BIOS 662 Fall 2018

Study Designs

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Types of Studies

- Definition 2.1. An *observational study* collects data from an existing situation. The data collection does not intentionally interfere with the running of the system.

  $\rightarrow$ beware *Hawthorne effect*.

- Definition 2.2. An *experiment* is a study in which an investigator deliberately sets one or more factors to a specified level.

  $\rightarrow$ leads to stronger scientific/causal inference

Types of Biomedical Studies

- Observational studies:
  - Cross-sectional
  - Longitudinal
  - Cohort
  - Case Control
- Experimental Studies:
  - Laboratory
  - Clinical Trials

Definition 2.5: An *experimental unit* or *study unit* is the smallest unit on which an experiment or study is performed.

$\rightarrow$ Distinct from the unit of observation.

Cross-Sectional Studies

- Definition 2.16: A *cross-sectional study* collects data on study units at a (single) fixed time.

- Purposes:

  1. To describe a population at a point in time; measure prevalence

     Examples:

     – U.S. Census

     – National Health and Nutrition Examination Surveys (NHANES)

  2. To examine associations

     Examples:

     – menopause status and blood cholesterol level

     – hyperactivity and blood lead levels

     – diet and blood pressure

Longitudinal Studies

- Definition 2.16: A *longitudinal study* collects information on study units on at least two occasions.
- Purposes:
  1. To measure change

     Examples:
     - change in height for each year of age
     - change in viral load in HIV+ individuals

  2. To develop predictions

     Example:
     - given blood pressure at age 10, what would we expect blood pressure to be at age 15?

3. To examine the association between the changes in 2 or more variables (explore temporal changes)

   Example:

   – is change in viral load associated with change in CD4+ T-cell count?

Cohort Studies

- Definition 2.10: A *cohort study* or *prospective study* is one in which a cohort of people is identified and followed to observe specified endpoints (e.g., occurrence of disease).

- Purposes:

  1. Estimate incidence of disease
  2. Relate baseline measures to the occurrence of disease

  Examples:

  – Framingham Heart Study
  – Atherosclerosis Risk in Communities (ARIC) Study

Question:

- Are cohort and longitudinal studies mutually exclusive?
- If not, how are they related?

Case-Control Studies

- Definition 2.12: A *retrospective study* is one in which people having a particular outcome or endpoint are identified and studied.

- Definition 2.13: A *case-control study* selects all cases, usually of a (rare) disease, that meet fixed criteria.

  A disease-free group, called *controls*, that serve as a comparison for the cases is also selected.

  The cases and controls are compared with respect to various characteristics (exposures, risk factors)

Case-Control Studies cont.

- Definition 2.14: In a *matched case-control study*, controls are selected to match characteristics of individual cases.

  The cases and controls(s) are associated with each other.

  There may be more than one control for each case.

  In an *individually-matched case-control study*, each control is matched with a specific case.

- Definition 2.15: In a *frequency-matched case-control study*, controls are selected to match characteristics of the entire case sample. A control is not matched with a specific case.

Case-Control Studies cont.

- Example: Investigators interested in the association between thromboembolic disease and oral contraceptive use
  - Cases: women aged 16-40 who had been discharged from one of 19 hospitals for deep vein thrombosis
  - Controls: women suffering acute medical conditions (other than thromboembosis) or elective surgery
  - Individual matching, with two controls per case; matched on age, date of hospital admission, parity
  - All participants asked about oral contraceptive history (50% cases, 14% controls)

Experimental Studies

- Definition: Interventions are applied by investigator
- Purpose: to compare outcomes between two or more interventions
- Example: Compared to placebo, does a candidate vaccine result in a lower incidence of HIV in high risk individuals?
- Usually interventions are assigned using *randomization*: a random but known process by which participants are assigned to different treatments or interventions

  For instance, each participant may be equally likely to be assigned to a medication or matching placebo

Randomization

- Attributed to R. A. Fisher
- "One of the great intellectual advances of the twentieth century."

  Lloyd D. Fisher

- Advantages:
  - Removes potential bias in allocating participants to different intervention groups
  - Tends to produce comparable groups on average
  - Provides a basis for statistical tests
- Disadvantages:
  - Ethical?

- RCT = randomized controlled trial

Clinical Trials

- Treatment trials – pharmaceutical, surgical, etc.
- Prevention trials
- Screening trials
- Diagnostic trials

Pharmaceutical trials

- Pre-clinical
- Phase I
- Phase II
- Phase III
- Phase IV

Parallel Group and Factorial Experiments

Crossover Experiment

- Definition 2.6: In a *crossover experiment* the sample experimental unit receives more than one treatment during non-overlapping time periods.
- Advantage: each experimental unit serves as its own control, eliminating subject-to-subject variability
- Disadvantage: possible carryover effects of treatment, calendar time effects
- Usually randomize the order of the treatments

Blinding / Masking

- Definition 2.19: A study is *single blind* if subjects being treated are unaware of which treatment (including any control) they are receiving
- A study is *double blind* if both the participants and the researchers are unaware of which treatment the subjects are receiving
- *Triple blind*: double blind plus those analyzing or reviewing the data (statistician/monitoring committee) are unaware of treatment assignments
- Sometimes impossible/infeasible: nutrition, circumcision
- Unblinded studies (aka "open label"):
  - Disadvantage: potential for bias (systematic error)
  - Advantages: reflects clinical practice, simpler

Endpoints

- Definition 2.9: An *endpoint* is a clearly defined outcome or event associated with an experimental or study unit
- Important considerations in choosing an endpoint:
  - Relevance
  - Reliability
  - Rate
- Hierarchy: primary, secondary, tertiary, etc.

Steps in Performing a Study

- Identify a question or problem area of interest
- Design a study to answer the question
  - Decide on the type of study
  - Identify the data to be collected
  - Determine appropriate analytical models
  - Determine the sample size required
- Conduct the study and collect the data
- Analyze the data and draw conclusions and inferences
- Use the results

Inferences from a Study

- What was the design?
- Guard against bias:
  - Comparability
  - Representative of target population
- Source of, control for, and quantification of uncertainty/variation

Some Considerations Related to Ethics

- Stakeholders in a study
  - Subjects / patients / participants
  - Population at risk
  - Funding agency
  - Scientific advancement
  - Study investigators
- Institutional Review Boards and external monitoring boards
- Principle of informed consent
- It is unethical to enroll participants in a study that is not designed appropriately to address the question of interest

BIOS 668 and 752

668 DESIGN OF PUBLIC HEALTH STUDIES (3). Prerequisites, BIOS 545, 550, or equivalents. Statistical concepts in basic public health study designs: cross-sectional, case-control, prospective, and experimental (including clinical trials). Validity, measurement of response, sample size determination, matching and random allocation methods. Spring.

752 DESIGN AND ANALYSIS OF CLINICAL TRIALS (3) Prerequisites, BIOS 660, and 661 or permission of the instructor. Description: This course will introduce the methods used in clinical trials. Topics include dose-finding trials, allocation to treatments in randomized trials, sample size calculation, interim monitoring, and non-inferiority trials. Fall. Ivanova.