

# Statistical Principles for Clinical Development

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**Clinical Investigator Training Course (CITC) – December 7, 2022**

# Learning Objectives



- To understand basic statistical principles relevant to clinical studies
- To understand the concepts of bias and variability
- To correctly understand p-values and hypothesis testing
- To understand issues around multiplicity

# Design and Conduct are more important than Analysis



- In other words: Analysis cannot make up for poor design and conduct
- Focus on good design and conduct, and analysis will be straightforward

# Stages of a Study

- Design: The conception, planning, and specification of the study
- Conduct: The running of the study
- Analysis: The analysis of the study (Number crunching)
- Reporting

# Adequate and Well-Controlled Study

## 21CFR314.126

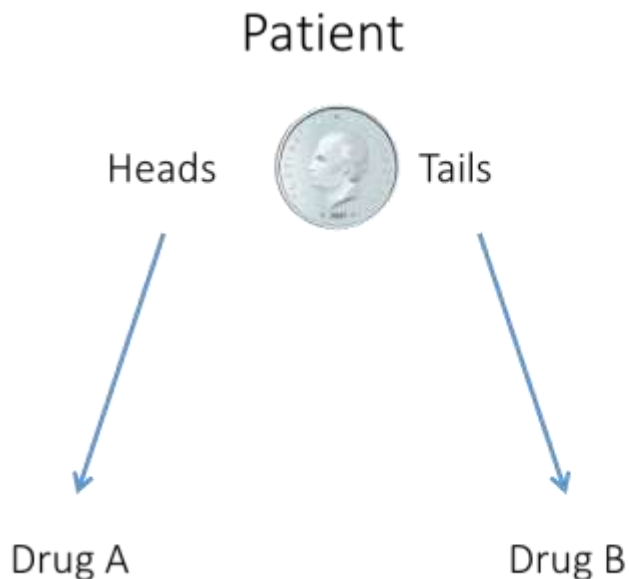


- Clear objectives, summary of methods and results
- Design permits a valid comparison with a control
- Adequate selection of patients
- Assigning patients to treatment and control groups minimizes bias
- Adequate measures to minimize biases on subjects, observers, and analysts
- Well-defined and reliable assessment of subjects' responses
- Adequate analysis to assess drug results

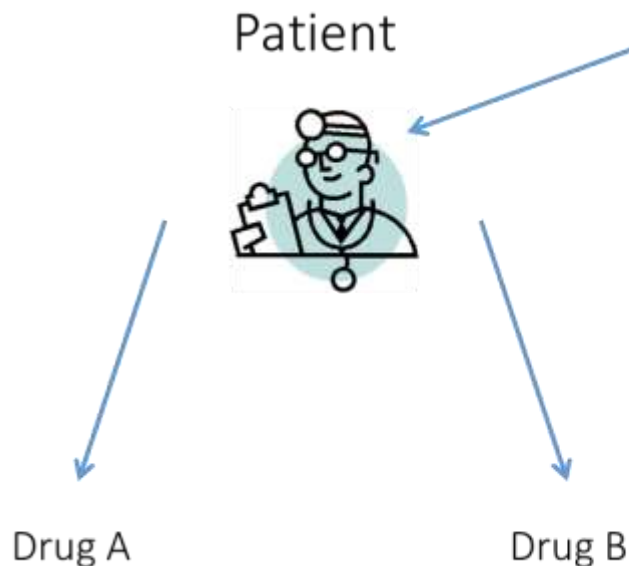
# Randomized v. Observational Studies



## Randomized Study



## Observational Study



Factors influencing assignment in an Observational Study:

- Lab tests
- Age
- Sex
- Race
- Medical history
- Family history
- Concomitant drug
- Insurance
- Convenience
- Geographic region
- Etc.

# Randomized v. Observational Studies



- Randomized study:  
characteristics of patients receiving drug A are similar to  
characteristics of patients receiving drug B
- Observational study:  
characteristics of patients receiving drug A may not be similar  
to characteristics of patients receiving drug B

# Confounding

- Without randomization there may be systematic differences (bias) when comparing people getting Drug A and people getting Drug B

This is known as confounding

Example: Drug A may be given to older sicker people.

Even if there was no differences between the effects of Drug A and Drug B, the comparison may show Drug A has worse outcomes

Note: There are other sources of biases to be concerned about that may exist even with randomization.

Example: Bias on part of observers (lack of blinding)

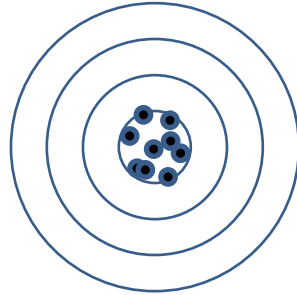
# The Health Benefits of Coffee

Drinking coffee has been linked to a reduced risk of all kinds of ailments, including Parkinson's disease, melanoma, prostate cancer, even suicide.

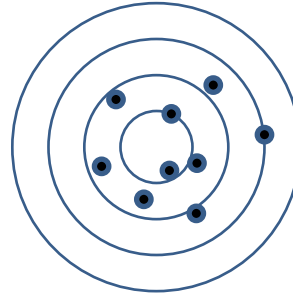


# Variability v. Bias

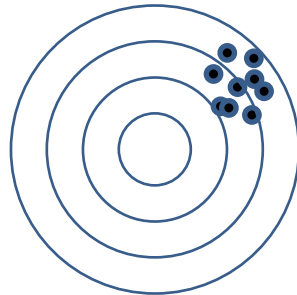
Low Variability,  
Low Bias



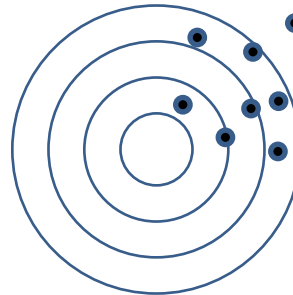
High Variability,  
Low Bias



Low Variability,  
High Bias



High Variability,  
High Bias



# Bias is worse than Variability



# Variability v. Bias

- Statistics helps to quantify variability (in the analysis stage)
- Design and conduct generally reduce bias  
Examples: randomization, blinding
- Note: Statistics helps reduce bias and variability at each stage, design, conduct, and analysis

# Reducing Variability with More Sample Size

- Sample size: number of people in study
- What is a better estimate of the average age of this session's attendees?
  - A. Pick a random sample of 5 attendees and calculate their average age
  - B. Pick a random sample of 20 attendees and calculate their average age

# Hypothesis Testing

- Null Hypothesis: Typically, what you are trying to show is **not** true

Ex: Drug A and placebo have the same effect (nothing)

- Alternative Hypothesis: Typically, what you are trying to show

Ex: Drug A has a better effect than placebo

# P-Values

- Probability of observing the effect or something more extreme, if the null hypothesis is true

Example: Study estimated drug effect is a reduction of 5mm of diastolic blood pressure.

P-value: probability of observing 5 or 6 or 7 or 8 ..., if the drug had no effect

# P-Values

- Small p-values are evidence **against** the null hypothesis (no drug effect)

Example: p-value = 0.02. If there was no drug effect, the chance of seeing what we saw or more extreme is 0.02. This is small. Leading us to doubt that there is no drug effect

- P-value is **not** the probability that the null is true (no drug effect)

# Decision Errors

- Type 1 error: Concluding the drug has an effect on when it does not  
(FDA and society's problem)  
(and drug company's)
- Type 2 error: Concluding drug does not have an effect when it does  
(Drug company's problem)  
(and FDA and society's)

# Hypothesis Testing

- Reject null hypothesis if  $p\text{-value} < \alpha$ .  
Equivalent to saying the drug has an effect.  
Example:  $\alpha = 0.05$

(Recall small p-values are evidence against the null hypothesis.)

# Sample Size and Power

- We can set the Type 1 error by choosing alpha
- We can limit the Type 2 error, by having larger sample size (more patients)
- More sample size = less variability = less likely to conclude drug has no effect when it really does (Type 2 error)



# Multiplicity

## (AKA: Multiple Bites from the Apple)

Example: Determining if a drug has effect

Drug has no effect

Study: Flip coin 4 times.

H = a good outcome, T = a bad outcome

If get 1, 2, or 3 H's, conclude drug has no effect.

If get 4 H's, conclude drug has effect.

Study 1: HHTH

Repeat study:

Study 2: HTTT

Study 3: THTH

Study 12: HHHH

# Multiplicity

- If you do enough studies or if you look at data in many ways, you will see an effect (even when there is no effect)
- This is known as data dredging or p-value hacking. It is a known problem with science

# Multiplicity

- Multiplicity can show up with multiple subgroups or endpoints

Subgroups: effect on males, effect on females, effect on people over 65

Endpoints: effect on blood pressure, effect on life expectancy, effect on happiness

- Prespecification: Tell the world ahead of time, what you will primarily look at  
Protocols and Statistical Analysis Plan (SAP) are how that is done.

# Challenge Question #1

**Which of the following does not reduce bias?**

- A. A larger sample size
- B. Randomization
- C. Blinding the knowledge of the drug from study participants and investigators
- D. Prespecification in the protocol and statistical analysis plan

# Challenge Question #2

**Which of the following addresses multiplicity?**

- A. A larger sample size
- B. Randomization
- C. Blinding the knowledge of the drug from study participants and investigators
- D. Prespecification in the protocol and statistical analysis plan

# Resources

- [Demonstrating Substantial Evidence of Effectiveness](#)
- [ICH E8\(R1\) General Considerations for Clinical Studies](#)
- [ICH E9 Statistical Principles for Clinical Trials](#)
- [ICH E9\(R1\) Estimands and Sensitivity Analysis in Clinical Trials](#)
- [Multiple Endpoints in Clinical Trials](#)
- [Adaptive Designs for Clinical Trials](#)
- [Adjusting for Covariates in Randomized Clinical Trials](#)

# Thank You!

