Statistical Principles for Clinical Development

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Clinical Investigator Training Course (CITC) – 2023

Learning Objectives

- To understand statistical principles for the design, conduct, and analysis of clinical studies
- To understand the concepts of bias and variability
- To understand issues around adherence, missing data, multiplicity

Stages of a Study (ICH E8 and E9)

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

Adequate and Well-Controlled Study

- 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

21CFR314.126

Purpose of Control Group (ICH E10)

- Allows for the discrimination of patient outcomes caused by the test treatment from other factors
  - Natural progression of the disease
  - Observer or patient expectations
  - Concomitant treatment

Similarity of Groups

- Similarity at baseline
  - Randomization
- Similarity post-baseline
  - Blinding
  - Compliance
  - Complete data and follow-up
  - Outcome assessment (ICH E8)

Randomized v. Observational Studies

Randomized Study

Patient

Heads  Tails

Drug A

Drug B

Observational Study

Patient

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

Drug A

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

PERSONAL HEALTH

The Health Benefits of Coffee

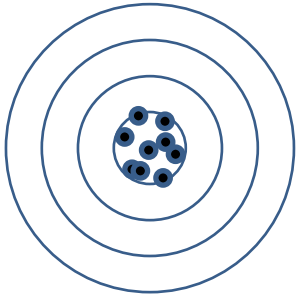
Drinking coffee has been linked to a reduced risk of all kinds of ailments, including Parkinson's disease, melanoma, prostate cancer, even suicide.

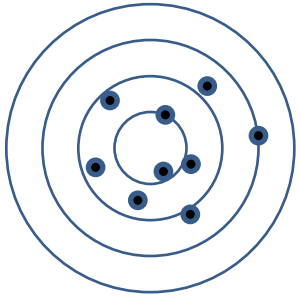
Blinding (ICH E10, E8, E9)

- Double blind: patients and investigators (and study staff) do not know treatment group membership
- Minimizes biases from differences in
  - Patient management
  - Assessment (efficacy and safety)
- Biases may be conscious or unconscious
- Even with blinding may, patients or investigators may guess what drug they are on

Variability v. Bias

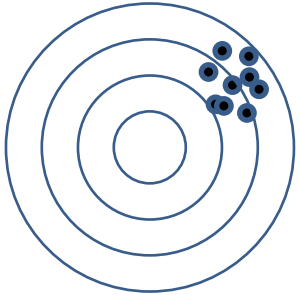
Low Variability,
Low Bias

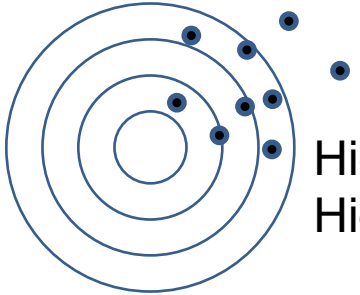




High Variability,
Low Bias

Low Variability,
High Bias





High Variability,
High Bias

Bias is Worse than Variability

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

Variability v. Bias

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

Adherence and Missing Data

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

Material and example adapted from Dr. Susan Ellenberg

Adherence and Missing Data Causes

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

Adherence and Missing Data Biases

- Patients with complete data may be different from those with incomplete (missing) data
- Treated group patients with complete data may be different from control group patients with complete data
- Analyzing of patients with complete data will likely produce biased results

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.

The Coronary Drug Project Research Group. N Engl J Med 1980;303:1038-1041.

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<80%	357	24.6±2.3 (22.5)		
⩾80%	708	15.0±1.3 (15.7)		
Total study group	1065	18.2±1.2 (18.0)	2695	19.4±0.8 (19.5)

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⩾80%	708	15.0±1.3 (15.7)	1813	15.1±0.8 (16.4)
Total study group	1065	18.2±1.2 (18.0)	2695	19.4±0.8 (19.5)

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Adherence and Missing Data Strategies ICH E9 and E9 R1

- First, want to get follow-up data regardless of treatment adherence
- Treatment Policy (Intent-to-Treat (ITT))
  - Patients analyzed according to random assignment regardless of adherence and missing data
  - What do you do for the missing data?
- There are other approaches depending on the situation

Multiplicity

(AKA: Multiple Bites from the Apple)

Study: Flip coin 4 times.
H = a good outcome, T = a bad outcome

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

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

Study 1: HHTH

Repeat study

Study 2: HTTT

Study 3: THTH

Study 12: HHHH

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

Multiplicity Solutions

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

Summary

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

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

References

- 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
- ICH E10 Choice of Control Group and Related Issues in Clinical Trials

U.S. FOOD & DRUG ADMINISTRATION

Good scientific practices (design, conduct, and analysis) will promote valid and reliable results!

U.S. FOOD & DRUG
ADMINISTRATION

Thank You!