

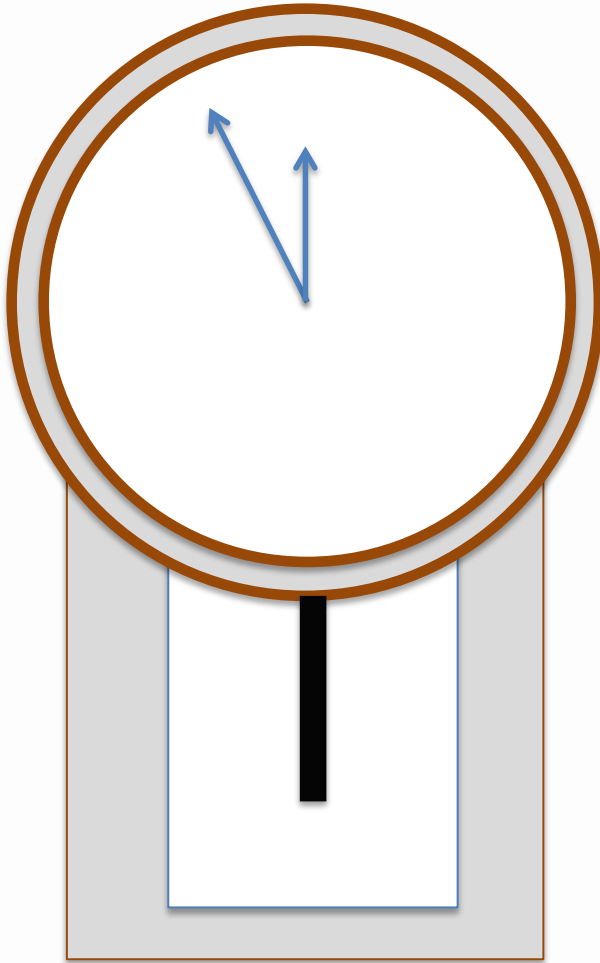
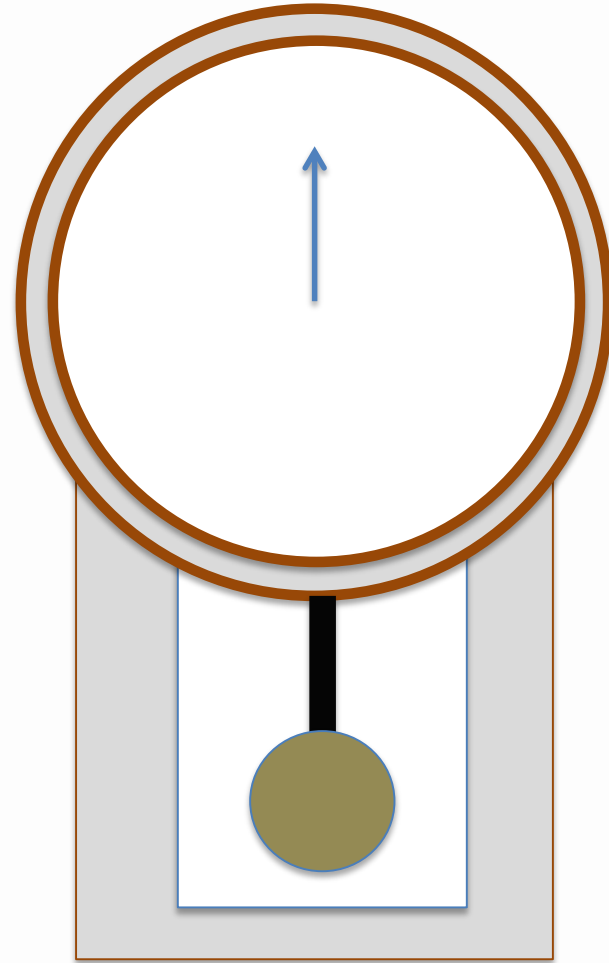
Randomized controlled trials

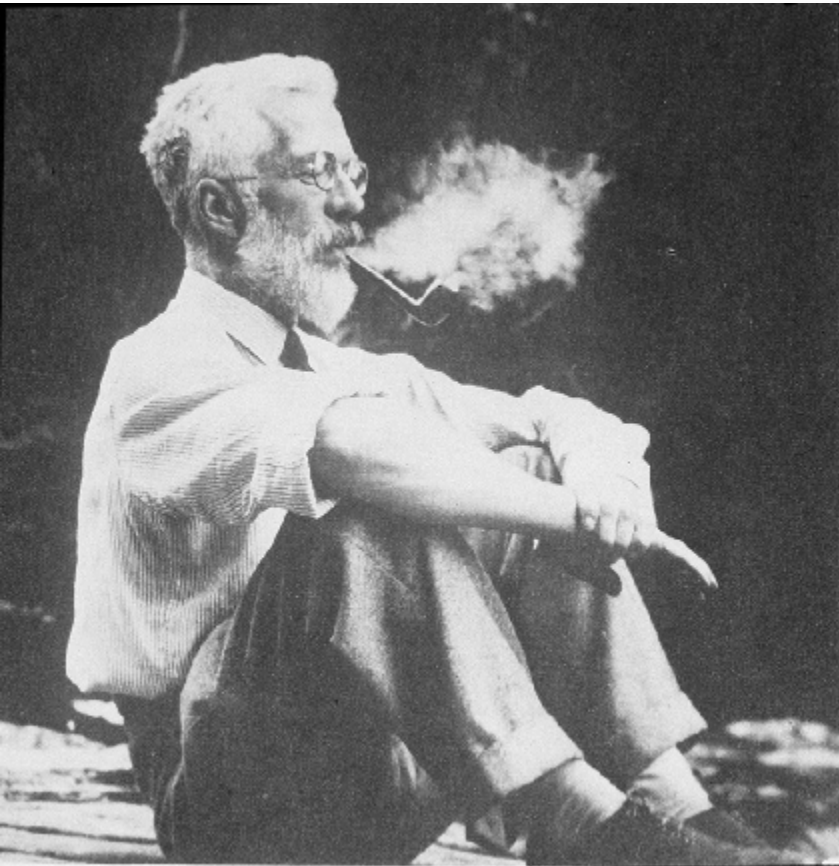
PH101

Spring quarter 2019

Lecture hall: PCB 1100

Causation

A**B**



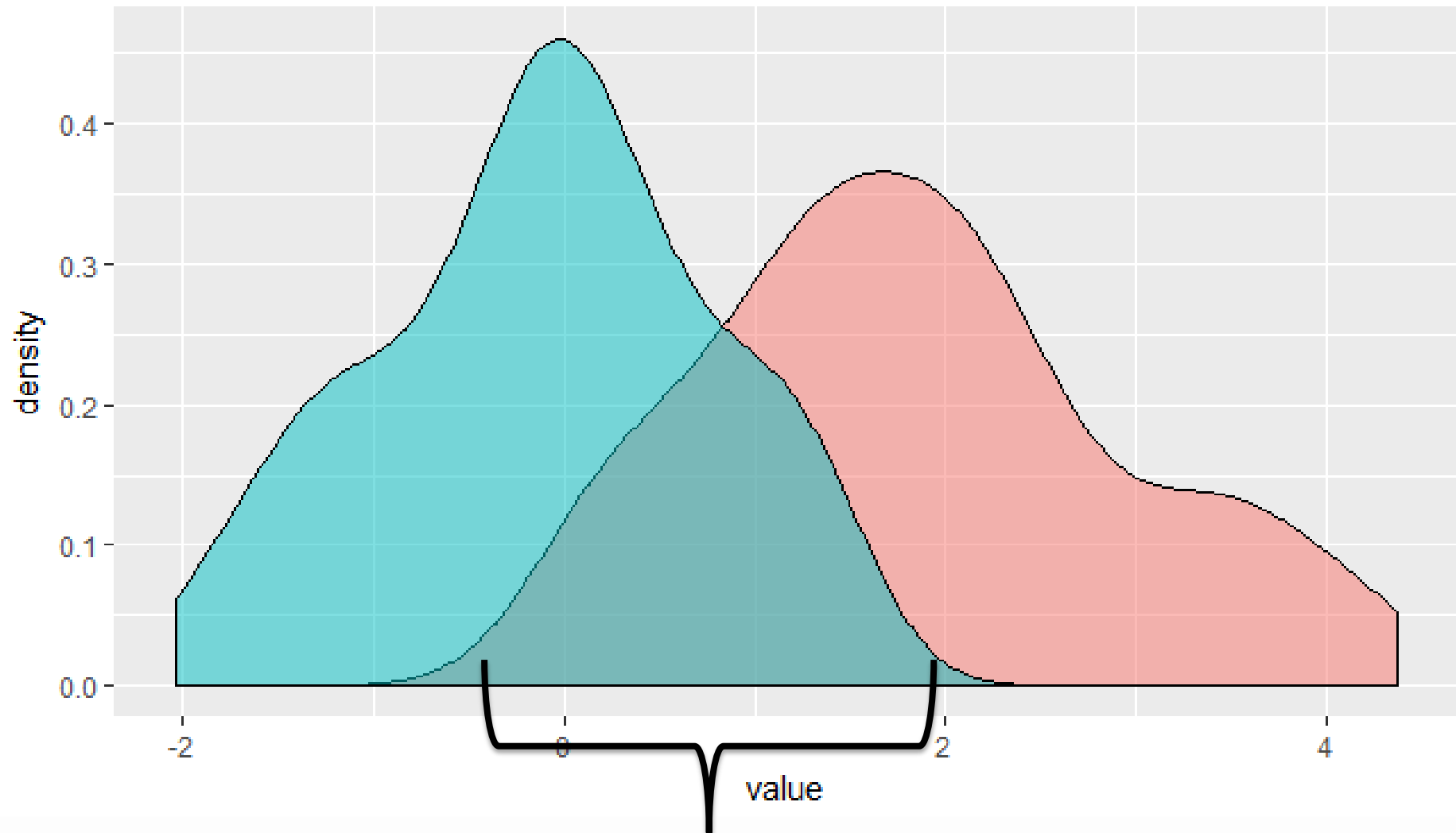
Ronald Fisher (1956)

$$H_0: \mu_1 = \mu_2$$

$$H_a: \mu_1 > \mu_2$$

$$H_a: \mu_1 < \mu_2$$

Is there a real difference between groups?



Study designs

- Observational
 - Researchers observe study subjects
 - Nothing is done to the subjects
- Experimental
 - Treatments are applied to some subjects

Study designs

- Observational
 - Cross sectional
 - Cohort
 - Case-control
- Experimental
 - Quasi-experimental
 - Randomized controlled trial

Observational designs

The six city study: Different cities, in very different environments and with different air qualities were chosen. A total of 8000 participants/subjects were followed over a period of 20 years. Air pollution measurements were predictive of shorter life spans.

Watertown, MA
Harriman, TN
St. Louis, MO

Steubenville, OH
Portage, WI
Topeka, KS

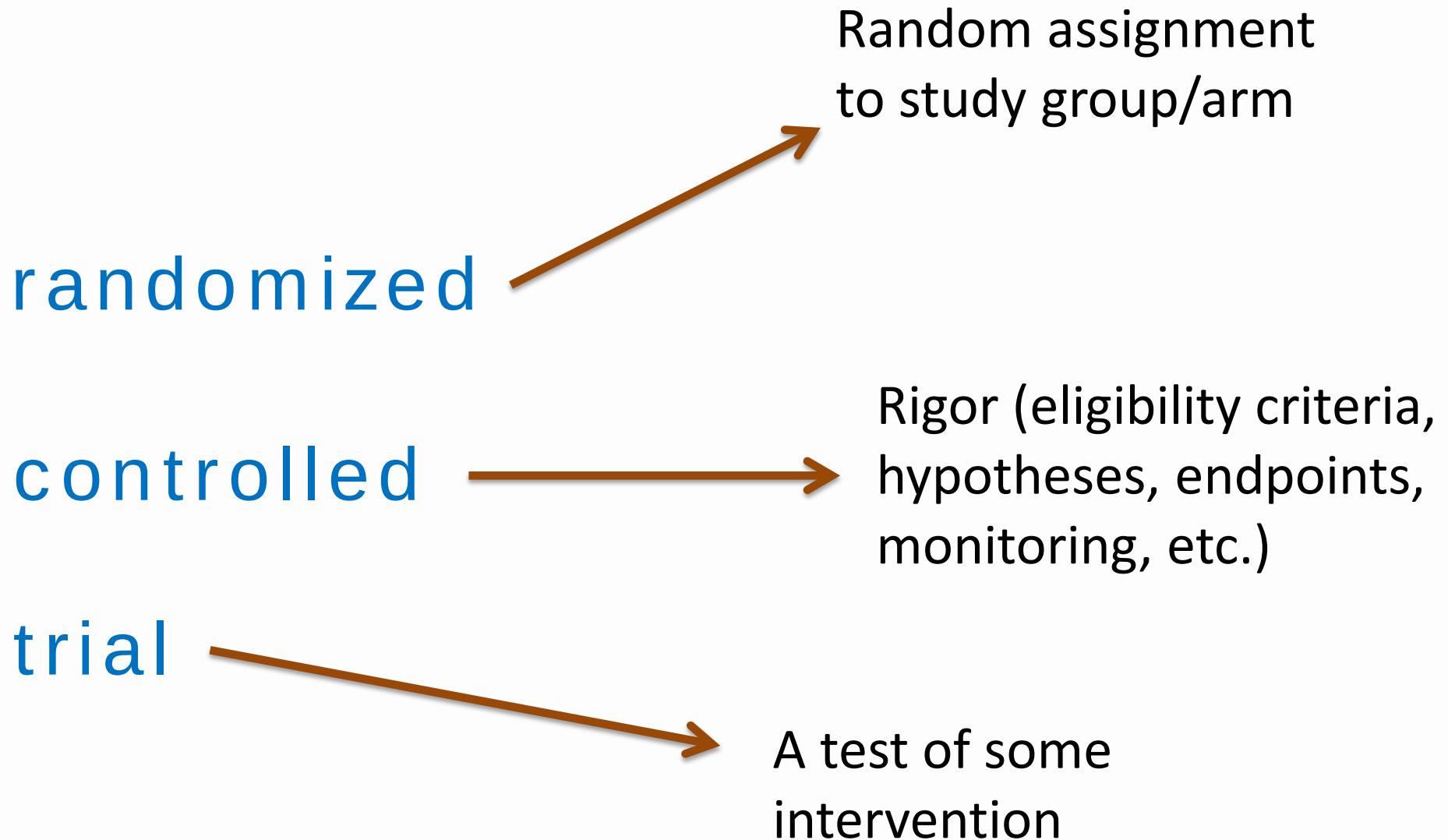
Experimental designs

50 cancer patients were recruited in a clinical trial for a new drug. 25 were randomly assigned to one arm of the study (receive the drug) while the remaining 25 received a placebo. All received normal standard of care. Health outcomes were measured between these two arms.

- Prospective
 - Looking forward
- Retrospective
 - Looking backward

You are conducting a research project on speech patterns and drinking. You have a hypothesis that drinking leads to an increased amount of words per minute among law students. You recruit some law students for your study and begin a conversation with them. After 1 hour you provide them with some beer and wine. You record the words per minute from law students before and after they have consumed alcohol. This type of study has an _____ design.

- A.) Educational
- B.) Experimental
- C.) Observational
- D.) Meta-analytic



Three main components of RCT

1. Interventions allocated to participants by investigator
2. There is a control group that is being followed and measured at the same time as the intervention group
3. Assignment to intervention or control group is done randomly
 - Only difference between groups is the treatment

The goal is to be as close to a laboratory experiment as possible

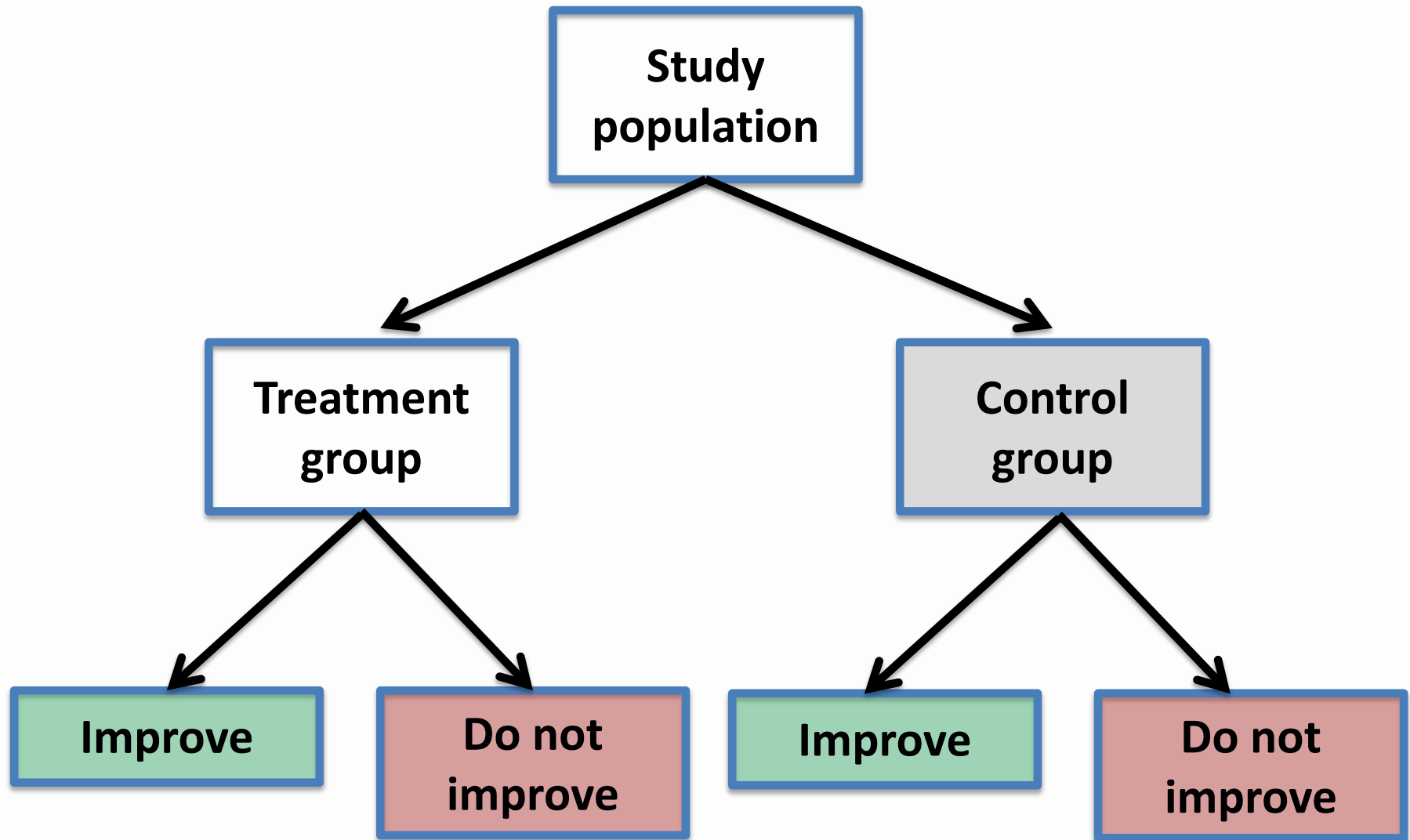
- we want to vary one factor, while keep all other factors constant

Comparison groups

- What happens when we have no “control”?
- We have no way to know if observed changes would or would not have occurred in the absence of treatment
- We can't really make causal associations

Comparison groups

- Historical control
- Use historical records to assess outcomes for the condition of interest (e.g. a disease)
- Compare these outcomes to individuals currently undergoing a treatment



components of a basic RCT

Study design

- Protocol:
 - Enrollment methods
 - Criteria for inclusion
 - Treatments and outcomes
 - Randomization approach
 - Follow up
 - Monitoring
 - Analytic plans and stopping rules

Recruitment of study subjects

Important to consider: How do people wind up in a RCT?

Recruitment of study subjects

- https://www.centerwatch.com/clinical-trials/listings/176994/tuberculosis-tbtc-study-31-rifapentine-containing/?section=elg&geo_lat=34.0522342&geo_lng=-118.2436849&radius=10

Allocation of study subjects to arms

- Allocation to study arms is done via randomization
- Random numbers
- Must avoid any systematic recruitment
- Occasionally will use matching or stratification (by age or sex)

Allocation of study subjects to arms

- Here we are mostly considering randomization at the individual level
- Sometimes randomization occurs to clusters (schools, communities, etc.)

Data recording

Participant characteristics

Data recording

Prognostic profile at entry

Also need to ensure that individuals in both arms of the study are equally as likely to have the same outcome

Data recording

Treatment

Assigned versus received

Data recording

Outcome

Clearly specified before the study begins

Measured equally in both arms

Follow up

Pre-determined intervals

Frequency and duration of follow ups

- Type of endpoint
- Risk associated with endpoint

Loss to follow up

- Remember our conversation in Lecture 6 about withdrawals in studies and censoring
- If there is something “informative” about the withdrawals, it can lead to analytic problems

Assumptions in the life table

- The “effect of time” is constant
- Those who are censored (for example, lost to follow-up) are not informative
 - Was the reason that they left the study related to the study outcome?
 - Did they leave because of illness?
 - Did they die as soon as they left?

Question

You are conducting a research project on speech patterns and drinking. You have a hypothesis that drinking leads to an increased amount of words per minute among law students. You go to a pub that is frequented by law students and record the number of words per minute before and after participants have consumed alcohol. This type of study has an _____ design.

- A.) Educational
- B.) Experimental
- C.) Observational
- D.) Meta-analytic

Masking/blinding

Bias can easily occur if:

Participant knows whether or not they are in the control or treatment group

Study investigators know who is in the control or treatment group

How to address this problem?

Blinding

Masking/blinding

Can be complicated or difficult operationally

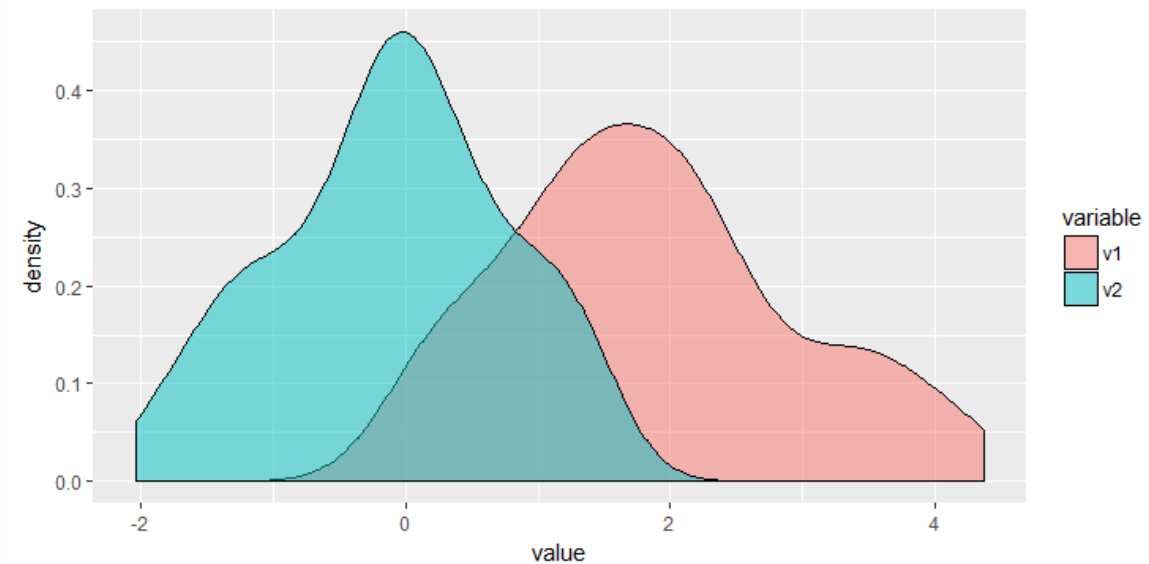
- Placebo may look or taste different than treatment
- Side effects can be informative
- Major interventions (surgery)

Trial monitoring

- Trials must be approved and monitored by IRBs (institutional review boards)
- Trials should report any adverse events, especially serious adverse events
- A data monitoring committee should monitor data and should have authority to terminate or change trial procedures

Noncompliance

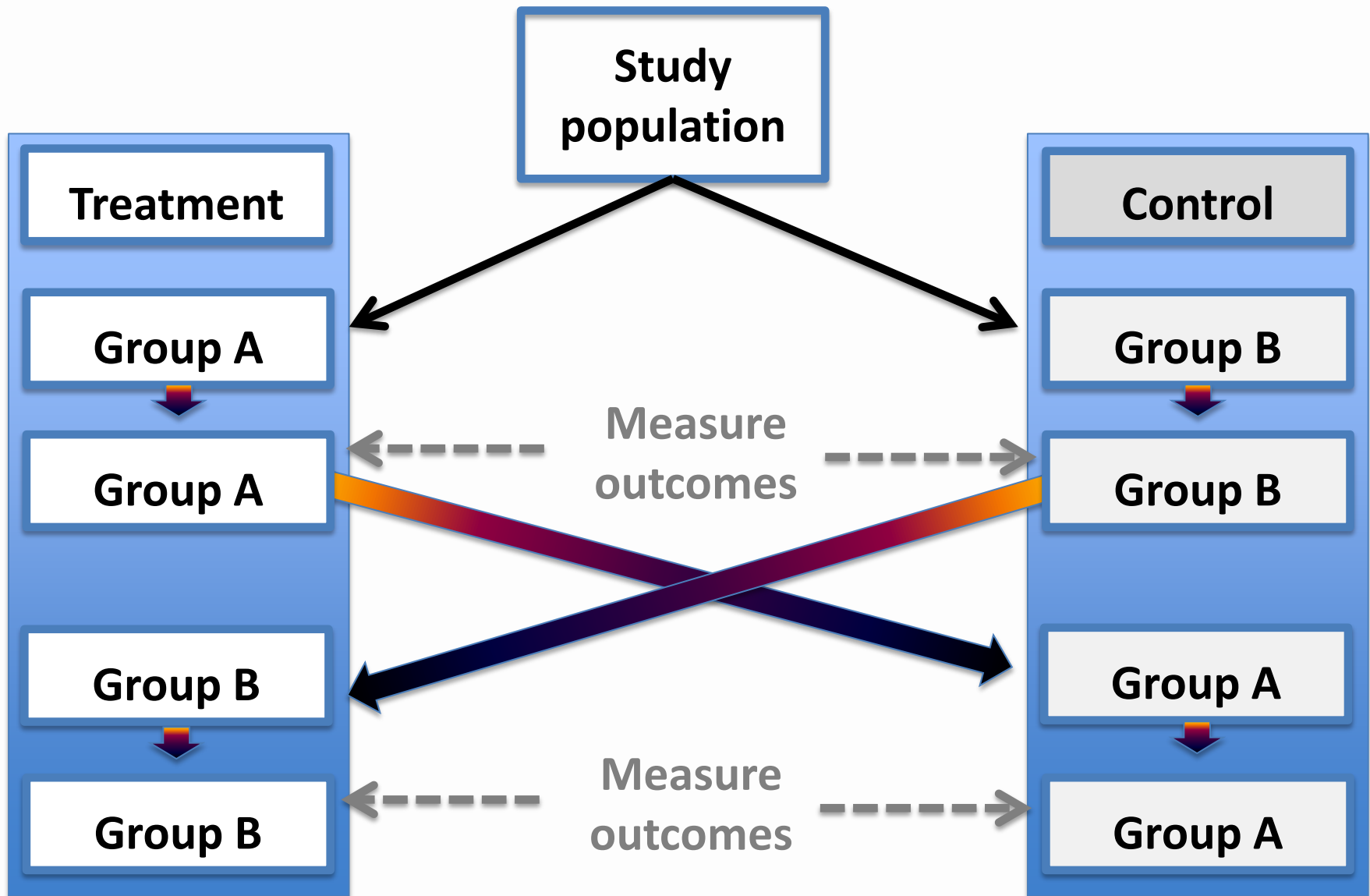
- People who don't do what they're supposed to do
- If it is rare, should not influence the results much



Validity

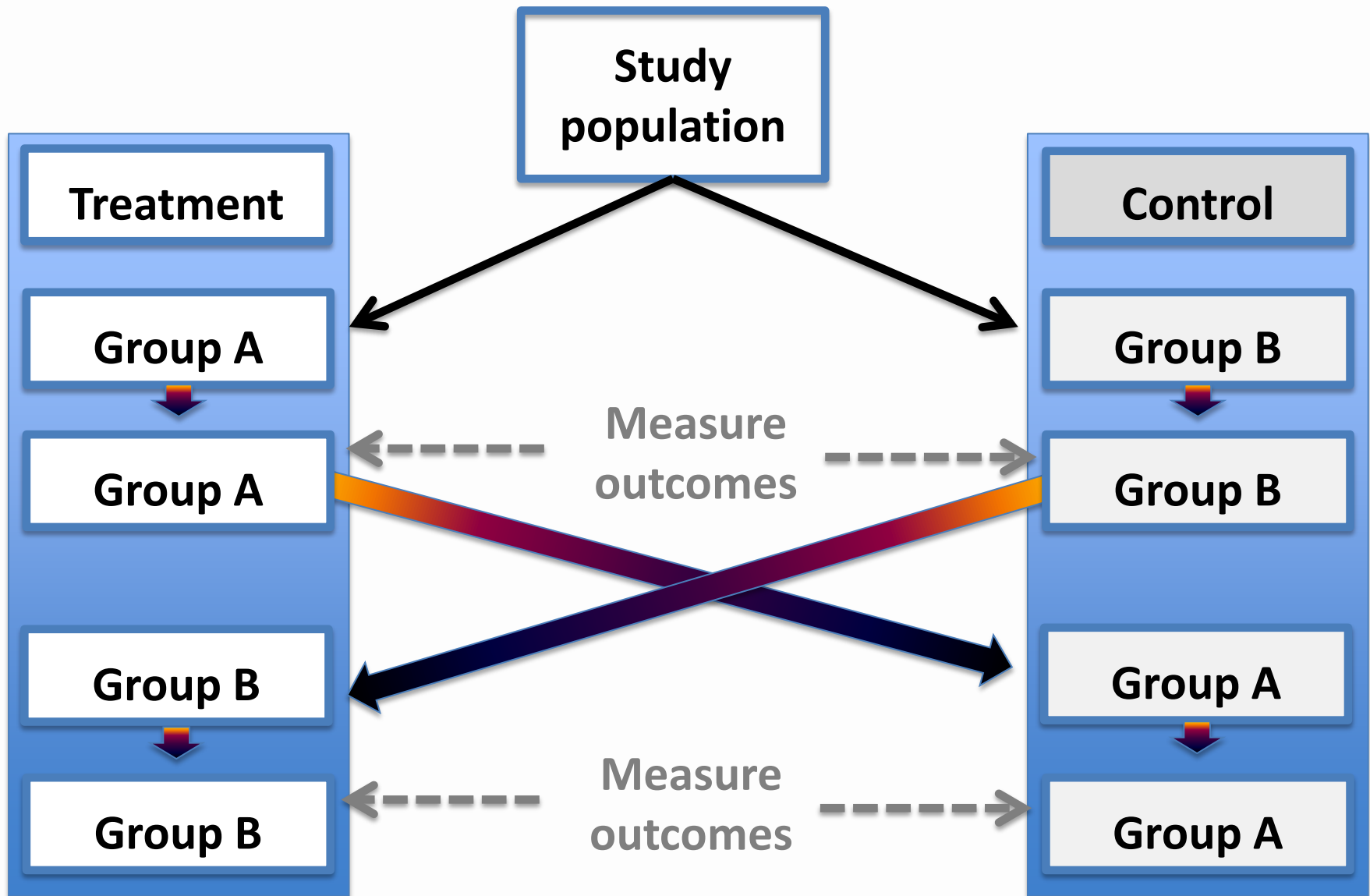
- Internal
 - Because of the RCT design, there is good internal validity
- External
 - Sometimes there is poor external validity
 - For example, is the study population representative of other population?

Variations on RCT design



Crossover

- Not only can we compare between treatment and control groups
- We can also compare within individuals who were exposed to treatment at one point and to control at another



Crossover

- Planned versus unplanned
- Problems?
 - Won't work if treatment is long lasting

Factorial design

Factorial design

		treatment A	
		yes	no
treatment B	yes	both A and B	B only
	no	A only	neither A nor B

Factorial design

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How similar are different treatments?

- The goal of some trials is to compare two different treatments
 - Could be two different drugs, or standard of care to a new drug, etc.
- Sometimes the result is inconclusive – a non-significant statistical test
- This does not necessarily mean that there is no difference!

How similar are different treatments?

- The goal of some trials is to compare two different treatments
 - Could be two different drugs, or standard of care to a new drug, etc.
- Sometimes the result is inconclusive – a non-significant statistical test
- This does not necessarily mean that there is no difference!
 - If we increased sample size, we would eventually find a significant difference...

- Superiority trial
 - To show that one treatment is superior than another
- Equivalence trial
 - To show that one treatment is not too different from another
- Non-inferiority trial
 - To show that one treatment is not worse than another

Lecture summary

- Causation/Assessing differences between populations
- Types of study design
- RCTs
- Study design
- Recruitment
- Data recording
- Randomization
- Follow up
- Blinding or masking
- Validity
- Variations on study design
- Crossovers
- Factorial designs
- Superiority, equivalence and non-inferiority