بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Epidemiological and Research Studies

Part 4

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~~Observational studies~~

- ~~Descriptive~~
  - ~~Case report~~
  - ~~Case series~~
  - ~~Epidemiological reports~~
  - ~~Cross-sectional~~
- ~~Analytical studies~~
  - ~~Cross-sectional~~
  - ~~Case-control~~
  - ~~Cohort~~

- Intervention(experimental studies
  - Clinical trials
  - Community trials

Intervention Studies

Observational studies

Descriptive

Case report

Case series

Epidemiological reports

Analytical studies

Cross-sectional

Case-control

Cohort

- **Intervention(experimental studies**
  - **Clinical trials**
  - **Community trials**

Randomised Controlled Study Design

Intervention Studies

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Randomised Controlled Study Design

Intervention Studies

- Intervention or experimentation
- involves attempting to change a variable in one or more groups of people.
- This attempt could mean;
  - the elimination of a risk factor e.g.
  - or testing a new treatment /intervention on a selected group of patients/persons.

- Intervention or experimentation could involve also testing exposure to risk factors
  - However, it is unethical to expose human subjects deliberately (purposefully) to potentially serious hazards.

effects of an intervention

- **The effects of an intervention are measured by:**
  - **comparing the outcome in the experimental group**
  - **with that in a control group.**
  - **Or and pre and post measurement**

- **Experimental studies are less susceptible to confounding because the investigator determines who is exposed and who is unexposed.**
  - In particular, if **exposure is allocated randomly** and the
  - **Number of groups or individuals randomized is large**
  - then **even unrecognized confounding effects become statistically unlikely**
  - **Informed consent from study participants is required in almost all circumstances.**

Cont. …intervention studies

- **Interventional studies are often performed in laboratories and clinical studies to establish beneficial effects of drugs or procedures.**

Types of experimental interventions may include:

- - Therapeutic agents
- - Prophylactic agents
- - Diagnostic agents
- - Surgical procedures
- - Health service strategies

Cont. …intervention studies

- **Intervention studies:** are considered to provide the most
- reliable evidence in epidemiological research. Either
- preventative or
- therapeutic

- Therapeutic trials
- conducted among individuals with a particular disease to assess the effectiveness of an agent or procedure
- So to;
  - * Diminish symptoms,
  - *Prevent recurrence, or
  - *Reduce mortality from the disease.

Cont. ..Intervention studies

- **Preventative trials**
  - conducted to evaluate whether an agent or procedure
  - ✓ reduces the risk of developing a particular disease among individuals free from that disease at the beginning of the trial,
  - ✓ for example, vaccine trials.

❖ Preventative trials may be
- ✓ conducted among individuals
- ✓ among entire communities

❑ Characteristics of an intervention study

❑ the intervention (the preventative or therapeutic measure) being tested, is

❖ allocated by the investigator to a group, of two or more study subjects

❖ Subjects are followed prospectively to compare the

❖ intervention vs. the control (standard treatment, no treatment or placebo).

Cont. ..Intervention studies

- **An interventional study could be classified according to:**
  - **Randomized controlled trial,**

(i) "**controlled clinical trials**" (or simply "clinical trials" or "trials"), in which individuals are assigned to one of two or more competing interventions, and

(ii)A field trial, or a community trial:

in which entire groups, e.g., villages, neighbourhoods, schools or districts, are assigned to different interventions.

- **Post test only or**
- **pre and post**
- **Cross-over trials**

The main intervention study design is The Randomised Controlled Trial (RCT).

❑ Cross-over trials

- A pre-post clinical trial/cross-over trial is one in which the
- subjects are first assigned to the treatment group and,
- after a brief interval for cessation of residual effect of the drug (washout period to get rid of the effect of the first intervention and to allow each participant to return to the baseline state)
- Shifted into the placebo /alternative group.
- Thus, the subjects act as their own control at the end of the study.

❑ However, such studies are not feasible

- ➢ if there is mortality, or
- ➢ if the disease is easily cured by one of the interventions.

Randomised Controlled Trials(RCT)

- ❖ is considered as the most rigorous method of determining whether
- ❖ cause-effect relationship exists between an intervention and outcome

- ❑ The strength of the RCT lies in the process of randomisation that is unique to this type of epidemiological study design.

- ❑ Generally, in a randomised controlled trial,
- ❖ study participants are randomly assigned to one of two groups:

experimental group

- experimental group receiving the intervention that is being tested
  - and a comparison group (controls) which receives a conventional treatment or placebo.
- These groups are then followed prospectively to assess the
- effectiveness of the intervention
- compared with the standard or placebo treatment.

- The Random Allocation of subjects is used to :
- Ensure that the intervention and control groups are similar in all respects (distribution of potential confounding factors)
  - with the exception of the therapeutic or preventative measure being tested.

The choice of comparison

- The choice of comparison treatments may include an
  - existing standard treatment or
  - a placebo (*a treatment which resembles the intervention treatment in all respects except that it contains no active ingredients*

Basic Outline Of The Design Of RCT

1. Development of a comprehensive study protocol.

- The study protocol will include:

- Aim and Rationale of the trial
- Proposed methodology/data collection
- Definition of the hypothesis
- Ethical considerations
- Background/review of published literature
- Quality assurance and safety
- Treatment schedules, dosage, toxicity data etc.

CONT. …Basic Outline Of The Design Of RCT

- 2. Formulation of hypothesis.
3. Objectives of the trial.
4. Sample size calculations.
5. Define reference population.
6. Choice of a comparison treatment placebo or current available best treatment.
7. Selection of intervention and control groups, including source, inclusion and exclusion criteria, and methods of recruitment
8. Informed consent procedures.

9. Collection of baseline measurements, including; all variables considered or known to affect the outcome(s) of interest.

Random allocatio

Con…Basic outline of the design of a randomised controlled trial

10. **Random allocation of study participants to treatment groups (standard or placebo vs. new).**

11. **Follow-up of all treatment groups,**

- **with assessment of outcomes**
  - ✓ **continuously or**
  - ✓ **intermittently**

12. **Monitor compliance and losses to follow-up.**
13. **Interim analysis.**
14. **Analysis - comparison of treatment groups.**
15. **Interpretation (assess the strength of effect, alternative** explanations such as sampling variation, bias).
16. **Publication.**

Randomised controlled trials (RCT)

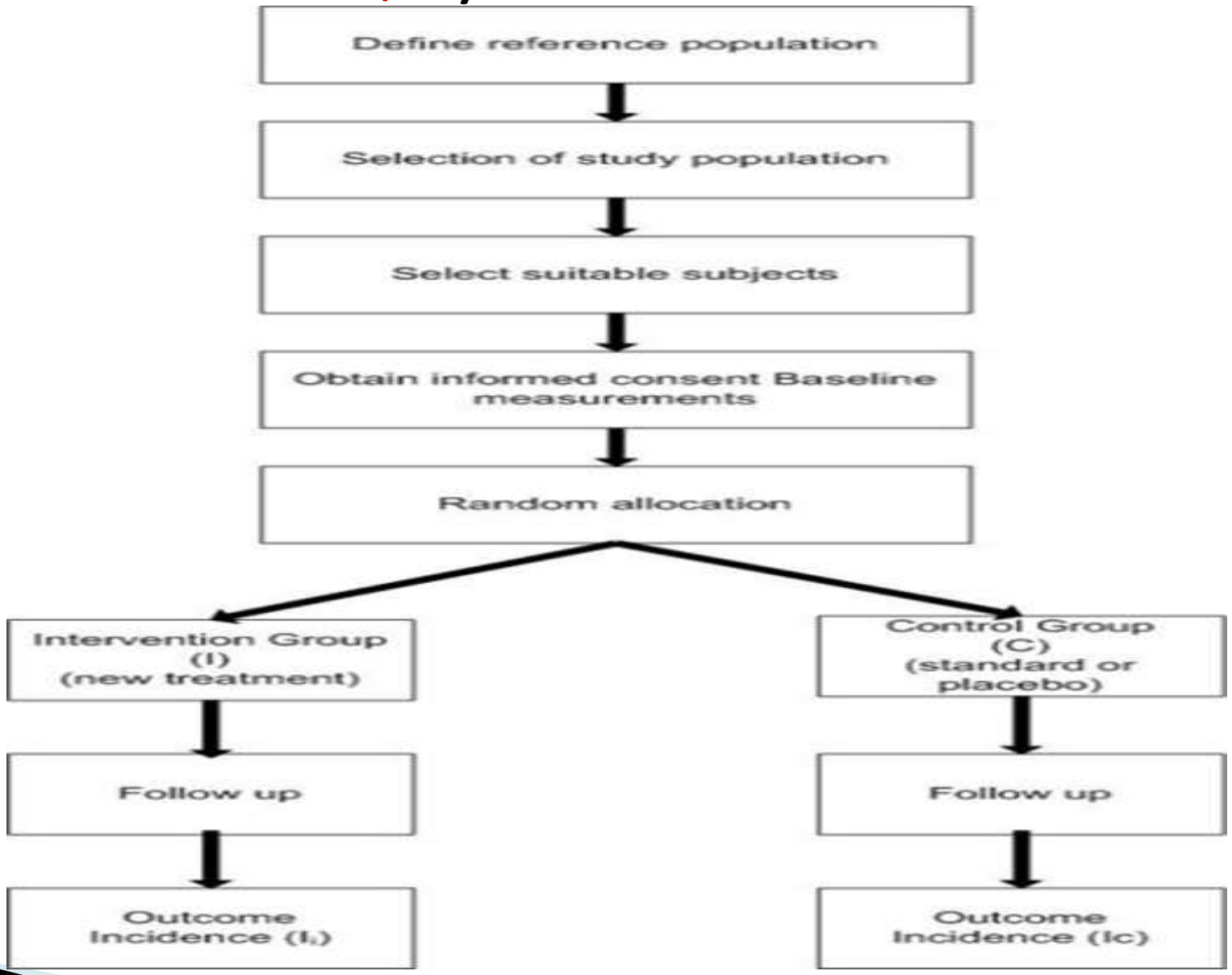

Figure 1. **General outline of a two armed randomised controlled trial.**

Randomisation

- The aim of randomisation is to ensure that
  - Any observed differences between the treatment groups are due to differences in the treatment alone and not due to the effects of confounding (known or unknown) or bias.
  - Groups are similar in all respects with the exception of the intervention under investigation.

- Methods of random allocation are used to ensure that
  - all study participants have the same chance of allocation to the treatment or control group,
  - and that the likelihood of receiving an intervention is equal regardless of when the participant entered the study.

Therefore, the probability of any participant

Cont. ..Randomisation

- Therefore, the probability of any participant
- receiving the intervention or the standard treatment/placebo is
- independent of any other participant being assigned that treatment.

- The assignment of study subjects to each intervention is determined by formal (strict) chance process and
- cannot be predicted or influenced by the
- investigator or participant.

- In a well designed RCT, random allocation is determined in advance.

Cont. ..Randomisation

❑ Advantages of randomisation

- ❖ **Eliminates confounding**
- ➢ tends to **create groups that are comparable(similar) for all factors** that **influence outcome, known, unknown or difficult to measure.**
- ❖ **Therefore, the only difference between the groups**
- ✓ **should be the intervention.**
- ❖ **•Eliminates selection bias.**
- ❖ **•Gives validity in statistical tests based on probability theory.**
- ❖ **Any baseline differences that exist between study groups** are **attributable to chance rather than bias.**

Though this should still be considered as a potential concern.

Disadvantages

Does not guarantee comparable groups as differences in confounding variables may arise by chance.

BLINDING In Randomised Controlled Trials

- Blinding is a process where the **critical information on allocation of treatment is hidden either:**
  - from the **patients,** or
  - from **observer** or
  - the **evaluator** in the study.

- The method of **blinding in RCT is used to ensure that**
  - **there** are **no differences in the way in which each group**
  - **is assessed or managed**, and
  - ***therefore minimize bias.**

cont.…Blinding in randomised controlled trials

- **Bias may be introduced, for example,**
  - if **the investigator** is aware of which treatment a subject is receiving, as **this may influence** (**intentionally or unintentionally**)
  - **the way in which outcome data is measured or interpreted**

- **Similarly, a subject's knowledge of treatment assignment may influence their response to a specific treatment**
- **Blinding also involves** ensuring that the **intervention and standard or placebo treatment appears the same.**
- **Double blinding**

is **when neither the**

*** investigator nor the**

****study participant**

is aware of treatment assignments.

However, this design is not always possible.

cont.…Blinding in randomised controlled trials

- **RCTs are classified into four types** on the basis of their level of blinding

- **Open-label RCTs:** employ no blinding and are thus the most susceptible to measurement bias
- **Single-blind RCTs:** the nature of the treatment is **concealed from either** the study **participants** or the **research team**
- **Double-blind RCTs:** **it is concealed from both the participants and the researchers, including those who administer the treatment**.
- **Triple-blind studies** entail concealing the nature of the treatment from **participants, researchers and administrators of the treatment**, and **data analysts.**
- **Triple-blind** studies, **data are analysed by codes** to prevent data analysts from **introducing judgment bias** because of their knowledge of group assignments.

❑ Strengths of a randomised controlled trial

- ❖ A well designed RCT **provides the strongest evidence of any epidemiological study** design that a given intervention has a postulated **effectiveness** and is safe.
- ❖ **RCT** provides the **best type of epidemiological study from which to draw conclusions on CAUSALITY**
- ❖ Randomisation **provides a powerful tool for controlling** (wash out) **for confounding**, even by factors that may be unknown or difficult to measure

- ❑ **Therefore, if well designed and conducted, a**
- ❖ **RCT minimizes the possibility that any observed association is due to confounding.**
- ➢ •**Clear temporal sequence - exposure clearly precedes outcome.**

Provides a strong basis for statistical inference.

Provides a strong basis

- **Provides a strong basis for statistical inference.**
  1. **Enables blinding and therefore minimizes bias.**
  2. Can **measure** disease **incidence** and **multiple outcomes**

Weaknesses of A Randomised Controlled Trial:

1.Ethical constraints - for example, it is not always possible or ethical to manipulate exposure at random.

2.Expensive and time consuming.

3.Requires complex design and

4.Loss to follow-up attributed to treatment

5.Inefficient for rare diseases or diseases with a delayed outcome

6.Generalizability - subjects in a RCT may be more willing to comply with the treatment regimen and therefore may not be representative of all individuals who might be given the treatment.

7.Volunteer biases: the population that participates may not be representative of the whole

Thank You

Thank You

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