Statistical Principles for Clinical Development

Mark Levenson, Ph.D.
Deputy Director
Office of Biostatistics
CDER | US FDA

Clinical Investigator Training Course (CITC) – 2024

Learning Objectives

- To understand basic statistical concepts such bias, variability, multiplicity
- To understand the role of statistical concepts in good study design, conduct, and analysis

Outline

- Quick review of good-study principles
- Statistical concepts and implications on study elements:
  - Bias v. variability
  - Variability, Z-statistic, sample size, and multiplicity
  - Bias types, sensitivity analysis
- Concluding statistical principles

Stages of a Study

- **Design**: The conception, planning, and specification of the study
- **Conduct**: The running of the study (recruitment, screening, intervention, concomitant care, outcome ascertainment, safety and study monitoring)
- **Analysis**: The analysis of the study
- **Reporting**

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
- Statistical concepts motivate good design and conduct

Study Design, Conduct, and Analysis Goals

- To address a specific clinical question
- To minimize bias and minimize variability
- To ethically, safely, and feasibly conduct the trial

- Note: There is some conflict among these goals

Enrichment v. Generalizability

- Interested in drug effect on cardiovascular events for all patients with Type II diabetes
- Event trials usually require a certain number of events to get necessary statistical precision
- You can get more events for the same number of patients if you study patients with additional CV risk factors
- Balance of feasibility and answering clinical question

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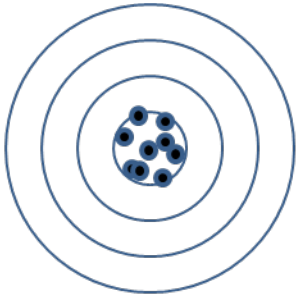
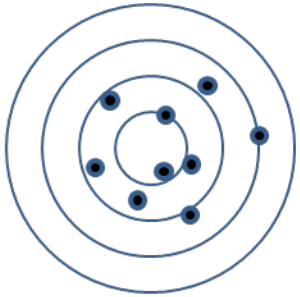
Variability v. Bias

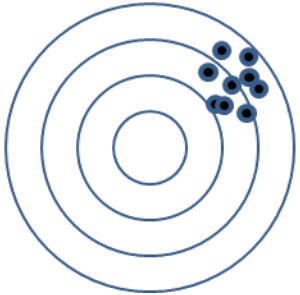
Low Variability,
Low Bias

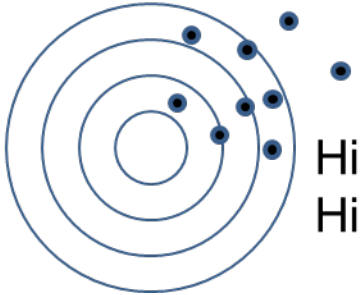




High Variability,
Low Bias

Low Variability,
High Bias





High Variability,
High Bias

Do These Data Have Low Bias?

Bias v. Variability

- We see and can measure variability
- We do not see bias
- Bias is mainly addressed in the design and conduct stages

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Variability and 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 50 attendees and calculate their average age

Variability and Sample Size

- $\hat{X}_5$ = mean of 5 people
- $\hat{X}_{50}$= mean of 50 people

- $\hat{X}_{50}$ has less variability than $\hat{X}_5$

Variability and Sample Size

- $standard\ error(\hat{X}_{50})$ is a measure of the variation of $\hat{X}_{50}$
- $standard\ error(\hat{X}_{50}) = \frac{SD(X)}{\sqrt{N}}$
- As sample size $N \uparrow$, *standard error* $\downarrow$

A Little Statistics

- $$Z = \frac{Effect\ Estimate}{Standard\ Error(Effect\ Estimate)}$$

- Assume observed *Effect Estimate* is 0.5 m.
- As sample size ↑
  - Standard error ↓
  - Z ↑
  - **P-value goes down (more significant).**

Sample Size, Significance, Power

- Typically, if there is no drug effect, then probability of seeing $|Z| > 2 = 0.05$
- If we observe $|Z| > 2$, then we say the finding was significant at the 2-sided 0.05 level
- For a given real effect, say 0.5m, the probability of a significant effect increase with sample size
- Larger sample sizes have higher *power*

Multiplicity

- AKA: Multiple bites from the apple

- A study found a drug had a statistically significant effect for females aged 51- 60 years

Multiplicity

Normalized Effect Measures (Z-Statistic)

	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	90+
Male	0.67	0.40	-0.74	-0.29	0.15	1.15	-0.04	-1.70	-0.08	-0.94
Female	-0.47	-0.29	-1.01	0.57	-0.75	2.49	-0.54	0.45	1.27	1.11

- Each of these cells gives you a chance $|Z|>2$ even if there is no drug effect.
- It is not surprising that some were $|Z|>2$

Multiplicity

- Even if drug has no effect, if you conduct enough statistical tests (without proper adjustment), you will find some results “statistically significant”
- This is known as multiplicity.

Multiplicity

- Multiplicity can show up with multiple subgroups, endpoints, or analyses.
- Subgroups: effect on males, effect on females, effect on people over 65
- Endpoints: effect on blood pressure, effect on life expectancy, effect on happiness
- Analyses: Multiple regression with different covariates

Multiplicity Solutions

- Prespecification: Tell the world ahead of time, what you will primarily look at
- Avoids fishing for p-values
- Protocols and Statistical Analysis Plans (SAP) are how that is done
- Statistical methods can handle multiple outcomes or subgroups
- Need to be prespecified too

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A Little Statistics: Review

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Bias Example

- Unblinded trial
- Effort dependent endpoint (6 min walk)
- Patients on experimental drug may try harder (let's say 0.5 meters on the average)
- Assume no drug effect.
- **This 0.5m bias will not likely be affected by sample size.**
- **P-values get smaller for larger sample size even though drug is not effective!**

Addressing Bias

- Sample size does not address bias
- Design and conduct should address bias
- Design methods: randomization, blinding, good outcome assessment
- Analysis cannot rescue poor design and conduct
- Analysis can address some bias and explore sensitivity to biases

Bias Types

- Confounding
  (Baseline differences between treatment groups)
  - Addressed by randomization
- Measurement
  (Endpoint ascertainment)
  - Addressed by blinding and reliable and valid measures
- Selection (baseline and post-baseline population issues)

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

PERSONAL HEALTH

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.

515

Selection Bias Type 1

Baseline study population not representative of intended population

- Easy to understand
- Example: Few people with co-morbidities in study
- Affects generalizability (external validity)

Selection Bias Type 2

Analysis population based on post-baseline information

- Harder to understand
- Examples
  - Analyzing adherers only
  - Analyzing those with no missing data
  - Analyzing those with initial response to treatment
- Biases causal relationships (internal validity)

Adherence May Be Related to Outcome

Table 1. Five-Year Mortality in Patients Given Clofibrate or Placebo, According to Cumulative Adherence to Protocol Prescription.

ADHERENCE *	TREATMENT GROUP			
	CLOFIBRATE		PLACEBO	
	no. of patients	*% mortality †*	*no. of patients*	*% mortality †*
Total study group	1065	18.2±1.2 (18.0)	2695	19.4±0.8 (19.5)

*A patient's cumulative adherence was computed as the estimated number of capsules actually taken as a percentage of the number that should have been taken according to the protocol during the first five years of follow-up or until death (if death occurred during the first five years).

†The figures in parentheses are adjusted for 40 base-line characteristics. The figures given as percentages ±1 S.E. are unadjusted figures whose S.E.'s are correct to within 0.1 unit for the adjusted figures.

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	no. of patients	*% mortality †*	*no. of patients*	*% mortality †*
<80%	357	24.6±2.3 (22.5)		
⩾80%	708	15.0±1.3 (15.7)		
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Adherence and Missing Data: Biases

- Patients who complete therapy may be different from those who stop therapy
- Treated group patients who complete therapy may be different from control group patients who complete therapy
- Analyzing of only patients who complete therapy (or complete data) will likely produce biased results

Adherence and Missing Data: Types

- Patients may stop treatment
- Patients may leave study (no more follow-up)
- Patients may miss a study visit (treatment or assessment)

- These are all *intercurrent events* and should be handled appropriately and not often the same

Adherence and Missing Data: Causes

- Random
  (not related to patient characteristics or patient outcome)
- Frailty of patient
- Lack of efficacy
- Side effects

What is Adherence?

- Adherence is not forcing patients to do something
- That is not ethical
- Protocol should allow for the best of interest of the patient
- Adherence is following the protocol, even if that means stopping therapy

Treatment Policy/Intent-To-Treat (ITT)

- First, want to get follow-up data regardless of treatment adherence
- Analyze patients according to random assignment regardless of adherence and missing data
- Answers the question: What is the effect of being assigned a therapy?
- Maintains randomization

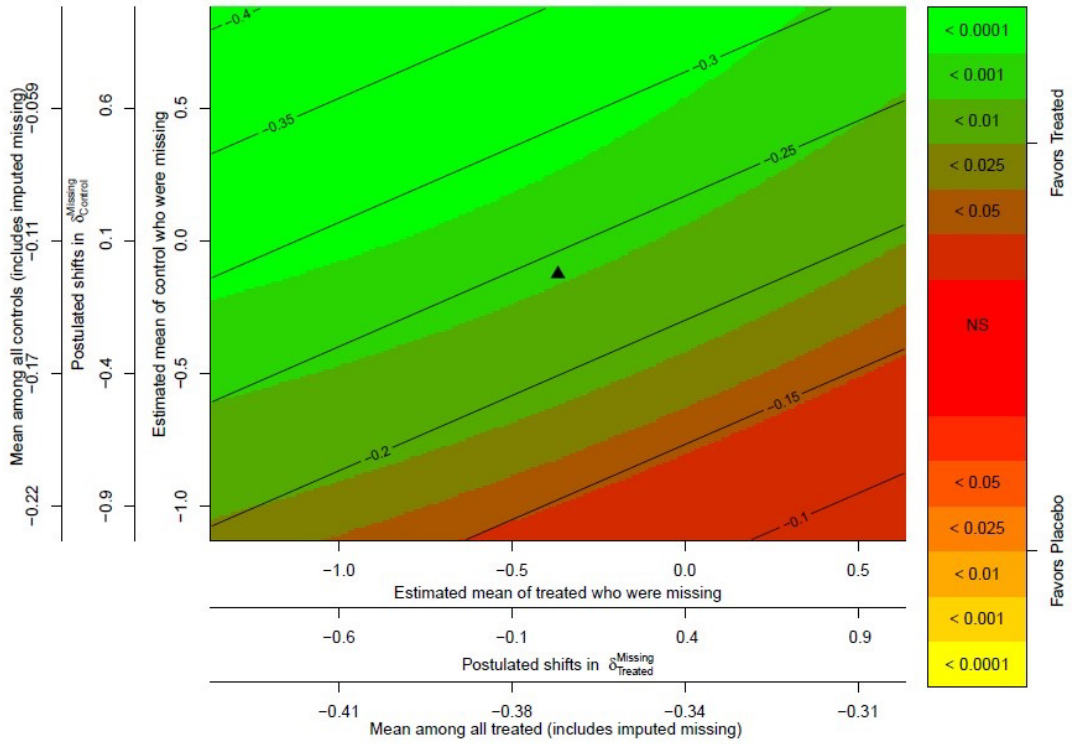
Treatment Policy/Intent-To-Treat (ITT)

- Problems
- Patients may stop therapy, cross over to other group's therapy, receive rescue therapy
- Still may have missing data
- Composite approach: stopping/changing/rescue therapy considered a failure in composite endpoint
- Approach should be tailored to specifics clinical question

Sensitivity Analysis

- Varying assumptions to explore potential biases
- Example: Drug effect for patients with missing data not the same as drug effect for patients with complete data

Sensitivity Analysis



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Summary

- Careful design and conduct are needed for reliable results
- Randomization addresses baseline biases
- Blinding, good adherence, good follow-up, and good endpoint ascertainment address post-baseline biases
- Prespecification is important to address multiplicity

Take Home

- Address the clinical question
- Minimize bias and minimize variability
- Careful design, conduct, and analysis will promote valid and reliable results!

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

Thanks!