Video 04 - Design of randomized studies

Steve Simon

Learning objectives

1. To define what a randomized study is and explain its advantages and disadvantages.
2. To describe how blinding, concealed allocation, and intention to treat analysis can improve the persuasiveness of a randomized trial.

Required reading

1. Chapter 5.

Recommended readings. Most of these are short and/or easy to skim. See the discussion section for assignments associated with these readings.

1. Richard Feinman. Intention-to-treat. What is the question?. Nutrition & Metabolism. 2009;6(1):1. Available in html format and PDF format.

…

Cameron and Pauling study of Vitamin C.

- Linus Pauling
  - Two-time Nobel prize winner (Chemisty, Peace)
  - Fervent advocate of mega-doses of Vitamin C
- Non-randomized study of cancer
  - All patients got Vitamin C
  - Ten controls per treated patient
- References
  - Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A. 1976 Oct;73(10):3685-9. PubMed PMID: 1068480; PubMed Central PMCID: PMC431183.

Birth control pills and cervical cancer

- Three groups of women
  - Oral contraceptives
  - Other forms of birth control
  - No birth control
- Differences in these three groups
  - Age at first intercourse
  - Number of secual partners
  - Use of tobacco, alcohol, other drugs
- Most importantly, number of pap smears
  - Oral contraceptives require regular doctor visits

Experimental versus observational

- Experimental: Active independent variable
- Observational: Attribute independent variable
- Who does the choosing?
  - Patients or doctors? = Observational
  - Researcher? = Experimental
- Patients in a randomized trial are giving you a gift.

Randomized versus quasi-experimental

- Quasi-experimental
  - Logistics prevent randomization
  - Very common in Quality Improvement

How to randomize

- Use of a random device
  - Physical devices (flip of a coin, balls in an urn)
  - Computer generated random numbers
- Avoid haphazard approaches
- Avoid alternating assignment
- Remember the law of large numbers

A fishy research story (part 1 of 7)

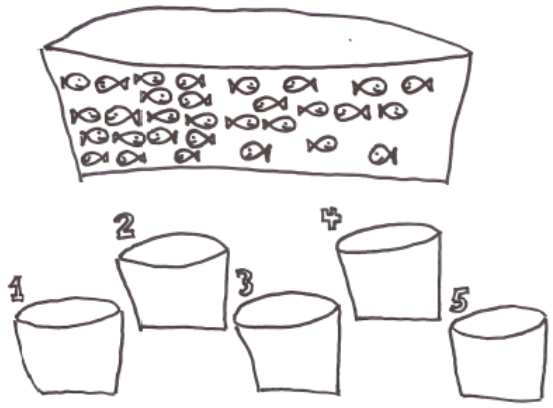

Figure 1. Thirty fish in a big tank

A fishy research story (part 2 of 7)

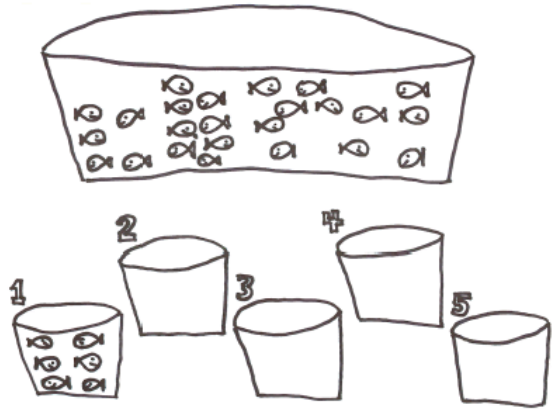

Figure 2. First six fish go in the first tank

A fishy research story (part 3 of 7)

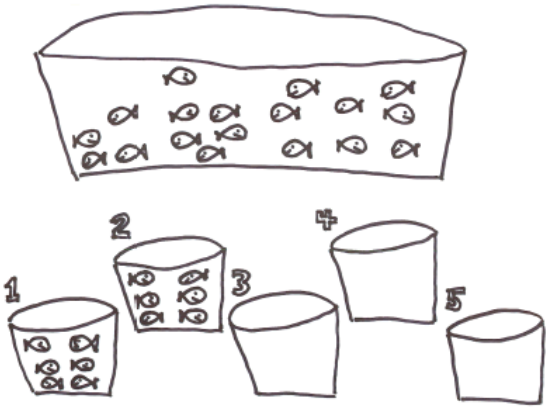

Figure 3. Next six fish go in the second tank

A fishy research story (part 4 of 7)

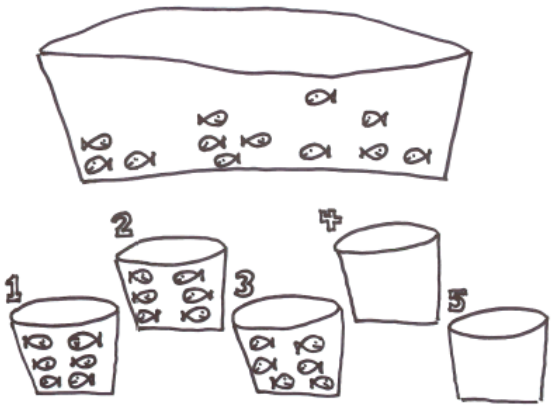

Figure 4. Next six fish go in the third tank

A fishy research story (part 5 of 7)

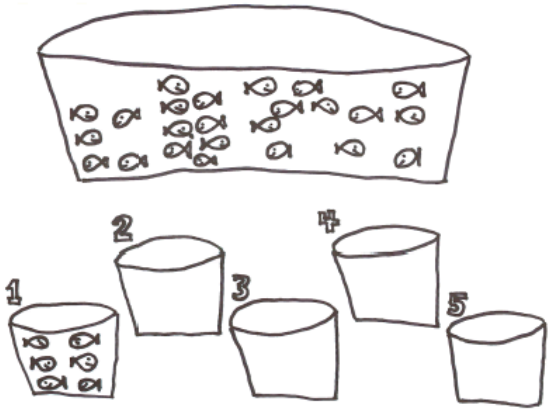

Figure 3. Next six fish go in the fourth tank

A fishy research story (part 6 of 7)

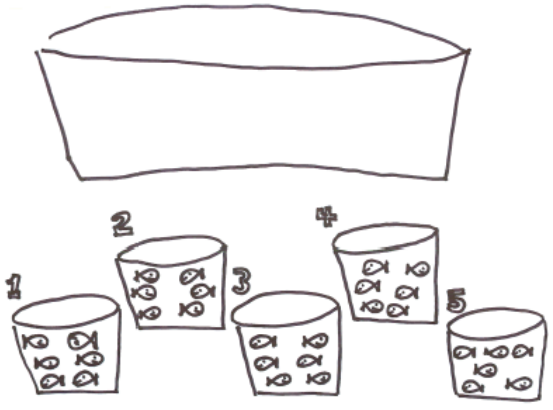

Figure 6. Last six fish go in the fifth tank

A fishy research story (part 7 of 7)

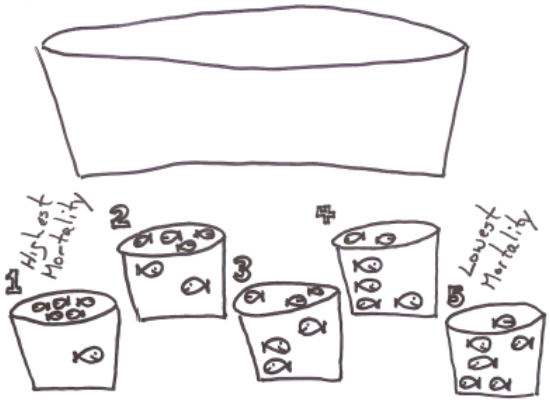

Figure 7. Final result-mortality hishest in first tank

Advantages of randomization

- Insures covariate balance
  - Smoking during pregnancy and Down's syndrome
- Difficult or impossible to measure covariates
  - Severity of illness
  - Co-medications
  - co-morbidities
  - Patient's psychological state
- Avoids selection bias

Disadvantages of randomization

- Expensive
- Artificial
  - Extra tests, extra attention
  - Explicit acknowledgement of uncertainty

When can't you randomize

- Unethical
  - Lack of equipoise
  - Harmful exposures
- Impractical
  - Too many patients
  - Too much time
  - Strong patient preferences
- Impossible
  - Attribute variables
  - Retrospective studies

Some alternatives

- Wait list control groups
- Intensive versus standard advice
- Randomly assign from a different end
- Early stopping

Blinding/partial blinding. Who knew what when?

- Hiding information (not deception)
- Not always possible (bilateral orchiectomy)

Types of blinding

- Double blind
  - Physician and patient blinded
- Single blind
  - Patient only
- Partial blind
  - Evaluators blinded

Hawthorne effect

- Series of studies at a GE factory.
  - Any change, no matter what, improved productivity
  - Positive response to attention.

Ascertainment bias

- The tendency to self deception.
  - "Linus Pauling actively promoted the use of massive doses of vitamin C during the last few decades of his life. He believed it could cure just about anything from the common cold to cancer. During one interview he explained that after he and his family started taking Vitamin C supplements, they never had colds. The interviewer was a bit surprised probed a bit further 'No colds? Ever?' Linus Pauling responded, 'Oh just an occasional sniffle.'"
- Steve Simon. StATS: Quantifying the ability of dreams to predict the future (April 10, 2007). Available in html format.

Confusion about the placebo effect

- Natural course of a disease
  - "If a doctor treats your cold, it will go away in fourteen days. If you leave it alone, it will go away in two weeks." Gloria Silverstein.
  - "The art of medicine consists in amusing the patient while nature affects the cure." Voltaire
- Regression to the mean
  - You're never as good as you think you are on your good days and you're never as bad as you think you are on your bad days.
- Hróbjartsson and Gøtzsche study of placebo effect

Subversion of the randomization process

- Physician subversion
  - Waiting until the right number pops up
  - Biased implementation of exclusion criteria
  - Not a problem in single investigator trials
- Hiding the randomization list.
  - Sealed envelopes
  - 800 number
- Patient subversion of the randomization process
  - Early anti-retroviral trials for AIDS

Problems with randomized trials

- Volunteer bias.
  - Willingness to endure painful procedures
- Professional volunteers
- Strong personal preferences
  - Birth control methods
  - Surgical versus non-surgical trials
  - Less invasive surgery

Intention to treat analysis

- Controversial
- Analyze in groups originally randomized to
  - Maintains benefit of randomization
  - Measures practical impact of treatment
- Alternative: per protocol analysis

Baseline measurements

- Not an absolute requirement
- Reduces variance
- Allows quality checks
  - Subversion of randomization
  - Differential dropout
- Several competing analysis strategies

Assignment

1. No homework this week, other than the discussion board. You will need to have a research question/hypothesis and a literature review completed by the end of the seventh week of class (Friday, March 08, 2019).

Discussion questions

1. Take one of the recommended readings and provide a brief summary (three or four sentences).

Extra credit. There are many peer-reviewed articles about issues and controversies associated with randomized trials. Find one (other than the ones listed under recommended reading this week) and share it with a brief summary. If the full free text is available, include a link. If not, please attach a PDF file.