9- Experimental studies

Learning objectives:

At the end of the lecture the students will be able to

- Understand the experimental studies feature and design.
- Recognize the value of clinical trials experimental studies.
- Identify the basic methodology of experimental studies.
- Recognize the advantages and disadvantages of experimental studies**.**

Experimental studies

Experimental" studies are referred to as "experimental epidemiology." They are applied as "clinical trials" to assess the efficacy of some intervention (or procedure), as surgical technique, type of facility, or type of health service, to name a few. The more common term used in Epidemiology is "randomized trial."

- Experimental studies are similar in approach to cohort studies except that the investigator directly controls exposure.
- Similar to laboratory experiments except living populations are the subjects
- They are the ultimate step in testing causal hypotheses.
- The effect of an intervention are measured by comparing the outcome in the experimental group with that in a control group. Since the interventions are strictly determined by the study protocol, ethical considerations are of paramount importance in the design of these studies.

Experiments or randomized trials are used for many purposes. Such purposes include:

1. Assessing new screening and early detection programs,
2. evaluating new drugs and other treatments of disease,
3. New ways of organizing and developing health services.

4. The randomized trial is considered the gold standard for evaluating the effectiveness of therapeutic, preventive and other measures, both in Clinical Medicine and in Public Health.

- Is used to study epidemics, the etiology of human disease, the value of preventive and therapeutic measures, and the evaluation of health services.
- Experimental studies are carried out under carefully controlled conditions. The investigator exposes an experimental group to some factors thought to cause disease, improve health, prevent disease, or influence health in some way (as in the Women's Health Study). Simultaneously, the investigator observes a control group that is similar in characteristics to the experimental group but without the exposure factor.
- Experiment—investigation designed to untangle cause from effect
  - **independent variable—imposed** treatment or special condition
  - **dependent variable** —specific behavior being studied
  - **experimental group** —participants who are given particular treatment
  - **comparison (control) group** —participants who are not given special treatment but are similar to experimental group in other relevant ways

WHAT ARE CLINICAL TRIALS?

- **Clinical trials or Randomized controlled trials** (**Experimental studies)** are research activities that involve the administration of a therapeutic or a preventive regimen to humans to evaluate its safety and efficacy.

- Experimental studies are the best epidemiological study design to prove causation.
- To ensure that the groups being compared are equivalent, patients are allocating to them randomly, i.e. by chance.

Types of Experimental studies:

- **Preventive trials**

These evaluate whether a preventive agent (e.g. Vaccine) or procedure reduces the risk of development of a particular disease.

We compare incidence rate among exposed and non-exposed

- **Therapeutic trials:**

Carried out among patients with a particular disease, to determine the ability of an agent or procedure to diminish symptoms, prevent recurrence, or decrease risk of death from that disease.

Examples of Experimental Epidemiologic studies:

- Prophylactic vaccines tested on children populations to prove the efficacy of the vaccines in preventing the diseases
- Prophylaxis with drugs in preventing diseases (i.e., penicillin to prevent rheumatic fever)

Values of Clinical trials

Clinical trials are useful for evaluating:

- New drugs or other treatments for disease.
- New medical/health care technology.
- New methods of prevention.
- New programs for screening and diagnosis.
- New methods of providing health care.

- New health care policies.

Phases of testing new agent

- Pre-clinical trials in animal and lab.
- Testing drugs in human

❋ **Pre-clinical trials**

- Before clinical trials of any medication in human subjects are undertaken, considerable research in experimental **animals** is essential.
- It includes pharmacological and toxicological studies.
- **Aims:**
  - To establish that the new agent is effective and may be suitable for human use.
  - To estimate roughly the dose to be used in man.

❋ **Testing drugs in human**

Clinical trials of new agents in human pass through 4 phases:

Phase I: Aims:

- To find a safe tolerated dose in man
- To test effects on body functions under close supervision.

- It is carried out on (20 to 25) of healthy volunteers
- They receive small doses of new drugs
- This phase is of short duration (one or two months)
- It is performed by clinical pharmacologists.

Phase II:

- It is carried out on 20 – 200 patients with relevant disease
- It lasts longer than Phase I trials (6 months to 2 years)
- The purpose of Phase II is:

- to assess therapeutic benefits & adverse reactions of the drug
- To establish a dose range and to investigate its side effects.

Phase III (The classical phase)

- Large scale, Randomised, Controlled Trials (RCTs)
- Target population: 250 – 1000 patients
- Performed by Clinicians in multi-centric hospitals.
- The purpose of this phase is to:
  - Assess the ***efficacy*** and safety.
  - Reduce the side effects & improve the quality of life.
- Results from Phase III trials are used to evaluate whether a new product or device should be licensed for general public use.

Phase IV: (*Post marketing Surveillance)*

It is a trial in normal field conditions when the drug is already available by prescription in the market.

The purpose of the Phase IV trial is to assess:

- ***Effectiveness*** under actual field conditions
- Safety& acceptability
- Long-term side effects.
- Rare adverse reactions and
- Drug interactions

Design of Randomized Clinical Trials (RCTs):

1. The first step is to identify the reference population (the target population).

The reference population is the population to which generalizations of the results of the experiment apply.

2. Second, Selection of a study population after defining inclusion/exclusion criteria.

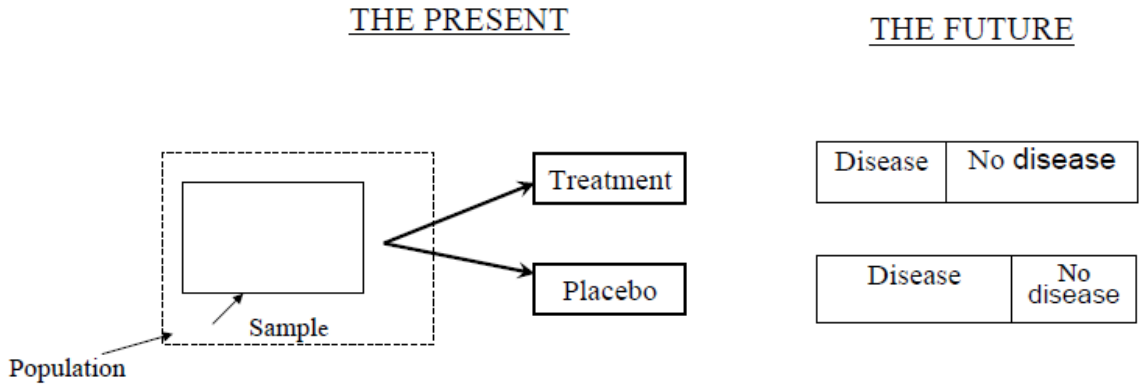
    - The inclusion criteria identify the target group or subgroup that will enter the study
    - The exclusion criteria are chosen to minimize potential dangers (e.g. elderly patients, pregnant women, children)

3. Getting ‘informed consent’ from the participants before they are subjected to experiments.
4. Random allocation of subjects to the experiment and control groups,
5. Follow up for a specified period of time under strict conditions
6. The outcome of the experiment is carefully measured.

The outcome may be a cure, recurrence of the disease, survival, relief of pain, or reduction in blood pressure, etc.

7. The outcome measures are compared between the groups using appropriate statistical methods.

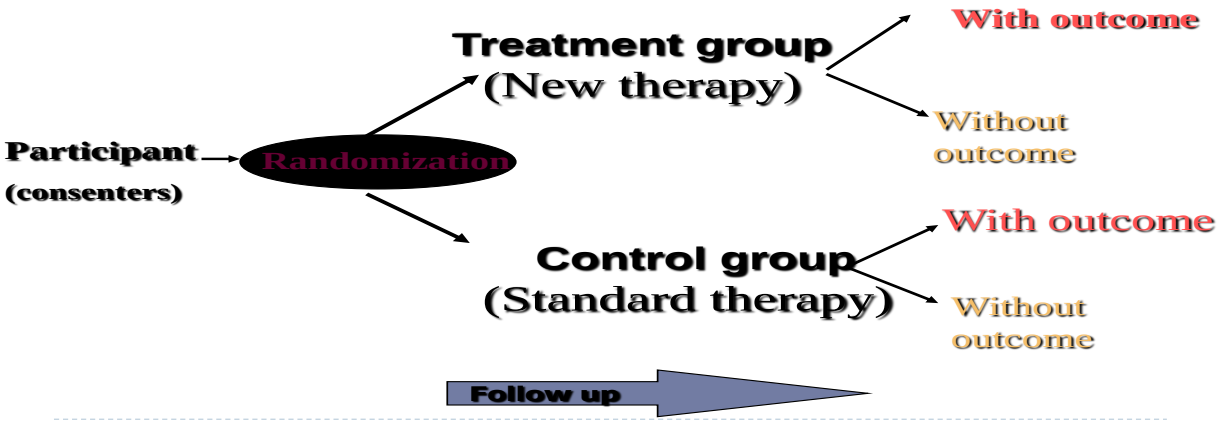
Experimental study (Clinical Trials)



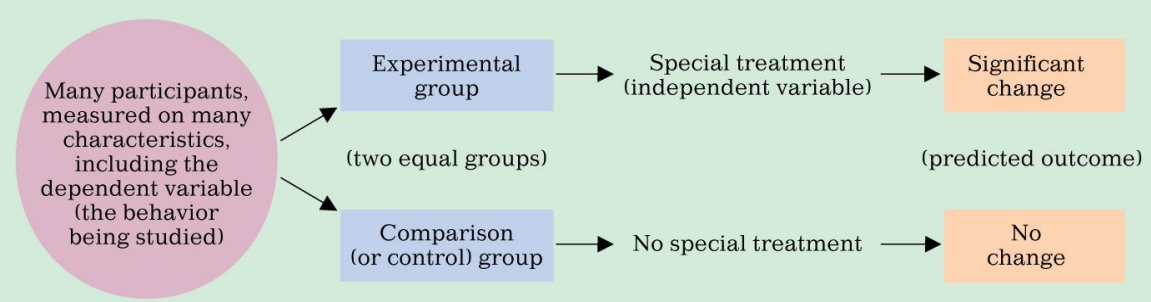
Steps:

1. Select a sample from the population
2. Measure baseline variables
3. Randomize
4. Apply interventions (one should be a blinded placebo, if possible)
5. Follow-up the cohort
6. Measure outcome variables (blindly, if possible)

Design of a Randomized Controlled Clinical trial



How to conduct an experiment



Procedure:

1. Divide subjects into two groups that are matched on important characteristics, especially the behavior that is the dependent variable of this research.
2. Give special treatment, or intervention (the independent variable), to one group (the experimental group).
3. Compare the groups on the dependent variable. If they now differ, the cause of the difference was probably the independent variable.
4. Publish the results.

Random allocation

- Random allocation is the method of assigning patients to treatment groups.
- Each subject has an equal chance of being assigned to any group in the study
- All groups in a study are similar in all characteristics
- It avoids selection bias on the part of the investigator or the patient.

Value of Randomization

Successful randomization tends to create comparison groups that are similar in terms of both known and unknown factors that may be related to outcome

(E.g. gender, age group, disease stage, or other prognostic factor).

Masking or "blinding

- It is a method of concealing (hiding) knowledge of treatment assignment to reduce bias in measuring outcome.
- *A Single masked study* – subjects are unaware of whether they are in the experimental or control group study.
- *A Double masked study* – the subject and the observer are unaware of the subject's group allocation.
- *A Triple masked study* – the subject, observer and data analyst are unaware of the subject's group allocation.

Methods of Blinding

- ❖ Masking is achieved by ensuring that all treatments appear identical (form & shape of drugs).
- ❖ A placebo is used for the comparison group if the objective is to evaluate a new drug in comparison with no treatment.
- ❖ A placebo is an inactive agent made to seem identical to the active agent in terms of appearance and mode of administration.

Relative Risk

Group	outcome		Total
	Positive	Negative	
Intervention	a	b	a +b
Control	c	d	c +d

Measures of effect size

Relative risk (RR)

Is the ratio of the incidence of a given outcome in experimental group compared to that in the control group

(a/(a + b)) / (c /(c + d))

Advantages of RCTS

- ✓ More scientifically valid (time relation is clearly established).
- ✓ Unbiased allocation of subjects through randomization. (No Selection Bias)
- ✓ Unbiased assessment of outcomes through blinding. (No measurement bias)

Disadvantages of RCTS

- Require large sample size.
- Time consuming and expensive.
- Non-compliance to treatment assignment
- Attrition (Losses to follow-up) may affect validity of results.
- Ethical issues may arise.
- ❖ **The ethical principles that apply to epidemiologic practice and research include:**
  - informed consent
  - confidentiality
  - respect for human rights
  - scientific integrity.

Major advantages & disadvantages of experimental study

Advantages	Disadvantages
Can produce the strongest evidence for cause and effect	Costly in time and money
Only possible design for some research question (new drug)	Many research questions are not suitable: ethical barriers or outcome too rare
Can sometimes be faster and cheaper	Reduced generalizability (standardized interventions may be different than common practice)
	Tend to restrict the scope and narrow the study question

References:

- Principles of Epidemiology in Public Health Practice *Third Edition* .An Introduction to Applied Epidemiology and Biostatistics

- ***www.giveto.pitt.edu/whocc.php super course in epidemiology***
- **Website http://faculty.ksu.edu.sa/73234/default.aspx**

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