Experimental Design

Corinne Riddell (Instructor: Alan Hubbard)

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Learning objectives for today

- Introduce terminology related to experiments
- Learn best practices for experimental designs, including randomized controlled trials, and why these practices reduce bias
- Discuss historical atrocities committed against marginalized racial and ethnic groups and how these atrocities affect regulations governing human experimentation today

Experimental Units

- Who is the treatment being applied to? Treatments can be assigned to individual people or to larger groups
- When individuals are the experimental unit, we call them participants, patients, or subjects
- Larger experimental units include hospitals, states, communities, schools, etc.
- In R, we often have one row of data for each experimental unit
- If you had multiple measurements per unit (say multiple hospital visits to each patient, or a row of data for each state-year), then you'd have multiple rows per experimental units in a "long" dataset (*shout-out for longitudinal data analysis*)

Randomization

- When the experimental unit is a person, they are **randomly assigned** to different levels of treatment
- In a lab setting, the experimental units themselves (like a mouse) are designed to be identical as possible
- The result of both (randomization and making the units as similar as possible) is to reduce the chance for confounding – or the chance that a unit's treatment is associated with another variable that affects their chance of experiencing the outcome.

Factor and treatment

- **Factor**: An explanatory variable that is being manipulated. There can be more than 1 factor variable being manipulated at once.
- **Treatment**: A specific experimental condition. When there is more than 1 factor, then the treatment is a combination of specific values of each factor.
- Factors and treatments are categorical variables. In R, we often refer to both of these variable types as Factors. Confusing, I know.

Example with two factors (Ex 8.2 pg 178 from Ed. 3)

- **Photoperiod** is the relative lengths of light and dark periods in a 24-hour cycle is a common environmental cue for flowering
- **Light wavelength** is also hypothesized to affect the flowering of Chrysanthemum flowers
- A plant physiologist grew chrysanthemums in **controlled** greenhouses under different combinations of photoperiods (short day, long day, continuous light, and interrupted night) and light wavelengths (blue light, red light, or blue + red light)
- The plants were kept in these conditions for 5 weeks and examined regularly to assess whether they had flowered

Check your understanding

- Who (or what) is the experimental unit in this study?
- What is the response variable?
- How many factors are there?
- How many levels does each factor have?
- How many treatment groups are there?

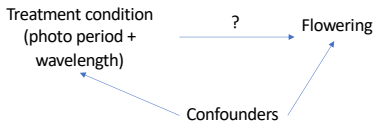
Example with two factors (Ex 8.2 pg 178 from Ed. 3)

- Is it better to assign one flower to each treatment group or multiple flower per treatment group?
  - What is a risk with assigning one flower per group?
  - What is a benefit of assigning one flower per group?
- More is often better → principle of **replication**

Benefits of experimental design

- When individuals are randomized to exposure conditions, you can avoid the issue of **confounding** (or "**lurking variables**")

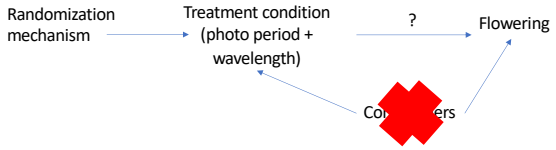
With **observational** data, there is often a risk of confounders that make the comparison across treatment conditions "unfair":



Benefits of experimental design

- When individuals are randomized to exposure conditions, you can avoid the issue of **confounding** (or "**lurking variables**")

With **experimental** data, the only thing that should affect whether a flower is treated is the randomization mechanism. Not other variables that increase/decrease the chance of flowering are also associated with the treatment the flower received



Benefits of experimental design

- When individuals are randomized to exposure conditions, you can avoid the issue of **confounding** (or "lurking variables")
- The environment can be tightly **controlled** so that everything is exactly the same except for the treatment applied
- Every experiment involves **comparison** between treatment groups – this allows you to see the effect of a treatment condition on an outcome vs. what would have occurred under another treatment condition

Uncontrolled experiments

- Uncontrolled experiments are a bad idea! They do not have a comparison group, but involve researchers still exposing experimental units to a treatment
- Suppose there is a vaccine trial where 50,000 people receive the vaccine. Suppose 0.1% of the study participants had an adverse outcome. Does this imply the vaccine is harmful? Why or why not?

Randomized controlled trial (RCT)

- Also called a randomized clinical trial
- Involve the randomization of study participation to at least two experimental conditions, these conditions are often called **study arms**
- If possible, both the individuals and the clinicians are **blinded** to the randomization; they don't know who is receiving the treatment and who is receiving the placebo

Randomized controlled trial (RCT)

- Oftentimes, the researchers are comparing a new medicine to what has been previously shown to best reduce the chance of the outcome of interest
- If no current treatment is available the researchers could compare the new treatment to a placebo treatment
- **Placebo:** An inactive treatment meant to mimic the look or feel of the treatment being tested in an RCT but that has no active ingredients
  - Examples: Sugar pill, saline injection
  - Can you think of an example of when a placebo treatment is hard to create?

Placebo effect

- The placebo effect is the measured effect on the outcome in the placebo "arm" of the RCT
- Placebo effects may be positive, such that individuals feel like they're getting better under the treatment and report less pain, improved well-being, better sleep, less anxiety, etc.
- Placebo effect may also be negative, and individuals might report more headaches, nausea, constipation, etc.

Research Ethics

In which of these cases can you do an experiment on humans?

- Is it ethical to randomize individuals to exposure to an incurable infectious diseases?
- Is it ethical to randomize individuals to exposure to lack of sleep?
- Is it ethical to randomize individuals to different levels of socio-economic status?
- Is it ethical to randomize fetuses to different levels of maternal alcohol or smoking exposure?

Tuskegee syphilis study

- From 1932 to 1972, several hundred black men were observed for the "natural progression" of syphilis in Tuskegee, Alabama.
- The men were told they were being treated, when they were not, and effective treatment was never provided
- In 1945 Penicillin was the treatment of choice for syphilis and very effective, but was not given to the men
- The study was planned to go on for 6 months but lasted 40 years and only ended when news articles were published that condemned the study.

More information: https://www.cdc.gov/tuskegee/timeline.htm

Similar to the US Public Health Service Syphilis Study at Tuskeegee (3) – which, in 1932, set out with the "best of intentions" to learn about the natural history of syphilis among black men in hopes of justifying a treatment program for them – Canadian researchers used Aboriginal children in residential schools to learn about malnutrition.

From https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3941673/pdf/pch19064.pdf

Major issues with the Tuskegee syphilis study

- **No informed consent**: The men were told they were being treated when they were not
- **Effective treatment was withheld**: A treatment existed during the study (penicillin) but was not offered to the men in the study
- **Underlying racism:** Why was the study performed only on Black men in the first place? Would this study had been performed on White men?

Background: Residential Schools in Canada for Indigenous children

- Approximately 1879-1979
- Over 150,000 children attended the schools
  - 80,000 still alive today
  - 6,000 estimated deaths during attendance by the Truth and Reconciliation Commission (TRC)
- Children could not speak their native languages or acknowledge their cultures
- Systemic physical, psychological, and sexual abuse
- Early mortality of 30-60% within 5 years of entry, as estimated by the Chief medical officer in 1909
- The TRC says 1 in 25 children died in these schools during all time
- Rates of TB very high. At one school, 50% of children had TB in early operation.

Residential Schools in Canada for Indigenous children

- Nutritional experiments were performed on the children
- One account of experiments between 1942 and 1952 led by the Department of Indian Affairs of Canada under two physicians, one a famed nutritionist and former president of the Canadian Pediatric Society
- Control and treatment groups of malnourished children were denied adequate nutrition
- The treatments provided were themselves inadequate and sometimes harmful and likely contributed to more death
- "…efforts were made to control as many factors as possible, even when they harmed the research subjects…dental care was denied…researchers wanted to observe the state of dental caries and gingivitis with malnutrition."

Major issues

- **No informed consent:** Who can give consent when the individuals are children? Here, the parents were not informed
- **Effective treatment was withheld:** All children in this study were undernourished and were denied other forms of healthcare (eg, dentistry)
- **Underlying cultural genocide:** The Truth and Reconciliation committee deemed the compulsory mandatory schooling of Indigenous children cultural genocide.

MacDonald NE, Stanwick R, Lynk A. Canada's shameful history of nutrition research on residential school children: the need for strong medical ethics in Aboriginal health research.

Nuremberg Code drafted in 1947

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

The **Nuremberg Code** aimed to protect human subjects from enduring the kind of cruelty and exploitation the prisoners endured at concentration camps

Nuremberg Code drafted in 1947

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

Nuremberg Code drafted in 1947

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Code of Federal Regulations

- The Nuremberg Code is the basis for Title 45 and 46 in the code of federal regulations.
- These regulations are used by institutional review boards. All studies of human subjects conducted in the United States must be approved by these review boards.

Data sovereignty

- The concept of data sovereignty "is linked with Indigenous peoples' right to maintain, control, protect and develop their cultural heritage, traditional knowledge and traditional cultural expressions, as well as their right to maintain, control, protect and develop their intellectual property over these".

The First Nations Indigenous Governance Centre. First Nations data sovereignty in Canada. Statistical Journal of the IAOS. 2019; 35:47-49.

Taylor J, Kukutai T, eds. Indigenous Data Sovereignty: Toward an Agenda. Centre for Aboriginal Economic Policy Research (CAEPR). Research Monograph No. 38. (Features a chapter, "Pathways to First Nations' data and information sovereignty", authored by FNIGC). Australian National University Press. 2016.

Saw-vern-tea!

Data sovereignty

1. Methods and approaches used to gather, analyze and share data on Indigenous communities has reinforced systemic oppression, barriers and unequal power relations.
2. Data on Indigenous communities has typically been collected and interpreted through a lens of inherent lack, with a focus on statistics that reflect disadvantage and negative stereotyping.
3. Data on Indigenous communities collected by nation state institutions has been of little use to Indigenous communities, further distancing Nations from the information.
4. Data on Indigenous communities collected by the nation state government has been assumed to be owned and therefore controlled by said government.
5. With a lack of a meaningful Nation-to-Nation dialogue about data sovereignty.

British Columbia First Nations' Data Governance Initiative (BCFNDGI). Decolonizing Data: Indigenous Data Sovereignty Primer. Prepared by Open North. April 2017.

Saw-vern-tea!

Clinical equipoise

- Requires general uncertainty in the medical (clinical) community if the newly proposed treatment will be beneficial
- The assumption that there is not one 'better' intervention present (for either the control or experimental group) during the design of a randomized controlled trial (RCT).
- What would happen if researchers enrolled participants in a study that compared the effect of Treatment A vs. Treatment B on mortality when there is moderate medical evidence that Treatment B is less effective or has many serious side effects?

https://ethics.gc.ca/eng/tcps2-eptc2_2018_chapter11-chapitre11.html#a (this is a Canadian reference, but is also required for trials in the United States)

Summary of lecture

- New terminology on experiments: experimental unit, factor, treatments, randomized controlled trials, blinding, placebo, placebo effects
- Research ethics
  - Fraught history of human experimentation
  - Today's regulation reflect this history, such as informed consent
  - Other issues like data sovereignty, clinical equipoise