

Experimental Studies

Learning Objectives:

To understand:

- What are experimental studies?
- The value of such studies
- The basic methodology
- Advantages and Disadvantages of such studies

Back ground:

- New treatments – pharmaceutical agents, devices, surgical procedures – are being developed every day.
- Before an intervention becomes standard practice, assessment of its efficacy and safety in comparison to standard therapy should be undertaken.

What are clinical trials?

- Experimental studies (clinical trials) 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

Common types of clinical trial (according to purpose):

- a. Prophylactic Trials, e.g. immunization, contraception.
- b. Therapeutic Trials, e.g. drug treatment, surgical procedure.
- c. Safety Trials, e.g. side-effects of oral contraceptives and injectables.
- d. Risk-factor Trials, e.g. proving the etiology of a disease by including it with the assumed agent in animals, or withdrawing the agent (smoking) through cessation.

Clinical trials are useful for evaluating:

- New drugs, 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 pass through four phases

Pre-Clinical Trials

- Enough knowledge about the safety and biologic activity of the treatment is essential to allow it to be administered to patients.
- In-vitro documentation is required before clinical trials of any medication in human subjects are undertaken.
- The next stage is animal studies.

Testing drug in human:

Phase I:

- Include studies of volunteers who receive small doses of new drugs to test effects on body functions under close supervision.
- This phase is of short duration (usually one or two months)

Phase II:

- Also carried out on volunteers.
- It lasts longer than phase I trials.
- The purpose of phase II is:
 - ✘ To assess the effectiveness of the drug or device.
 - ✘ To determine the appropriate dosage, and to investigate its side effects.

Phase III:

- This is the classical phase. It is performed on patients, who should consent to being in a clinical trial.
- The purpose of this phase is to assess the efficacy and to assess safety. It looks for ways to reduce the side effects and 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.

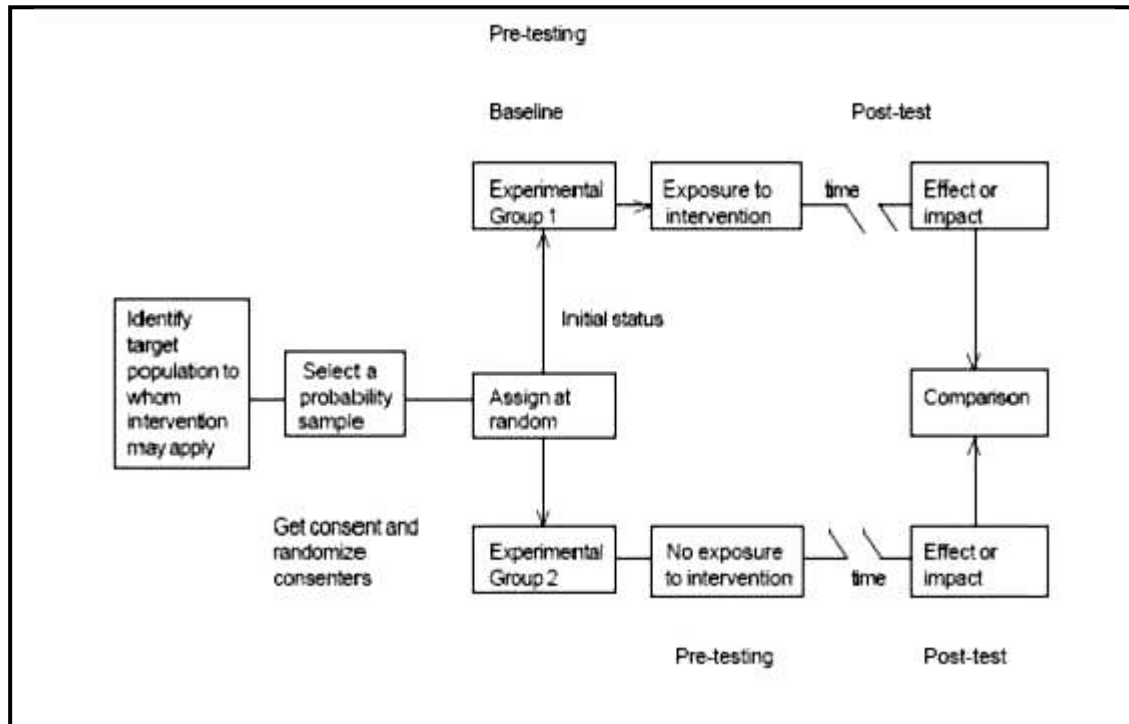
Phase IV:

- 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 re-assess the effectiveness, safety, acceptability and long-term side effects of continued use of the drugs or devices under actual field conditions.

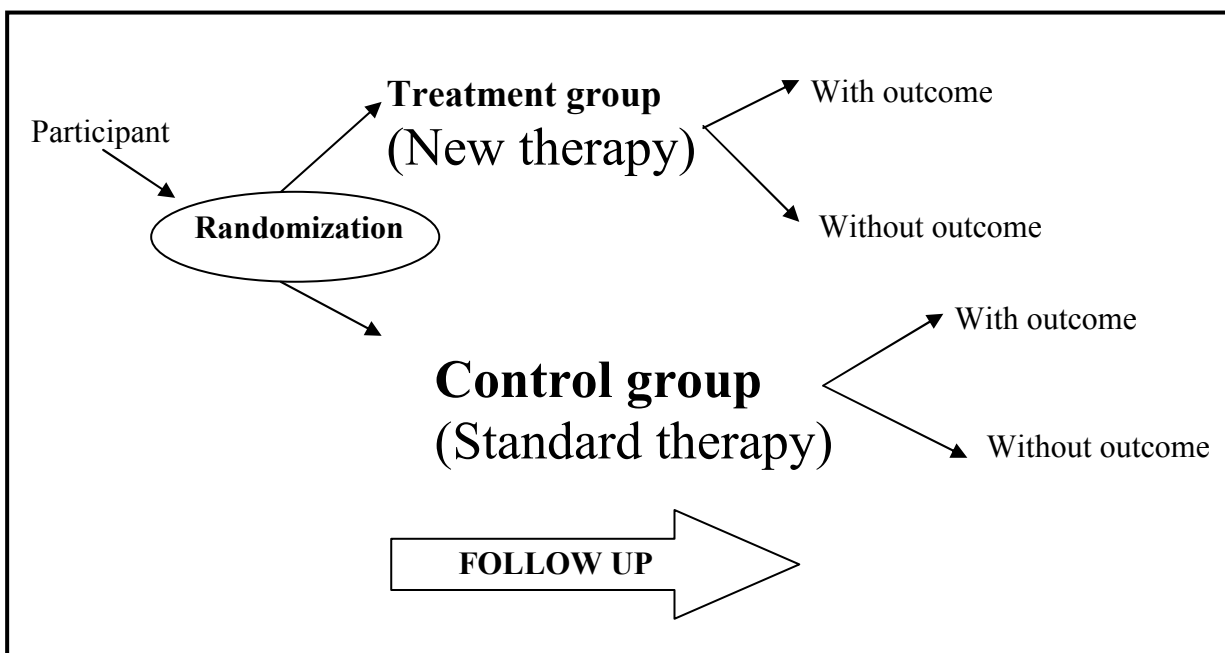
Randomized Clinical trials (RCTs) design

- The first step in any experimental design will be to identify the reference population (or the target population).
 - The reference population is the population to which generalizations of the results of the experiment apply.
- 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 and pregnant women)

- Getting "informed consent" from the participants before they are subjected to experiments.
- Allocation of subjects to the experiment and control groups.
- Follow up for a specified period of time under strict conditions
- The outcome of the experiment is carefully measured.
 - The outcome may a cure of the disease, relief of pain, or reduction in blood pressure, etc.
- The outcome measures are then compared between the groups using appropriate statistical methods.



Design of a Randomized Controlled Clinical trial



Random allocation:

- Random allocation – Each subject has an equal chance of being assigned to any group in the study, so that all groups in a study are similar in all characteristics
- Avoid selection bias on the part of the investigator or patient.

Value of Randomization

- Successful randomization tends to create comparison groups that are balance 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).

Data collection on Subjects:

- Baseline characteristics should be measured before patients are randomized.
 - First analysis is done. After random allocation, the two groups should be comparable in demographic and other variables
 - Thus, the differences in outcomes from the treatments can be ascribed to the treatment rather than to differences in the individuals in the groups.

Data Collection on Outcome:

- After assigning treatment, the outcome; both beneficial and adverse effects are measured.
- Outcome measures must be decide before conducting the study.
- All patients should be followed in the same way, with the same test, and at the same intervals after treatment.

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 weather 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 Trip masked study – the subject, observer and data analyst are unaware of the subject's group allocation.

Examples of Blinding:

- Masking may be achieved by ensuring that all treatments appear identical.
- If the objective is to evaluate a new drug in comparison with no treatment, a placebo is used for the comparison group.
- A placebo is an inactive agent made to seem identical to the active agent in terms of appearance and mode of administration.
- Sometimes blinding of all parties may not be feasible.
 - For example, in most surgical trials, or trials involving medical devices, it may be obvious to which group the patient has been allocated.
- Thus masking may be limited ti the individuals who are assessing the outcome.
 - For example, in a clinical trial of eye surgery, the technician measuring visual acuity would be masked as to treatment assignment



Advantages of RCTS:

- 1- More scientifically valid.
- 2- Unbiased allocation of subjects through randomization.
- 3- Unbiased assessment of outcomes through blinding.

Disadvantages of RCTS:

- 1- Require large sample size.
- 2- Time consuming and expensive.
- 3- Non-compliance to treatment assignment.
- 4- Loss to follow-up
- 5- Ethical issues may arise.

Community intervention trials

- The major difference from the RCT is that the randomization is done on communities rather than individuals.
- Examples of Community intervention trials are:
 1. Trials for testing a vaccine.

Some communities will be randomly assigned to receive the vaccine, while other communities will either not be vaccinated, or will be vaccinated with a placebo.

2. Testing of whether the introduction of iron-fortified salt in the community would reduce the incidence of anaemia in the community.

- ***In summary***, there is a hierarchy of studies from ones that open up a question to ones that may be the definitive answer, or as close to that as is possible.
- With increasing certainty comes increasing complexity and attention to detail (and increasing expense, time and cooperation).

