Study design

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Sampling in the ideal world

- In an ideal world,
  - We have a list of everyone in the population of interest
  - We randomly sample these people
  - It is equally costly to sample one person as it is another
  - No one ever refuses to be sampled

Sampling in the real world

- In the real world, all of these assumptions may fail:
  - We have to get access to people somehow in order to sample them
  - It is often more cost effective to sample certain groups of people than other groups of people
  - Not all people are equally likely to participate in your study
- All of these factors may create bias

Example: The 1936 Presidential Election

- In 1936, Franklin Delano Roosevelt was completing his first term of office as president of the United States, and was up for re-election
- The Republican candidate that year was Alfred Landon
- The country was still in the Great Depression, with 9 million unemployed and real income only two-thirds of what it was in 1929
- Roosevelt and Landon had different views about how active the government should be in terms of enacting policies to bring the country out of the depression

Example: The 1936 Presidential Election (cont'd)

- The *Literary Digest* magazine had predicted the winner in every presidential election since 1916
- For the 1936 election, the *Digest* sampled 2.4 million people and predicted a landslide victory for Landon: 57% to 43%
- In the actual election, Roosevelt won 62% to 38%

What went wrong?

- How could this poll have been so incredibly far off?
- The poll had an enormous sample size; variability of the estimate is not the issue
- Instead, the flaw was bias

Where the bias came from, Part I

- The *Digest* mailed 10 million questionnaires to addresses gathered from telephone books and club membership lists
- This tended to screen out the poor, who were less likely to belong to clubs or to own telephones (at the time, only one out of every four households owned a telephone)
- This is called *selection bias*: instead of random sampling, certain subgroups of the population were more likely to be included than others

Where the bias came from, Part II

- The *Digest*'s poll contained another flaw: only 2.4 million people replied, out of the 10 million who got the questionnaire
- Nonresponders can differ from responders in many important ways
- This type of bias is called *nonresponse bias*
- Thus, the 2.4 million respondents in the *Digest*'s poll do not even represent the 10 million people who were polled, let alone the entire population of voters

Pharmaceutical trials and children

- Sample estimates only describe the population they are sampled from; attempts to generalize to other populations may be biased
- The issue of pharmaceutical trials and children is a biostatistical example of this last point
- For practical, ethical, and economic reasons, clinical trials usually involve only adults – children are excluded (only about 25% of drugs are subjected to pediatric studies)
- Physicians, however, are allowed to use any FDA-approved drug in any way that they think is beneficial, and aren't required to inform parents if the therapy hasn't been tested on children

Propofol

- For example, propofol is a sedative that has consistently proved safe in adults
- In 1992, after several children who received propofol in the ICU died, the British government recommended against using it on patients under 16
- In the U.S., however, propofol continued to be widely used
- In 2001, the manufacturers of propofol conducted a randomized, controlled trial and found that 9.5% of children on propofol died, compared with 3.8% of children on a different sedative
- The FDA has now added a warning indicating this, although the administration of propofol to children in the ICU is still legal (and controversial)

The method of comparison

- Identifying patients to sample is not the only important question in study design, however
- Suppose a new therapy is developed; how should we design an experiment to test whether or not it is effective?
- The only meaningful way to do this is to compare it with something else
- Thus, we are going to have to obtain two samples (or one sample, then split it into two groups):
  - The therapy is given to subjects in the *treatment group*
  - The other subjects are not treated and are used as *controls*

Assigning treatment

- Subjects should be assigned to treatment or control *at random*
- Furthermore, the experiment should be *double blinded*:
  - The subjects should not know which group they are in
  - The doctors should not know which group the subjects are in

The U.S. polio epidemic

- A polio epidemic hit the United States in 1916
- During the next forty years, hundreds of thousands of people, especially children, fell victim to the disease
- By the 1950s, several vaccines had been developed
- One in particular, developed by Jonas Salk, seemed very promising based on laboratory studies

Field trials

- In 1954, the Public Health Service organized an experiment to see whether the Salk vaccine would protect children from polio outside the laboratory
- The subjects were children in the most vulnerable age groups: grades 1, 2, and 3
- Two million children were involved: some were vaccinated, some refused treatment, and some were deliberately left unvaccinated

Ethical issues

- This raises issues of medical ethics, which are always a consideration in medical studies
- Is it ethical to leave some children deliberately unvaccinated?
- Maybe a more ethical design would be to offer the vaccine to all children, and the children whose parents refused vaccination would serve as the controls

Confounding

- There is a big problem with the "ethical" design
- Higher-income parents are more likely to consent to treatment, and their children are more likely to suffer from polio
- The reason for this is that children from poorer backgrounds are more likely to contract mild cases of polio early in childhood, while still protected by antibodies from their mothers
- Thus, differences between treatment and control groups could be due to parental income, not the treatment
- Family background here is said to be a *confounding factor*; confounding is a major source of bias

Making treatment and control groups similar

- So, the "ethical" design isn't really all that ethical, in the sense that it won't correctly determine whether the vaccine works or not
- To avoid bias and confounding, it is important that the treatment and control groups be as similar as possible – except for the treatment
- It is necessary, then, that both treatment and control groups be chosen from the same population: children whose parents consented to treatment

Ethical issues, Part II

- This means that in order to truly learn whether the vaccine works or not, it is necessary to withhold the vaccine from consenting patients
- This certainly raises ethical considerations, but it is important to remember that when a new therapy first emerges, no one really knows whether or not its benefits will outweigh its risks
- This uncertainty is what justifies withholding treatment from the control group

How to choose who receives treatment?

- As we have said, it is important that the treatment and control groups be as similar as possible except for the treatment; but how should we decide which children go in which group?
- One approach would be to use human judgment to try to make the treatment and control group as similar as possible with respect to all the relevant variables
- Experience shows, however, that this is a bad idea
- Human judgments often result in substantial bias

Randomized controlled trials

- It is much better to use a carefully designed random procedure
- For the Salk vaccine trial, this is equivalent to flipping a coin: heads, the child gets the vaccine; tails, the child does not
- Experiments in which an impartial chance procedure determines whether a subject is placed into the treatment or control group are called *randomized controlled* experiments

Placebos

- Another basic precaution is the use of a *placebo*
- In the Salk vaccine trial, children in the control group were given an injection of salt dissolved in water
- Therefore, the children did not know whether they had received the treatment; this ensures that their response is due to the vaccine itself, not the idea of treatment
- This may not seem important, but the placebo effect can be surprisingly strong

Double-blinding

- To see whether or not polio was being prevented, physicians would have to determine whether or not the children had contracted polio
- Many forms of polio are hard to diagnose, and borderline cases could be influenced by a physician's knowledge of whether the child was vaccinated
- So, another precaution taken in the Salk vaccine trial is that the doctors were not told which group the child belonged to
- Thus, neither the subjects nor the doctors knew who was in the treatment group and who was in the control group
- The Salk vaccine trial was therefore a randomized controlled double-blind experiment
- This is pretty much the best design there is

The results of the trial

	Size of group	Polio cases per 100,000 children
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

Another design

- Randomized controlled double-blind experiments are now recognized to be the gold standard for experiments, but this was not the case in the 1950s
- There was a lot of disagreement over the best way to design this study
- In addition to the design we just talked about, a second design proposed by the National Foundation for Infantile Paralysis (NFIP) was carried out
- In the NFIP design, all second graders would be offered the vaccine, and children in grades 1 and 3 would serve as controls

Results of both trials

Randomized controlled double-blind experiment

	Size	Rate
Treatment	200,000	28
Control	200,000	71
No consent	350,000	46

NFIP study

	Size	Rate
Grade 2 (vaccine)	225,000	25
Grades 1 & 3 (control)	725,000	54
Grade 2 (no consent)	125,000	44

Conclusions

- We observed lower incidence of Polio in the vaccine group than the placebo group; what could be causing it?
  - Confounding? No
  - Perception bias? No
  - Diagnostic bias? No
  - Chance?
- The incidence of Polio could be lower in the vaccine group simply by random chance
- Next week, we will investigate whether or not this is a plausible explanation

Clofibrate

The Coronary Drug Project Research Group published an article in the *New England Journal of Medicine* (1980) describing a randomized controlled double-blind experiment involving the drug clofibrate, which reduces the level of cholesterol in the blood

	Clofibrate	
	Number	Deaths
Adherers	708	15%
Nonadherers	357	25%
Total	1,103	20%

Subjects who took more than 80% of their prescribed medicine were called "adherers"

Interpreting the clofibrate results

- This looks like strong evidence that clofibrate is effective, but caution is in order
- Subjects were randomized with respect to whether they received the drug; they were **not** randomized with respect to their adherence
- Thus, confounding is possible

Clofibrate and placebo results

	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Adherers	708	15%	1,813	15%
Nonadherers	357	25%	882	28%
Total	1,103	20%	2,789	21%

- Taking into account the placebo results as well, clofibrate no longer looks effective
- One possibility is that adherers are more concerned with their health, and take better care of themselves in general
- Take-home message: comparing subjects *as they were randomized* is the only completely valid way of carrying out a controlled experiment; all other comparisons are subject to confounding and bias

Portacaval shunts

- Patients with cirrhosis of the liver may start to hemorrhage and bleed to death
- One treatment involves surgery to redirect the flow of blood through what is called a *portacaval shunt*, a long and hazardous operation
- A bunch of studies were done in the 1950s and 1960s trying to determine whether the benefits of this surgery outweighed its risks

Portacaval shunt studies

	Degree of enthusiasm		
Design	Marked	Moderate	None
No controls	24	7	1
Controls, but not randomized	10	3	2
Randomized controlled	0	1	3

Conclusions

- The poorly designed studies greatly exaggerated the value of the surgery
- One possible explanation is that in an experiment without randomized controls, many physicians have a natural tendency to treat only the patients who are in relatively good shape
- This biases the study in favor of the treatment

Diethylstibesterol

- DES (Diethylstibesterol) is an artificial hormone used to prevent miscarriage in pregnant women
- Five studies of DES were carried out using "historical controls" (outcome rates of patients from the past); all had favorable conclusions regarding the value of the therapy
- Three randomized controlled designs were carried out, and all were negative about the value of DES
- Doctors paid attention to the positive studies and ignored the randomized controlled studies, giving the drug to 50,000 women each year throughout the 1960s
- This turned out to be a medical tragedy – DES has the disastrous side effect of causing cancer in female offspring; DES was banned in 1971

Summary

- Poor study design can bias results
- Samples are subject to selection bias and nonresponse bias
- Bias arises whenever the sample is not representative of the population
- Another source of bias is the perception of benefit from a treatment (placebo effect)
- Randomization is the only way to guarantee the similarity of the treatment and control groups
- Randomized controlled double-blind experiments reduce bias to a minimum, and that is why they are the most convincing study design
    - Sometimes, controlled randomized experiments are not possible/ethical and observational studies are necessary; we will discuss such studies in an upcoming lecture