Family& Community medicine department

Experimental Epidemiology

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Epidemiological studies:

1-Observational studies:

a- Descriptive studies: (limited to a description of the occurrence of a disease in population.)

b- Analytical studies: (analyzing relationship between health status and other variable).

2- Experimental studies:

Intervention studies involve an active attempt to change a disease determinant or the progress of disease.

The investigators intervene in the natural history by actively altering one of the variables and then making inference on the relationship between the variables based on the outcomes.

Aims of experimental studies:

1-to provide "scientific proof" of aetiological (or risk) factor which may permit the modification or control of disease.

2-To provide a method of measuring the effectiveness and efficiency of health services for the prevention, control and treatment of disease and improve the health of community.

Animal studies:

-To confirm aetiological hypothesis and to study the pathogenetic mechanisms

-Testing the efficacy of preventive and therapeutic measures.

-Completing the natural history of disease.

Advantages:

- Easy manipulation
- Rapid multiplication to provide outcome

Disadvantages :

- Not all diseases reproduced in animals
- Conclusion may not be applicable in human (e.g.Typhoid vaccine)

Human experiments:

These studies are more essential in the investigation of diseases that cannot be reproduced in animal.

Types of experimental studies:

1- Randomized control trials.

2- Non – randomized trials.

-A trial is an experiment.
-A clinical trial is a controlled experiment having a clinical event as an outcome measure, done in a clinical setting, and involving persons having a specific disease or health condition
-A randomized clinical trial is a clinical trial in which participants are randomly assigned to separate groups that compare different treatments

Randomized control trials:(RCT)

The basic steps in conducting a RCT include the following:

1- Drawing up a protocol (proposal of the research).

2- Selecting reference and experimental populations.

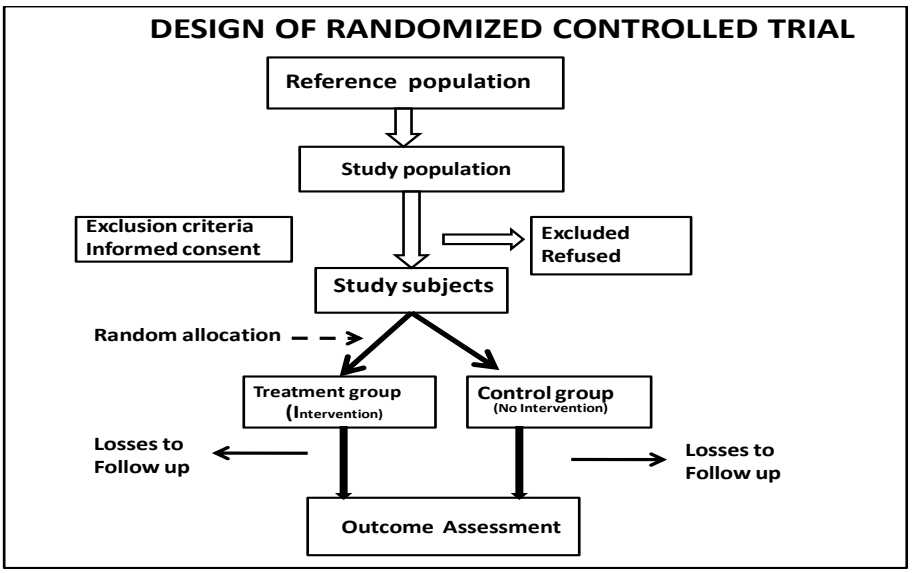
3- Randomization.

4- Manipulation or intervention.

5- Follow-up.

6- Assessment of outcome.

Design of RCT:



General outline of a protocol for a clinical trial:

1- Rationale and background for study.
2- Specific objectives of study.
3- Concise statement of the study design (randomization schemes, types of treatment, No. of patients)
4- Criteria for including and excluding subjects.
5- Outline of treatment procedures.
6- Definition of all clinical, laboratory methods.
7- Methods of assuring the integrity of the data.
8- Major and minor end points.
9- Provisions for observing and recording side effects.
10- Procedures for handling problem cases.
11- Procedures for obtaining informed consent of subjects.
12- Procedures for analyzing results.

****Elements of an informed consent:**

- Background and invitation to participate
- Explanation of procedures
- Potential risks and discomforts
- Potential benefits
- Rights of inquiry and withdrawal
- Signatures of subject and witness

***Pilot (preliminary)** studies have to be made to find out the feasibility or operational efficiency of certain procedures or unknown effects.

Steps of RCT:

1-Selecting reference and experimental populations:

a)- Reference or target population:

it is the population to which the finding of the trial, are expected to be applicable.

Reference population may comprise the population of a whole city, or specific group.

b)- Experimental or study population:

Study population is derived from the reference population, randomly chosen.

****Study Populations should be:**

1- Chosen randomly

2- Stable population (to avoid losses)

3- Informed (Written consent)

4- Representative

5- Eligible

2-Randomization: (heart of RCT)

It is statistical procedure to eliminate bias and allow comparability.

By random allocation every individual gets an equal chance of being allocated into any of trial groups.

**It is the only step in RCT that not under control of investigator.

Aims of randomization:

1- Eliminate selection bias
2- Increase comparability
3- …….
4- …… (complete)

3-Manipulation:

Manipulate the study group by application or withdrawal or reduction of the suspected causal factor. Manipulation creates an independent variable (drug, vaccine, a new procedure) whose effect is then determined by measurement of final outcome (dependent variable) e.g., incidence of disease, survival time

4-Follow -up:

Examination of the experimental and control group subjects at defined intervals of time, in standard manner, with equal intensity, under the same given circumstances, in the same time frame till final assessment of outcome.

Attrition: = Losses to follow-up = drop-out

What are the causes of drop-out?.....

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5-Assessment:

1- Positive results.

2- Negative results.

**Bias may arise from errors of assessment of out come due to human element.

Sources of bias:

1- **Subject variation or bias**: the participants subjectively feel better or report improvement if they knew that they were receiving a new form of treatment

2- **Observer bias**: the investigator measuring the outcome of a therapeutic trial / intervention may be influenced, if he knows beforehand the particular procedure or therapy to which the patient has been subjected.

3- **Evaluation bias**: the investigator may subconsciously give a favourable report of the outcome of the trial if the evaluator is aware of the details of the study.

These biases cannot be prevented by randomization or by increasing the size of the sample, but can be minimized by a technique known as blinding.

Blinding:

1- Single blind trial: the participant is not aware whether he belongs to the study group or control group

2- Double blind trial: neither the doctor nor the participant is aware of the group allocation & treatment received

3- Triple blind trial: the participant, doctor & person analyzing data are all blind

Types of Randomized control trials:

1- Clinical trials.

2- Preventive trials.

3- Risk factors trials.

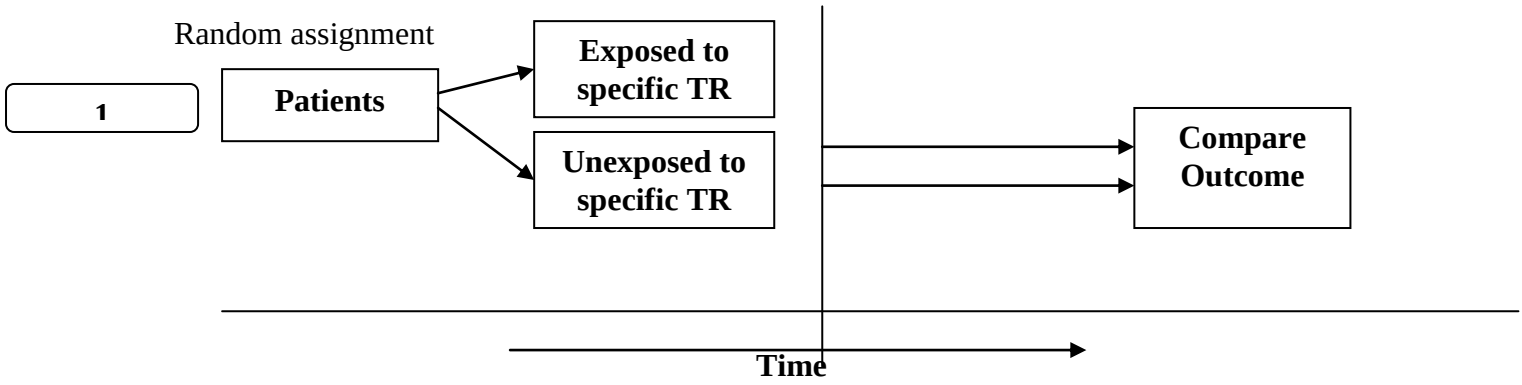
4- Cessation experiments.

5- Trial of aetiological agents.

6- Evaluation of health services.

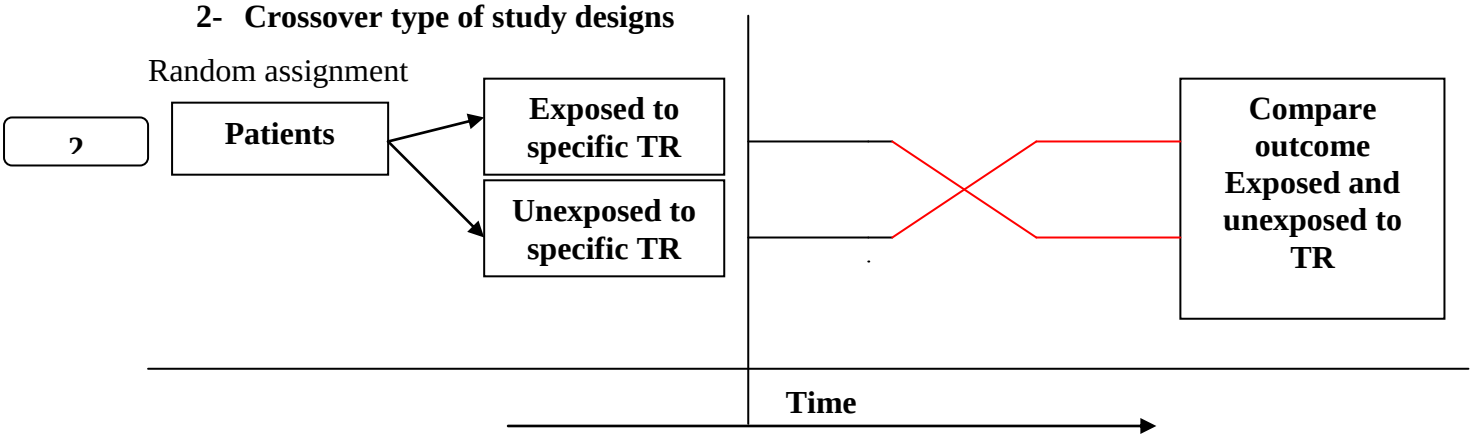
Some study designs:

1- **<u>Concurrent parallel study design.</u>**



In this situation, comparisons are made between two randomly assigned groups, one group exposed to specific treatment (study group), and the other group not exposed (control group). Patients remain in the same group for entire duration of the investigation (trial). Periodically follow-up is done and outcome is measured & compared between the groups

2- **Crossover type of study designs**



In this type of study design, each patient serves as his own control. In first step, the patients are randomly selected to study and control groups, the study group receive the treatment under consideration. The control group receives some alternate form of active treatment or placebo. The two groups are observed over time. Then the patients in each group are taken off their medication or placebo to allow for elimination of the medication from the body and for the possibility of any "carry over" effects. The length of the interval is determined by the pharmacologic properties of the drug being tested, In the second step, the two groups are switched over (those who received the treatment under study are changed to control group therapy or placebo, and vice versa).

What are advantages & limitation of <u>cross over type</u> of RCT?

……

Advantages and disadvantage of RCT:

Advantages:

1- Randomization tends to balance prognostic factors across study group.
2- Detailed information can be collected on baseline and subsequent characteristics of participants.
3- Dose levels can be predetermined by investigator.
4- Blinding of participants can reduce distortion in assessment of outcomes.
5- Allows comparison of multiple outcomes
6- Protection against confounders, both known and unknown
7- Able to directly estimate risk

Disadvantages:

1- Subject exclusions may limit ability to generalize findings to other patients.
2- Long period of time often is required to reach a conclusion.
3- Large No. of participant may be required.
4- Cost.
5- Ethical concerns may arise.
6- Not suitable for rare disease
7- Not suitable for outcomes requiring long or extensive follow-up
8- Subjects may not comply with treatment

Non – randomized trial:

Randomized trial sometimes is not possible because of:

- Administrative cause.
- Some of study need preventive measures can be applied only to group or community, e.g., community trial of water fluoridation.
- When disease frequency is law and natural history is long (ca. cx) need prolonged period for follow up.
- Cost.

In non-randomized trial or non experimental study the degree of comparability is law and the chance of spurious result higher than where randomization had taken place.

Types of Non – Randomized trial:

1- Uncontrolled trial.
2- Natural experiment.
3- Before and after comparison studies:

a)- before and after comparison studies without control.

b)- before and after comparison studies with control.

1- <u>un controlled trial:</u>

There is no comparison group.
it may be useful in evaluating whether specific therapy appears to have any value in particular disease to determine proper dose or to investigate side effect.
Historical control:
Subject in a clinical study who was previously treated with the standard therapy before the new experimental treatment was introduced.

2- <u>Natural experiment:</u>

Where experimental studies are not possible in human population , the epidemiologist seeks to identify natural circumstances that mimic an experiment.
People have separated themselves naturally into two groups, populations involved in natural experiments comprise the following groups:
1-Migrants 2- Religious & social groups 3- Earthquakes

3- <u>Before and after comparison studies: (community trial)</u>

a) Before & after comparison without control:

- Comparing the incidence of disease before and after introduction of preventive measures, e.g., prevention of scurvy among sailors by James Land in 1750 by providing fresh fruit. prevention of polio by Salk and Sabin vaccines.
- To establish before and after comparison studies the following are needed:

  - Data regarding the incidence of the disease before and after introduction of preventive measures must be available .
  - Manipulation of only one factor.
  - Diagnostic criteria should be the same.
  - Adoption of preventive measures should be over a wide area.
  - reduction in the incidence must be large following the introduction of the preventive measure, because there is no control
  -several trials may be needed before the evaluation is considered conclusive.

Table (I):Effect of adoption of compulsory seat-belt legislation in Victoria, Australia

	1970	1971	% change
Deaths	564	464	_ 17.7
Injuries	14620	12454	_ 14.8

b)- **Before and after comparison studies with control:**

Use of natural control group i.e. the one provided by nature or natural circumstances. If the preventive programme is to be applied to an entire community select another community as similar as possible , particularly with respect to frequency & characteristics of the disease to be prevented.

e.g. : seat-belt legislation in Victoria in Australia in 1971, compared with other states where similar legislation was not introduction.

Table (II): Effect of adoption of compulsory seat-belt legislation in Victoria, 1971 compared with other states where similar legislation was not introduced.

	1970	1971	% change
Deaths : Victoria	564	464	_17.7
Deaths: other state	1426	1429	0.2
Injuries: Victoria	14620	12454	_14.8
Injuries: other state	39980	40396	1

Good luck