EPID600 (Spring 2007) module on Intervention studies

Objectives:

- List the characteristics of (a) community trials and (b) clinical trials.
- Identify the advantages and disadvantages of (a) community trials and (b) clinical trials.
- State how a community trial is different from a clinical trial.
- Differentiate experimental studies from observational studies.
- Describe how randomization of subjects is accomplished.
- Describe the purpose of randomization.
- Explain the implications of different ways of handling unplanned crossovers in the analysis.
- Understand the relation between statistical power and the sample size of a study.
- Define the term masking (blinding).
- Identify the purpose of masking (blinding).
- Explain the "placebo effect."
- Identify factors which make the results of a study externally valid (generalizable).
- Identify the advantages and disadvantages of clinical trials and explain how they apply to a particular study.

Instructions:

1. **Read**: Aschengrau and Seage, ch. 6 - Overview of Epidemiologic Study Designs, and ch. 7 - Experimental Studies . Answer the practice questions at the end of the chapter or at http://publichealth.jbpub.com/aschengrau/student_resources.cfm and check your answers (recommended, but optional) (animated flashcards, weblinks, and Powerpoint slides from the authors] can also be found at that URL)

2. Look over the case study questions and then read the case study reading: John M. Colford, Jr., Timothy J. Wade, Sukhminder K. Sandhu, Catherine C. Wright, *et al*. A randomized, controlled trial of in-home drinking water intervention to reduce gastrointestinal illness. *American Journal of Epidemiology* 2005;161(5):472-482. (abstract, full text)

3. (Optional, but earns credit) Before lab, submit the answers to the starred case study questions (numbers 1, 2, 4, 6, and 9).

4. Read the lecture slides and attend the lecture (or read the speaker notes).

5. Work on the rest of the case study questions in **lab** and afterwards.
6. Agree on the answers, so the facilitator can submit the group's consensus answers by the following Sunday evening (EST).

Case Study Questions (NOTE: For some of these questions there may not be one "right answer".)

1. A **randomized trial, as in the typical clinical trial, and a (nonrandomized) **crossover trial** are both methods for attempting a causal comparison by ensuring a valid substitute population to represent the counterfactual condition for the index (exposed) group. This question, which is not directly focused on the study article, asks about the respective advantages of these two techniques (randomized trial, crossover trial) for making a valid comparison for inferring causality. (60 words overall maximum).

1a. What is an advantage that is afforded by the typical randomized trial and that is not provided by a (nonrandomized) crossover trial?

1b. What is an advantage that is afforded by a (nonrandomized) crossover trial and that is not provided by the typical randomized trial?

**2. Why is blinding so important in the Colford *et al.* study? Give two (2) specific sources of error or improper influence that could result if the blinding were compromised? (100 words maximum)

3. The investigators employed a number of procedures to achieve and maintain the triple-blinding (of installers, participants, and investigators). State three (3) procedures the investigators employed for this purpose. (100 words maximum)

**4. In selecting the community for this study, the authors had to balance diverse and somewhat conflicting objectives. Some of the selection criteria pertain to the cooperativeness of the water utility and availability of monitoring data. Others were presumably intended to to increase the power of the study to detect an effect of water filters, whereas others were presumably intended to make the results more generalizable.

4a. What is an example of a selection criterion, other than population size, intended to increase the statistical power of this study?

4b. What is an example of a selection criterion intended to increase the generalizability of the results of this study?

5. Use the data in Table 1 to estimate the average household size (number of study participants per household) separately for the active device group and the sham-device group. Show the calculation.

**6. Participants in the trial were asked to guess whether they thought they were using the active device or the sham device. Suppose we regard guessing as a "screening test" for detecting an active filter device in the participant's home (on analogy to mammography as a screening test for breast cancer). (For all parts of this question, treat the responses "Sham device" and "Don't know" as equivalent, and ignore the fact that participants share households.)

6a. What was the "sensitivity" of guessing as a test for detecting the active device during the first month of Cycle 1? Show the calculation (as a percentage with one decimal place) and state the meaning of your result, without using the word "sensitivity".

6b. What was the "specificity" of guessing as a test for detecting use of the active device during the first month of Cycle 1? Show the calculation (as a percentage with one decimal place) and state the meaning of your result, without using the word "specificity".

6c. What was the positive predictive value of "guessing" for detecting use of the active device during the first month of Cycle 1? Show the calculation (as a percentage with one decimal place) and state the meaning of your result, without using the words "predictive value" or PPV.

6d. How did "sensitivity" and "specificity" change between the first month of Cycle 1 and the first month of Cycle 2?

7. The precise meaning of the term "rate" is, according to Regina Elandt-Johnson (see "Definition of rates: some remarks on their use and misuse", *Am J Epidemiol* 1975;102:267-271), the "ratio of a change in one quantity to a change in another quantity, with the denominator quantity often being time" (see *Understanding the Fundamentals of epidemiology: an evolving text*, chapter on "Measuring Disease and Exposure"). Have Colford *et al.* presented any incidence rates derived from their data (look only in the Results section, tables, and figures)? (Select A or B)

A. The paper contains at least one such rate (give an example, including page and column).

B. The paper contains no such rate(s).

8. Suppose that the authors wanted to estimate HCGI incidence in this trial with a cumulative incidence (CI)-type measure.

8a. How could they define and calculate a CI-type measure for HCGI in the context of this trial?

8b. What data that are not provided in the paper are needed to estimate a CI-type measure for HCGI incidence for the active device participants during Cycle A (Cycle 1)?

**9. Use the data in table 4 to estimate the following (crude) incidence rates of highly credible gastrointestinal illness (HCGI). Show calculations and units.

9a. rate of HCGI during Cycle A among active device participants

9b. rate of HCGI during Cycle A among sham device participants

9c. rate of HCGI in both cycles combined among active device participants

9d. rate of HCGI in both cycles combined among sham device participants

10. Use your results from the preceding question to show the calculation for the following crude statistics, giving units where appropriate. Use the active device participants as the reference group.

10a. For both cycles combined, what was the crude rate ratio for HCGI comparing sham device participants to active device participants? How does your result compare with the comparable estimate ("device only") from the authors' mathematical model?

10b. What was the crude rate difference for HCGI in both cycles combined comparing sham device participants to active device participants?

11. It turns out that the article has some incorrect numbers. In one case the correct value can be calculated using numbers in the article and information that this course has touched upon. In two cases there are inconsistent numbers, and in another the number seems quite improbable. The authors told me about others that cannot be detected by the reader (the lead author is sending the journal a letter with the corrections). Without spending too much time, try to identify one of the incorrect values and make a case for why the number you have identified is suspect. (60 words maximum)

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A Randomized, Controlled Trial of In-Home Drinking Water Intervention to Reduce Gastrointestinal Illness

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Trials have provided conflicting estimates of the risk of gastrointestinal illness attributable to tap water. To estimate this risk in an Iowa community with a well-run water utility with microbiologically challenged source water, the authors of this 2000–2002 study randomly assigned blinded volunteers to use externally identical devices (active device: 227 households with 646 persons; sham device: 229 households with 650 persons) for 6 months (cycle A). Each group then switched to the opposite device for 6 months (cycle B). The active device contained a 1-μm absolute ceramic filter and used ultraviolet light. Episodes of "highly credible gastrointestinal illness," a published measure of diarrhea, nausea, vomiting, and abdominal cramps, were recorded. Water usage was recorded with personal diaries and an electronic totalizer. The numbers of episodes in cycle A among the active and sham device groups were 707 and 672, respectively; in cycle B, the numbers of episodes were 516 and 476, respectively. In a log-linear generalized estimating equations model using intention-to-treat analysis, the relative rate of highly credible gastrointestinal illness (sham vs. active) for the entire trial was 0.98 (95% confidence interval: 0.86, 1.10). No reduction in gastrointestinal illness was detected after in-home use of a device designed to be highly effective in removing microorganisms from water.

drinking; epidemiologic studies; gastrointestinal diseases; intervention studies; randomized controlled trials; water; water supply

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; EPA, US Environmental Protection Agency; HCGI, highly credible gastrointestinal illness.

Although infectious disease outbreaks can result from mistakes in the management of drinking water systems, there are questions regarding the extent to which such illness can be attributed to drinking water in systems that operate properly (1, 2). Previous drinking water trials produced conflicting results (3–6). In 1996, the US Congress amended the Safe Drinking Water Act (7). One of the Act's provisions that focuses on the above uncertainties (Section 1458 (d) (1)) required the Centers for Disease Control and Prevention (CDC) and the US Environmental Protection Agency (EPA) to conduct studies on waterborne disease occurrence and to provide a national estimate of waterborne disease. After a lengthy public discussion and planning process (8, 9), the CDC and the EPA funded a pilot and a large-scale drinking water trial as well as several smaller studies to estimate the risk of illness from using municipal tap water.

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Principles of Epidemiology for Public Health (EPID600)

Study designs: Intervention trials

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Signs from around the world – East Africa

"In an East African newspaper:
A new swimming pool is rapidly taking shape since the contractors have thrown in the bulk of their workers."

Topics for this lecture

- Causality - the counterfactual model
- Experimental and observational epidemiologic study designs
- Types of intervention trials
- Importance of randomization
- Other issues

Causality - the counterfactual model

- How do we discover causation?
- Toddler playing with a lamp switch
- Causation is not observed but inferred
- Conceptual models and frames of reference underlie causal inference

Counterfactual model for causal inference in "modern epidemiology"

- Compare the outcome in "exposed" group to what the outcome would have been if had not been exposed
- Compare the outcome in "unexposed" group to what the outcome would have been if had been exposed
- These comparisons are counterfactual

In practice: use a substitute population

- Since can't compare to counterfactual, compare the outcome for the "exposed" group to the outcome in a "substitute" population
- Substitute population represents the "exposed group without the exposure".
- Validity of inference depends on finding a valid substitute population

Experimental and observational studies

Both compare "exposed" and "unexposed" groups

In experimental (intervention) studies, researcher determines who is exposed.

Most epidemiologic studies are observational – but intervention studies have a special status

Analytic study designs

- Intervention trials (experimental)
- Cohort studies (observational)
- Case-control studies (observational)
- Cross-sectional studies (observational)

Types of intervention studies

Therapeutic trials vs. preventive trials

Example of a therapeutic trial:

The Beta-blocker Heart Attack Trial (B-HAT)

Types of intervention studies

Example of a prevention trial:

Perinatal transmission of HIV (ACTG 076)

Randomized trials that I have done

- *Free & Clear* – self-help smoking cessation program
- *Quit for Life* – self-help smoking cessation program for African Americans
- Partner notification for HIV-infected persons

Types of intervention studies

The distinction between therapeutic and preventive is not always a clear one

Examples:

HDFP, MRFIT, LRC-CPPT

Periodic screening for breast cancer

Types of intervention studies

- Single site – interventions provided from a single center
  - *Free & Clear*
- Multi-site – multiple centers and a coordinating center
  - LRC-CPPT, ACTG

Types of intervention studies

Clinical trials – intervention is applied to individuals (patients, students, workers)

- Multiple Risk Factor Intervention Trial (MRFIT)

Community trials – intervention is applied to groups (schools, worksites, communities)

- Smoking prevention & cessation (COMMIT)

Types of intervention studies

- Intervention randomly assigned
- Intervention not randomly assigned

Randomization is a key feature

Randomization

Why is randomized assignment of intervention so important?

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Randomization is so important because overall, it provides the strongest evidence for causal inference

Why is randomized assignment of intervention so important?

1. Best assurance that control group (unexposed) is a valid substitute population (avoids self-selection of exposure)

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4. Avoids ambiguity of time order of exposure and outcome (most intervention studies achieve this)
5. Provides foundation for statistical tests – valid quantification of uncertainty

Experiments and control

Experimental method tries to control all unwanted influences

Benefits of randomization require strict adherence to protocol

Difficult to exercise control, especially over people

Statistical “proof”

Randomized trial is a “true experiment” designed to “prove”, so follow Neyman-Pearson hypothesis testing to preserve the actual significance level:

1. *a priori* specification of hypothesis
2. primary outcome variable and test
3. pre-specified rules for early termination
4. intention to treat analysis

(for notes page)

"Listen to your statistician."

Statistical "proof"

Coronary Primary Prevention Trial (CPPT) – Lipids Research Clinics (LRC) trial

Hypothesis: reducing serum cholesterol with cholestyramine will reduce CHD incidence

Outcome: CHD incidence, based on specific diagnostic criteria

Analysis: cholestyramine group vs. placebo group

Stopping rules: Interim analyses, declining alpha

Demonstrate each link in chain of inference

1. Intervention was received, only by intervention group
2. Effect was mediated by the expected mechanism

Verify the difference between intervention and control groups

Process evaluation:

- Compliance – did intervention participants receive the intervention?
- Crossovers (unplanned) – did control participants receive the intervention?

Crossovers

- Crossover design – planned reversal of intervention and control treatments
- Unplanned crossovers – intervention participants do not comply, control participants obtain the treatment
- Unplanned crossovers weaken or can obscure a true effect

Document exposure

- Ask –
  - "How many of your pills did you take?"
  - "Did you watch the program?"
  - "How much of the manual did you read?"
- Pill count, serum assay, behavioral analog
- May do same for control participants

Demonstrate each link in chain of inference

- Intention-to-treat analysis
- Treatment-received analysis

Measure mediating variables

- Try to demonstrate the chain of inference or to find out why expected effect did not occur
- CPPT – reduction in serum cholesterol was an intermediate outcome
  - Cholestyramine had greater reduction in cholesterol
  - 2% reduction in CHD incidence for each 1% reduction in cholesterol

Issues in interpretation

- Participants often highly selected
- How far can one generalize
  - E.g., CPPT –
    - top 15% of cholesterol distribution
    - men
    - middle-aged

Ethical issues

- Equipoise – there must be genuine uncertainty about which treatment is better
- Is it ethical to test something other than the best?
- After the trial, who will receive the benefits? The control group? Everyone?

The Water Pistol

When a 3-year-old boy opened his birthday gift from his grandmother, he discovered a water pistol. He squealed with delight and headed for the nearest sink.

The boy's father was not so pleased. He turned to his mother and said, “I'm surprised at you. Don't you remember how I used to drive you crazy with water guns?”

Mom smiled and then replied … “I remember.”