# Experimental Studies

Dr Amna Rehana Siddiqui
Dr Abdul Aziz Bin Saeed

# Objectives

At the end of session students will be able to

1. Explain the design of a Randomized Trial.
2. Justify the methodological issues for,
   - Randomization of intervention & comparison group
   - Masking (blinding)
   - prognostic and outcome variables measurement
   - the assumptions needed for sample size
   - compliance and non-compliance

# What is a clinical trial?

**A prospective study comparing the effect and value of intervention(s) against a control in human beings**

# Why experimental study methods are important ?

Before any new intervention *(drug, diagnostic or therapeutic equipment)* becomes a standard practice, assessment of its efficacy and safety in comparison to standard therapy should be undertaken.

# Intervention studies

Intervention studies are similar in approach to cohort studies except that the investigator assigns exposure.

# Design of a Clinical Trial

Defined population

**Randomized**

EXPOSED to Drug or New therapy

NOT EXPOSED / PLACEBO*

With Outcome

Without Outcome

With Outcome

Without Outcome

**PLACEBO is an inert substance that is similar to the intervention medicine in color, weight, size, shape, and flavor; but does not contain the active substance*

# Studies done prior to any clinical trial

- research in experimental animals is essential.
- pharmacological and toxicological studies.
- 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.
- Clinical trials of new agents in humans pass through phases; actual trial is phase II and Phase IV is post marketing surveillance

# Design of Randomized Clinical Trials (RCTs):

1. Identify the **reference population** for generalization

2. Select **study population -** sampling technique

3. Define inclusion/exclusion criteria.

   - The inclusion criteria for, who will be study participants
   - The exclusion criteria are chosen to minimize potential dangers in being lost to follow up, hazardous effects (e.g. elderly patients, pregnant women, children)

## Design of Randomized Clinical Trials (RCTs):

4. Getting **'informed consent'** from the participants
5. **Random allocation in** experiment & control groups
6. **Follow up** for a specified period of time
7. The **outcomes** may be a cure, recurrence of the disease, survival, relief of pain, or reduction in blood pressure, etc.
8. The outcome measures are **compared** between the groups using appropriate statistical methods.

# Major STEPS

Defined population

Consenters

1 RANDOMIZED ⇩ Selection bias

2 MASKING /BLINDING ⇩ Information bias

INTERVENTION | NO INTERVENTION

3 COMPLIANCE & FUP ⇩ Loss to follow up

| % with Outcome | % with out Outcome | % with Outcome | % with out Outcome |
|---|---|---|---|

PRIMARY END POINT (Outcome) NEEDS DEFINITION AND CLARITY

## Design of an Experimental Study

# Fundamentals of Randomization process

- Tends to produce comparable groups
- Removes investigator bias
- Statistical tests will be valid
- If predictable, selection bias will occur
- Similarly if balance is not achieved for risk factors or prognostic factors bias will occur

# How would you randomize?

- Fully Informed consent is to be taken
- Coin toss ; not feasible
- Alternating assignments ABABAB; predictable , select an unpredictable method
- Random digit table – better
- Random number producing algorithm

**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 | 76129 |
| 05 | 16263 | 35632 | 88105 | 59090 |
| 06 | 62032 | 90741 | 13468 | 02647 |
| 07 | 48457 | 78538 | 22759 | 12188 |
| 08 | 36782 | 06157 | 73084 | 48094 |
| 09 | 63302 | 55103 | 19703 | 74741 |

## Baseline characteristics of patients in Placebo and (intervention) Pravastatin groups (NEJM 1996)

| Characteristic | Placebo | Pravastatin |
|---|---|---|
| 1. Mean Age (yrs) | 59± 9 | 59± 9 |
| 2. Male Sex (%) | 86 | 86 |
| 3. Race White (%) | 92 | 93 |
| 4. Current Smoker (%) | 21 | 21 |
| 5. Hypertension (%) | 34 | 34 |
| 6. Diabetes Mellitus (%) | 15 | 14 |
| 7. Body Mass Index (Mean) | 28± 4 | 28± 4 |
| 8. Angina (%) | 20 | 21 |
| 9. Medication Aspirin (%) | 83 | 83 |
| 10. On Oral Hypoglycemic agent (%) | 7 | 5 |

Original Table Shown For Your Interest

**TABLE 1.** BASE-LINE CHARACTERISTICS OF PATIENTS IN THE PLACEBO AND PRAVASTATIN GROUPS.*

| CHARACTERISTIC | PLACEBO (N = 2078) | PRAVASTATIN (N = 2081) |
|---|---|---|
| **General** | | |
| Age (yr) | 59±9 | 59±9 |
| Sex (%) | | |
| Female | 14 | 14 |
| Male | 86 | 86 |
| Race (%) | | |
| White | 92 | 93 |
| Other | 8 | 7 |
| Country of residence (%) | | |
| United States | 66 | 66 |
| Canada | 34 | 34 |
| Hypertension (%) | 43 | 42 |
| Current smoker (%) | 21 | 21 |
| Diabetes (%) | 15 | 14 |
| Body-mass index† | 28±4 | 28±4 |
| Blood pressure (mm Hg) | | |
| Systolic | 129±18 | 129±18 |
| Diastolic | 79±10 | 79±10 |
| **Cardiovascular status** | | |
| Months from myocardial infarction to randomization | 10±5 | 10±5 |
| Type of myocardial infarction (%) | | |
| Q wave | 61 | 61 |
| Other | 38 | 38 |
| Angina (%) | 20 | 21 |
| Congestive heart failure (%) | 4 | 4 |
| CABG (%) | 28 | 26 |
| PTCA (%) | 32 | 34 |
| CABG or PTCA (%) | 54 | 54 |
| Thrombolysis (%) | 40 | 42 |
| Ejection fraction (%) | 53±12 | 53±12 |
| **Medication use** | | |
| Aspirin (%) | 83 | 83 |
| Beta-blocker (%) | 39 | 41 |
| Nitrate (%) | 33 | 32 |
| Calcium-channel blocker (%) | 38 | 40 |
| ACE inhibitor (%) | 14 | 15 |
| Diuretic agent (%) | 11 | 11 |
| Insulin (%) | 2.6 | 2.4 |
| Oral hypoglycemic agent (%) | 7 | 5‡ |
| Estrogen (% of women) | 10.3 | 8.4 |
| **Plasma lipids§** | | |
| Cholesterol (mg/dl) | | |
| Total | 209±17 | 209±17 |
| VLDL | 27±16 | 27±16 |
| LDL | 139±15 | 139±15 |
| HDL | 39±9 | 39±9 |
| Triglycerides (mg/dl) | 155±61 | 156±61 |

*Plus–minus values are means ± SD. Except for the use of oral hypoglycemic agents, differences between the groups were not significant. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, ACE angiotensin-converting enzyme, VLDL very-low-density lipoprotein, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡$P<0.05$ for the comparison with the placebo group.

§To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

# Masking

- Single blind
- Double blind
- Triple blind
- Placebo characteristics

To minimize information bias

# Masking: Safety of participants

- Protection and safety of study participants is to be ensured
- Minimization of risks, fear, pain and distress
- Appropriate expertise is available at all trial sites .
- Study participants can contact appointed study team member at any time for any advice or reporting adverse effect (ensures compliance)

# Checklist for sample size

- Estimate the outcome/event rate for control group by extrapolation from a similar population
- Define the primary outcome
- Difference in response rate to be detected

  **(Define the smallest difference between intervention & control groups that will be of clinical significance)**
- Adjust for the expected level of noncompliance

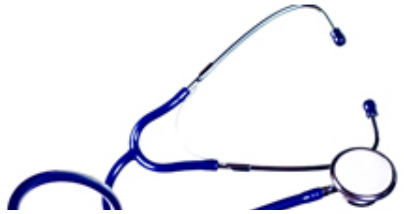

**TABLE 8–4** Number of Patients Needed in Each Group to Detect Various Differences in Cure Rates; $\alpha = .05$; Power $(1 - \beta) = .80$ (Two-sided Test)

| Lower of the Two Cure Rates | Differences in Cure Rates Between the Two Treatment Groups | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | .05 | .10 | .15 | .20 | .25 | .30 | .35 | .40 | .45 | .50 | .55 | .60 | .65 | .70 |
| .05 | 420 | 130 | 69 | 44 | 36 | 31 | 23 | 20 | 17 | 14 | 13 | 11 | 10 | 8 |
| .10 | 680 | 195 | 96 | 59 | 41 | 35 | 29 | 23 | 19 | 17 | 13 | 12 | 11 | 8 |
| .15 | 910 | 250 | 120 | 71 | 48 | 39 | 31 | 25 | 20 | 17 | 15 | 12 | 11 | 9 |
| .20 | 1,090 | 290 | 135 | 80 | 53 | 42 | 33 | 26 | 22 | 18 | 16 | 12 | 11 | 9 |
| .25 | 1,250 | 330 | 150 | 88 | 57 | 44 | 35 | 28 | 22 | 18 | 16 | 12 | 11 | – |
| .30 | 1,380 | 360 | 160 | 93 | 60 | 44 | 36 | 29 | 22 | 18 | 15 | 12 | – | – |
| .35 | 1,470 | 370 | 170 | 96 | 61 | 44 | 36 | 28 | 22 | 17 | 13 | – | – | – |
| .40 | 1,530 | 390 | 175 | 97 | 61 | 44 | 35 | 26 | 20 | 17 | – | – | – | – |
| .45 | 1,560 | 390 | 175 | 96 | 60 | 42 | 33 | 25 | 19 | – | – | – | – | – |
| .50 | 1,560 | 390 | 170 | 93 | 57 | 40 | 31 | 23 | – | – | – | – | – | – |

Modified from Gehan E: Clinical trials in cancer research. Environ Health Perspect 32:31, 1979.

# Considering Methods in Analysis

## Interim analysis

- Reasons to stop trial when
  - Beneficial effects appear earlier than expected
  - Harmful or adverse effects appear
- Primary end point evaluation

# Compliance of groups

- Differences in outcome in important subgroups
- Mortality differential when sub groups were analyzed for good compliance or bad compliance

Coronary drug Trial: Five year Mortality in Groups

| | # of patients | Mortality (%) |
|---|---|---|
| Clofibrate Drug | | |
| Poor Complier | 357 | 24.6 |
| Good complier | 708 | 15.0 |
| Placebo | 2695 | 19.4 |

# Expressing results of a Clinical Trial

- Risk of death or complication
- Relative risk
- Efficacy of vaccine (in vaccine trial)

  = disease rate in placebo takers – disease rate in vaccine takers
  disease rate in placebo takers

- Generalizability

# Relative Risk: Measure of Association

| Group | outcome | | Total |
|---|---|---|---|
| | Cured/ Positive | Not Cured / Negative | |
| Intervention | a | b | a +b |
| Control | c | d | c +d |

**Relative risk (RR): Ratio of the incidence of an outcome in experimental group compared to that in the control group**

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

# Pravastatin Study Results (NEJM 1996)

| Outcomes | # | Placebo | # | Pravastatin |
|---|---|---|---|---|
| Death CHD | 274 | 13.2 % | 212 | 10.2% |
| Fatal MI | 207 | 10% | 157 | 7.5% |
| Stroke | 78 | 3.8 % | 54 | 2.6% |

Calculate RR (incidence in exposed/Incidence in unexposed ) for all outcomes

What is exposure here ?

# Summary

- Experimental Studies like Clinical Trials are a powerful design
- This design helps to  estimate the superiority of one treatment on the other
- Role in determining new methods of treatment, prevention, and diagnosis
- Its randomization process  helps to reduce selection bias
- Masking reduces information bias
- Efficacy of vaccines and Number needed to treat translate in setting health care priorities

# Reference book & page number for the lecture resource

- Epidemiology by Leon Gordis Third Edition Elselvier Saunders 2004 . Chapter 7& 8

- Sacks-FM; Pfeffer-MA; Moye-LA; Rouleau-JL; Rutherford-JD; Cole-TG; Brown-L; Warnica-JW; Arnold-JM; Wun-CC; Davis-BR; Braunwald-E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N-Engl-J-Med. 1996 Oct 3; 335(14): 1001-9.

# Terminologies

- Protocol: The planned course of action for the clinical trial
  The protocol is established prior to the start of the trial and states the number of participants, eligibility requirements, agents that will be used, dosages, duration, how data is collected, etc.

- Investigator: A researcher in a clinical trial.

- Sponsor: Responsible for funding the clinical trial.

- Institutional Review Board (IRB): An independent board of scientists, physicians, and nurses who review the clinical trial protocol to ensure patient safety.

- Informed consent: A patient's decision to participate in the clinical trial after being informed of the potential benefits and risks of participation. Participants may withdraw their consent at any time and leave the trial.

# Terminologies

- Double blind : Term used to describe a clinical trial in which neither the patient nor the researcher knows which agents are being administered to which patients. This helps prevent bias.
- Intervention group: The group of participants receiving the new preventive or treatment agent that is being evaluated in the clinical trial.
- Control group: The group of participants receiving a standard treatment or placebo that is being compared to the new agent in the clinical trial.
- Randomization: Assigning participants by chance to either the intervention group or the control group. Randomization is often done with a computer.
- Placebo: An inactive substance that may be given to participants in a clinical trial.
- Follow-up: Monitoring of participants for a specified time after the clinical trial is completed.

# Quiz Question

- Consider that undiagnosed hypertension is the only risk factor for immediate death by stroke in a city. Health department implemented a successful program that made identification and control of hypertension mandatory for all population above 15 years of age to prevent immediate death in stroke related mortality.
- Which of the following measures will increase after three years for stroke in this city?
- Exposure (Undiagnosed HTN) …….. outcome (immediate death by stroke)
- Undiagnosed HTN leads to immediate death by stroke / stroke assoc with death
- Control undiagnosed HTN leads to reduction in "immediate death by stroke" (stroke will occur…..but immediate death by stroke will not occur)
- Period of three years passes away that covers period for initial increase in incidence of HTN & stroke incidence
- Then stroke cases will accumulate in population over time as stroke related mortality is reduced as they are not dying of stroke but surviving
-