Intervention vs. Observational Trials: A Brief Introduction

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Introduction

Just like an architect translates a vision for a building into blueprints, so an investigator translates their research idea into a study design.
How do you translate your research ideas into a 'blueprint'? 

- By defining the specific aims of the study.
- Write out the specific aims of your study in no more than one or two sentences.
- Be as specific as possible!
And when you don’t plan...
Overview

Intervention vs. Observational Trials:

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Intervention Trials
- Clinical trials (gold std)
- Community trials
- Therapeutic/preventive trials
- Single/multi-site trials

Observational Trials
- Cohort studies
- Case-control studies
- Nested case-control studies
- Cross-sectional studies
A Taxonomy of Epidemiologic Study Designs

(c) 2004, James N. Hyde, M.Sc., M.A.
Objectives

- Define unique characteristics of intervention trials.
- Define randomization and explain its purpose.
- Define blinding and explain its purpose.
- List advantages and disadvantages of intervention trials.
Intervention Trials – General Structure

- Researcher selects and **randomly** assigns individuals (or groups) to treatment or non-treatment groups.
  - Select participants by defining specific exclusion/inclusion criteria.
  - Perform sample size/power calculations to define the number of subjects to be selected.
- Participants are followed forward in time.
- Incidence of outcome (i.e., disease, survival, death) are compared between groups.
Randomization eliminates the influence of confounding variables that are present at the time of randomization. It makes treatment groups comparable with respect to these potential confounders (ie., eliminates selection bias).

Provides strongest evidence for causal inference.

What can potentially happen without randomization?

- Trial studying the effects of bacille Calmette-Guerin (BCG) vaccination against TB in children from TB families. Physicians were told to divide the children into treatment and control groups. Study results indicated that TB mortality was almost 5x higher in controls than in vaccinated children. It was later discovered that physicians tended to inoculate children of the more intelligent and cooperative parents who were probably also more conscious of health and related issues. Those in the treatment group may have done better not because of the vaccination but because the parents were more health-conscious and, therefore, the children simply had a lower risk of mortality from TB.
Simple randomization of individual participants in an equal ratio to each intervention group. When the sample size of the trial is small, SR could result in imbalance in the #/trt or you could have different distributions of a trait like race in the two arms.

Block randomization ensures close balance in the # of participants in each study group. Block of pre-determined size with half in block on treatment and half on non-treatment. BR does reduce the unpredictability of randomization which could lead to issues in blinding. Varying the size of the blocks would help alleviate this.

Stratified block randomization ensures that an important predictor of the outcome is more evenly distributed between the study groups than chance alone would dictate. Tends to be used with small trials. Need to be sure stratification variable has a large effect on prognosis. The number of strata needs to be kept to a minimum, and the variable cannot be evaluated in the analysis.

Ex: In a study of the effect of a drug to prevent fractures, having a prior vertebral fracture is a strong predictor of outcome and response to treatment. To ensure that similar numbers of people with vertebral fractures are in each group, stratify by whether patient has had a vertebral fracture and then carry on block randomization in each strata.
Intervention Trials – Blinding

- Randomization does not deal with confounding variables that may surface after randomization.

- **Purpose** - To reduce bias in
  - **Measurement**: Especially if the outcome is subjective, patients who know they are on treatment may indicate better outcomes than those in the untreated group.
  - **Classification**: If a patient knows they are on placebo, they may be more likely to seek out other treatments independent from the trial that could affect the outcome.
  - **Analysis**: In an unblinded study, the researcher may not treat both groups equally but rather look for the outcome more carefully in the untreated group than in the treated group. (e.g., In a study of persons with MS in which some were randomized to treatment and some to placebo, neurologists who were not blinded to treatment assignment concluded from their structured examinations that those on treatment did statistically better than those not on treatment. Neurologists blinded to treatment assignment saw no difference using the same examination.)
Intervention Trials – Blinding[2]

- Single – Subject does not know his treatment assignment.
- Double – Subject and researcher do not know treatment assignments.
- Triple – Subject, researcher, nor analyst know treatment assignments.
Advantages

- Gold standard for evaluating efficacy of therapeutic or preventive measures.
- Provides strongest evidence for causality.
- Reduces influence of other determinants of exposure and outcome (confounding) due to randomization.

Disadvantages

- Expensive, time-consuming.
- Subjects may not be representative of all people who might eventually be put on the treatment.
- Ethical considerations (equipoise necessary) – believe new treatment is at least as good as old treatment or placebo.
Objectives

- Define the unique characteristics of cohort, case-control, nested case-control, and cross-sectional studies.
- List factors that should be considered when determining which type of observational trial is most appropriate for a given study.
- List outcomes available for different types of observational studies.
Observational Trials – Points to Consider

- What is your outcome of interest?
  - Common or rare
  - Descriptive (incidence, prevalence) or analytic (association)

- Time frame
  - Retrospective (past) or prospective (future)
  - Interested in changes over time or a single point in time?

- Natural grouping of subjects
  - Exposed vs. unexposed
  - Diseased vs. non-diseased
Cohort Studies – General Structure

- Start with exposed vs. unexposed
- Similar to intervention trials except patients are not randomized to groups.
- Need to have a good idea of which exposures are suspected as possible causes of disease.
- Retrospective or prospective
Cohort Studies – General Structure [2]

- Outcome is common. Prevents having to recruit excessive number of subjects or following patients for exceedingly long periods of time to have sufficient numbers with the disease.

- Prospective design is ideal for estimating incidence (\# of newly diagnosed cases in population) of disease since new cases can only be clearly identified prospectively.

- Prospective and retrospective can be used to estimate prevalence (proportion of individuals in population with the disease) or association of outcome with a specific candidate of predictors. Factors are associated if:
  - The distribution of one factor is different for different values of another.
  - Knowing the value of one factor gives information about the distribution of the other.
Intervention vs. Observational Trials:

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Cohort Studies (prospective)

Cohort Studies (retrospective/historical)
Outcome measures in cohort studies

- **Odds ratio** – compares the odds of disease in the exposed group to the odds of disease in the unexposed group.

- **Relative risk (risk ratio)** – ratio of risk of disease in exposed to risk of disease in unexposed. In a cohort study, it can be calculated directly by taking the incidence of disease in the exposed group and dividing it by the incidence of disease in the unexposed group. **Incidence** is simply the proportion of people who developed the disease from the population at risk (new cases, not existing ones).

- **Risk difference** – represents the absolute difference in risk and can be calculated using the cumulative incidence. **Cumulative incidence** is the incidence calculated using a period of time during which all of the individuals in the population are considered at risk for the outcome.

- **Incidence density ratio** – ratio of the incidence rate in the exposed to the incidence rate in the unexposed. **Incidence** assumes that any individual in the denominator has the potential for being in the numerator. **Incidence rate** is useful when individuals in the denominator were not followed for the full time period due to loss to follow-up, etc. In this case, the denominator consists of the sum of the different times each individual was at risk. This is often expressed in terms of person-years.
Cohort Studies – Potential Issues

**Weaknesses**

- Causal inference challenging to impossible, often muddied by influences of confounding variables.
- Prospective studies are expensive and inefficient for rare outcomes.
- Retrospective studies give limited control over how the population of interest was sampled and over the nature and quality of the predictors.

**Potential biases**

- Information bias – when the quality and extent of information obtained is different for exposed and unexposed subjects.
- From non-response and losses to follow-up (e.g., if people with disease are selectively lost to follow-up, incidence rates in the two groups will be hard to interpret).
Case-control studies – General Structure

- Start with diseased (case) vs. non-diseased (control).
- Examine the relationship of exposure status to disease status.
- Efficient when outcome is rare.
- Match controls to cases based on major factors related to the disease but not of interest to the investigator. The number of controls per case can be different than 1:1.
Case Control Studies (retrospective)
Challenges to case-control studies

- **Selection of cases**
  - Where/how to locate sample of interest. If all subjects chosen from a single facility, you may find that risk factors are unique to that location limiting the generalizability of the study.
  - Do you select incident (ie., newly diagnosed) cases or prevalent cases? Incident cases may lengthen the time of your study as you wait for cases to be diagnosed. Prevalent cases not ideal for studies focusing on the etiology of the disease as risk factors in prevalent cases may be more related to survival than development of the disease.
Challenges to case-control studies [2]

- Selection of controls
  - Must be sampled independently of exposure status.
  - Should estimate the distribution of exposure in the source population.
- Type of matching to controls:
  - Group matching – select controls such that the proportion of controls with a certain characteristic matches the proportion of cases with that characteristic.
  - Individual matching – control matched to individual case based on similarities in potential confounders.
- Ratio of controls to cases – 1:1 is the most statistically efficient; typically not much gain in power is seen past a 4:1 ratio. If larger than a 1:1 ratio is used, could use controls of different types (e.g., In a study of brain tumors in children (cases), matched to children without cancer (normal controls) and children with cancer but not a brain tumor (cancer controls).
Odds ratio (OR) compares the odds of exposure in the diseased (case) group to the odds of exposure in the non-diseased (control) group.

Unlike in cohort studies, unable to calculate relative risk in case-control study designs because there is no time element in this type of study.

OR is a good estimate of the relative risk when:
- Incident cases selected
- Cases and controls selected independently of their exposure status
- The disease is rare ($\approx \leq 10\%$)
Case-control Studies – Potential Issues

- **Weaknesses**
  - Limited to one variable
  - Sequence of events unclear. Therefore, no ability to determine causation.

- **Potential biases**
  - Sampling bias
  - Recall bias which potentially affects cases and controls differently
Nested Case-control Studies

- A case-control study nested within a cohort study.
- Ideal for predictor variables that are expensive to measure and that can be assessed at the end of the study on subjects who develop the outcome during the study (cases) and on a sample of those who do not (controls).
- Because the number of cases is probably fairly small, can match multiple controls to a given case to increase the power.
Why use a nested case-control study?

- Removes recall bias because data collected before development of disease.
- Allows for the time element to be included in the case-control. Therefore, if abnormal biologic characteristics were found years before the disease developed, these findings could now be attributed to risk factors for the disease rather than potential developments of early, subclinical disease.
- Often more cost-effective than a cohort. Not all samples collected are tested. Rather they are stored until the disease has developed at which time analysis begins.
Cross-sectional Studies – General Structure

- Snapshot of the population in which the exposure and the outcome are measured at the same time.
- Useful for describing variables and their distribution patterns.
- e.g., National Health and Nutrition Examination Survey (NHANES) a major source of information about the health and habits of the US population. Collected year to year but is a snapshot of the health and habits.
Common Outcome Measures in Cross-sectional Studies

- Prevalence
- Odds ratio
Cross-sectional Studies – Potential Issues

- Impractical for rare diseases unless sample drawn from a population of diseased patients.
- Cannot establish causal relationships.
Conclusion

- The beginning of good study design is a good plan – define your specific aims writing them out in no more than 1-2 sentences per aim.
- The choice of intervention or observational trials will be guided by the questions your specific aims raise.
- Intervention trials good for determining causality; however, randomization not always ethical.
- A variety of observational trials are available. The best choice is determined by your outcome of interest and what, if any, time frame that is of interest.
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