ASA Biopharmaceutical Section Workshop

Washington, DC

13 Sep 2018

Causal versus Casual Inference

What Happens When I Take This Medication?

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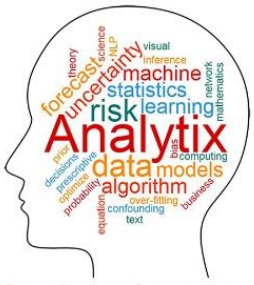


Bringing data to life.

ACKNOWLEDGEMENTS

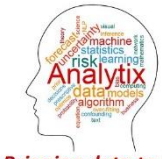
Eli Lilly

Yongming Qu

Haoda Fu

Sanofi

Junxiang Luo (work completed while at Lilly)



Outline

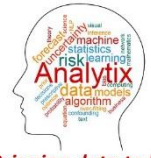
Motivation

Tripartite Approach

Estimators for Causal Inference

Example

Discussion



Bringing data to life.

Climbing Mt Kilimanjaro

How long is the hike on Mt. Kilimanjaro?

19,341 feet

On day 6, hikers take on average 4.65 hours.

Climbing Mt Kilimanjaro

How long is the hike on Mt. Kilimanjaro?

19,341 feet

20%
4 hours
Lack endurance

45%
7 hours
Stick to the plan

35%
2 hours
Adverse event

What Is the Right Answer?

"Intent to hike" estimate? (4.65 hrs)

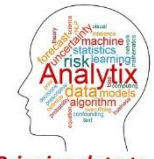
Completers/adherers estimate? (7 hrs)

The whole story? (all three parts)

What does the traveler (i.e. patient) want to know?

WHAT DO YOU WANT TO KNOW?

What would you tell your loved one?



Bringing data to life.

What are the Right Questions?

Patient / Physician

What happens when I take this medication?

Researcher

What are the causal effects of treatment?

Regulator

What are the benefits and risks of treatment?

Bringing data to life.

ICH Draft Addendum

A.3 ESTIMANDS

A.3.1 Description

"A central question for drug development and licensing is to **quantify treatment effects**: how the outcome of treatment compares to what would have happened to the same subjects under different treatment conditions (e.g. had they not received the treatment or had they received a different treatment)."

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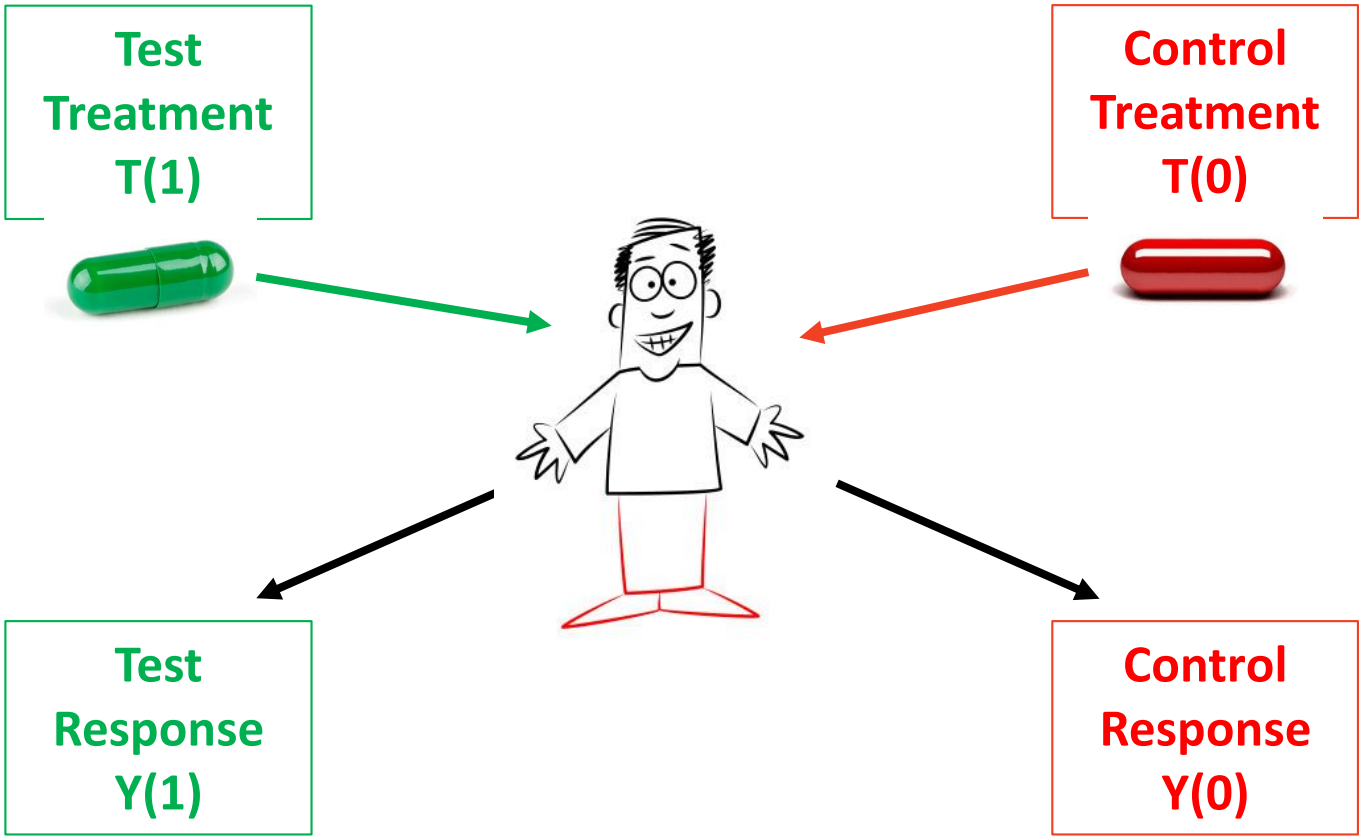
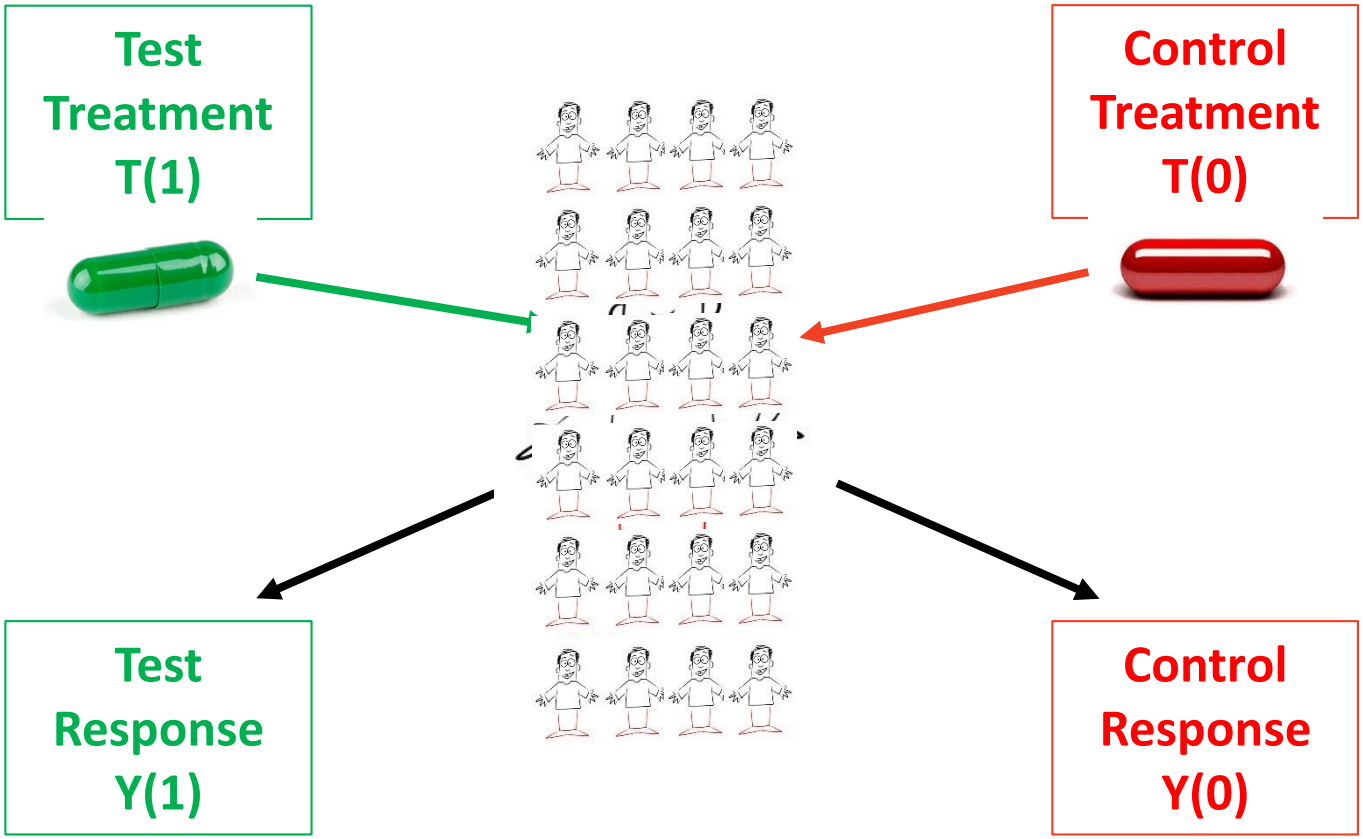
Treatment Effect



Treatment Effect = Y(1) – Y(0)

Bringing data to life.

Treatment Effect



$$\text{Estimator} = \Sigma \left[Y_i(1) - Y_i(0) \right] / N$$

Bringing data to life.

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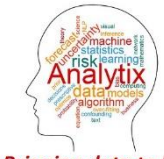

Bringing data to life.

The Tripartite Approach*

Three Causal (and clinically meaningful) Estimands

1. The proportion of patients that discontinue treatment due to adverse effects
   - Can also assess time to discontinuation
2. The proportion of patients that discontinue treatment due to lack of efficacy
   - Need to assess time to discontinuation
3. For those who could adhere to their treatment, what is the treatment difference for the primary efficacy response
   - Must assess safety in this group as well

Akacha, Bretz, Ruberg (2017). Estimands in clinical trials – broadening the perspective. Stat in Med 36:1, 5-19.
Ruberg, Akacha (2017). Considerations for Evaluating Treatment Effects from Randomized Clinical Trials. Clin Pharm & Ther 102:6, 917-923.

Bringing data to life.

The Tripartite Approach

Estimands (1) and (2) are pretty easy

- All randomized patients provide a response
- Categorical or survival analysis
- Can include models for important covariates
- Could consider competing risks as a more complex assessment

Estimand (3) is more difficult

- Patients are self-selected (i.e. non-randomized)
- ***Akin*** to an observational study
- **Casual** inference approach – Completers Analysis
- **Causal** inference approach – Counterfactual / IPW

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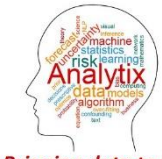

Causal Inference

For T(0) [CONTROL]
A(0) = 0 for non-adherence
= 1 for adherence

For T(1) [EXPERIMENTAL]
A(1) = 0 for non-adherence
= 1 for adherence

	Experimental Treatment Adherence		
Control Treatment Adherence	**A(1) = 0**	**A(1) = 1**	**A(1) ∈ {0, 1}**
A(0) = 0	NA	NA	NA
A(0) = 1	NA	A++	A+*
A(0) ∈ {0, 1}	NA	A*+	A**

Population of patients who can adhere to Experimental AND Control treatments.

Bringing data to life.

Causal Inference

For T(0)
A(0) = 0 for non-adherence = 1 for adherence

For T(1)
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A(0) = 0	NA	NA	NA
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Population of patients who can adhere to the Experimental treatment *regardless* of adherence to the Control treatment.

Bringing data to life.

Causal Inference

For T(0)
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For T(1)
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Causal Inference

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A(0) = 0	NA	NA	NA
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Population of All Randomized patients.

Causal Inference

General Framework

Let $S \in \{ A{+}{+}, A{*}{+}, A{+}{*}, A{*}{*} \}$

$$E [Y(1) - Y(0) \mid S]$$

Causal Inference

Estimand definition requires POPULATION

It's more than Inclusion/Exclusion criteria!

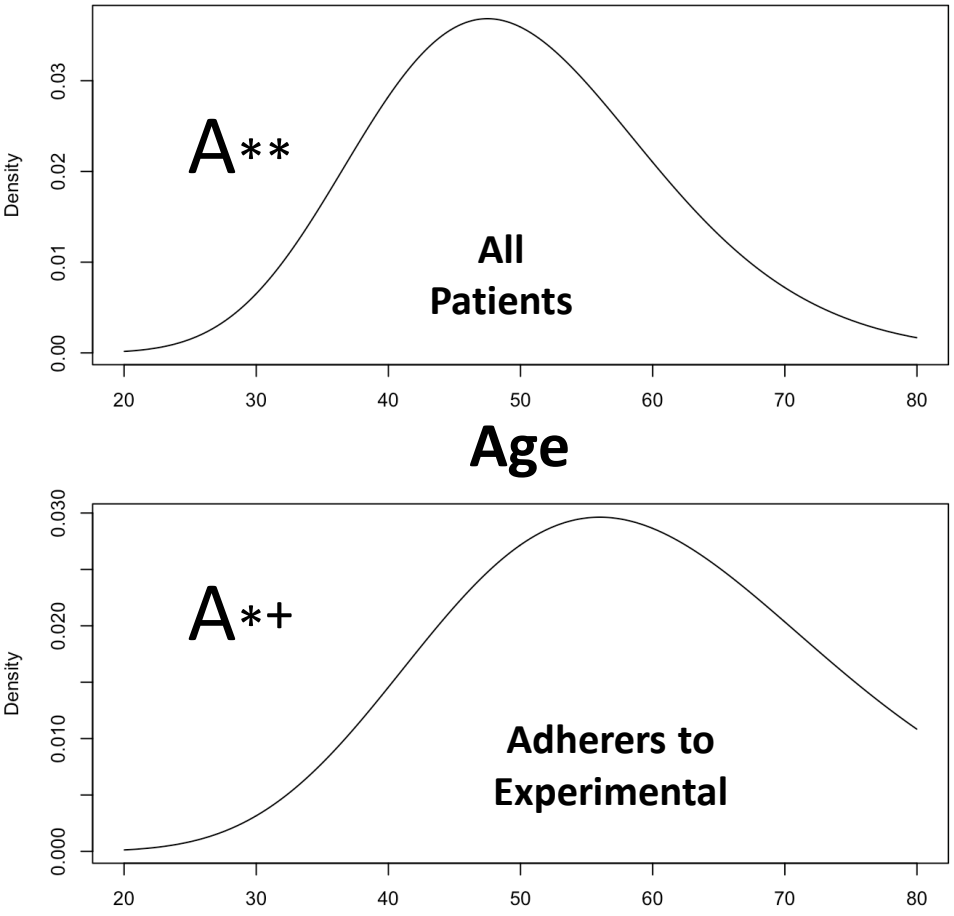
WHAT $S \in \{ A{+}{+}, A{*}{+}, A{+}{*}, A{*}{*} \}$ are you interested?

$$\mathbf{E [Y(1) - Y(0) \mid S]}$$

Placebo controlled trials

The population of patients adherent to Experimental treatment regardless of adherence to Placebo.

Causal Inference



Causal Inference

Estimand definition requires POPULATION

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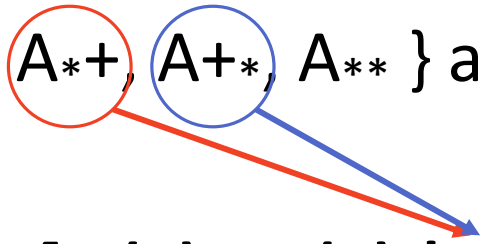
WHAT S $\in$ { A++, A_{*+}, A_{+*}, A_{**} } are you interested?

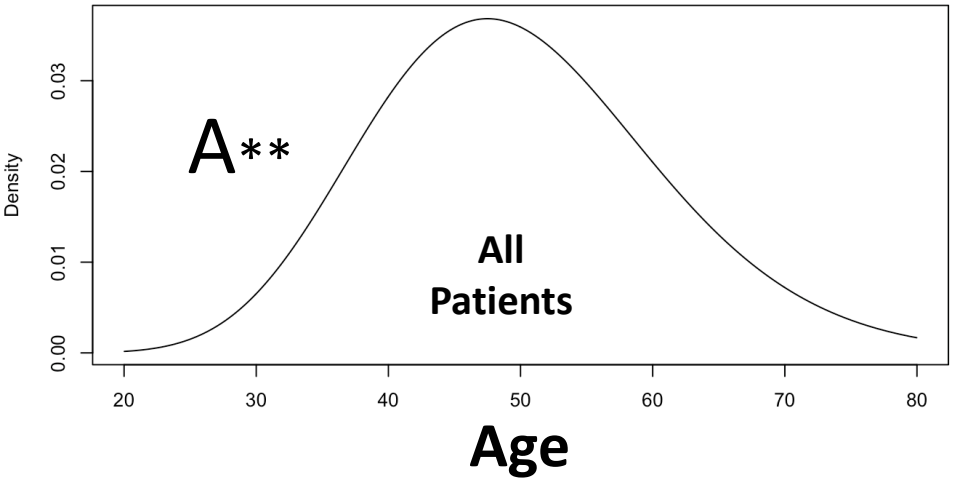


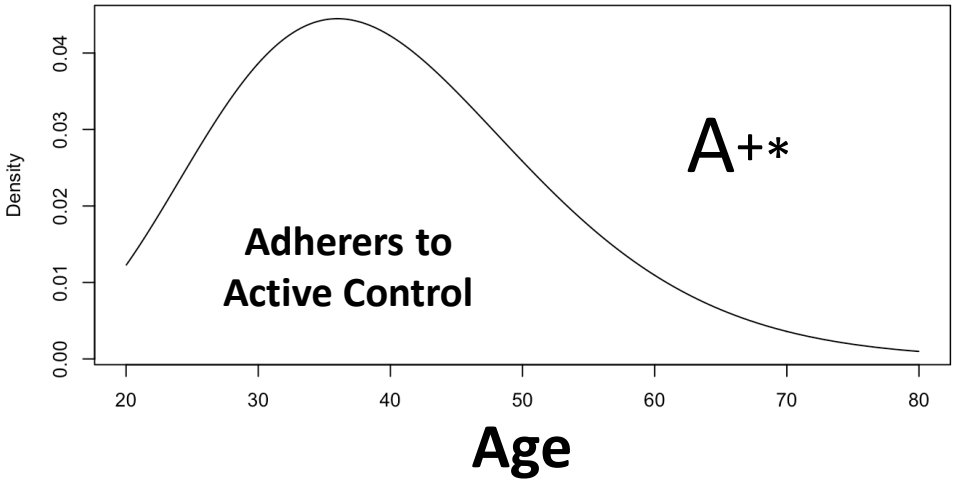
E [Y(1) – Y(0) | S]

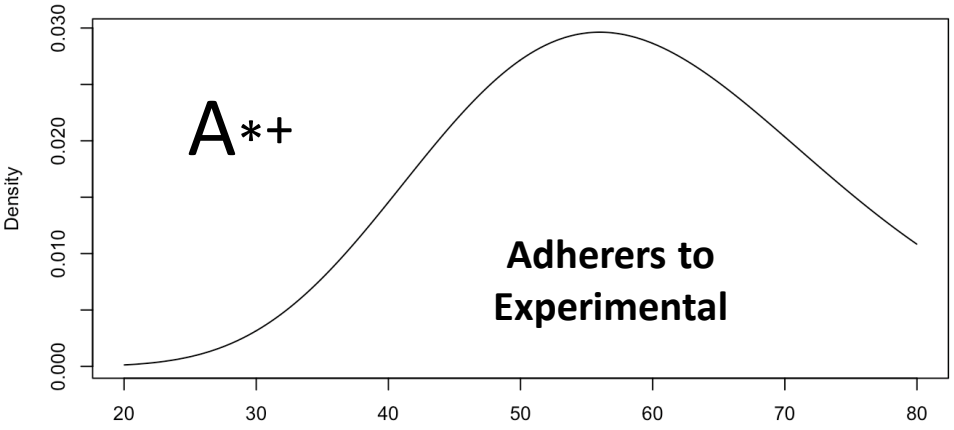
Active controlled trials

?? ?? ?? ?? ?? ?? ?? ?? ?? ?? ?? ?? ??

Causal Inference







Causal Inference

Estimand definition requires POPULATION

It's more than Inclusion/Exclusion criteria!

WHAT $S \in \{ A{+}{+}, A_{*}{+}, A{+}_{*}, A_{**} \}$ are you interested?

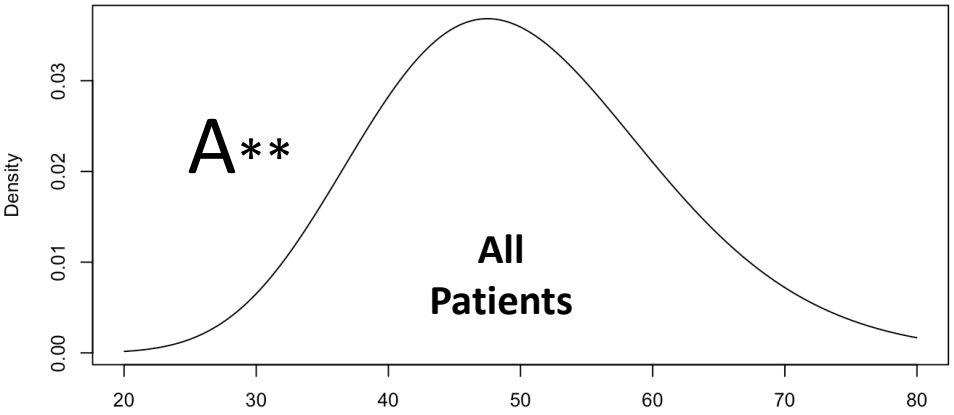
$$\mathbf{E\{ Y(1) - Y(0) \mid S \}}$$

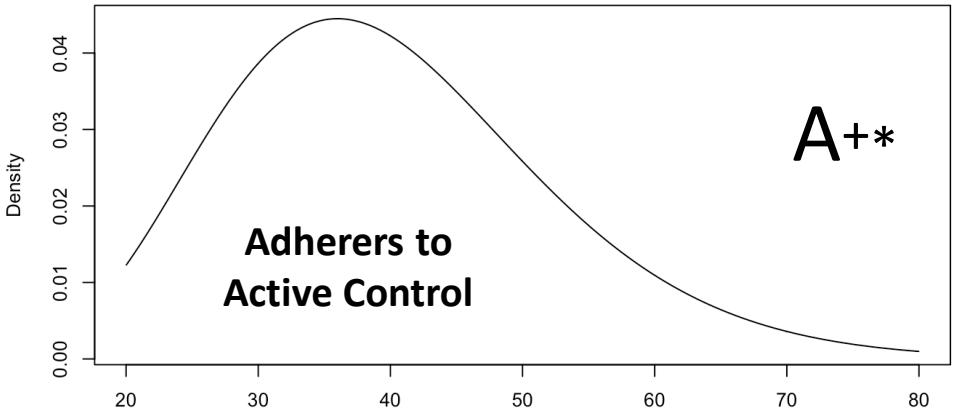
Active controlled trials

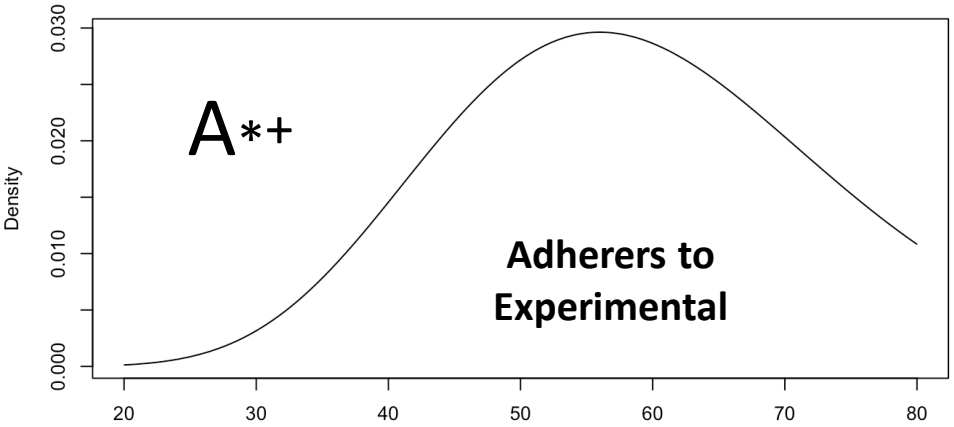
The population of patients adherent to both the Experimental treatment and the Active Control treatment.

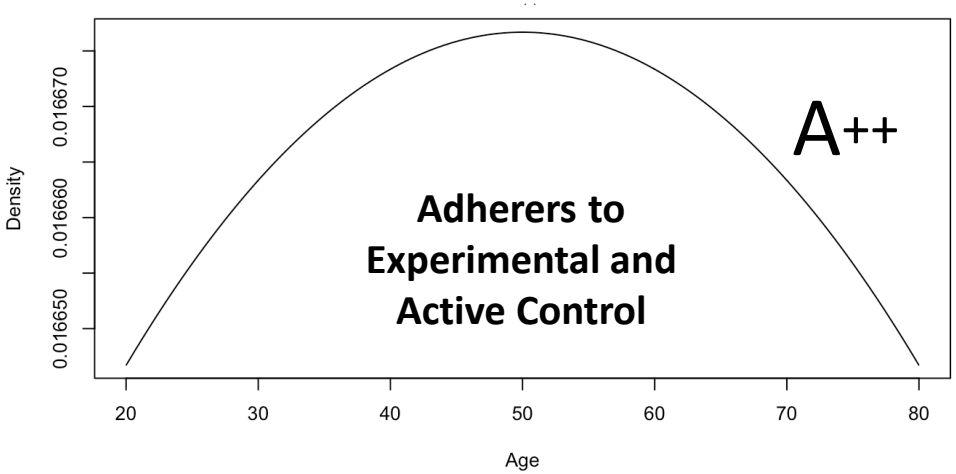
Bringing data to life.

Causal Inference









Causal Inference

Estimand definition requires POPULATION

It's more than Inclusion/Exclusion criteria!

WHAT $S \in \{ A{+}{+}, A{*}{+}, A{+}{*}, A{*}{*} \}$ are you interested?

$$\mathbf{E [Y(1) - Y(0) \mid S]}$$

The Intent-to-Treat Population (all randomized patients).

Estimators Based on Adherence

Method A – Counterfactual

- Build a model of response (Y) based on baseline covariates (X) and post-randomization data (Z)
- Create a "virtual twin"
- Predict response on the unobserved treatment
- Compare observed response with predicted response of "twin"

This is consistent with the ICH-E9(R1) statement:

- "quantify treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under different treatment conditions (e.g. had they not received the treatment or had they received a different treatment)."

Estimators Based on Adherence

Method B – Inverse Probability Weighting (IPW)

- Estimate the probability that a patient from the unobserved treatment (e.g. Control) would adhere to the observed treatment (e.g. Experimental)
- Use IPW to estimate the average response for the population (A_{ij}) of interest.

This is consistent with the ICH-E9(R1) statement:

- But takes a different approach

Estimators Based on Adherence

Population	Method A: Estimator Based on Distribution of (X, Z, Y)
A_{**}	$\frac{1}{n_1}\sum_{j\in\{j:T_j=1\}}\hat{\psi}_1(X_j,Z_j)-\frac{1}{n_0}\sum_{j\in\{j:T_j=0\}}\hat{\psi}_1(X_j,Z_j).$
A_{*+}	$\frac{1}{n_{11}}\sum_j T_jA_jY_j-\frac{1}{n_{11}}\sum_j\hat{\phi}_0(X_j)$
A_{+*}	$\frac{1}{n_{01}}\sum_j\hat{\phi}_1(X_j)-\frac{1}{n_{01}}\sum_j(1-T_j)A_jY_j$
A_{++}	$\frac{\sum_j\hat{\varphi}_1(X_j)(1-T_j)A_j}{\sum_j\hat{h}_1(X_j)(1-T_j)A_j}-\frac{\sum_j\hat{\varphi}_0(X_j)T_jA_j}{\sum_j\hat{h}_0(X_j)T_jA_j}$

Population	Method B: Estimator Based on Distribution of (X, Z, A)
A_{**}	$\frac{1}{n_1}\sum_{j\in\{j:T_j=1,A_j=1\}}\frac{Y_j}{\hat{g}(X_j,Z_j)}-\frac{1}{n_2}\sum_{j\in\{j:T_j=0,A_j=1\}}\frac{Y_j}{\hat{g}(X_j,Z_j)}$
A_{*+}	$\frac{1}{n_{11}}\sum_j T_jA_jY_j-\frac{n_1}{n_0n_{11}}\sum_j\frac{\hat{h}_1(X_j)(1-T_j)A_jY_j}{\hat{g}(X_j,Z_j)}$
A_{+*}	$\frac{n_0}{n_1n_{01}}\sum_j\frac{\hat{h}_0(X_j)T_jA_jY_j}{\hat{g}(X_j,Z_j)}-\frac{1}{n_{01}}\sum_j(1-T_j)A_jY_j$
A_{++}	$\frac{\sum_j\hat{h}_0(X_j)T_jA_jY_j}{\sum_j\hat{h}_0(X_j)T_jA_j}-\frac{\sum_j\hat{h}_1(X_j)(1-T_j)A_jY_j}{\sum_j\hat{h}_1(X_j)(1-T_j)A_j}$

Estimators Based on Adherence

Population	Method A: Estimator Based on Distribution of (X, Z, Y)
A_{**}	$\hat{\psi}_1(X_j, Z_j)$.
A_{*+}	
A_{+*}	Y_j
A_{++}	$\sum_j h_1(X_j)(1-T_j)A_j \qquad \sum_j h_0(X_j)T_jA_j$

An extension of MMRM

Population	Method B: Estimator Based on Distribution of (X, Z, A)
A_{**}	$\frac{Y_j}{(X_j,Z_j)}$
A_{*+}	
A_{+*}	
A_{++}	$\sum_j \hat{h}_0(X_j)T_jA_j \qquad \sum_j \hat{h}_1(X_j)(1-T_j)A_j$

An extension of Marginal Structural Models

Estimators Based on Adherence

Under certain reasonable assumptions, these estimators are consistent

Our simulations studies show they are unbiased

- Even with modest sample sizes (N = 150 / treatment)
- For different discontinuation patterns
  - Differential discontinuation on Experimental and Control Treatments
  - Discontinuations ranging from ~10% to ~50%

Method A and Method B perform similarly

- Method A is easier computationally when the outcome is normally distributed.

Outline

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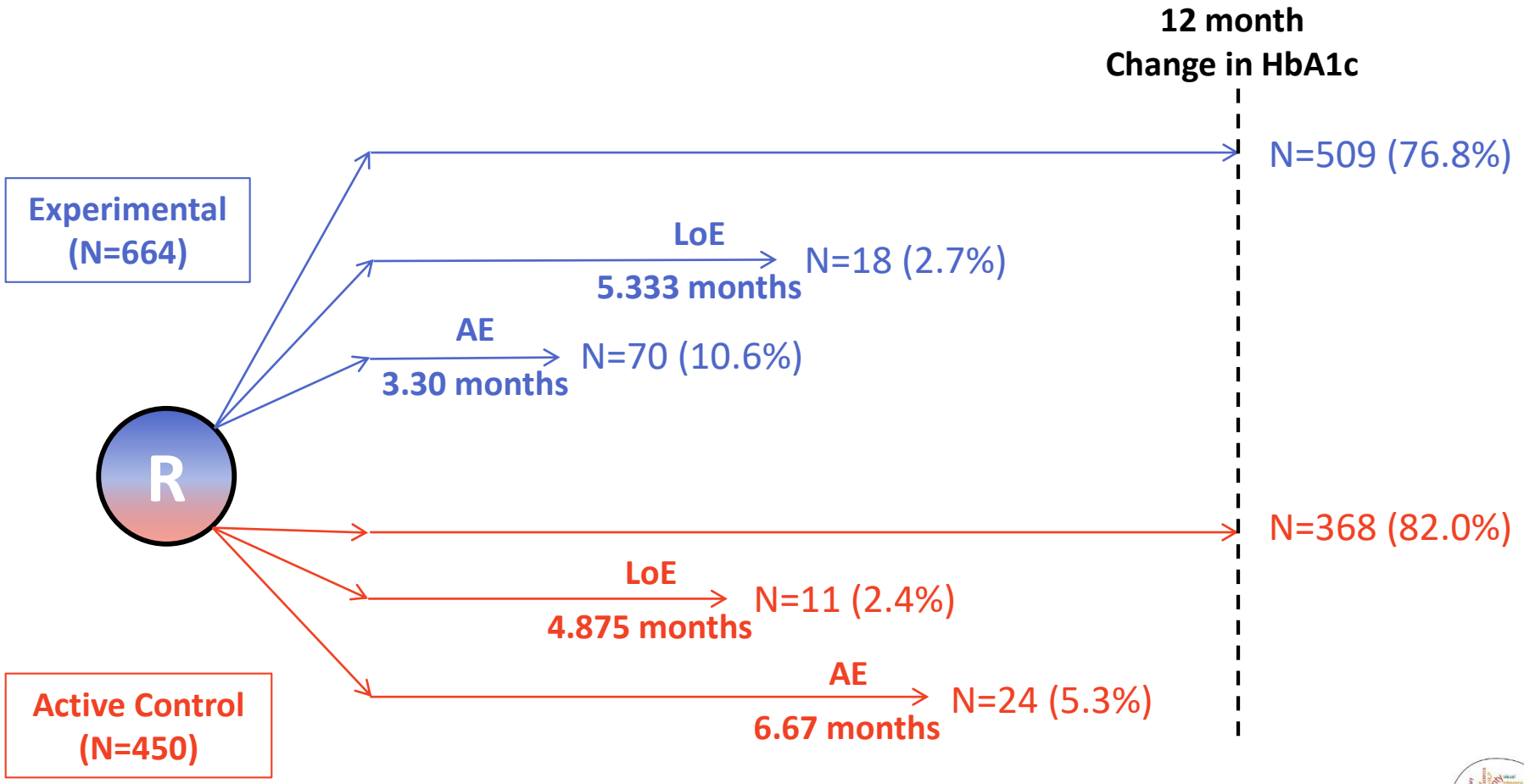
Example

Discussion

Example (Diabetes)



Discontinuation due to administrative reasons occurred in ~11% of each treatment group and were randomly distributed over the course of the study.

Bringing data to life.

Example (Diabetes)

In **WHAT** Population are we interested?

$$E\{ Y(1) - Y(0) \mid S = A{+}{+} \}$$

(adherent to experimental **and** active control)

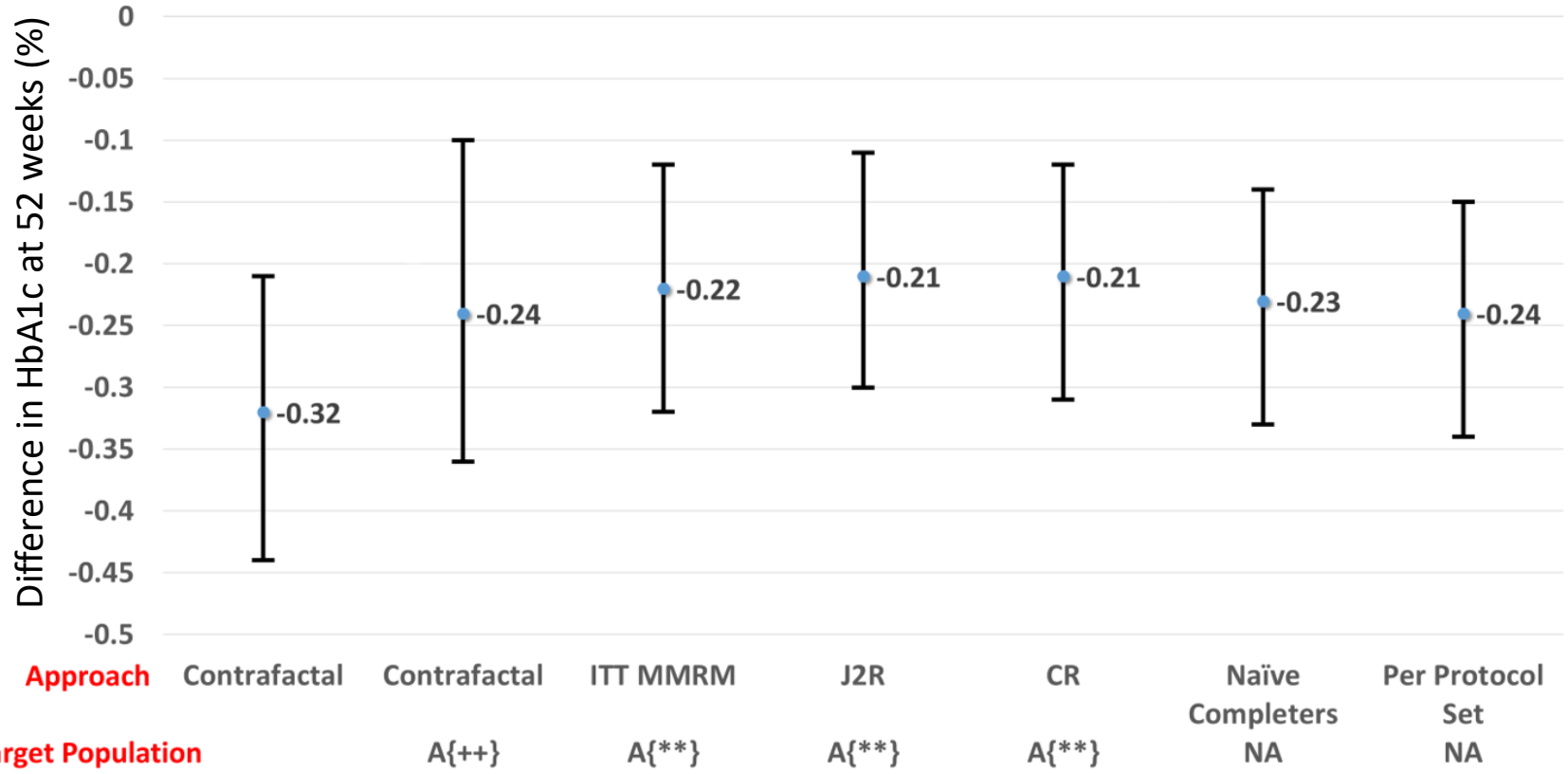
- - - - - - - - -

We could examine …

$$E\{ Y(1) - Y(0) \mid S = A{*}{+} \}$$

(adherent to experimental **regardless** of active control adherence)

Treatment Difference between Experimental and Active Control in HbA1c at 52 Weeks



Abbreviations: NA = not applicable; ITT = Intent-to-Treat; MMRM = Mixed Model Repeated Measures; J2R – Jump to Reference; CR = Copy Reference

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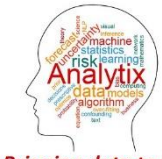


Discussion

Casual Inference – Completers Analysis

$$E[Y(1) \mid A(1)=1] - E[Y(0) \mid A(0)=1]$$

Causal Inference

$$E\,[\,Y(1) - Y(0) \mid S\,]$$

More work on variance of these estimators

Discussion

Missing at Random assumption

- Quite reasonable to believe that discontinuations of treatment are related to the efficacy and safety of the treatment
- Some data MCAR (administrative drop-outs)

Causal Inference

- It's more complicated, but …

  worth it given the cost of clinical trials.

Bringing data to life.

What are the Right Questions?

Patient / Physician

What happens when I take this medication?

Researcher

What are the causal effects of treatment?

Regulator

What are the benefits and risks of treatment?

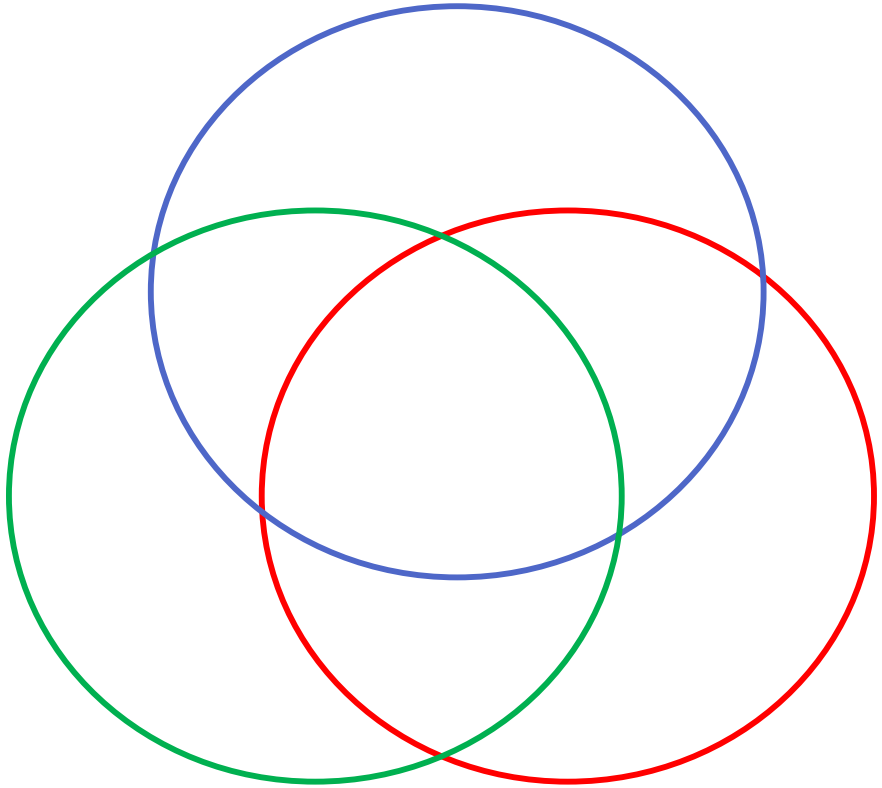
Tripartite Estimands

Bringing data to life.

What are the Right Questions?

Benefit (and Risk)
Given Adherence

Probability of
Lack of Efficacy



Probability of
Adverse Event

Tripartite Estimands

Bringing data to life.

Discussion

Why can't Estimand 3 be the gatekeeper to regulatory review (i.e. $p < 0.05$)?

(PS: It can!)

(PPS: Physicians think this

is what we give them.)

… Then assess risks in this context.

The Final Answer

"… I hope we also recognize when what's meaningful to our patients trumps anything medical that we can offer."

Mikkael A. Sekeres, M.D.
"The Best Medicine? What's Meaningful to Our Patients"
New York Times
3 May 2018
Stephen J. Ruberg
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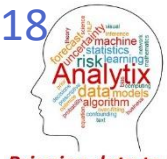

Presentation Estimands

1. Proportion of those who had an adverse reaction to these concepts/recommendations
2. Proportion of those who tuned out due to lack of interest
3. For those who followed this presentation to the end …

THANK YOU.

I hope the expected change in your thinking

is scientifically meaningful !!