Randomized Clinical Trials

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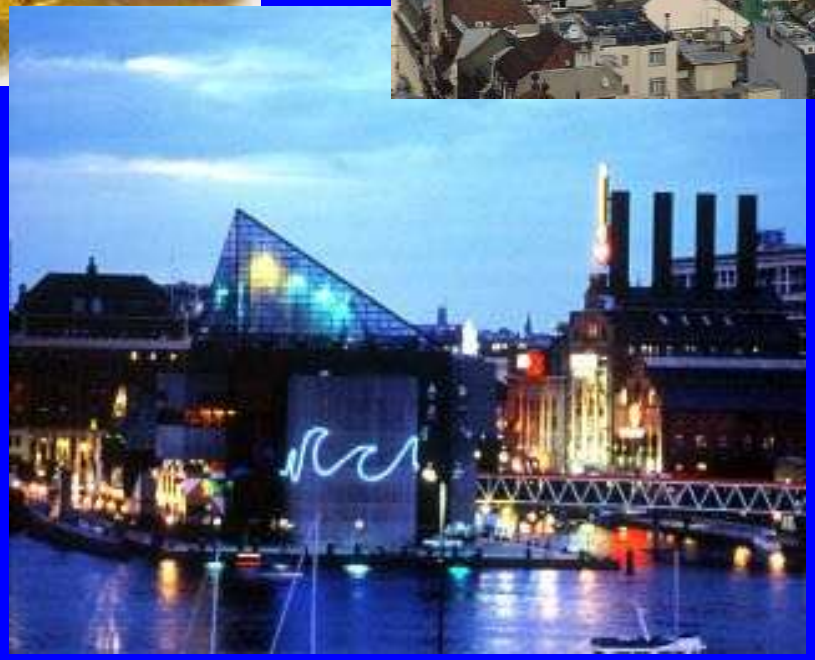

1) In the study of the causes of a disease, the essential difference between an experimental and an observational study is that in the experimental investigation

A) The study is prospective
B) The study is retrospective
C) The study and control group are of equal size
D) The study and control groups are selected on the basis of history of exposure to the suspected causal factor
E) The investigators determine who is and who is not exposed to the suspect causal factor

2) Randomization is a procedure used for assignment or allocation of subjects to treatment and control groups in experimental studies. Randomization ensures:

A) That assignment occurs by chance

B) That treatment and control groups are alike in all respect except treatment

C) That bias in observations is eliminated

D) That placebo effects are eliminated

E) None of the above

3) In a study of the cause of lung cancer, patients who had the disease were matched with controls by age, sex, place of residence, and social class. The frequency of cigarette smoking was there compared in the two groups. What type of study was this?

A) Cohort (concurrent)
B) Cohort (non concurrent)
C) Clinical trial
D) Case control
E) Non of the above

4) A randomized blinded trial of aspirin to prevent myocardial infarction fails to find a difference between aspirin and placebo group after 5 years (N=100 per group).

Select the choice that might best explain it.

A) Ecologic fallacy

B) Type 1 error

C) Type 2 error

D) Selection bias

E) Misclassification bias C

Rationale

- To evaluate the efficacy of a drug or a procedure in the treatment or prevention of disease
- We compare a new drug with the one currently in use or, if no such drug exits, to a placebo (inert substance)

The groups

- The treatment group is given the drug being tested
- The comparison group is given the drug in current use or a placebo

Experiment

- All the participants in the study are assigned to either the treatment group or the comparison group
- Then the participants are followed over the same time period to determine if there are differences in the outcome of interest between the treatment and control group
- The investigator has direct control over the assignment of subjects to study groups (this is the main difference from observational studies)

Not a new idea: Ambroise Paré at the battle of Villaine (1537)

The Battle of Moncontour, Oct. 3, 1569

- “I raised myself very early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen not inflamed, and having slept through the night...

- ...The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses”.

Randomization

- Random assignment (by chance) of individuals to the treatment and comparison groups

Why randomization?

- We want the treatment and comparison groups to be comparable in all respects except the one being studied
- We try to ensure as much as possible that the distribution of all factors and population characteristics, except for the therapy being studied, is based on chance and it is not due to some other factor such as patient or investigator preference (bias)

Randomization and trial results

- The process of randomization will provide comparable groups for most factors so that differences in outcomes at the end of the trial can be attributed to the intervention being tested
- Preventing biased assignment is important as it permits a more definitive interpretation of the trial results

Randomized trials are not only about treatment

- Therapeutic trials evaluate the efficacy of drugs or procedures to cure the disease
- Preventive trials evaluate the efficacy of drugs or procedures to prevent a disease (e.g. Calcium supplementation for the prevention of preeclampsia)
- Intervention trials evaluate the efficacy in treating the risk factors of a disease by an intervention (somewhere between the two)

Procedures

The protocol

- Contains the objective and specific procedures to be used in the trial (scientific rationale, methods for patient selection and allocation, validity of clinical and laboratory procedures, administration of the intervention)
- Must be written before the start of the trial (justification for a new trial, guarantee of the quality and integrity of the study, scientific and ethical approval of the proposed study, funding, publication)

The manual of operations

- Detailed description of all the procedures presented in the protocol
- Intended for the study personnel implementing the study activities
- It is the guide for what the investigator is supposed to do

Selection of study subjects

- The investigator decides, on the basis of the purpose of the study and the difficulty of recruitment, the characteristics of the population to be studied
- Eligibility criteria
- Exclusion criteria
- Internal vs. External validity (typical problem in epidemiology)

Sample size

- “A difference to be a difference must make a difference”
- The study must have a sufficient sample size to have adequate statistical power so that if the treatment being studied is effective, its efficacy will not be mistakenly missed in the trial

Possible outcomes of a trial

	Treatment is effective	Treatment is not effective
Results show treatment is effective	Correct conclusion	False positive (Type I error)
Results show treatment is not effective	False Negative (Type II error)	Correct conclusion

Factors determining the sample size calculation

- With a sample size calculation the investigator determines the number of patients required to detect a designated treatment difference in a specific outcome with specified levels of Type I and Type II protection

Informed consent

- The study subjects must be clearly and understandably informed of the risks and possible benefits of the trial intervention
- Informed consent must be obtained and documented for all study subjects
- Requested by scientific institutions (Ethical review board), funding agencies, and journals

Random allocation

- Eligible subjects who consent to participate in the study are recruited and randomly assigned to the treatment and comparison groups
- Random allocation can be done in different way (computer generated list of subject numbers)
- Stratification for some factors known to influence the outcome (more needed for small studies)

Preventing bias in the assessment of the effect: Masking

- Knowledge of whether the participant was in the treatment or comparison group can influence the perception of the benefit by the subject or the observation and care by the investigator: biased assessment of the effect
- Single masking (subject)
- Double masking (subject and observer)
- Triple masking (subject, observer, and data reviewer)

Follow up

- Follow up patients from recruitment to the end of the study
- Main purpose: assess how many patients will develop the outcome of interest

Compliance or Adherence

- We must be sure that the treatment group is actually receiving the intervention
- Compliance must be constantly assessed during the study
- Different strategies can be used:
  - count unused tablets
  - biological methods

Analysis of the results. Are the two groups comparable?

- Are there differences in the characteristics of the two groups at baseline?
- If there are no differences it means that randomization resulted in the formation of comparable and evenly balanced groups

Analysis of the results. Was the intervention effective?

- Incidence rate for the development of the disease are calculated among the subjects in the treatment and control group
- If the incidence rate of the disease is greater among the persons in the control group than among the ones in the treatment group, we have evidence that the intervention decreased the risk of disease

What is an incidence rate?

- Number of cases of a disease occurring in one of the study groups

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- Number of persons in the study group

Incidence rates of preeclampsia

- Incidence rate = cases/number of subjects
- Incidence rate in calcium group 119/4250 = 0.028
- Incidence rate in placebo group 170/4250 = 0.040
- The incidence rate is greater in the placebo than in the calcium group
- We have evidence that calcium supplementation is effective in reducing the risk of preeclampsia

How strong is the treatment effect?

- The relative risk measures the strength of the treatment effect
- Incidence rate in the treatment group / incidence rate in the control group
- In our example 0.028 /0.040 = 0.7

How to interpret relative risk?

- If relative risk is = 1 there is no evidence of an effect of the treatment (the incidence rate in the treatment group is the same as in the control group)
- If relative risk is < 1 the treatment is beneficial (decreases the risk of disease)
- If relative risk is > 1, the treatment is associated with an increased risk of disease

Other way to assess treatment effectiveness

- Comparison between average values of an outcome between the two groups (e.g. average blood pressure levels)
- If the study is longitudinal we can perform a survival analysis or use longitudinal data analysis

A major source of difficulty

- Maintaining the follow up of the individuals in the study (assure compliance with treatment and study procedures, minimize drop outs and lost to follow-up)
- It is important to trace as many subjects as possible
- Try to get information on the individuals lost to follow up and look if they are somehow different from the individuals who stay in the cohort

Other important issues

- Adequate sample size (can be very big if the outcome is rare)
- Ethical considerations (is it correct to withhold a treatment that is potentially beneficial?)
- Expensive
- Generalizability of the results (multicentre trials)

How randomized clinical trials differ from observational studies?

- The investigator has direct control over the assignment of subjects
- Random allocation of study subjects to treatment and control group
- Preventing biased assignment and outcome assessment permits a more definitive interpretation of the results

Important

- Randomized clinical trials provide strong epidemiological evidence but always consider all the criteria of causality.

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