Randomized Control Trial (RCT)

Dr Alpesh Patel
Asst. Professor
Dept. of Community Medicine

Why RCT ?

Comment

- An advertisement in a medical journal stated that “2000 subjects with sore throats were treated with our new medicine. Within 4 days 94 % were asymptomatic” The advertisement claims that the medicine was effective. Based on the evidence given, give your comments

Animal studies

- Throughout history animals have played an important role in men's quest for knowledge about himself and his environment.
- Animal studies have contributed to our knowledge of anatomy, physiology, pathology, microbiology, immunology, genetics, chemotherapy and so many others.

Important application of animal experiments

(a) experimental reproduction of human disease in animals to confirm etiological hypotheses and to study the pathogenetic phenomena or mechanisms

(b) testing the efficacy of preventive and therapeutic measures such as vaccines and drugs,

(c) completing the natural history of disease.

Advantages of animal studies

- The experimental animals can be bred in laboratories and manipulated easily according to the wishes of the investigator.
- A more important point is that they multiply rapidly and enable the investigators to carry out certain experiments (e.g., genetic experiments) which in human population would take several years and involve many generations.

The limitations of animal studies

- Not all human diseases can be reproduced in animals.
- Secondly, all the conclusions derived from animal experiments may not be strictly applicable to human beings.

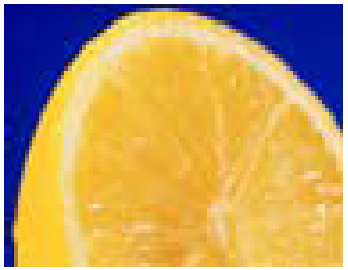
Human experiments

Human experiments

- Human experiments will always be needed to investigate disease etiology and to evaluate the preventive and therapeutic measures.
- More essential in the investigation of diseases that cannot be reproduced in animals.

Early Clinical Trial: Scurvy

1747 James Lind "On the 20th of May 1747 I took 12 patients in the Scurvy on board the Salisbury at sea" **These cases were as similar as I could have them ... and had one diet common to all."**



- Two patients: A quart of cider
- Two patients: 25 gutts tid Elixir vitrol
- Two patients: Two spoonfuls vinegar
- Two patients: Half pint sea water
- Two patients: Two oranges and 1 lemon
- Two patients: Nutmeg and Barley water tid

Type of study	Alternate name	Unit of study
Observational studies		
Descriptive studies		
Analytical studies		
Ecological	Correlational	Populations
Cross-sectional	Prevalence	Individuals
Case-Control	Case-Reference	Individuals
Cohort	**Follow-up/ Longitudinal**	**Individuals**
Experimental/ intervention Studies		
Randomized Controlled Studies	Clinical Trial	**PATIENTS**
Field Trial		**Healthy person**
Community Trial	Community intervention studies	**Communities**

Experimental studies

- In observational studies (eg. Descriptive, case-control and cohort) no action is taken . The epidemiologist observe only the natural course of event.

- The Experimental studies are similar to cohort studies except they involve some action, intervention, or manipulation

Aims of experimental studies

- To provide scientific **proof of etiological (or risk) factor** which may permit modification or control

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

Types of Experimental studies

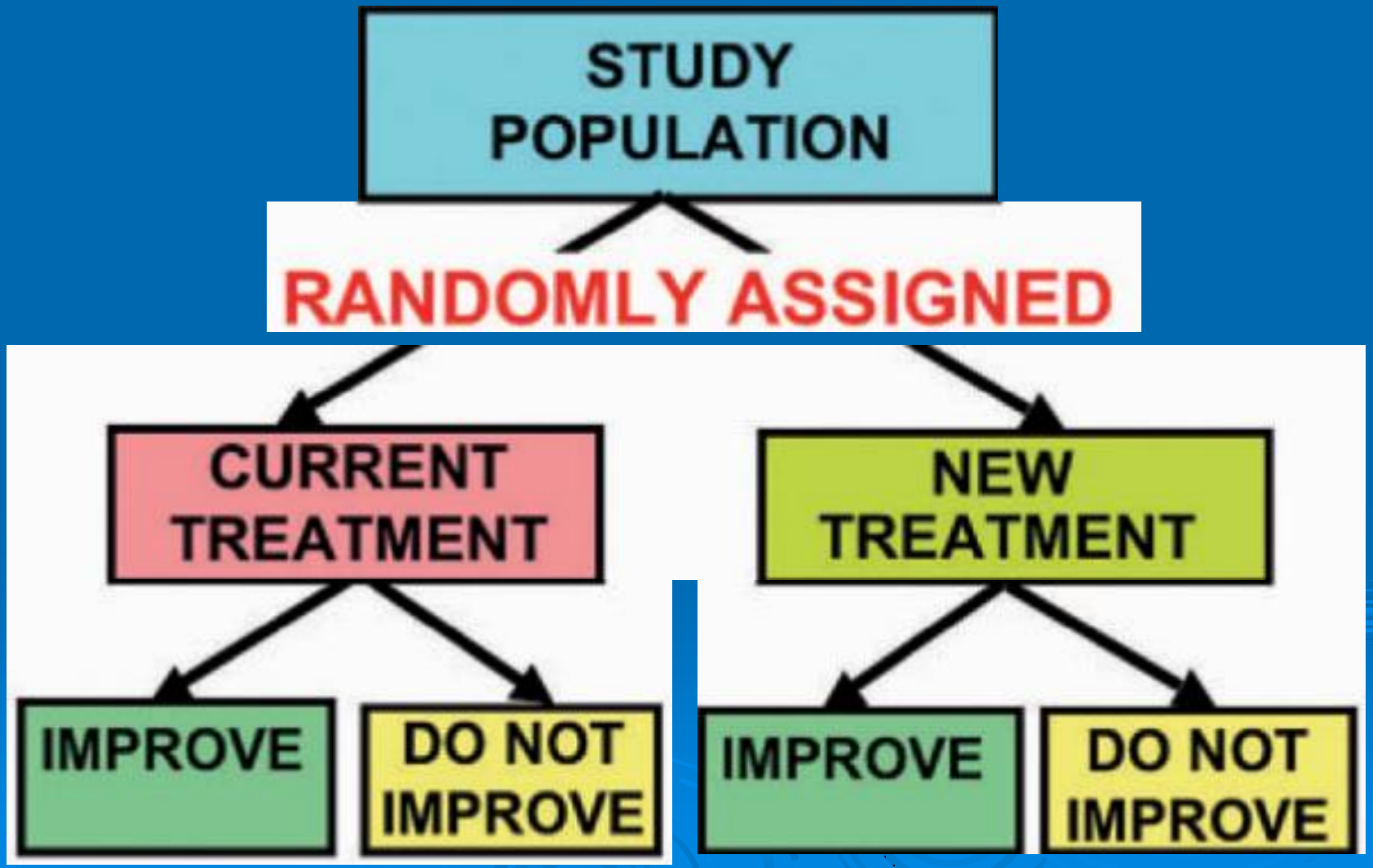
- Randomized Controlled Trials
- Non- Randomized or “Non- Experiment” trials (those departing from strict randomization for practical purposes)

Randomized Controlled Trial (RCT) (Synonym: Randomized Clinical Trial)

”An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called *study* and *control* groups to receive and not receive an experimental preventive or therapetuic procedure, maneuver, or intervention”

John M.Last, 2001

Design of a randomized trial




Systematic Reviews and Meta-analyses
Randomized Controlled Double Blind Studies
Cohort Studies
Case Control Studies
Case Series
Case Reports
Ideas, Editorials, Opinions
Animal research
In vitro ('test tube') research


Establish causality
Generate hypotheses

Why RCT?

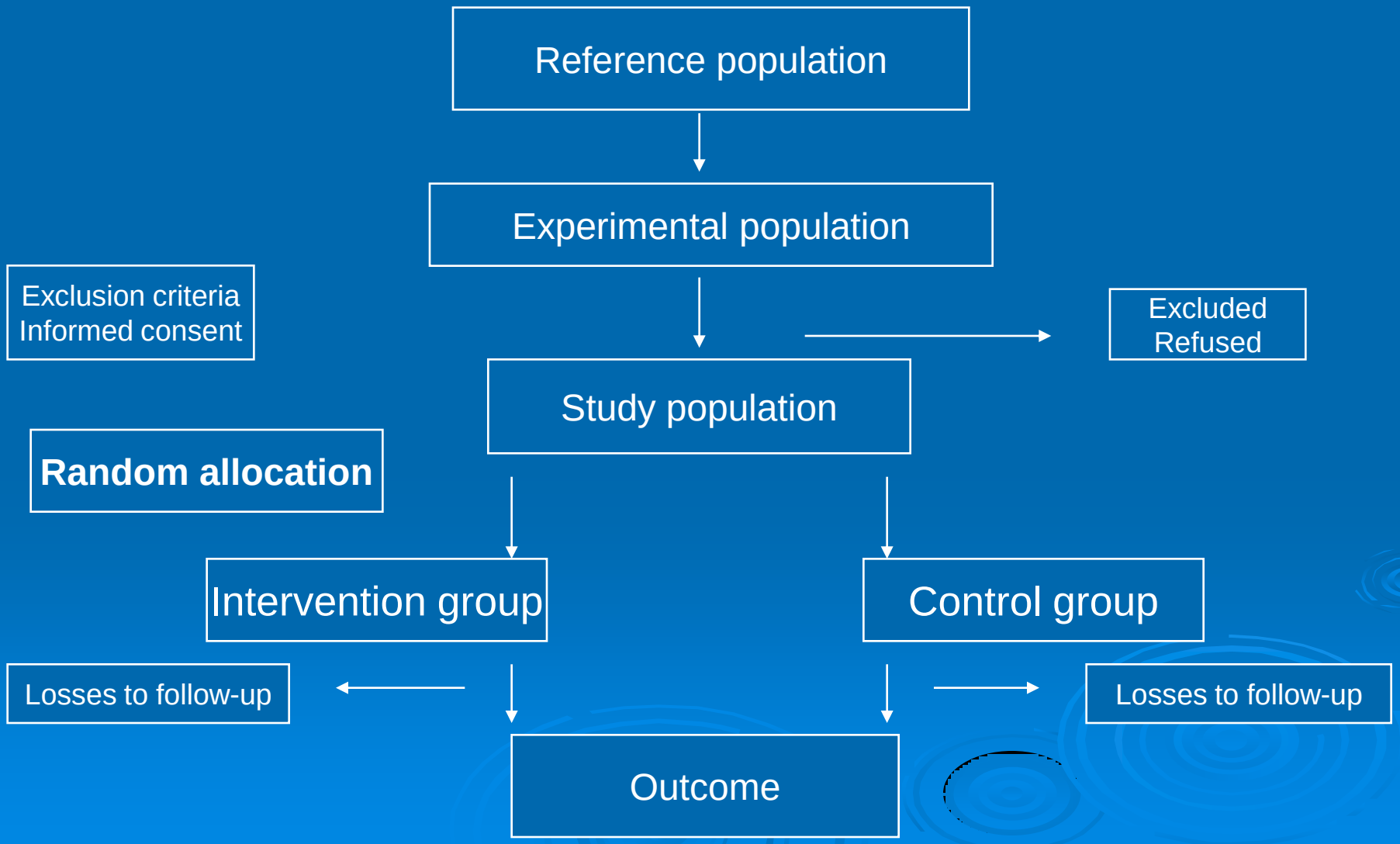
- GOLD STANDARD of study design

- Makes group comparable
  - Controls for confounding (known and unknown)
  - Prevents selection bias

Basic steps of RCT

1. The protocol
2. Selecting reference and experimental populations
3. Randomization
4. Intervention
5. Follow up
6. Assessment

Population hierarchy for intervention study



1. The protocol

- Rationale
- Aims and objectives, Research questions
- Design of the study: selection of study and control groups
- Ethics: patient consent, adverse events
- Documentation
- Procedure

2. Selecting Reference and Experimental Populations

a. Reference or target population - population to which the findings of the trial, if found successful, are expected to be applicable (eg. drugs, vaccines, etc.)

b. Experimental or study population - actual population that participates in the experimental study

Participants must fulfill the following criteria:

- Must give informed consent
- Should be representative of the population
- Should be qualified or eligible for the trial

3. Randomization

- Heart of the control trial
- Procedure: Participants are allocated into study and control groups
- Eliminates bias and allows comparability
- Both groups should be alike with regards to certain variables that might affect the outcome of the experiment
- Best done by using table of random numbers

Both groups should be alike with regards to certain variables that might affect the outcome of the experiment

4. Manipulation / Intervention

- Deliberate application or withdrawal or reduction of a suspected causal factor

- It creates an independent variable

Types of Interventions

- Interventions
  - Pharmaceutical (Therapeutic or Preventive)
  - Device
  - Procedure
  - Behaviour modification

5. Follow Up

- Implies examination of the experimental and control group subjects
  - at defined intervals of time,
  - in a standard manner, with equal intensity, under the same given circumstances

- Attrition: Inevitable losses to follow up

6. Assessment

a) Positive results : *that is benefits of the experimental* measure such as reduced incidence or severity of the disease, cost to the health service or other appropriate outcome in the study and control groups,

b) Negative results : *that is, severity and* frequency of side-effects and complications, if any, including death. Adverse effects may be missed if they are not sought.

6. Assessment

- Biases: Subject variation, Observer bias, Evaluation bias

- Can be corrected by blinding

Double-Blinded

Single-Blinded

~~Blinding~~/ MASKING

- Single
  - patient doesn't know
- Double
  - neither patient nor investigator knows
- Triple
  - none of the patients, investigators or analysts know

Randomization is a **key feature**

And heart of RCT

Random = governed by chance

Randomization = allocation of individuals to groups by chance

Each sampling unit has the same chance of selection

Makes intervention and control group comparable at the start of the investigation

Why is randomized assignment of intervention so important?

- Randomization is so important because overall, it provides the strongest evidence for causal inference

What does random allocation mean?

- Random allocation means that all participants have the same chance of being assigned to each of the study groups
- Allocation is not determined by the investigators, the clinicians, or the study participants

How randomization is done

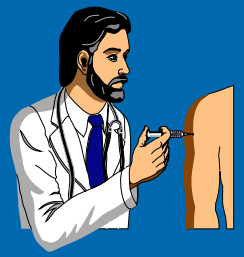
- Table of Random numbers
- Computer generated list
- According to date of birth (odd or even years), the number of their hospital records, the date at which they are invited to participate in the study (odd or even days), or alternatively into the different study groups

Ensures unpredictabilty

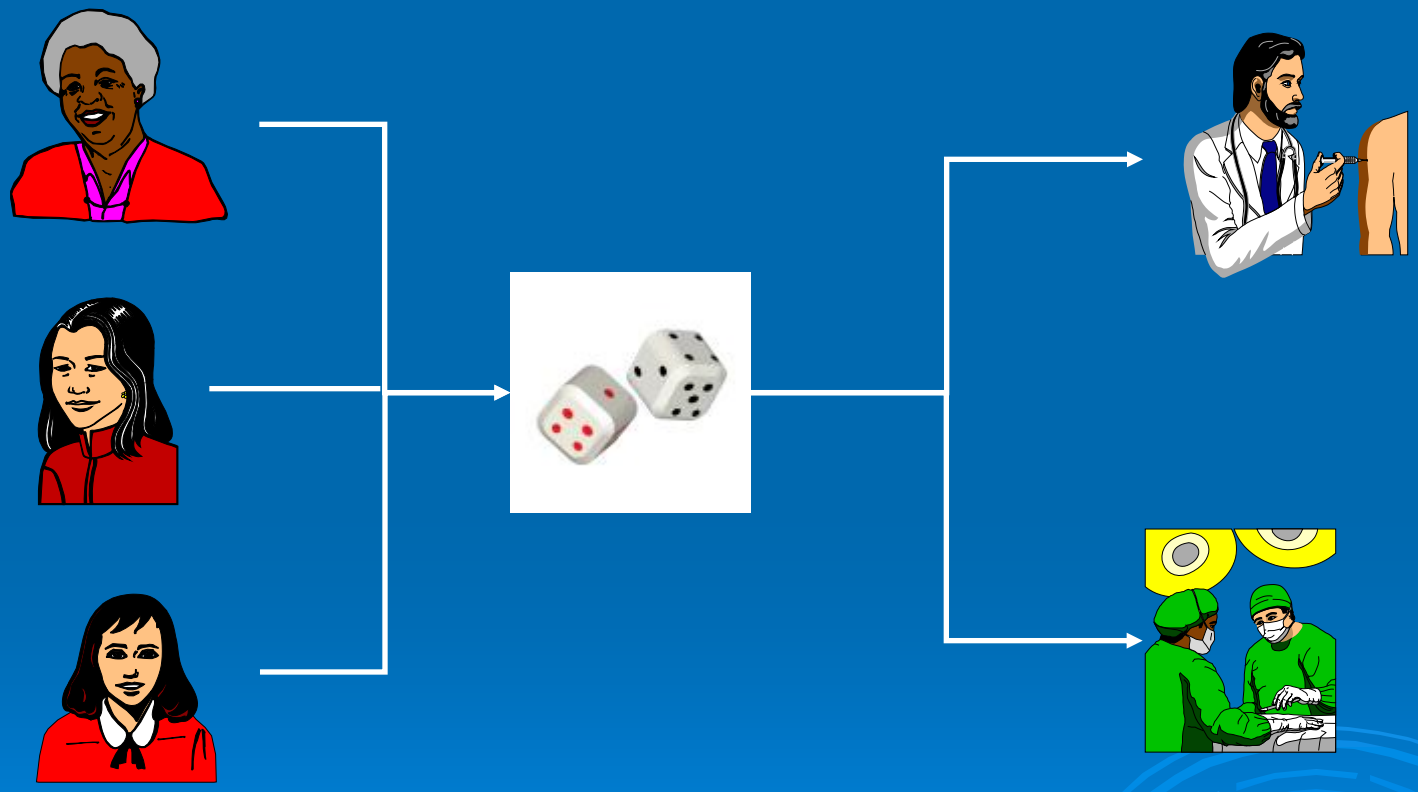
TABLE 7–3 A Table of Random Numbers

	00–04	05–09	10–14	15–19
00	56348	01458	36236	07253
01	09372	27651	30103	37004
02	44782	54023	61355	71692
03	04383	90952	57204	57810
04	98190	89997	98839	75129
05	16263	35632	88105	59080
06	62032	90741	13468	02647
07	48457	78538	22759	12188
08	36782	06157	73084	48094
09	65302	55103	19703	74741

Simple randomisation

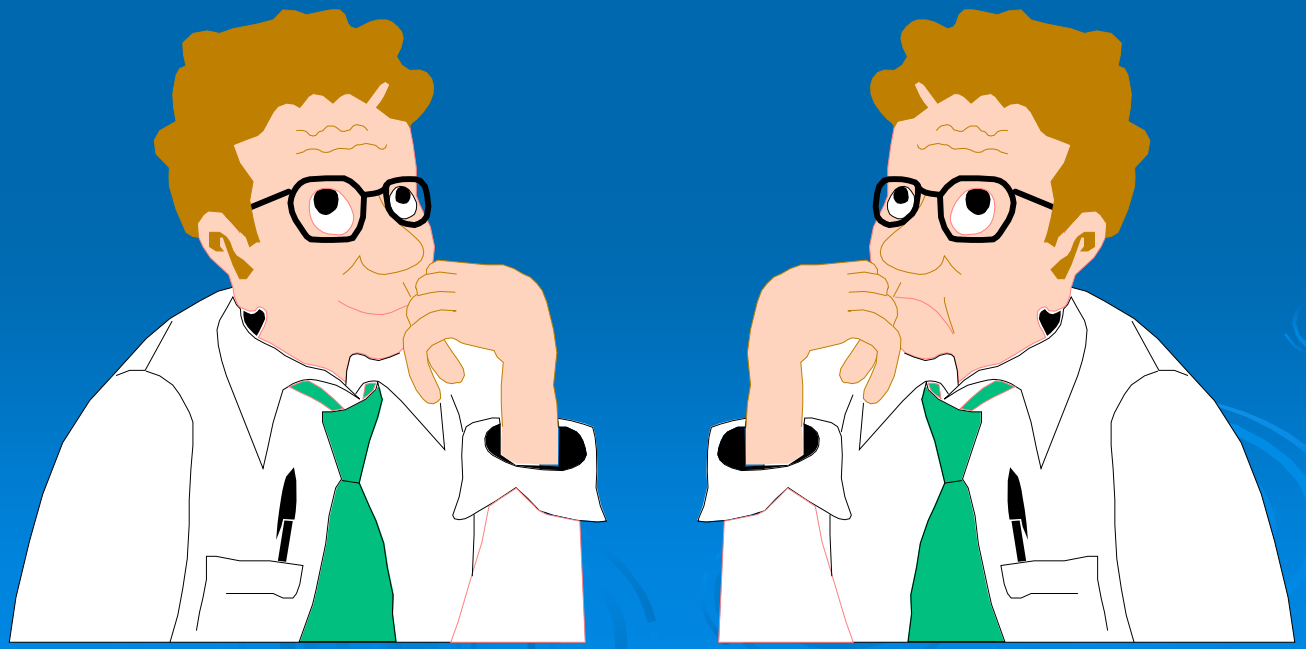


Stratified randomisation

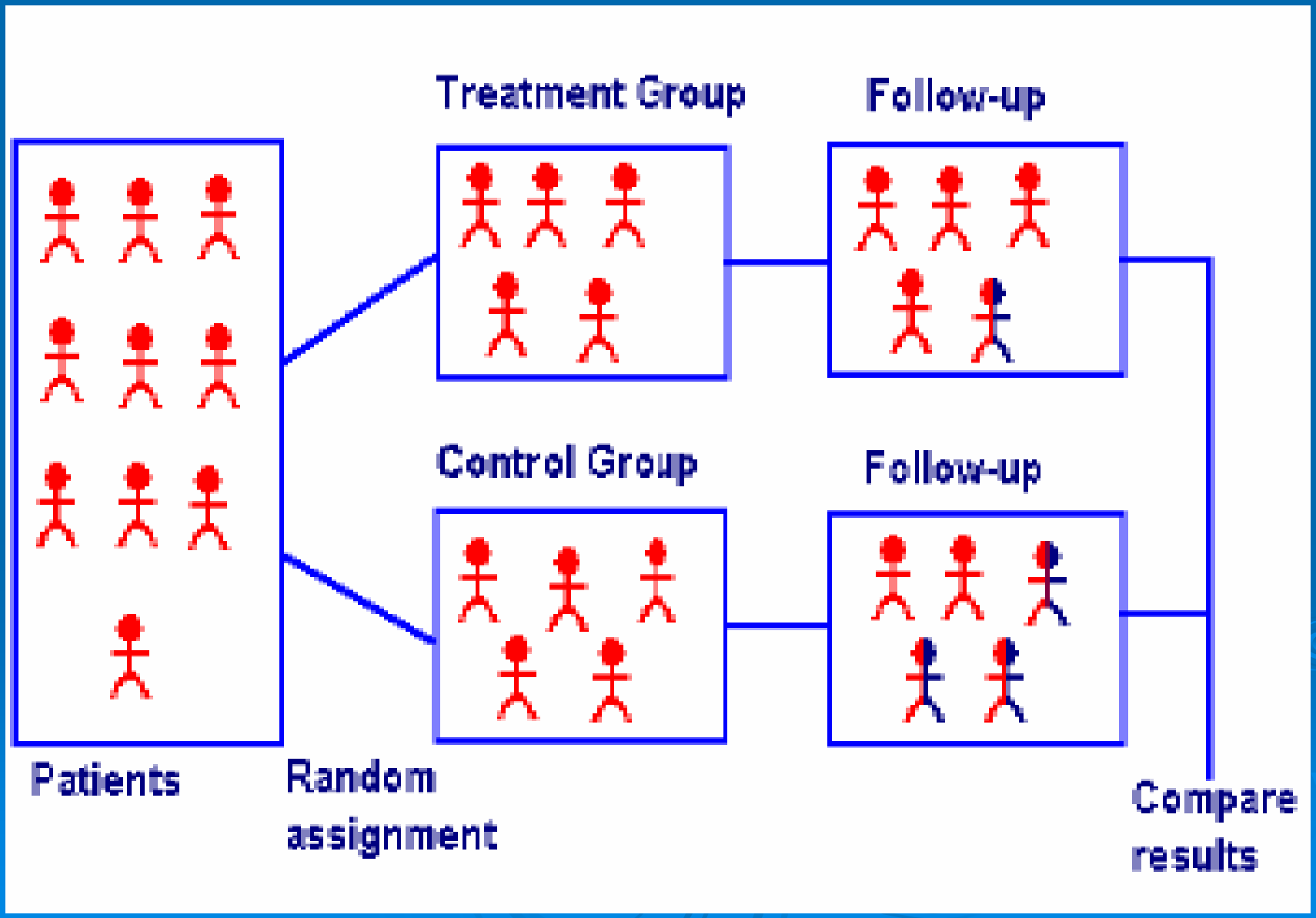


Design variations

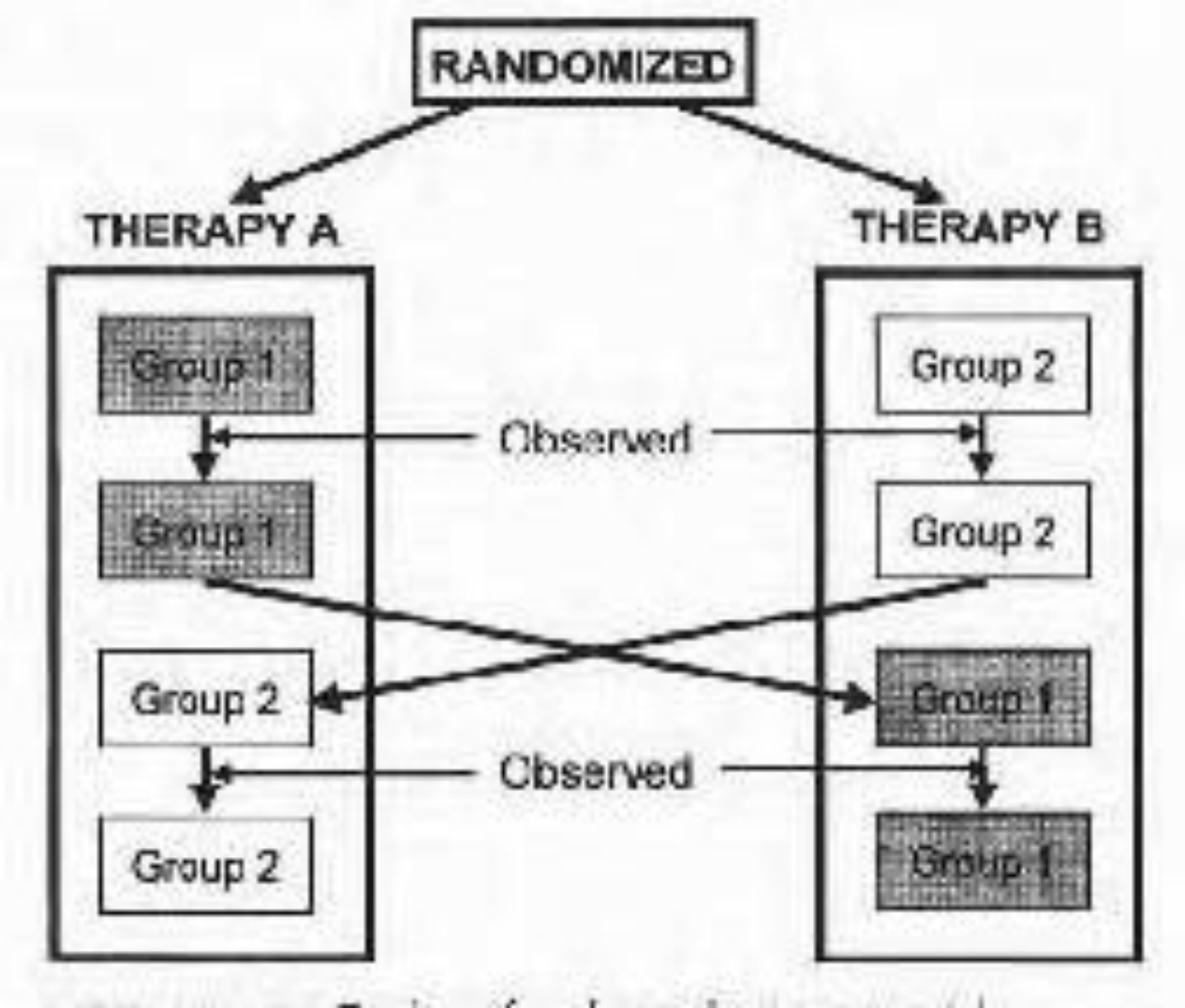
- Concurrent Parallel study designs
- Cross over designs



Randomized Controlled Trial (RCT)



Cross over


RANDOMIZED
THERAPY A
THERAPY B
Group 1
Group 1
Group 2
Group 2
Observed
Observed
Group 2
Group 2
Group 1
Group 1

Types of RCT

- Clinical Trials- *Diagnostic, Therapeutic, Prophylactic, Devices, Procedures, Regimens, Protocols* streptomycin for treating TB
- Preventive Trials- pertusis vaccine
- Risk factor Trials- MRFIT
- Cessation Experiments- eg smoking
- Trial of aetiological agents- eg. Retrolental fibroplasia
- Evaluation of health services- DOTS

Types of Randomized Controlled Trials:

1. Clinical Trial

- Concerned with evaluating therapeutic agent, mainly drugs

  eg. Evaluation of beta-blockers in reducing cardiovascular mortality

- Not all clinical trials are susceptible to being blinded

2. Preventive Trials:

- Trial of primary preventive measures eg. Vaccines

- Analysis of preventive trials must result in clear statement about benefits to community, risk involved and cost to health

3. Risk Factor Trials:

- Investigator intervenes to interrupt the usual sequence in the development of disease for those individuals who have risk factor for developing the disease

- Primary prevention of CHD using clofibrate to lower serum cholesterol

4. Cessation Experiment:

- An attempt is made to evaluate the termination of a habit which is considered to be causally related to disease
- Cigarette smoking and lung cancer

5. Trials of Etiological Agents:

- To confirm or refute an etiological hypothesis

6. Evaluation of Health Services:

- Domiciliary treatment of PTB was as effective as more costlier hospital or sanatorium treatment

Efficacy and effectiveness

- Efficacy – Does the intervention work in IDEAL situations

- Effectiveness – Does the intervention work in ‘real world’ conditions?

Study Phase

In Phase I :

Researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase II :

The study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

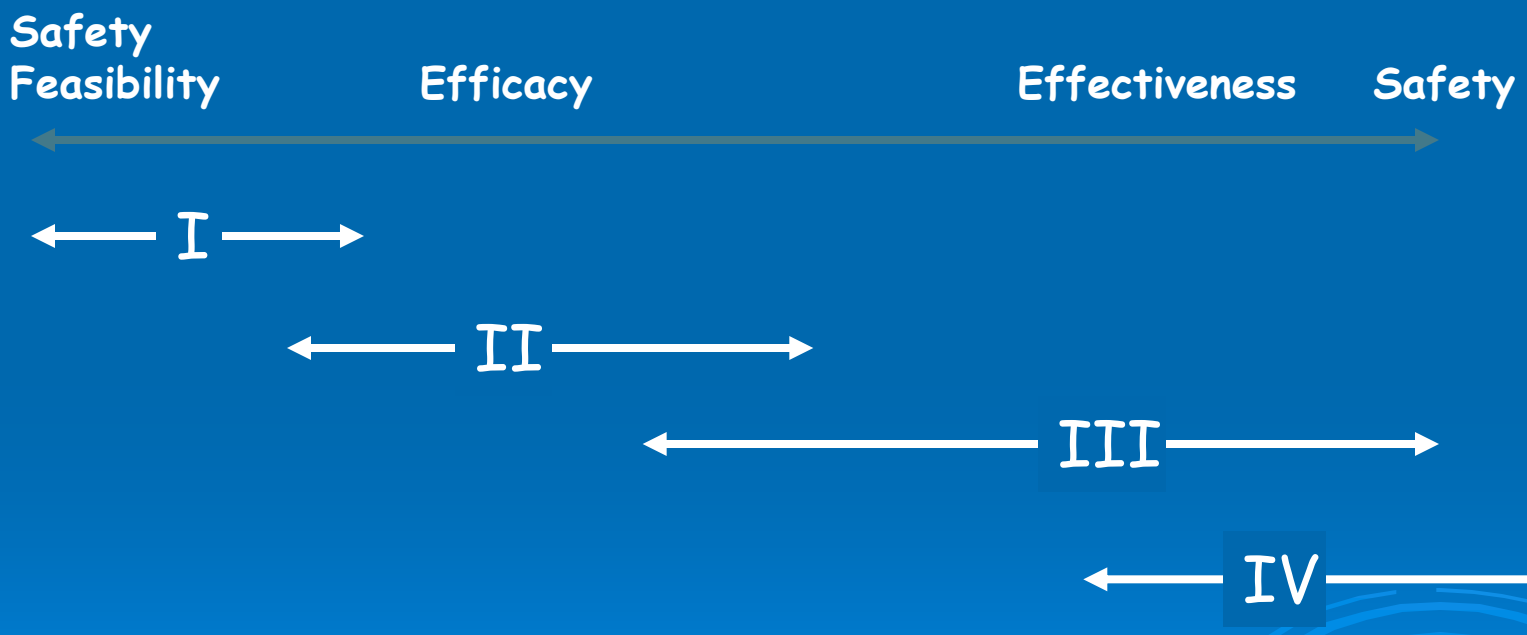
In Phase III :

The study drug or treatment is given to large groups of people (1,000 -3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

In Phase IV :

Post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Clinical Trial Phases
An overlapping continuum

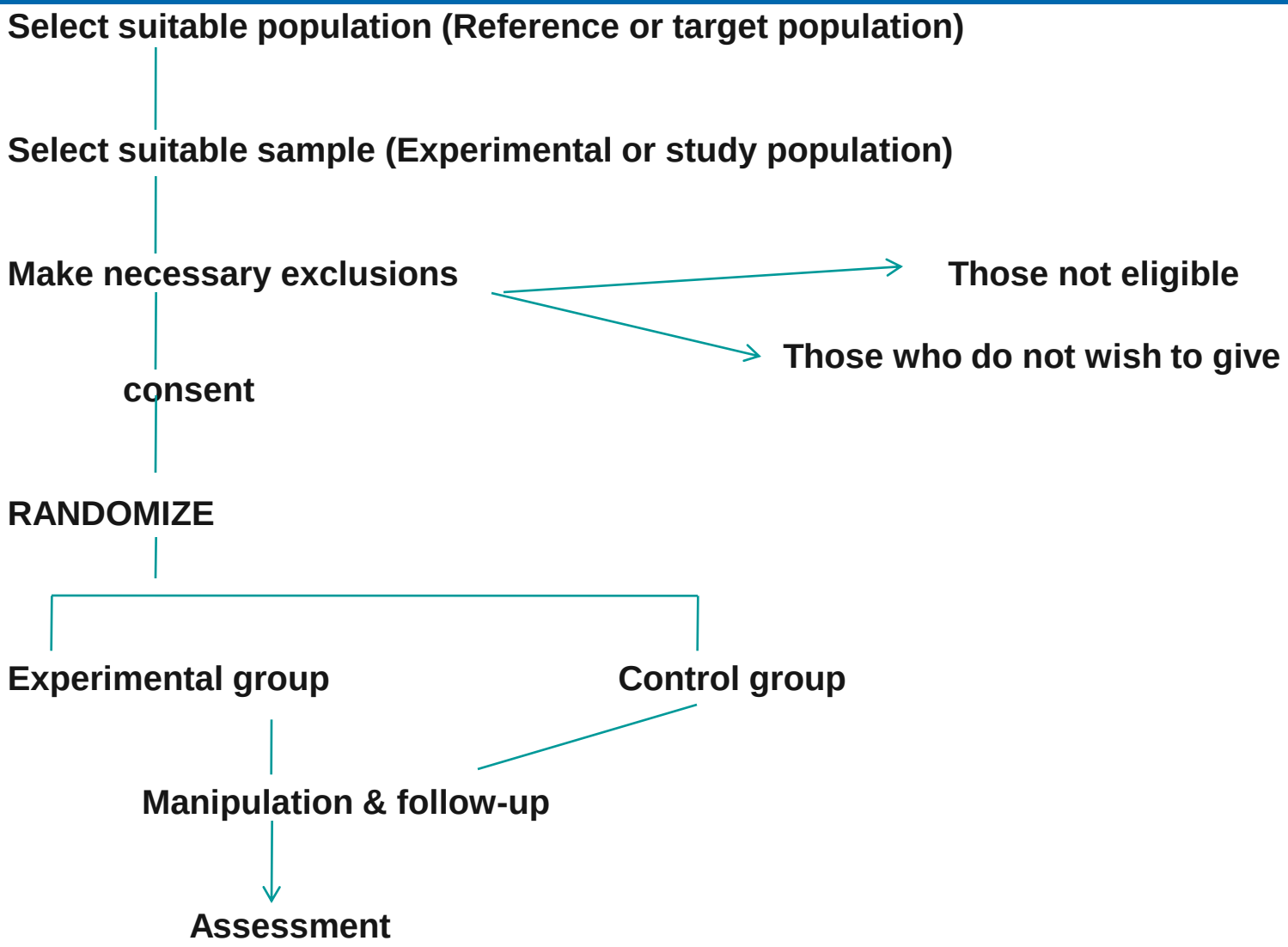


Other types of evaluation designs

- Uncontrolled Trials
- Natural Experiments
- Before after study
- Non randomized trials

Conclusion

- Well-conducted double-blind randomised controlled trials are gold standard for studies of efficacy
  - Minimise bias
  - Maximise attribution


Select suitable population (Reference or target population)
Select suitable sample (Experimental or study population)
Make necessary exclusions
Those not eligible
Those who do not wish to give consent
RANDOMIZE
Experimental group
Control group
Manipulation & follow-up
Assessment

Thank You .....