

Experimental designs

Sources of Bias

Ethics

Ethical principles and
current regulations

Randomized designs, bias and ethics

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Learning objectives for today

Randomized
designs, bias and
ethics

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- ▶ Understanding different types of experimental designs
- ▶ Thinking about sources of bias
- ▶ Ethics in experimental studies

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Randomization indicates that the treatment(s)/exposure(s) of interest have been assigned randomly, or by chance alone. Why do we do this? What advantage does this have?

A very simple example of a randomized trial would be one in which:

- ▶ the units of randomization are nearly identical
- ▶ only one treatment/exposure group and one control group
- ▶ simple randomization
- ▶ effects are immediate or in the short term

Level of randomization

When we are assigning an exposure/treatment we can do this for different levels (think about our units of analysis).

These could be:

- ▶ Individuals
- ▶ Households
- ▶ Groups
- ▶ clinics

If we think about our resulting data, each of these might be a row in our data frame.

What are some examples of exposures we might randomize at these different levels?

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Uncontrolled trials

Imagine that we had a vaccine trial where we recruited 50,000 individuals who received a vaccine. Suppose that 0.1% of our participants experienced an adverse event in the 3 weeks following vaccination. Does this give us evidence that the vaccine is harmful? Why or why not?

Comparison group

In every calculation of measure of effect, we must choose a comparison group. Under the best of circumstances this group would be a “counterfactual” meaning that they would represent the experience that the treated group would have had, if they had an alternate exposure (had not been treated).

Control group

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Usually in a trial, we recruit our participants and randomize them to either an intervention or a “control” condition.

Blinding

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When we talk about blinding we are talking about keeping the treatment assignment hidden. There are multiple groups we might want to consider keeping this knowledge from.

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- ▶ In a single blind trial it is usually the participants who are blinded
- ▶ In a double blind trial we are generally talking about blinding of the participants and the people doing the assessment of outcomes
- ▶ Triple blinding is often referring to blinding the participants, study staff, and also the investigators and statistical analysts.

Why do you think blinding is important?

Why might we have a trial where we do not blind?



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A placebo is a non-active substitute for treatment. In a drug trial, the placebo is usually a pill made to look identical to the medication being tested, but that does not have the active ingredient.

What is the placebo effect?

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- ▶ from New York Times Magazine, November 2018:



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Sampling bias

If our sampling frame does not cover our target population, this is a bias in the sampling process.

Your book refers to this as under-coverage bias.

What might be an example of this?

Small size

As we saw previously in our example of online reviews, small samples often give unpredictable results. The smaller an effect is, or the more rare the conditions you are studying, the larger the sample needs to be in order to draw conclusions.

We will talk much more about sample size later in the course.

Often trials are designed to find a **statistically significant** difference between treatment and control. This means an observed effect so large that it would rarely occur by chance.

As we move into the next sections we will talk more about probability and assessing the role of chance. In part III of the course we will talk more about statistical significance in assessing differences between groups.

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Participation

Once sampled an individual may not agree to participate.

This is referred to as **response bias** or **non-response**. If there is enough information about who did and did not respond, the data may be adjusted to try and compensate for this type of bias. This kind of adjustment is common in survey samples.

Participants may also start the study and then drop out or become **lost to follow up**. If one of your study groups is more likely to be lost this can create bias.

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When either the study participants randomized to control receive the medication or exposure that was intended to be given only to treatment arm participants.

Examples:

- ▶ MRFIT trial
- ▶ SHAZ!

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Once a participant is randomized to a given treatment, they do not always **adhere** to that treatment.

Often we do two types of analyses with trial data when there are issues of adherence.

Intention to treat and **Per protocol**

Errors associated with imperfect measurement including:

- ▶ imprecise measurement equipment
- ▶ poorly designed or worded questions
- ▶ responses of the individual to the measurement process
 - ▶ white coat hypertension
 - ▶ sleep studies in lab environments

Important to distinguish errors that are systematic

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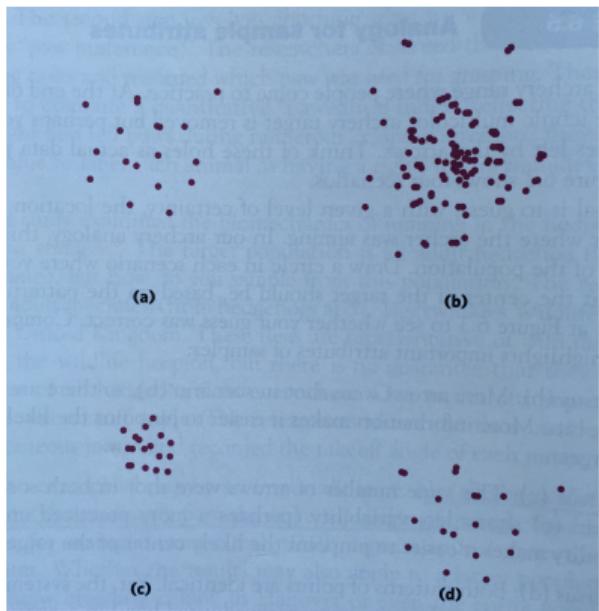
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The process of drawing conclusions about a population based on a sample

Where is the target?

- ▶ Four samples are shown. Imagine guessing the location of the center of the population from the center of the sample distribution



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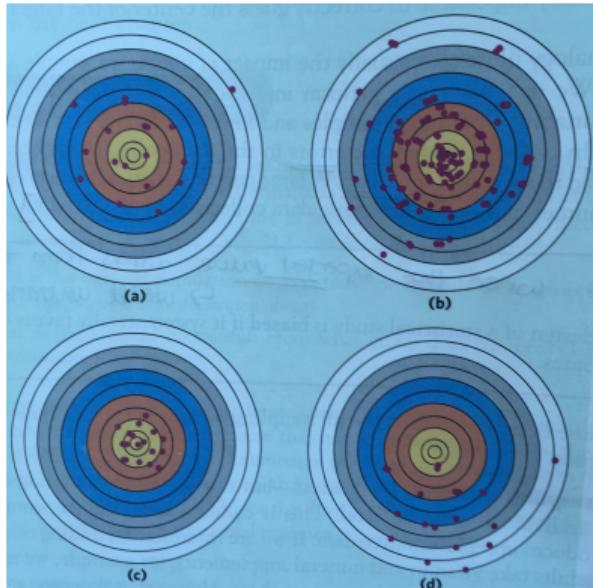
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Where is the target?

- ▶ The samples are now superimposed on archery targets representing the target population. Sample (d) in this analogy is a biased sample



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Where is the target?

Key takeaways from the previous figures:

1. A vs. B: More arrows make it easier to pinpoint the center of the target (assuming the archer has good aim)
2. A vs. C: Less variability makes it easier to pinpoint the center of the target
3. A vs. D: Systematic downward misses in scenario D bias our best guess of where the target is.

In real life we do not know where the target actually is, so we can't be sure whether our guesses are biased or not. But we can discuss the possibility of bias, and quantify how much bias would be required to negate a conclusion

Which of these is precise and which is accurate?

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Issues with self report

In addition to the biases that may come with the design of questions you ask a participant in surveys, there can be biases associated with willingness or ability to report information:

- ▶ social desirability biases
- ▶ poor recall
- ▶ biased recall
- ▶ diary compliance

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Ethical issues in trials

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While this is primarily a methods course, I feel it is important to highlight some of the ethical issues in study design.

This section of the lecture includes some examples of atrocities committed against marginalized groups. The goal is to provide some of the background context for regulations that now govern experimental trials.

If you need to step away from the lecture please do so.

Tuskegee syphilis study

Famous example of an unethical trial is the Tuskegee syphilis study which started in 1932 and ended in 1972. Several hundred black men were observed for the “natural progression” of syphilis in Tuskegee, Alabama.

The men were told that they were being treated, when they were not, and effective treatment was never provided.

Penicillin became the treatment of choice for syphilis in 1945. It was very effective, but was not given to the men in the study.

The original study was planned for 6 months, but instead lasted 40 years and only ended after news articles were published that condemned the study.

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There were many ethical issues with the Tuskegee study including

- ▶ Lack of informed consent
- ▶ Withholding of effective treatment (lack of equipoise)
- ▶ Underlying racism: why was this study performed only on Black men? Would this study have been performed in the same way if the participants had been White men?
- ▶ timeline of the study is here [CDC](#)

Nutritional experiments among residential schools for Indigenous children in Canada

- ▶ Approximately 1879-1979
- ▶ Over 150,000 children attended these schools
- ▶ Children forbidden to speak their native languages or acknowledge their cultures
- ▶ Nutritional experiments performed on the children
- ▶ Control and treatment groups of malnourished children were denied adequate nutrition
- ▶ Treatments provided were inadequate, sometimes harmful and likely contributed to deaths
- ▶ “... 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”

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Nutritional experiments among residential schools for Indigenous children in Canada

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- ▶ No informed consent: Who can give consent? Here the parents were not informed
- ▶ Effective treatment withheld
- ▶ Underlying cultural genocide: The Truth and Reconciliation Committee deemed the compulsory schooling of Indigenous children a 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.

Ethical principles and current regulations

Key influential documents

The *Nuremberg Code* - following the trials of Nazi doctors after World War II

The *Declaration of Helsinki* adopted for the first time in 1964.

The *Belmont Report* - published in 1978 following scandals in the 1970s.

Core principles

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The Belmont Report established three core principles of research:

- ▶ respect for persons
- ▶ beneficence
- ▶ justice

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1st principle of the Nuremberg code: voluntary consent of the individual is absolutely essential.

- ▶ what information is required for “informed” consent?
- ▶ who can provide informed consent?

Vaccine trials in institutionalized children

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In the 1960s many vaccines against childhood illnesses were developed. Including the mumps vaccine. Like many other vaccines and medications of that time period, the mumps vaccine was initially tested in children with intellectual disabilities who lived in group homes. The rationale for this was that given the poor hygiene and cramped quarters in the group homes, they were at much higher risk of infectious disease.

Vaccine trials in institutionalized children

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What issues does this raise given the ethical principles we have discussed?

When is it ethical to randomize an exposure?

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Is it ethical to randomize individuals to lack of sleep?

Is it ethical to randomize individuals to be exposed to an infectious disease?

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Equipoise in the context of trials

Unethical not to give a treatment or exposure condition that is known to be better.

If the incentives to join a study are too strong, participants may be willing to consent (even with informed consent) to conditions they would not otherwise accept.

- ▶ Large payments
- ▶ Access to treatment not otherwise available
- ▶ Fear of losing medical care

Who benefits from the study, who is included

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There is also a larger issue of justice and ethics related to who benefits from the trial.

- ▶ Is there a direct benefit to participants?
- ▶ Is there a potential benefit to individuals who are similar to the study participants?
- ▶ Is there a group that is excluded from participation unfairly?

Who owns the data?

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.

Data sovereignty

- ▶ Methods and approaches used to gather, analyze and share data on Indigenous communities has reinforced systemic oppression, barriers and unequal power relations.
- ▶ 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.
- ▶ Data on Indigenous communities collected by nation state institutions has been of little use to Indigenous communities, further distancing Nations from the information.
- ▶ Data on Indigenous communities collected by the nation state government has been assumed to be owned and therefore controlled by said government.
- ▶ 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

Parting humor

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**"Miss Peterson, may I go home? I can't assimilate
any more data today."**

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