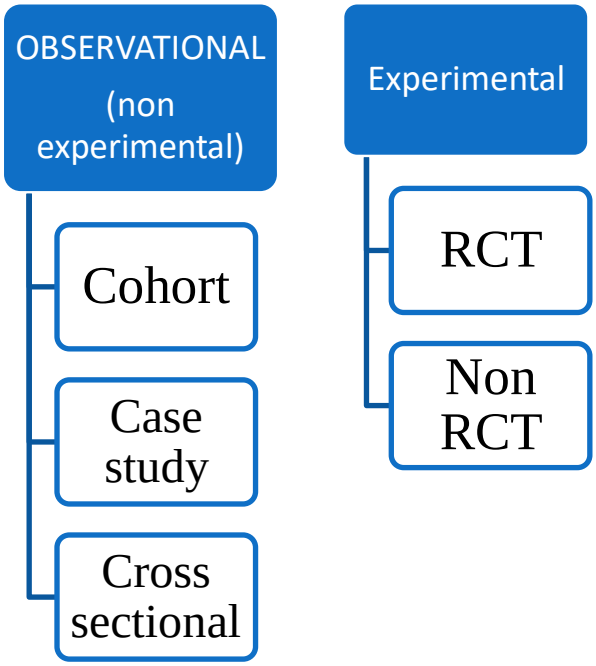
The idea of randomization was introduced in 1923. However, the first randomized control trial of streptomycin in pulmonary tuberculosis was carried out in 1946 by MRC of the UK.[6,7] The MRC Streptomycin in Tuberculosis Trials Committee (1946) was chaired by Sir Geoffrey Marshall, and the statistician was Sir Austin Bradford Hill and Philip Hart, who later directed the MRC's tuberculosis research unit, served as secretary.

TYPES OF CLINICAL TRIALS

	Phase I	Phase II	Phase III	Phase IV
Objectives	Determine the metabolic & pharmacological actions & the maximally tolerated dose	Evaluate effectiveness, determine the short-term side effects & identify common common risks for a specific population & disease	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risks- benefit ratio in a dermatography diverse sample .	Monitor ongoing safety in large populations & identity additional uses of the agent that might be approved by the FDA .
Factors to be identified	a)Bioavailability b)Bioequivalence c)Dose proportionality d)Metabolism e)Phamacodynamics f)Phamacokinetics	a)Bioavailability b)Drug -Disease Interactions c)Drug -Drug Interactions d)Efficacy at various doses e)Patient Safety f)Phamacodynamics g)Phamacokinetics	a)Drug -Disease Interactions b)Drug -Drug Interactions c)Dosage intervals d)Risk -benefit information e)Efficacy & safety for subgroups	a)Epidemiology data b)Efficacy & safety within large, diverse populations c)Pharmacoeconomics
Data factors	• Vital signs , • Plasma & serum levels • Adverse events	• Dose response & tolerance • Adverse events • Effects	• Laboratory data • Efficacy • Adverse events	• Efficacy • Pharmacoeconomics • Epidemiology • Adverse events

	Phase I	Phase II	Phase III	Phase IV
Design features	• Single, asacending dose tiers • Unblinded • Uncontrolled	• Placebo controlled comparisons • Active controlled comparisions • Well defined entry criteria	• Randomized • Controlled • 2-3 treatment arms • Broader eligibility criteria	• Uncontrolle • observational
Duration	Up to 1 month	Several months	Several years	Ongoing (following FDA approval)
Population	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders,etc
Sample size	20 to 80	200to 300	100-1000	>1000
Example	Study of a single dose of drug X in normal subjects	Double blinded study evaluatng safety and efficacy of drug X vs . Placebo in patients with hypertension.	Study of drug X vs, Standard treatment in hypertension study	Stu dy of economics benefit of newly approved drug X vs .

DESIGN OF CLINICAL TRIALS



EXPERIMENTAL STUDY DESIGN

The basic concept of experimental study design is to study the effect of an intervention. In this study design, the risk factor/exposure of interest/treatment is controlled by the investigator. Therefore, these are hypothesis testing studies and can provide the most convincing demonstration of evidence for causality. As a result, the design of the study requires meticulous planning and resources to provide an accurate result.

The experimental study design can be classified into 2 groups, that is, controlled (with comparison) and uncontrolled (without comparison).[1] In the group without controls, the outcome is directly attributed to the treatment received in one group.

Randomization

Randomization is the random allocation of treatment, which means all participants have the same chance of being assigned to each of the study groups. The allocation, therefore , is not determined by the investigators , the clinicians or the other participants.

The basic benefits of randomization include

- Eliminates selection bias
- Balance arms with respect to prognostic variables(known & unknown).
- Forms basis for statistical tests, a basis for an assumption- free statistical test of the equality of treatments.

There are various ways to randomize and it can be as simple as a 'flip of a coin' to use computer software and statistical methods. To better describe randomization, there are three types of randomization: simple randomization, block randomization and stratified randomization.

Simple randomization

In simple randomization, the subjects are randomly allocated to experiment/intervention groups based on a constant probability.

This can be performed in multiple ways, and one of which being as simple as a 'flip of a coin' to using random tables or numbers.[17] The advantage of using this methodology is that it eliminates selection bias. However, the disadvantage with this methodology is that an imbalance in the number allocated to each group as well as the prognostic factors between groups.

Block randomization

In block randomization, the subjects of similar characteristics are classified into blocks. The aim of block randomization is to balance the number of subjects allocated to each experiment/intervention group. For example, let's assume that there are four subjects in each block, and two of the four subjects in each block will be randomly allotted to each group. Therefore, there will be two subjects in one group and two subjects in the other group.[17] The disadvantage with this methodology is that there is still a component of predictability in the selection of subjects and the randomization of prognostic factors is not performed.

Stratified randomization

In stratified randomization, the subjects are defined based on certain strata, which are covariates.[18] For example, prognostic factors like age can be considered as a covariate, and then the specified population can be randomized within each age group related to an experiment/intervention group. The advantage with this methodology is that it enables comparability between experiment/intervention groups and thus makes result analysis more efficient.

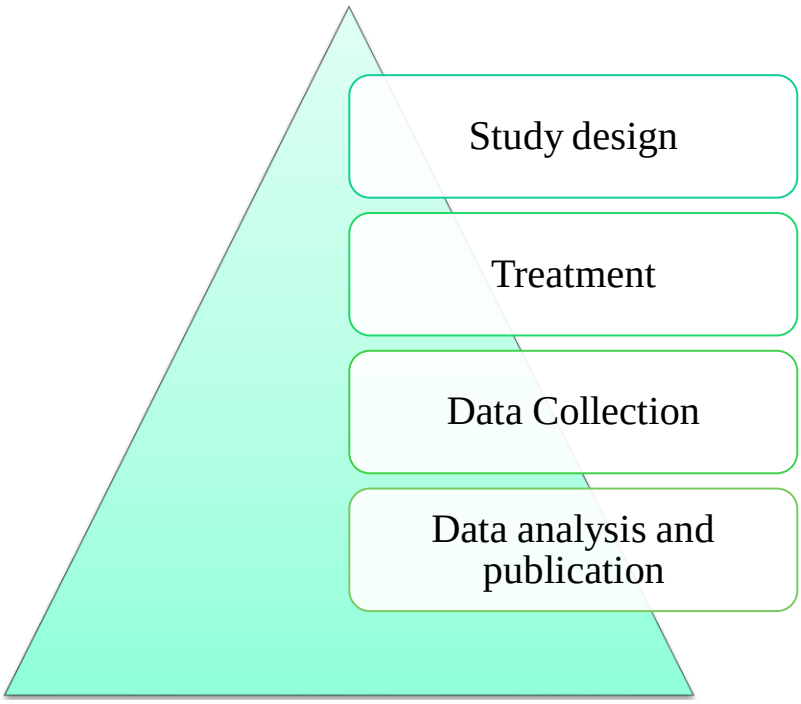
Placebo

Placebo is defined in the Merriam-Webster dictionary as 'an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (such as drug)'.[20] A placebo is typically used in a clinical research study to evaluate the safety and efficacy of a drug/intervention.

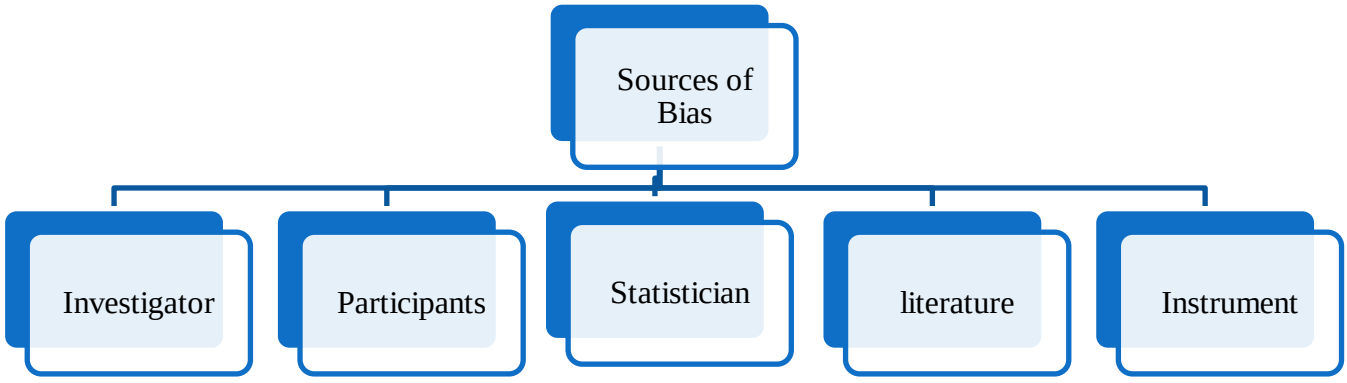
Bias

- Any systemic deviation from the true results.
- It may be any error in the design, conduct or analysis of a study that results in distortion of truth.

- **Where bias can happen ?**



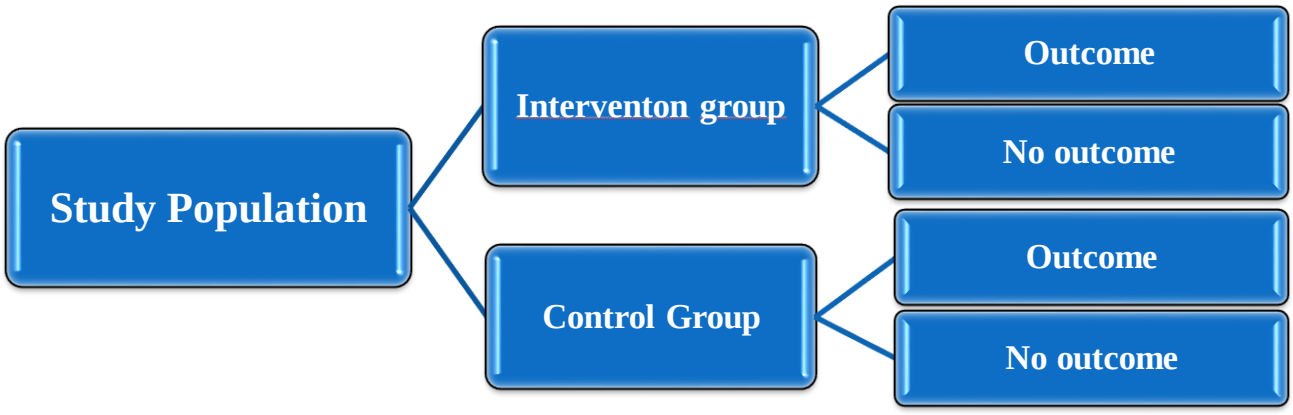
Sources of Bias



RCT (Randomized Control Trial)

An epidemiology experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic.

Patients are randomly assigned to the study all groups that help in avoiding bias in patients.



Advantages of randomised control trial study design –

Comparitive –

One treatment is directly compared to another establish superiority.

Minimises bias –

Randomisation minimization allocation bias and selection

Blinding minimises performance bias.

Minimises confounding factors

Randomisation makes groups comparable according to both known and unknown factors.

Statistical reliability

Statistical test of significance is readily interpretable when the study is randomized.

Disadvantages of randomised control trial study design

1. Might demand vast sample size, which require more resources from the investigators.
2. Sometimes allocation of participants may be predictable and result in selection bias when the study groups are unmasked.
3. Trials are of longer duration and more expensive
4. Results may not always mimic real life treatment situation (e.g. inclusion, exclusion criteria: highly controlled setting).
5. Ethical limitation: some reserch can not ethically performed as an RCT.

TYPES OF RCT

Randomised controlled clinical trial – includes diagnostic, therapeutic and prophylactic'

e.g. evaluation of nitrates in reducing cardiovascular mortality.

Randomized controlled field trial – similar to RCCT except that the intervention is preventive and not therapeutic.

e.g. in this, efficacy of a preventive such as a new vaccine is tested in one study group and the other group recive a placebo or standard.

Preventive trial- trial of primary preventive measure

e,.g. vaccines

Risk factor trial – investigator intervenes to interrupt the usual sequence in the development of disease for those individuals who have risk factors for developing the disease

e.g. primary prevention of CHD using simvastatin to lower serum cholesterol.

Classification according to level of blinding

Open Blind	• In open RCT, everybody involved in the trial knows which intervention is given to each paticipants.
Single Blind	• Patients or evaluator is blind as to treatment but not both.
Double Blind	• Neither patient nor the outcome evaluator knows to which treatment patient was assigned.
Triple blind	Patient, physician and data analyst are blind as to treatment identity.

According to participants exposure-

Parallel

A parallel study is a type of clinical study where treatment and controls are allocated to different individual.

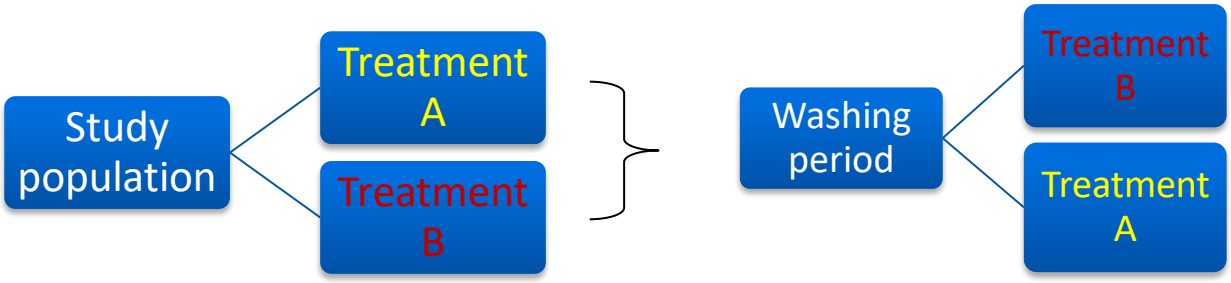
In this groups treatments, a & b, are given s that one group receives only a while another group receives only b .

Advantages	Disadvantages
• This is unlike a crossover study where at first one group receives treatment A, followed by treatment B later, while the other group receives vice –versa. • Key element of this design is randomization. • One treatment group & one treatment-as- usual group.	• These studies generally require large number of patients for the analysis.

Cross- over design

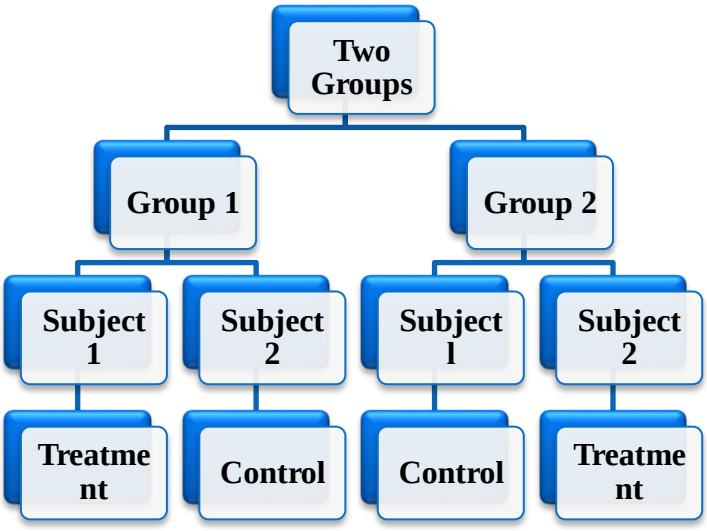
In these type of studies each patient serves as his own control. Each patient gets both treatments.

Each patient receive first treatment then washout time is provided then other treatment is provided to the same.

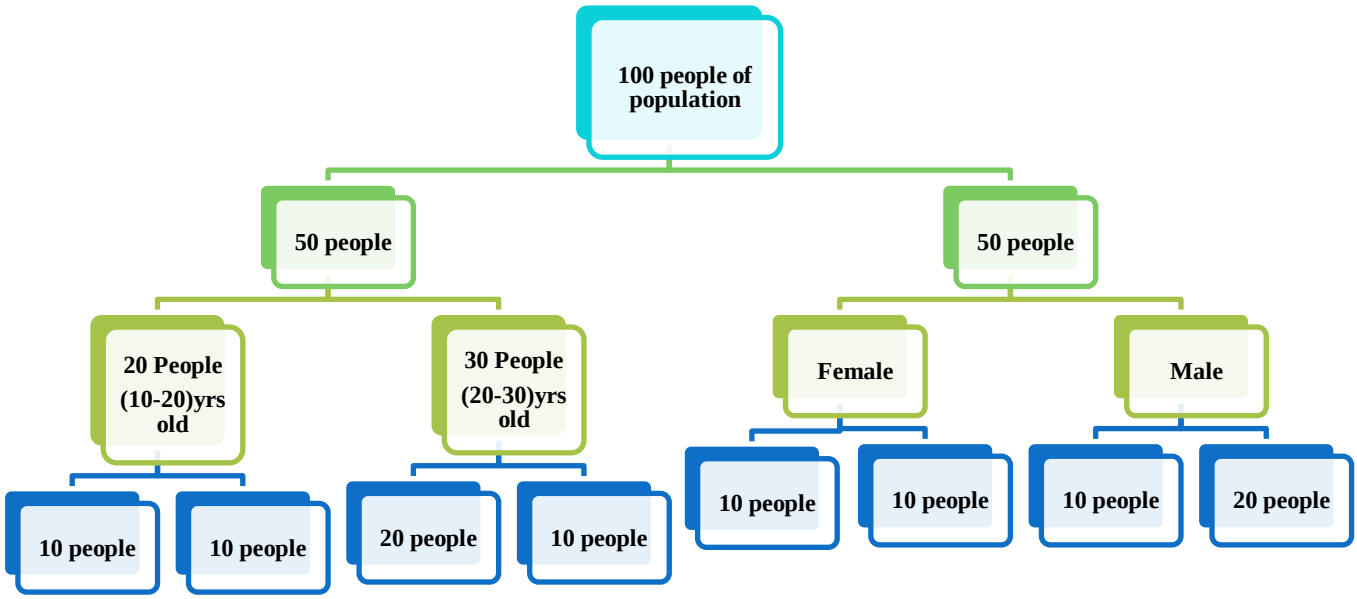


Matched Pair

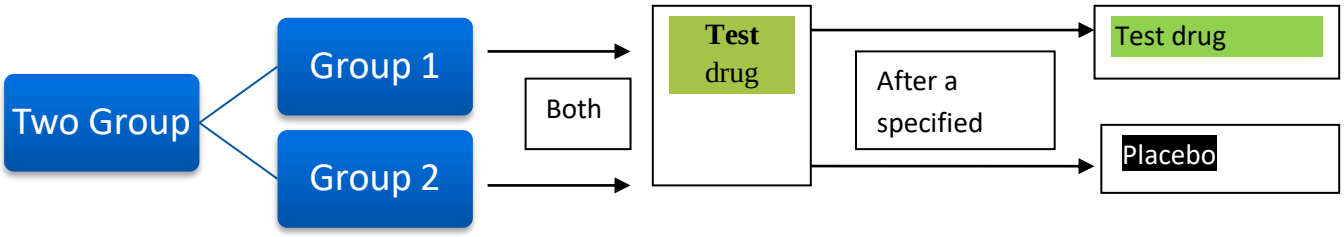
In these type of study two pair of groups are prepared. Then one subject of each group are administered treatment and another subject are administered control & then compared the result.



Stratification

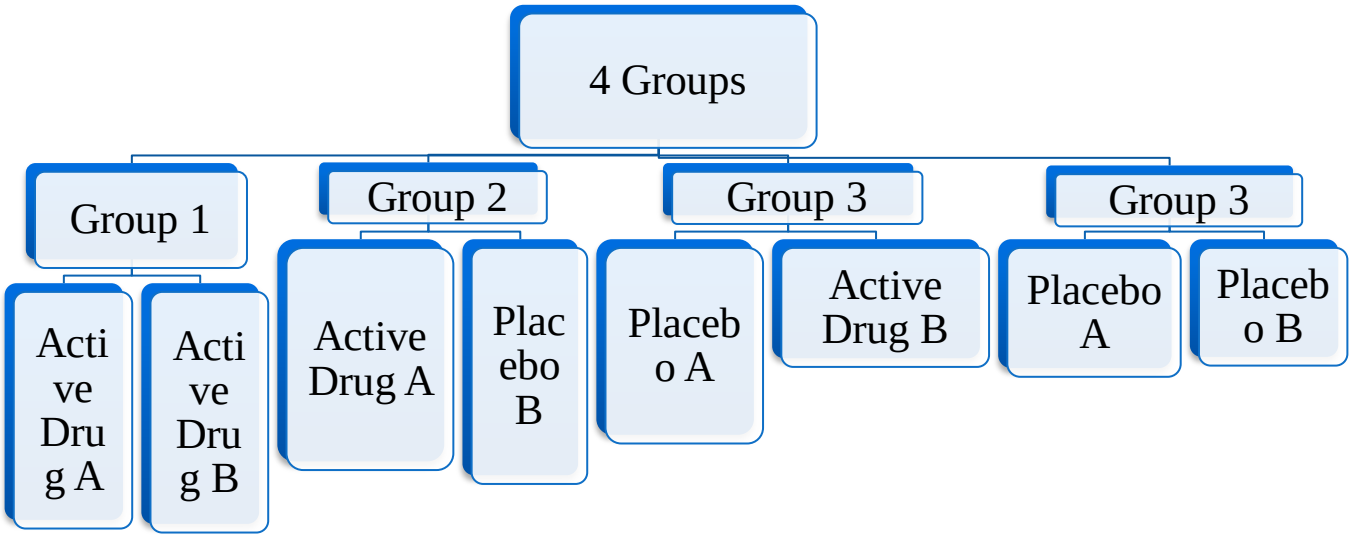


Withdrawal design



Factorial Design

In these study Drug A & Drug B with Placebo of drug A & placebo of Drug B.



According to number of participants

1. N- of one trial	• An N of 1 trial is a clinical trial in which a single patient is the entire trial, a single case study. • In which one participants receives the experimental and the control interventions.
2. Mega trial	• A massive clinical trial assessing the value of the therapeutic interventions by enrolling 10,000 or more subjects.
3. Sequential trial	• It is a statistical analysis where the number of participants is not specified by the investigators beforehand. • Instead, the investigators continue recruiting participants until a clear benefirt of one of the interventions is observed.

According to the magnitude of activity

Superiority	• Test medicine better than control medicine .
Equivalent	Test medicine equivalent to controlled drug
Non **inferiority**	• Find out the effect by comparison with prevesiouly marketed medicine,
Dose response relationship	• Find out stating dose and maximum dose by comparing with control drug.

Non randomized Trial

- A study where the participants have been assigned to the treatment, procedure ,or intervention alternatives by a method that is nor random. The investigator defines and manages the alternatives.
- A clinical trial in which the participants are not assigned by chance to different treatment groups. Participants may choose which group the want to be in, or they may be assigned to the group by the researchers.
- The non randomized interventional study design also called Quasi- experimental designs.
- It is used to estimate the casual impact of an intervention on its target population without random assignment.

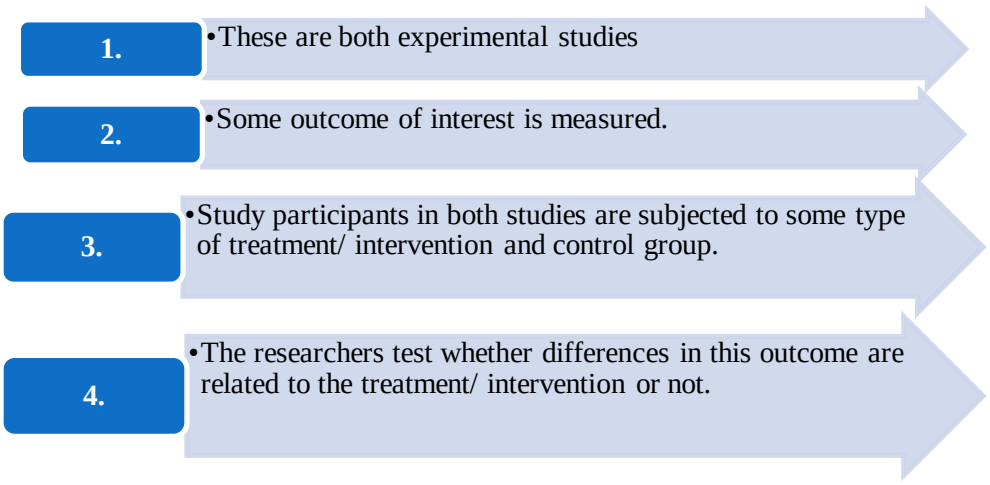
Reasons to do Qausi Experimental Study

- When the act of random allocation may reduce the effectiveness of the intervention(occurs when the effectiveness of the intervention depends on the partipants's active participation which is influenced by their beliefs and preferences.
- When it would be unethical to do random allocation.
- When it is impractical to do random allocation(e.g cost or convenience factors).
- When there are legal or political obstacles to random allocation.
- When the researchers can't manipulate the independent variables.
- When the researchers can't randomly assign participants to groups.

Disadvantages of Nonrandomized Clinical Trial-

1. • It is the potential for bias from confounding. The direction of this bias is unpredictable from the study to study.
   • e.g.- clinicians may differentially include the sicker patients in the intervention trial to provide the "best chance" for the patient, thus biasing the trial against the intervention.
2. • The design can never ensure that unmeasured or imprecisely measured social, cultural, or clinical variables do not account for the apparent treatment effect.
3. • Thus the results of these trials must be evaluated in a larger context, & internal & external validity may be best assessed through the replication of results in a variety of clinical settings.

Similarities between RCT & Non RCT



	Randomized	**Non- Randomized**
1.	RCT is an experimental study design where the subjects in a population are randomly allocated to different groups.	Non- RCT is an experimental study design where the subjects in a population are non randomly allocated to different groups.
2.	Also known as randomized study	Also known as Quasi experimental study
3.	Study population are selected are randomly	Study population are chosen.
4.	Randomization is the main ingredient of RCT.	Randomization is not the main ingredient of NON RCT.
5.	It is less potential for bias,or confounding and study validity is not compromised.	It has relatively increased potential for bias, or confounding and study validity is compromised.
6.	Have a scientific validity	Has moderate scientific validity
7.	It provide the best scientific evidence to any study.	Evidence generated from this design are relatively of low significance while compared to RCT.
8.	It is considered as an ideal design for evaluating both the effectiveness and side effects of interventions.	It is not considered as an ideal design for evaluating both the effectiveness and side effects of interventions.
9.	These are generally quite expensive.	These are generally less expensive.
10.	RCT can be used up to a point unless there is any real world constraints for random assignment.	NON RCT is real world constraints like ethical, political or logistical constraints do not allow for randomization.

OBSERVATIONAL (non experimental)

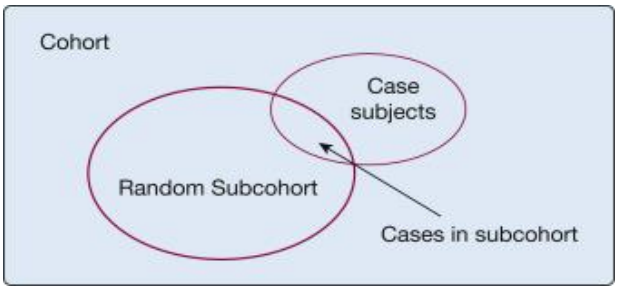
COHORT STUDY

Cohort studies are types of observational studies in which a cohort, or a group of individuals sharing some characteristic, are followed up over time, and outcomes are measured at one or more time points.

The term "cohort" in modern epidemiology refers to "a group of people with defined characteristics who are followed up to determine the incidence of, or mortality from, some specific disease, all causes of death, or some other outcome."[1] A cohort study observes people as two or more groups, from exposure to outcome.

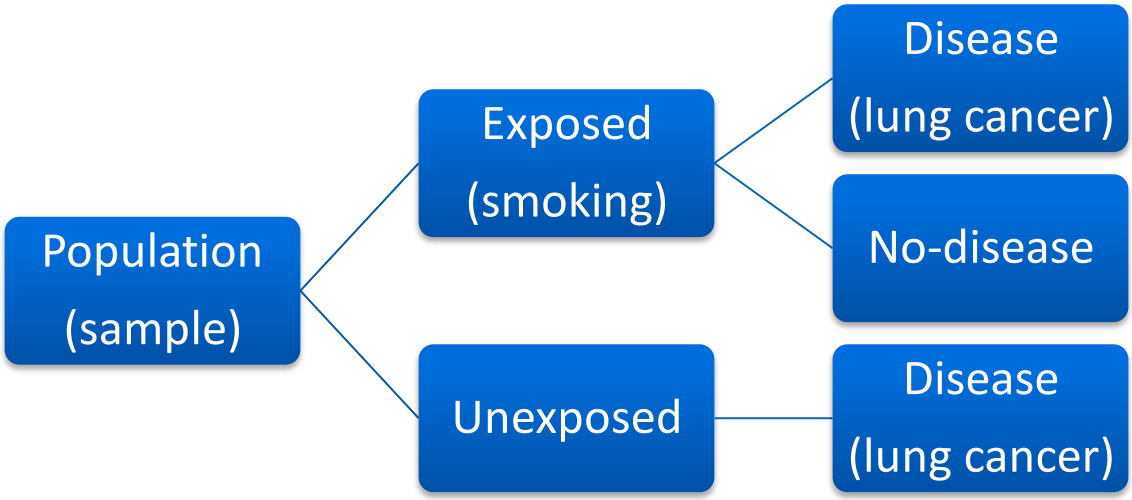
A key feature of the cohort study design is that subjects are followed up over time. It begins with subjects who are exposed and not exposed to a factor and then evaluates the subsequent occurrence of an outcome. Unlike cross-sectional studies, which are often used to determine prevalence, cohort studies are used to study incidence, causes, and prognosis.

Cohort studies allow us to calculate the incidence rate, cumulative incidence, relative risk, and hazard ratio. Causality cannot be established definitively through a cohort study.

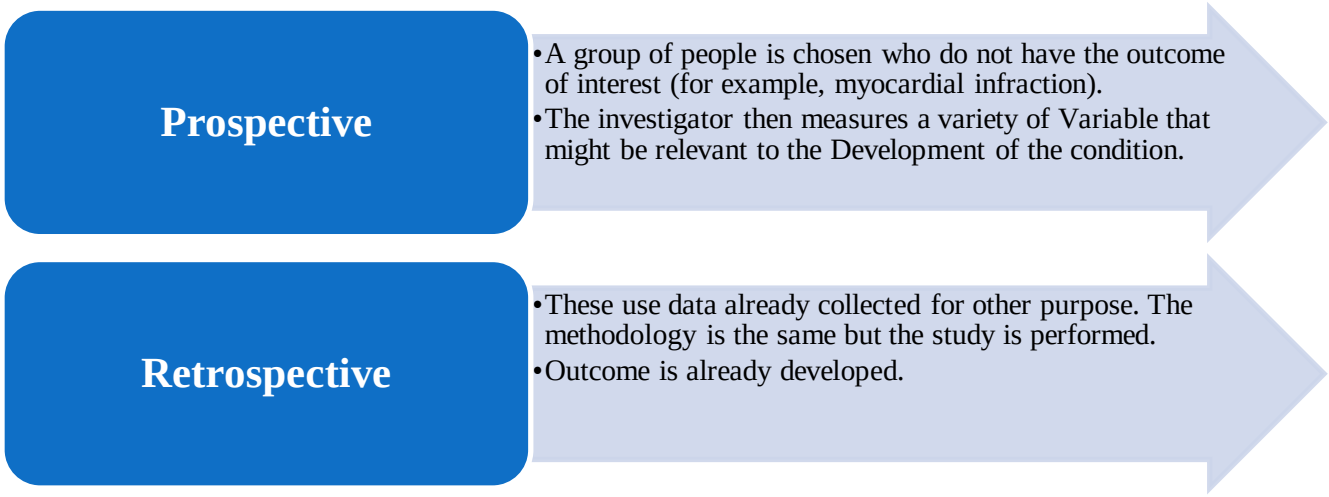


Cohort studies follow a defined group of subjects (cohort) over a defined time period. The usual approach is to start with healthy subjects, or subjects without the disease under study. The main purpose is usually to assess the possible effects of different external or internal factors on the risk of disease.

- A population at risk for the disease events is followed over time for the occurrence of disease of events.
- This study used to estimate how often disease or life events happen in a certain population .
- These are the best method for determining the incidence and natural history of a condition.



The studies may be; Prospective or retrospective



Prospective & Retrospective

- ❖ Studies carried out from present time to future.
- ❖ Can be tailored to collect specific exposure rate.
- ❖ But long wait for events to occurr
- ❖ Expensive
- ❖ Prone to high dropout rates.

Retrospective

- ❖ Look at medical events from past to present
- ❖ Information is available immediately
- ❖ Difficult in tracing subjects and doubt on quality of recorded information.

Advantages

1. The principal advantage of cohort studies is that they include the dimension of time, which permits the researcher to draw conclusions about causal relationships.
2. A major advantage of the cohort study design is the ability to study multiple outcomes that can be associated with a single exposure or multiple exposures in a single study.
3. Cohort study designs also allow for the study of rare exposures.
4. Cohort studies are intuitively easy to understand, numerous variables can be assessed at the same time, and one can apply standardized methods with clear definitions with regard to both exposure and endpoints.
5. Ascertainment of exposure and endpoints are independent, as all exposure data are collected while the subjects are still healthy.
6. Both incidence rates and incidence rate ratios can be estimated from cohort studies.
7. Large cohort studies allow for the assessment of more than one endpoint. In this way multiple disease problems can be examined as different exposures.
8. Able to study the change in exposure and outcome over time
9. Good for examining rare exposures.
10. Can measure incidence of outcome.
11. May be able to infer causality.

Prospective Study	Retrospective Study
Able to control design, sampling, data collection, and follow-up methods	Time-efficient and inexpensive
Can measure all variables of interest	Easy to obtain large sample

Disadvantages

1. Cohort studies have several practical and inferential problems. First, cohort studies on diseases with low incidence rates are not amenable to drawing conclusions on causal relationships, as too much time is needed to accrue a sufficient number of events. On the other hand, cohort studies are suitable to the examination of exposures that are stable over time, or of diseases that are either relatively frequent or of a certain duration.
2. Susceptible to loss to follow-up compared with cross-sectional studies.
3. Confounding variables are the major problem in analyzing the data compared with RCTs
4. Cohort studies are relatively costly and usually require long follow-up, as well as an infrastructure for follow-up and database updating. In addition, the recording of exposure data can be inflexible.
5. Exposure data are collected only at baseline, and are used to construct different exposure categories.

6. Therefore, any changes in exposures the subjects may undergo during follow-up, such as change in their area of residence or occupation (if occupational exposure is of interest), cannot be taken into account.
7. Without follow-up, these changes are unknown to the researcher and can lead to an underestimation of the risk assigned to a particular exposure.

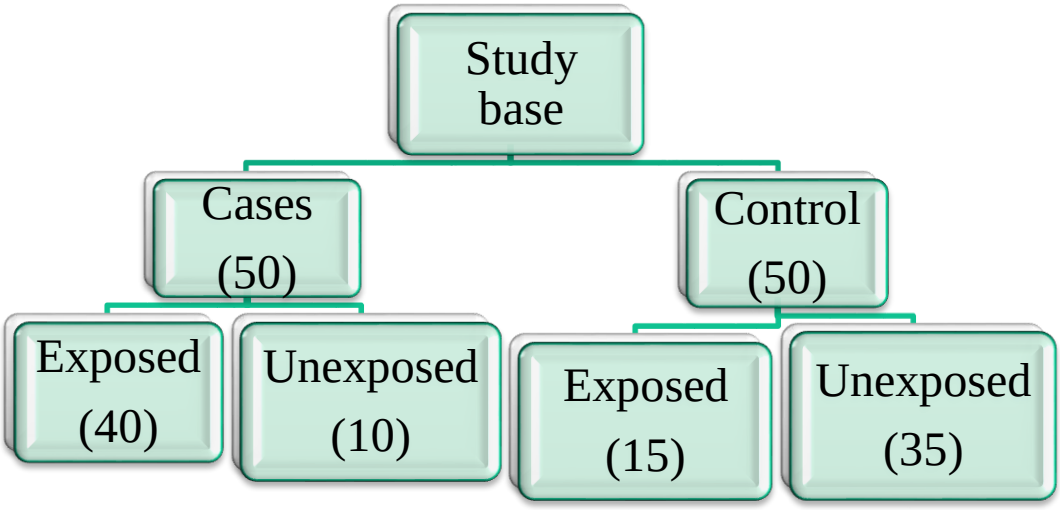
Prospective Study	**Retrospective Study**
May be expensive to conduct	Less control over variables
Time-consuming	Susceptible to information bias and recall bias

As with all other epidemiological studies, cohort studies contain three principal elements:

1-Choice of target population, which contains the source population
2-Methods for ascertainment of exposure
3-Registration of endpoints

CASE CONTROL STUDY

An observational study that compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls) & looks back retrospectively to compare how frequently the exposure to risk is present in each group.



$$\text{Odd ratio} = \frac{\text{no of exposed cases) / (no. of unexposed cases}}{\text{no of exposed cases) / (no. of unexposed cases}}$$

Odds Ratio ; 40/10X 35/ 15 = 4X 2.33 = 9.33 0dds of exposure for cases is 9.33 times that of controls

Exposure is associated with 9x greater chance of disease.

Key Points

- ❖ Case control studies are usually retrospective.
- ❖ In this study the only outcome is presence or absence of the disease or whatever criteria was chosen to select the cases.
- ❖ Aim to identify predictors of an outcome
- ❖ Permit assessment of the influence of predictors on outcome via calculation of an odd ratio.
- ❖ Can only look at one outcome.
- ❖ Bias is an major problem.

Advantages

- Efficient –saves time and energy
- Used for rare diseases, small sample sizes.
- Can generate hypothesis for future study.

Dis-Advantages

- Susceptible to bias- recall, reporting
- Prone to methodological errors
- Selection of an appropriate comparison group may be difficult.

Cross sectional study

The cross-sectional study is an observational study that assesses exposure and the outcome at one specific point in time in a sample population. There is no prospective or retrospective follow-up.

The cross-sectional study cannot be used to infer causality because a temporal sequence cannot be established. Nevertheless, this type of study is used to generate descriptive statistics regarding the disease/outcome burden in a population, or to determine background exposure rates.

- ❖ Is a type of observational study that are primarily used to determine prevalence.
- ❖ Prevalence equals the number of cases in a given point in time.
- ❖ All the measurements on each person are made at one point in time.

Advantages of Cross-Sectional Study

The advantages of cross-sectional study include:

- Used to prove and/or disprove assumptions
- Not costly to perform and does not require a lot of time
- Captures a specific point in time
- Contains multiple variables at the time of the data snapshot
- The data can be used for various types of research
- Many findings and outcomes can be analyzed to create new theories/studies or in-depth research

Disadvantages of Cross-Sectional Study

The disadvantages of cross-sectional study include:

- Cannot be used to analyze behavior over a period to time
- Does not help determine cause and effect
- The timing of the snapshot is not guaranteed to be representative
- Findings can be flawed or skewed if there is a conflict of interest with the funding source
- May face some challenges putting together the sampling pool based on the variables of the population being studied

	Cohort	Cross sectional
Study group	Population at risk	Entire population
Common measures	Risk and rates	Prevalence

Comparison of observational studies			
	Cohort study	**Case-control study**	**Cross-sectional study**
Design	Participants are selected based on the exposure status of the individual. They are then followed over time to evaluate for the occurrence of the outcome of interest Prospective cohort study Retrospective cohort study	Participants are selected for the study based on their outcome status. The investigator then assesses the exposure in both these groups	In a cross-sectional study, the investigator measures the outcome and the exposures in the study participants at the same time
Strengths	The temporality between exposure and outcome is well defined We can study multiple outcomes in the same exposure If the exposure is rare, then a cohort design is an efficient method to study the relation between exposure and outcomes	Can be conducted relatively and are inexpensive – particularly when compared with cohort studies (prospective) Useful to study rare outcomes and outcomes with long latent periods Useful to study multiple exposures in the same outcome	Can usually be conducted relatively faster and are inexpensive May be used before cohort studies May be used for public health monitoring and planning
Limitations	Time-consuming and costly In a retrospective cohort study, the measurements of exposure and outcome may not be very accurate or according to our requirements Cohort studies may not be very efficient for rare outcomes except in some conditions	It is, in general, not useful to study rare exposures We are not able to estimate the incidence or prevalence in a case–control study Design is not useful to study multiple outcomes Sometimes, the temporality of the exposure and outcome may not be clearly established They may also be prone to certain biases - selection bias and recall bias	It is difficult to derive causal relationships from cross-sectional analysis
Analysis	Incidence ratio and rate Incidence rate ratio Advanced modeling methods - Cox regression, survival analysis, fixed and random effects models	Odds ratio Logistic regression models	Prevalence Odds ratio Logistic regression models

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