Unit 9. Introduction to Experimental Studies/Intervention Studies - Part 2

- Randomized Clinical Trials
- Community Trials

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NO AUDIO ON THIS SLIDE

1950's Salk's Polio Vaccine Trial

Field trial in 600,000 school children. What's interesting ... is that
- in some communities (N=84 test areas in 11 states) children in grades 1-3 were randomized to receive vaccine or placebo
- and some (N=127 test areas in 33 states) weren't. In these communities, 2nd graders received the vaccine while grades 1 & 3 did not.

1950's Salk's Polio Vaccine Trial: results

In the randomized communities, the results were crystal clear. The vaccine protected against polio. In the non-randomized communities, results, though still slightly in favor of vaccine, were much more ambiguous and would not have allowed investigators to conclude that the vaccine worked. Why? We'll never know for sure.

Alternatives to Randomization: Why don't they work?

- Historical controls: you compare your study patients with information on previous patients, taken from patient records or the literature.
  - Copied From Pocock-Clinical Trials: There are two major sets of problems with historical controls
  - Problem Set 1. Patient selection
  - Problem Set 2. Experimental Environment

Patient Selection

1. A historical control group is less likely to have clearly defined criteria for patient inclusion, since such patients on standard treatment were not known to be in the clinical trial when their treatment began. (historical controls would tend to be less healthy)

2. Since historical controls were recruited earlier and possibly from a different source, there may be a change in the type of patient available for selection.

3. There is danger that the investigator may be more restrictive in his choice of patients for a new treatment. (historical controls would tend to be more healthy).

Experimental Environment

1. Quality of historical data is inferior. A clinical trial requires data entry and case report forms.
2. Outcome definition may differ between the two groups of patients.
3. Ancillary patient care may improve on the new treatment. It is difficult to assure that all aspects of managing the patient, other than treatment, remain constant.
4. There is a tendency to invalidate more patients on a new treatment than in historical controls. Patients on new therapy who fare badly may be excluded after subsequent inquiry reveals protocol violations whereas the exclusion of any historical controls is difficult.
Matching: Pair each exposed person with a similar unexposed person (eg. same age, same gender, same diet)

1. Doesn't in itself address the problem of who gets which treatment. Still need a random allocation schedule for each pair.
2. It is difficult to match on more than two or three factors.
3. Confounding is only addressed for the factors that were matched on.

Use of birth dates or social security numbers or odd day-even day, or alternate (every other person) control schemes.

- The major problems with these schemes is that they are inherently unblinded.
- Pocock says: The main problem with all these methods is that the investigator can easily know in advance which treatment a patient would receive if he entered the trial, and this prior knowledge may affect the investigator's decision regarding entry or not.

About Alternatives to Randomization

- When two or more treatments are being compared in a clinical trial, there simply are NO alternatives to randomization that are accepted by the general scientific community.

Placebo Controlled: Haygarth

- 1799 Haygarth, in one of the earliest (single) blinded placebo controlled studies recorded,

Tested metal tractors --metallic rods used to stroke the body of an ailing person, believed to relieve pain against imitation tractors made of wood.

Imitation tractor = Placebo

Haygarth 1799

"All the patients were in some measure not more relieved by the second application, except one, who received no benefit from the former operation, and who was not a proper subject for the experiment, having no existing pain, but only stiffness of her ankle."

Placebo Effects

This section is taken from Clark and Leaverton: Scientific and ethical issues in the use of placebo controls in clinical trials. Annu Rev Public Health 15, 19-38 1994

A Placebo is an "inert" substitute for a treatment or intervention. "Inert" means the compound has no known activity that would be expected to affect the outcome.

Need for inclusion/exclusion criteria.
Placebo Effects (cont.)

- In actuality, a placebo effect is a psychosomatic effect brought about by relief of fears, anxiety or stress because of study participation.
- It's not just the little white pill that brings about the effect; it's the additional attention and the belief that your condition might be being treated with a superior new treatment.
- All outcomes affected by psychosomatics are prone to placebo effects.

Clark and Leaverton note:

"Placebos have been noted to be effective in the treatment of arthritis, angina pectoris, peptic ulcer, asthma, diabetes, high blood pressure, multiple sclerosis, Parkinson's disease, radiation sickness, postoperative pain, insomnia, hay fever, common cold, cough, seasickness, anxiety, depression ... not exhaustive."

Clark and Leaverton conclude that:

"A component of every specific treatment effect can be attributed to the placebo response." The question that a study should be asking is whether the treatment has any effect on outcome aside from the stress-relieving effect of study participation.

NO treatment is NOT the same as placebo treatment

- To determine if improvement in the treated group is due to drug effect rather than the act of being treated, a placebo must be used.

Alternative: Positive (active) Control

An active control is another treatment that is known to have efficacy.

An active control group may be used instead of a placebo group when use of a placebo is deemed unethical, namely when withholding treatment from a patient could produce irreversible harm.

Eg. Test of cocktail in HIV infection: control group is given AZT

Problems with the use of an active control

1. The effect both treatments may be due to a placebo effect.
2. The new treatment must be shown to be better than the active control. This is not normally an FDA requirement for approval. Suppose the treatment is an herbal remedy that appears half as efficacious but has fewer side effects than the standard drug. In reality, because no placebo was used, we have no idea whether the herbal remedy really was efficacious or not.
Blinding, also called Masking

If the outcome can conceivably be affected by patient or investigator expectations, then blinding is important.

Types of Blinding

- Single Blind: The patient is blind.
- Double Blind: The patient and the investigator are blind.
- Triple Blind: The patient, investigator and data-cleanup people are blind. The statistician can only be partially blinded since he/she has to know which patients are in the same treatment group.

Learning Activity

- Why are clinical trials important?
- When should we choose to conduct a clinical trial?
- Why are clinical trials often considered the ‘gold standard’ of epidemiologic study designs?

Study Designs

There are only two major types of designs for clinical trials. These are the Parallel design and the Crossover design.

Parallel Design

- In a parallel design, a participant is assigned to receive only one of the study treatment-regimens.
- The term comes from a flow chart in which the different treatment groups are denoted by parallel lines.
- The term "treatment group" refers to the group of patients all assigned to the same treatment.

Parallel Design

- Studies with two treatment groups, active treatment and placebo, are most common. Studies with three treatment groups, often consisting of a new treatment, a placebo and a standard treatment ("active control") are also common.
- Example: Fred, Brian and Dawn receive our wonder drug. Chris, Jill and Julie receive placebo.
**Crossover Design**

- Definition: In a crossover design, a volunteer or patient receives two or more of the treatments being compared in random order.
- A cross-over design can be complete meaning each volunteer/patient receives all study treatments, or incomplete, meaning each volunteer/patient receives a subset of all treatments.

**Crossover: Period**

- The term "period," (meaning time-period) is used in conjunction with crossover designs. A "two period crossover" design means that each patient takes two treatments (for example active and placebo) in randomly assigned order. A three period crossover design means that each patient takes three treatments in randomly assigned order, etc.

**Crossover Washout**

- There is a washout (drug-free) period between treatment periods. Thus if a volunteer is supposed to take a drug for three weeks, a two period cross-over would be seven or eight weeks long: three weeks for treatment 1; one or two weeks washout and three weeks for treatment 2.

**Crossover Example**

- Example: Fred, Brian and Dawn receive our wonder drug, followed in one week by placebo. Chris, Jill and Julie receive placebo followed in one week by our wonder drug.

**Summary – consolidate your understanding: Strengths of the RCT**

- Control for confounding is inherent in the design. For something to be a confounder, it must be associated with both the exposure and the outcome. In an RCT, nothing is associated with the exposure, because the exposure was assigned randomly.
- Provides strongest evidence for causality in terms of clear temporality and control for unknown confounders. No longer can the statistician or anyone else tell you that "predisposition to the disease caused the exposure," because you know what caused the exposure: You did.

**Limitations are Obvious**

- Generally can't be done. People are usually already exposed & unexposed. Applicability is limited (artificial settings)
- Expensive and time consuming
- All of the extra benefits only hold for the exposure you randomized on. For other exposures you may be interested in, after the fact, consider it to be a cohort study.
- Sometimes you can randomize, but can't blind. Patient expectations are powerful. If you randomize and don't blind, patient expectations may be a powerful confounder, and you've lost the benefit of randomizing.
- Bias: non-compliance, withdrawals after randomization, attrition/losses to follow up, ineligible patients enrolled, misclassification of outcome.
- Limited external validity: volunteers, eligibility criteria.
Example of an Unblinded Catastrophe

- MRFIT. Multiple risk factor intervention trial (1975).
- In MRFIT, one group was randomized to quit smoking, exercise and go on a low fat diet. The other group was randomized to a control group which was supposed to stay the same.

Problem: the control group also quit smoking, exercised, and went on a low-fat diet.

Next up: Community Trials

- Entire "community blocks" are randomized to receive an intervention… or not.
  - Community blocks can be:
    - Cities
    - Townships
    - Villages
    - Counties
    - States
    - School districts
    - Classrooms
    - Occupational groups
    - Hospitals
    - Nursing homes

- Distinguish from large clinical trials with the word "Community" in the name

An experiment where the unit of analysis are entire communities of group of people

Community Trials

- Two major objectives:
  - Test etiologic hypotheses (health-related exposures and outcomes)
  - Evaluate impact of health-related programs, projects or campaigns.

First type: true epidemiologic study
Second: evaluation study that uses epidemiologic methods

Community Trials

- Study protocol
  - Developing a research hypothesis
  - Selecting communities
  - Collecting baseline data on outcomes
  - Allocating communities
    - Experimental group
    - Control group
  - Applying the intervention
  - Assessing outcomes

- Selection of experimental and control communities
  - Communities should be similar (confounders: age, race, gender, income, pop. size, access to health or PH care)
    - Relatively stable populations
  - Willingness of the communities to participate (think about the logistic: authorities, leaders, members, media)
  - Sufficient evidence that the communities are experiencing high enough levels of the study exposures and outcomes to:
    - Justify the experiment
    - Allow the investigator to detect significant changes over time
  - Sample size to ensure sufficient power

RCT may have problems with generalizability

- Selection of patients and lack of generalizability are commonly cited problems with RCT's.
- Investigators often choose the rare patients that
  - (1) have the disease under study and no other ailments and
  - (2) have a high likelihood of compliance and
  - (3) agree to participate.
Community Trials

- Strengths and Weaknesses
  - Strengths over RCTs:
    - Prevent more cases than could be achieved targeting only individuals
    - Outcome influenced by social context (better response by community)
    - Less costly than a clinical intervention (public service announcements of risk factors for HIV than treatment in a large population).
  - Weaknesses:
    - Changes on outcomes may be due to causes other than intervention
    - Depending on type of intervention expensive and time consuming
    - Randomization not always be feasible
    - Possibility of committing an ecological fallacy (drawing inferences about i____ based on c_______ may be incorrect since associations are based on aggregate data).

Stages

- Stage 1. Three sets of 1st grade class rooms
  - Test an intervention to address aggressive behavior and
  - Test an intervention to address poor reading skills
  - Controls

- Stage 2. Test synergism between the two interventions: Does intervention for aggressive behavior help reading skills and vice-versa? Class-rooms with both interventions, class-rooms with behavioral intervention, class-rooms with reading intervention, class-rooms with neither

- Stage 3. Fine tune/practice

Community Trial Example

- The Center for Integrating Education and Prevention Research in Schools (ongoing)
  - Three stage trial in 1st grade school children
  - 20 schools participated. Each school has multiple 1st grade classrooms.

Community Trials, more examples

- Examples of two communities studies:
  - Newburgh-Kingston study-NY,1944 (epi study; adding ?; 10 years; 58% reduction of ?)
  - Pawtucket Heart Health Program-Rhode Island (evaluation study; educational, screening and counseling approach)
  - North Karelia Project-Finland (evaluation study; educational and screening approach)

- Example of multiple communities:
  - Communities Mobilizing for Change on Alcohol study (? communities; multiple interventions, educational approach)

Summary: Know these terms

- Clinical Trial
  - Keywords
    - Randomized
    - Placebo Controlled
    - Blinded
  - Clinical Trial Designs
    - Parallel
    - Crossover (periods, washout)
    - Strengths and weaknesses
    - Community trial definition

Learning Activity

- What are some of the advantages and disadvantages of these experimental designs?
- What are the ethical issues when conducting clinical trials?
- Why is IRB approval and study monitoring important?
Articulate Quizmaker Quiz Placeholder - review2_lecture9