Causal estimands and inference for a principal stratum of adherers in clinical trials

Stephen J. Ruberg, Analytix Thinking, LLC

Yongming Qu, Eli Lilly and Company

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Outline

Stephen Ruberg

Overview and motivation for the Adherence Average Causal Estimands

Yongming Qu

Technical details and examples

Perspective

Science is fundamentally about understanding the true cause-and-effect relationships in nature

Statistics is the science of inferring what is likely to be true

Drug Development Goal

Does this treatment ***cause*** that outcome?

- Efficacy
- Safety/adverse events

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)

MORE IMPORTANT

- ***WHAT IS THE RIGHT QUESTION?***
  - ***WHAT*** does the traveler want to know?
  - ***WHAT*** DO YOU WANT TO KNOW?
  - ***WHAT*** would you tell your companions?

ICH E9(R1) Addendum

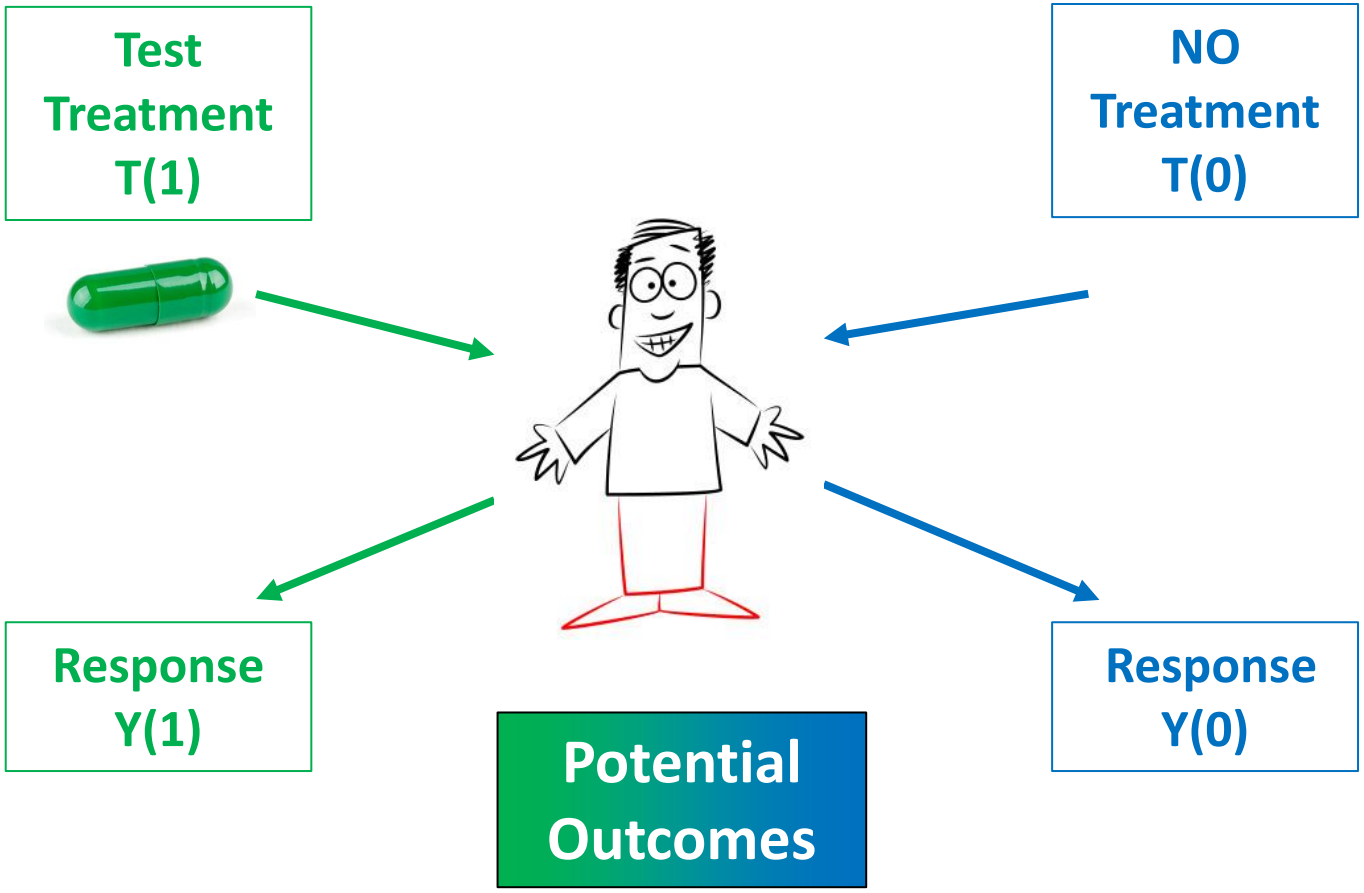
A.3 ESTIMANDS

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)."

Treatment Effect

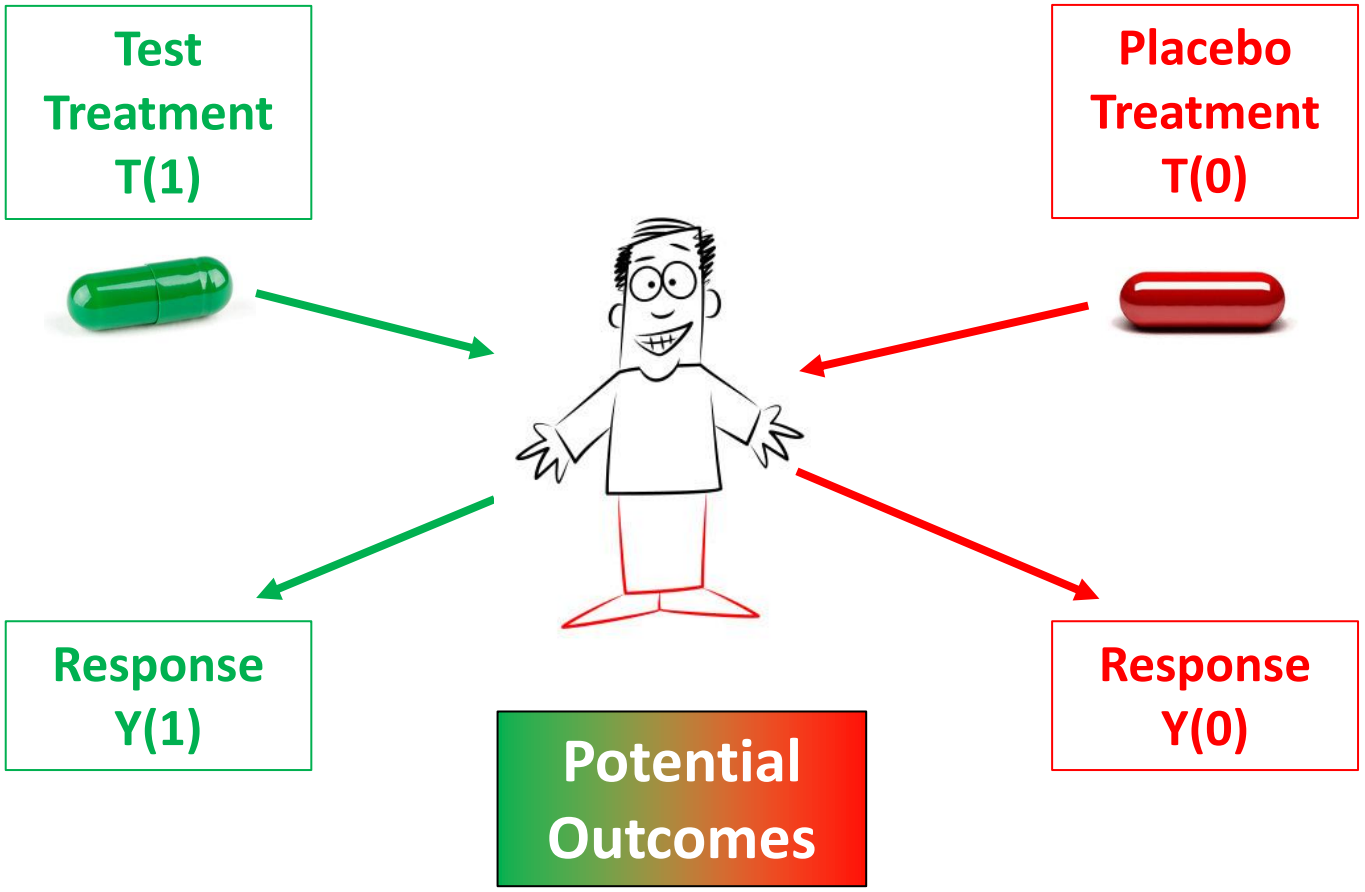
Ideal



Treatment Effect = $Y(1) - Y(0)$

Treatment Effect

First Approximation



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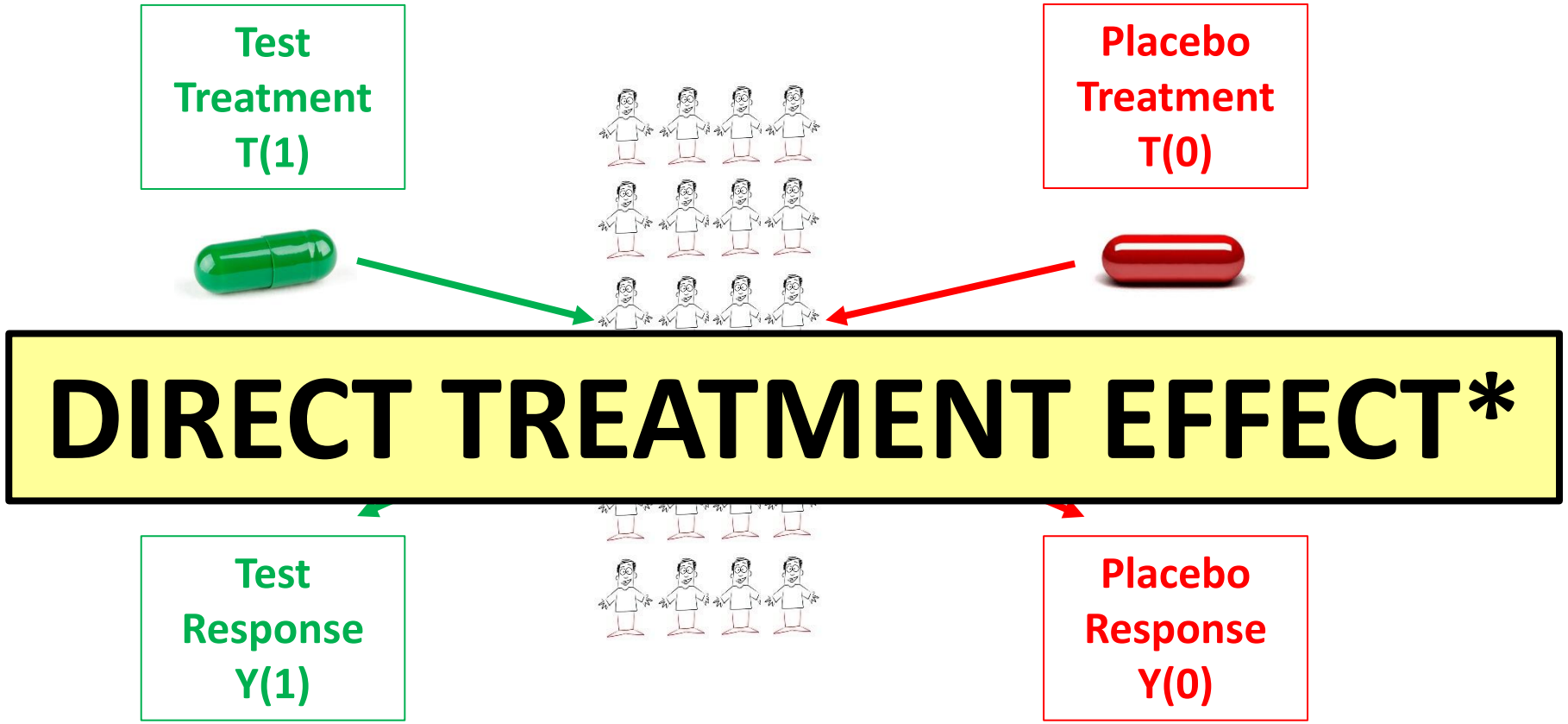
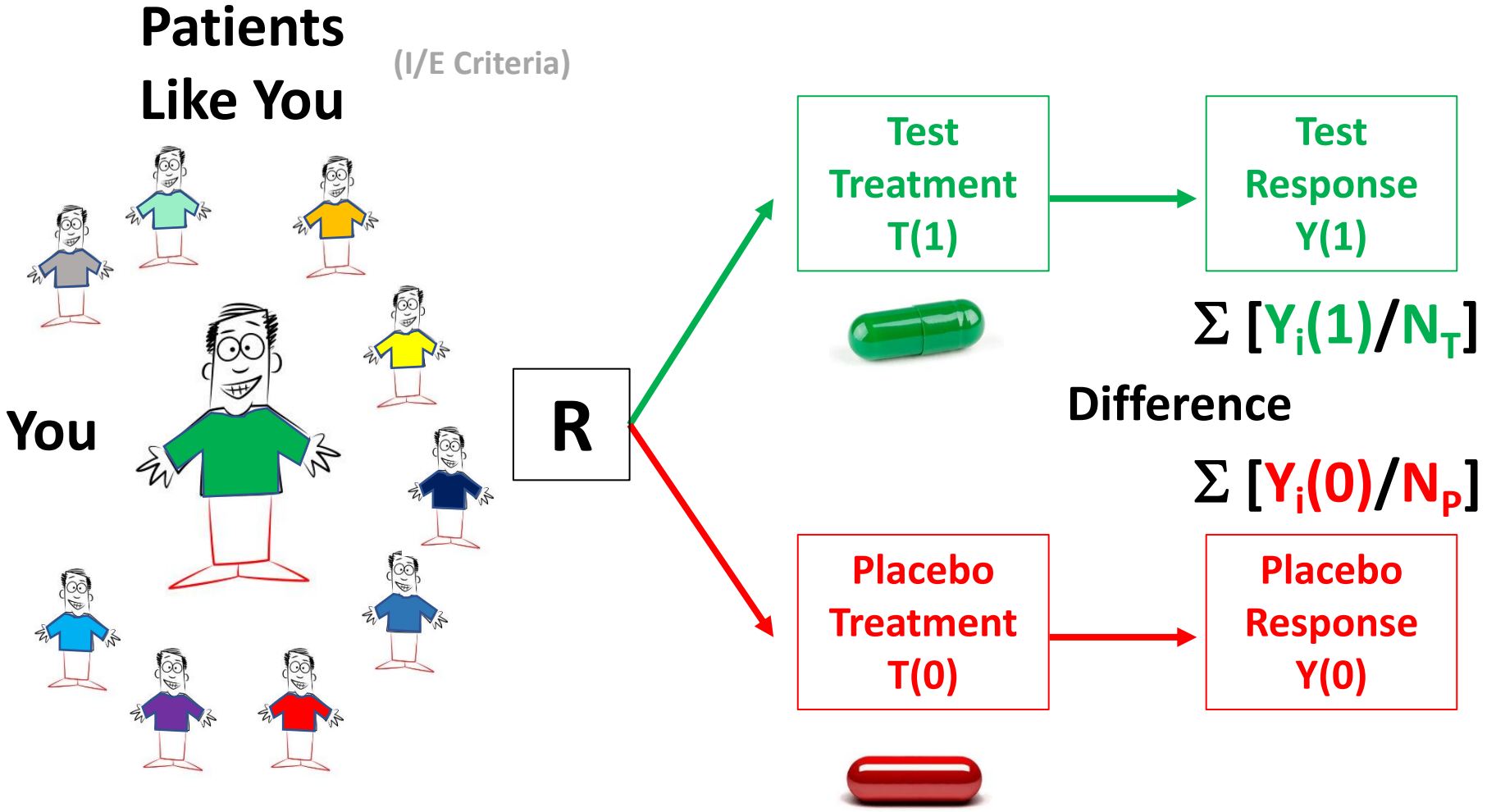
Treatment Effect



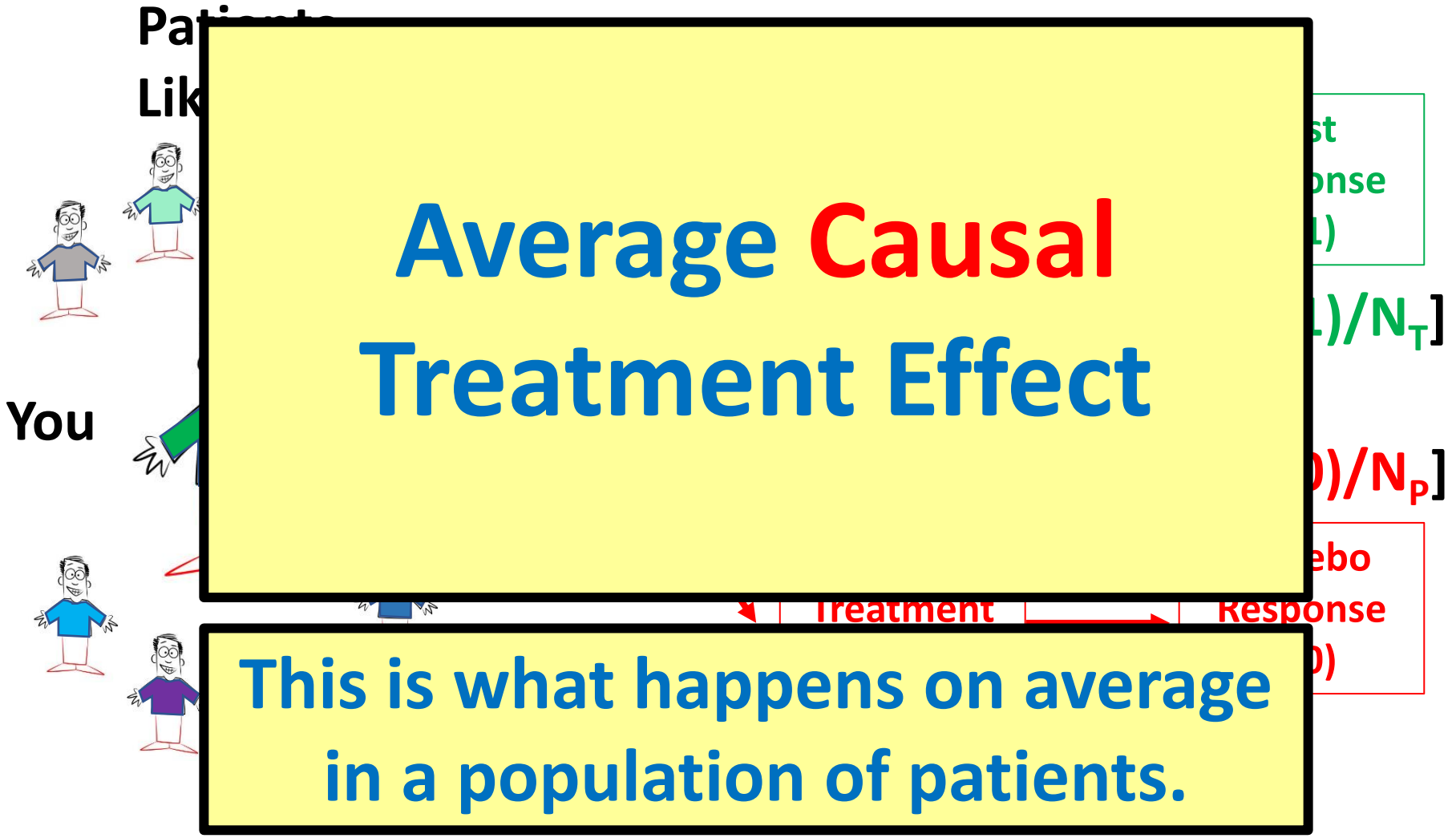
$$\text{Estimator} = \Sigma\,[Y_i(1) - Y_i(0)] \,/\, N$$

*"Controlled Direct Effect" as defined in
Pearl, J. (2009) Causal Inference in Statistics: An Overview. *Statistics Surveys Vol. 3.* pp. 96–146.

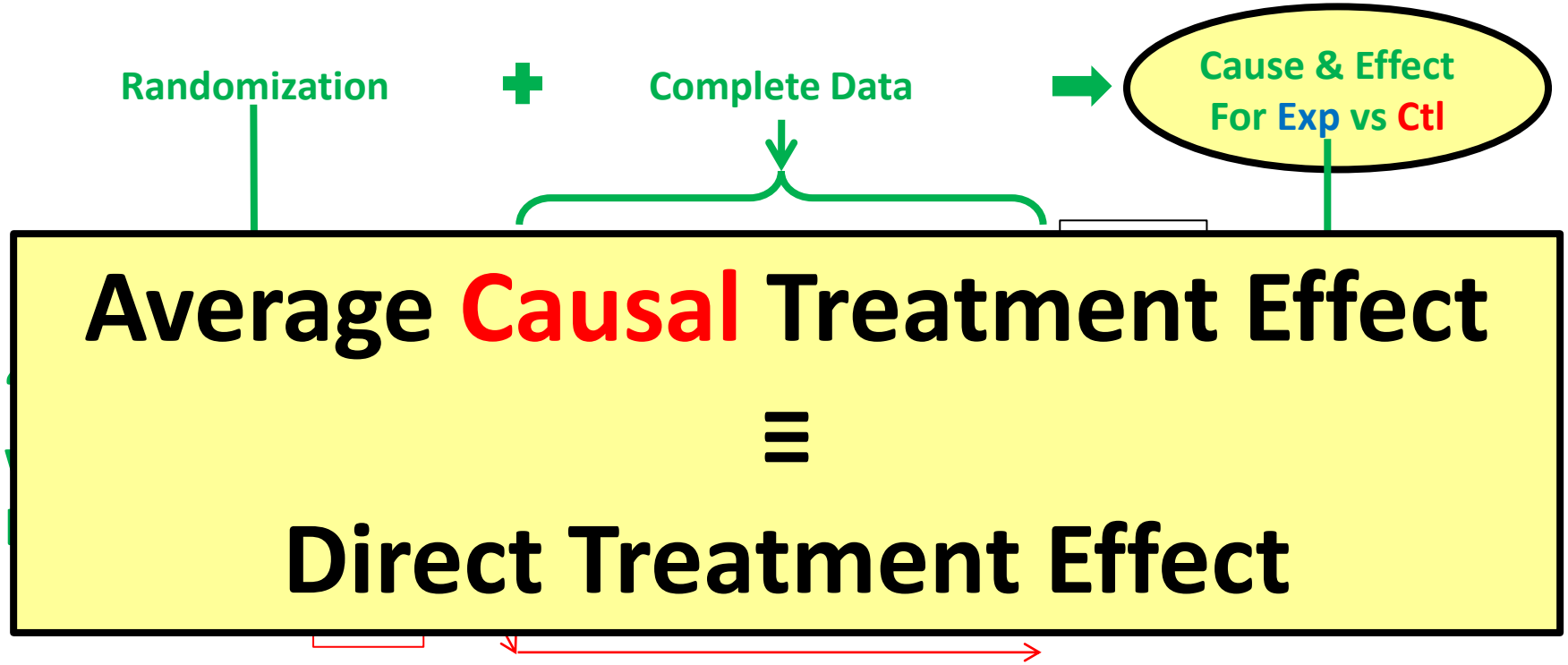
Treatment Effect in Randomized Trials



Treatment Effect in Randomized Trials



Treatment Effect in Randomized Trials



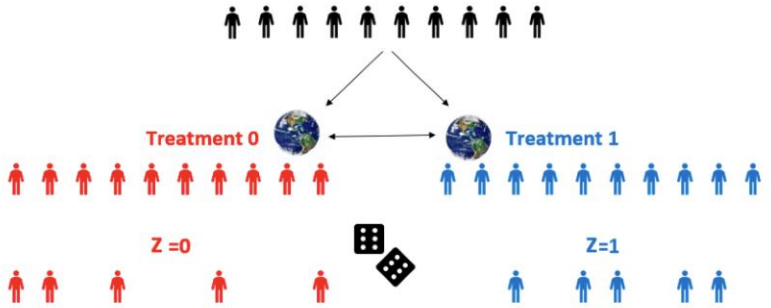
Charles Sanders Peirce & Joseph Jastrow (1885). On Small Differences in Sensation. First published in Memoirs of the National Academy of Sciences, 3, 73-83. (Presented 17 October 1884)

Fisher, R. A. *Statistical Methods for Research Workers*. (Oliver & Boyd, Edinburgh, 1925).

Kelly Van Lancker

causation $\neq$ association? (1)

Consider a randomized trial



- In real life, patients are randomized to only one group.
- Randomization ensures that causal contrasts correspond to statistical contrasts:
  - $E\left(Y^1\right) - E\left(Y^0\right) = E\left(Y|Z=1\right) - E\left(Y|Z=0\right)$.

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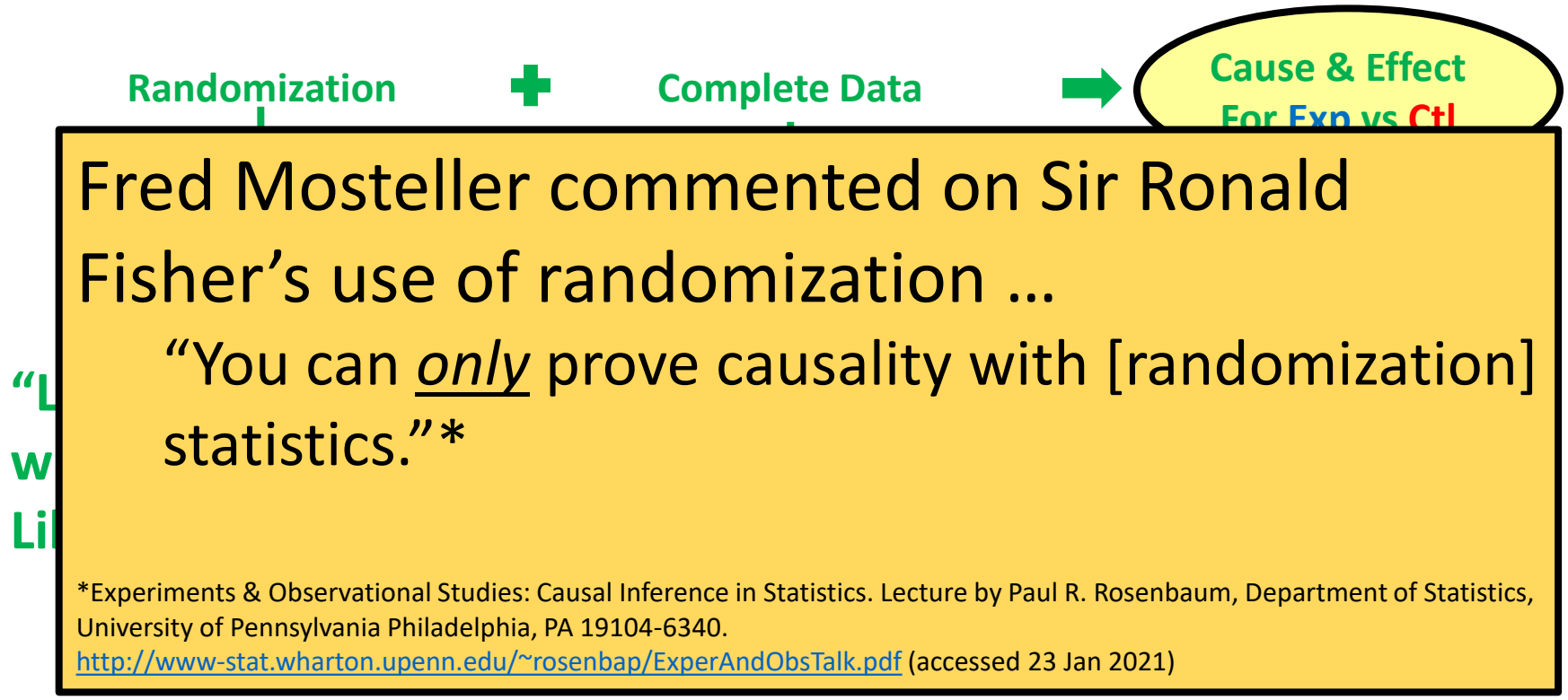
Treatment Effect in Randomized Trials



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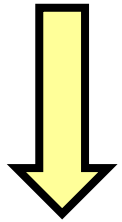
Summary So Far

Goal: Estimate the Direct Treatment Effect (DTE)

- The basis for cause and effect

Randomization is THE tool for estimating DTE

- **Requires** complete data
- **Requires** adherence to randomized study treatment



Average Causal Treatment Effect ≡ Direct Treatment Effect

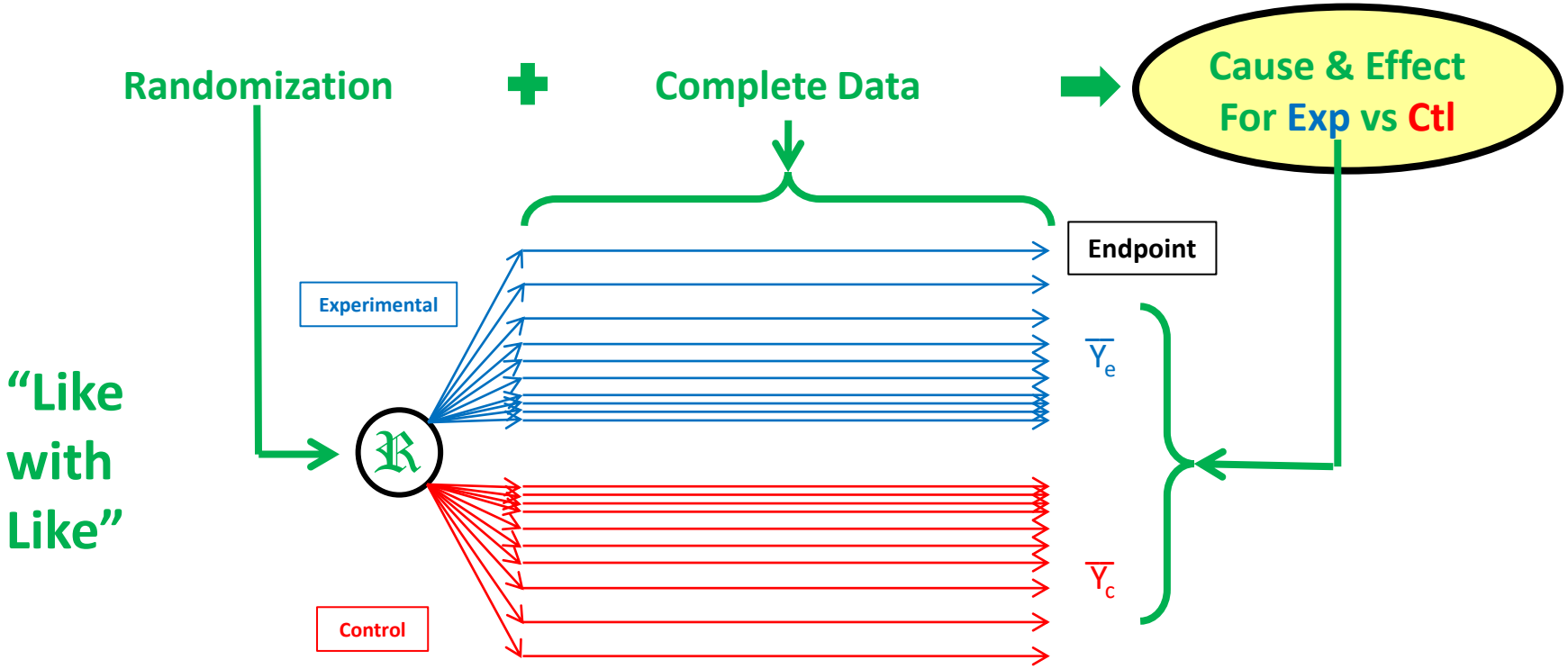
Treatment Effect Questions

What is the Study Treatment effect …

- *Regardless* of whether/how the study treatment is taken
- *If* the study treatment is taken as directed
- *When* the patient takes the study treatment
- *While* the patient is taking the study treatment
- For patients who *adhere* to the study treatment

If all randomized patients complete the trial as planned (i.e., take all their study medication, follow the protocol visits to the end, etc.), **then these are all the same questions.** There is no controversy as to what to estimate.

Treatment Effect Questions



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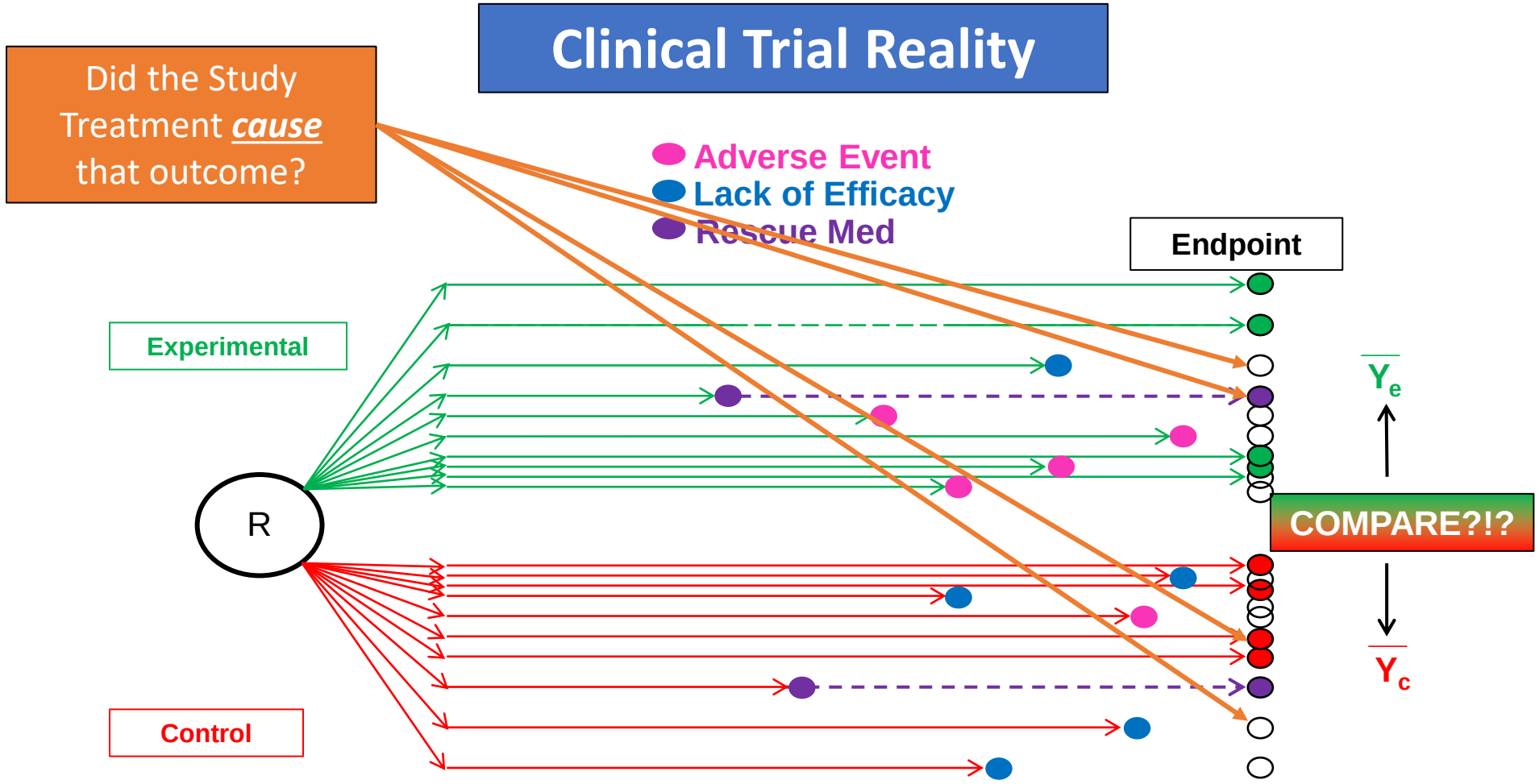
Treatment Effect Questions



Kelly Van Lancker

causation $\neq$ association? (2)

- So, do we need to care about the question whether causation $\neq$ association in a randomized trial?
- Yes!
- Randomization can be broken
  - due to intercurrent events,
  - missing data, or
  - when interest lies in generalizing trial results.

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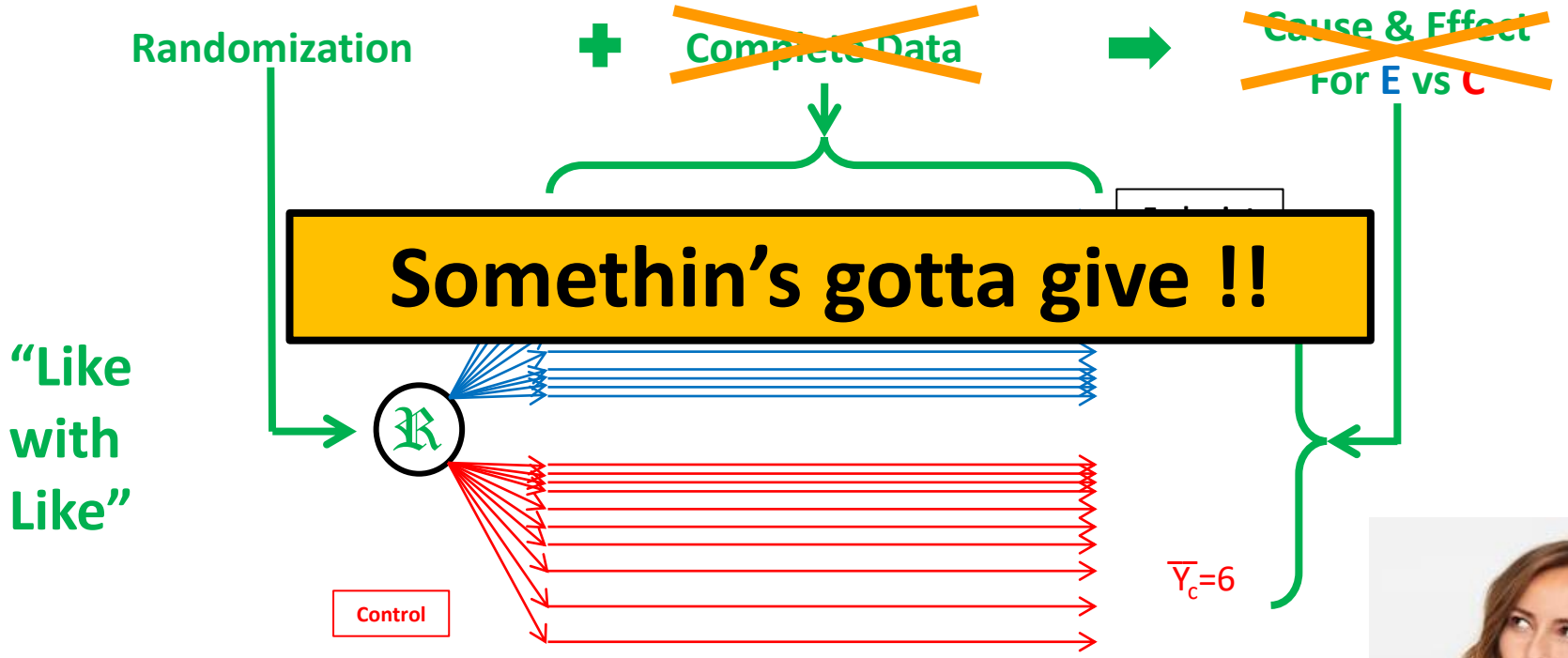
Treatment Effect Questions

… in the presence of intercurrent events.



Treatment Effect Questions

Bold Proclamation #1

Discontinuation of the "estimand-defined study treatment" breaks the logic of causal inference.

Therefore, the only Intercurrent Event of interest is discontinuation of the estimand-defined study treatment (EDST).

There are multiple reasons for DC of the EDST, …
Adverse events, lack of efficacy, administrative reasons, …
but the central issue is DC of the EDST.

Treatment Effect Questions

Bold Proclamation #2A

All of ICH E9(R1)
is about how to handle discontinuation of the estimand-defined study treatment (EDST).

Treatment Effect Questions

Bold Proclamation #3B

All the strategies in ICH E9(R1)
are an attempt
to "create" complete data and
restore the logical basis
for causal inference.

Estimation Strategies

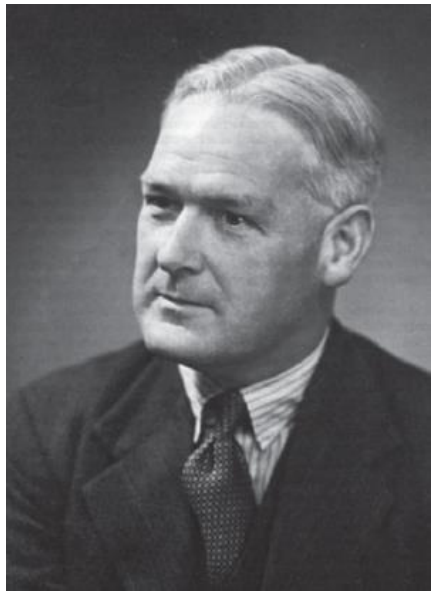
- **Treatment policy** (change treatment definition)
  - There are no DC of the EDST
  - Follow all patients regardless of treatment or protocol violations
  - Obtain outcome measure at the end of the trial for all patients
- **Hypothetical** (change the analysis approach)
  - For those who DC their EDST, predict/impute/model their endpoint outcome
- **Composite** (change the primary outcome variable)
  - Create a new response variable that is defined for all patients
- **While on Treatment** (change the duration of assessment)
  - Measure outcome on their EDST up to the occurrence of the first ICE
- **Principal Stratum** (change the population of interest)
  - Assess population of adherent patients – all have complete data*

* See Ilya Lipkovich's presentation. There are other PS that can be defined for which complete data may not exist (e.g., the PS that achieves some early response to treatment).

Treatment Effect Questions

- "… in the strictly controlled trial of a new treatment we almost invariably seek to measure its strength and, sometimes, its dangers …"

- "In many trials the original careful **randomization** of patients to treatment and control **can be later disturbed by selective withdrawals of patients who cease to take a treatment or** are proved sensitive to it so that they **have to be withdrawn**. **The experiment is necessarily weakened—indeed we may on occasions have to assess the value of an *intent* to treat rather than a treatment."**



Sir Austin Bradford Hill

10th Alfred Winston Memorial Lecture to the Institute of Actuaries, 1962

Treatment Effect Questions

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Your Run-of-the-Mill Statistician

PSI Causal Inference Webinar, 2023

Some Final Thoughts (1)

The Tripartite Approach (TEA)

Three Causal (and clinically meaningful) Estimands

1. The proportion of patients that discontinue study treatment due to adverse effects
   - Can also assess time to discontinuation
2. The proportion of patients that discontinue study treatment due to lack of efficacy
   - Need to assess time to discontinuation
3. For those who could adhere to their study 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.

Some Final Thoughts (2)

Tripartite Estimand Approach (TEA)

What can I expect when I take this treatment you are recommending?

Well, here is the best way I can describe it to you, using the best data from clinical studies.

First, I know safety is an issue for you, and there is a 10% chance that you could have an adverse reaction that will prevent you from taking this medication.
{goes on to explain what adverse reactions and their characteristics}

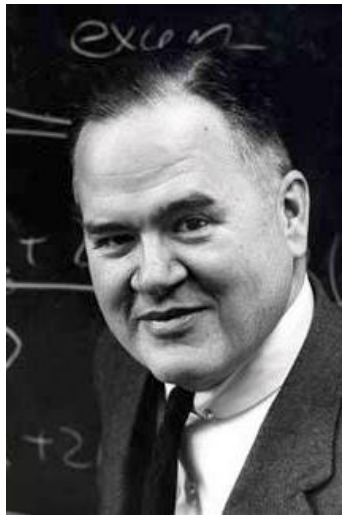
Second, this drug does not work for everyone, and there is about a 20% chance that you or I might choose to try something else. But, let's give it at least 3 months to see how it works.

Third, 70% of patients can 'stick with this treatment' and do quite well. On average, those patients experienced a 60% improvement over doing nothing (i.e. placebo) and a 30% improvement over Drug X."
{goes on to explain long-term adverse reactions and their characteristics}

Some Final Thoughts (3)

Far better an approximate answer to the *right* question, which is often vague, than an *exact* answer to the wrong question, which can always be made precise."

John Tukey
The Future of Data Analysis
The Ann of Math Stat (**1962**, pp. 13-14)



Yongming Qu

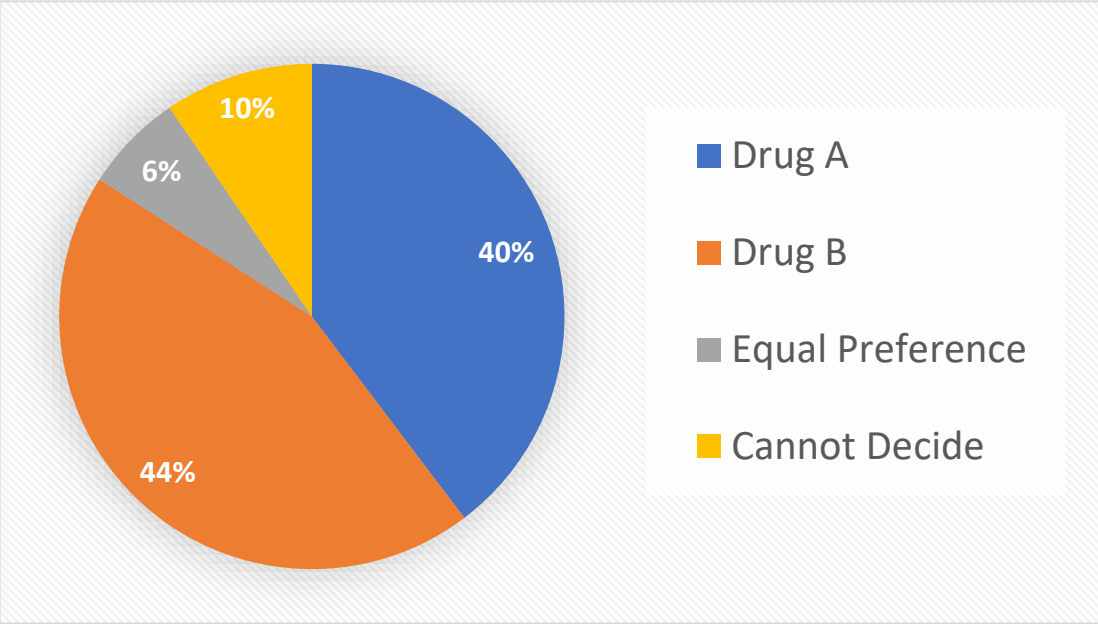
Adheres Average Causal Effect Estimators Statistical Methods and Examples

All randomized patients vs. adherers

Adherers: Patients who complete the randomized treatment without intercurrent events

- Suppose we have 2 anti-diabetes drugs
  - Drug A: Only 50% of patients can tolerate the drug (adherers), and on average it can reduce HbA1c by 2% for adherers
  - Drug B: Every patient can tolerate the drug, and on average it can reduce HbA1c by 1%
- If you were to treat a diabetes patient, which drug do you prefer to try first?

A simple survey for researchers in diabetes



N = 63

Some Comments

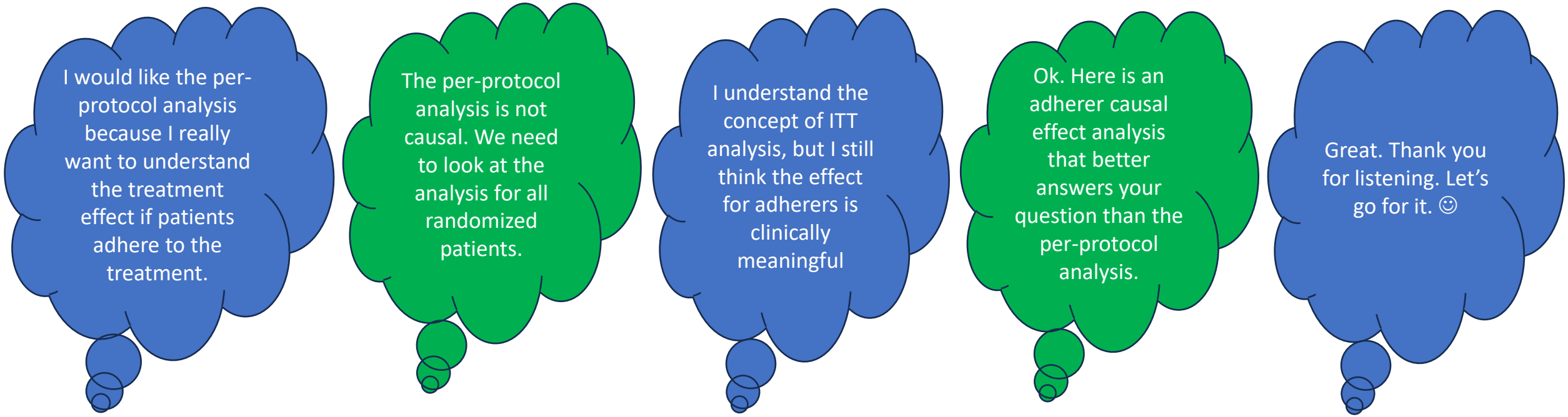
- "It depends on patients' baseline information. If a patient had high HbA1c, I would start Drug A; Otherwise, I would start Drug B"
- "What type of tolerability? It is important for my decision"

Estimands for adherers (based on principal strata) are equally important as estimands for all randomized patients

Clinical questions

- Physicians: What is the treatment effect for adherers? (a very vague question)
- Traditionally, the so-called per-protocol analysis
  - Using the regulaor statistical models (e.g., linear models) by only including those patients who adhere to the study medication during the study
  - It is not “causal”
- What is the new analysis to replace the non-causal per-protocol analysis?

A real dialogue between study physician and statistician for a phase 2 study



Physician **Statistician** **Physician** **Statistician** **Physician**

Principal Strata based on Adherence

***A*(*T*) is the indicator of adherence on treatment *T* (*T* = 0, 1)**

Adherence to Control Treatment	Adherence to Experimental Treatment		
	$A(1) = 0$	$A(1) = 1$	$A(1) \in \{0,1\}$
$A(0) = 0$			
$A(0) = 1$			
$A(0) \in \{0,1\}$			

Principal Strata

Frangakis, C. E., & Rubin, D. B. (2002). Principal stratification in causal inference. *Biometrics*, *58*(1), 21-29.

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	$A(1) = 0$	$A(1) = 1$	$A(1) \in \{0,1\}$
$A(0) = 0$			
$A(0) = 1$		S_{++}	S_{+*}
$A(0) \in \{0,1\}$		S_{*+}	S_{**}

Patients that would adhere to both treatments

Patients that would adhere to experimental treatment

All randomized patients

Estimands based on Adherence

Y(t) is the potential outcome on treatment t (t=0,1)

Adherence to Control Treatment	Adherence to Experimental Treatment		
	$A(1) = 0$	$A(1) = 1$	$A(1) \in \{0,1\}$
$A(0) = 0$			
$A(0) = 1$		$E[Y(1) - Y(0)\|S_{++}]$	$E[Y(1) - Y(0)\|S_{+*}]$
$A(0) \in \{0,1\}$		$E[Y(1) - Y(0)\|S_{*+}]$	$E[Y(1) - Y(0)\|S_{**}]$

Patients that would adhere to both treatments

Patients that would adhere to experimental treatment

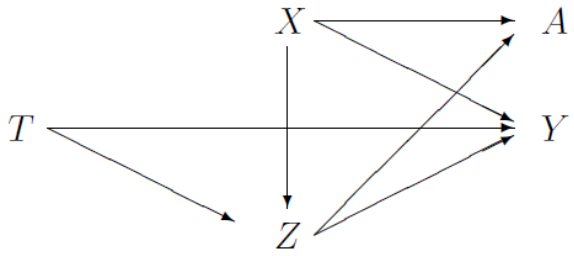
All randomized patients

Existing methods for estimating treatment effect for principal strata

- Estimators using the monotonicity assumption
  - For any patient, $A(0) = 0 \Rightarrow A(1) = 0$ or $A(1) = 0 \Rightarrow A(0) = 0$ Drawback: a simplistic deterministic relationship on random variables of A(0) and A(1)
- Estimators based on principal scores
  - Model the probability of principal stratum membership through baseline covariates: $\Pr(A(1) = 1|X) = g(X)$
  - Drawback: assuming the principal stratum membership can be directly modeled through only baseline covariates
- We introduce a method using intermediate outcomes to utilize the predictive model and improved estimation for the principal score (Qu et al 2000, Luo et al 2021, Zhang et al 2022, Chen et al 2023)

Assumptions

***X* is the baseline covariates**
***Z*(t) is the potential intermediate outcome on treatment t**
***A*, *Y*, *Z* are the outcome under the actual assigned treatment**



A1: $Y = Y(1)T + Y(0)(1-T)$

A2: $Z = Z(1)T + Z(0)(1-T)$

A3: $A = A(1)T + A(0)(1-T)$

⇒ Stable unit treatment value assumption (SUTVA)

A4: $T \perp \{Y(1), A(1), Z(1), Y(0), A(0), Z(0)\}|X$ ⇒ Ignorable treatment assignment assumption

A5: $A(i) \perp \{Y(1), Y(0), Z(1-i)\}|\{X, Z(i)\}, \quad \forall i = 0, 1$ ⇒ Ignorable adherence assumption

A6: $Y(i) \perp Z(1-i)|\{X, Z(i)\}, \quad \forall i = 0, 1$

A7: $Z(0) \perp Z(1)|X$

⇒ Conditional potential outcome cross-world independence assumption

Key ideas

- Use X, Z, and Y to build predictive models
  - $f(y|x,z)$
  - $f(y|x) = \int f(y|x,z)dz$
- Use X, Z, and A to build models for the probability of principal stratum membership (principal score)
  - $\Pr(A = 1|x,z)$
  - $\Pr(A = 1|x) = \int \Pr(A = 1|x,z)\, dz$

Notation

Notation	Description
$g(X,Z) \coloneqq \Pr(A=1\|X,Z)$	The probability of being adherent given X and Z
$h_i(X) \coloneqq E\{(g(X,Z(i))\|X\}$	The conditional probability of being adherent only conditional on baseline covariate X, for treatment i
$F_{Z(i)\|X}$	CDF of $Z(i)$ given X
$\psi_i\big(X,Z(i)\big) = E\{Y(i)\|X,Z(i)\}$	The conditional expectation of the outcome given baseline covariate X and the intermediate outcome $Z(i)$
$\phi_i(X) = E\big\{\psi_i\big(X,Z(i)\big)\big\|X\big\}$	The conditional expectation of the outcome given the covariate X
$\varphi_i(X) = E\big\{g(X,Z(i))\psi_i\big(X,Z(i)\big)\big\|X\big\}$	The conditional expectation for the potential outcome under treatment i for patients who are adherent to treatment i

Adherence causal estimators (ACEs)

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

Mixed Model Repeated Measures (MMRM)

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

Marginal Structural Model (MSM)

Estimator for $E[Y(1) - Y(0)|S_{*+}]$ based on Method A

$$\frac{1}{n_{11}} \sum_{j \in \{j:T_j=1, A_j=1\}} Y_j - \frac{1}{n_{11}} \sum_{j \in \{j:T_j=1, A_j=1\}} \hat{\phi}_0(X_j)$$

Step	Data Used	Estimator for Parameter or Model
1	*X* and *Z* from the **control** group	$\hat{F}_{Z(0)\|X}$: Conditional distribution of $Z(0)$ given X
2	*X*, *Z* and *Y* from the **control** group	$\hat{\psi}_0\big(X, Z(0)\big) = E\{Y(0)\|X, Z(0)\}$
3	$\hat{F}_{Z(0)\|X}$ (Step 1) and $\hat{\psi}_0\big(X, Z(0)\big)$ (Step 2)	$\hat{\phi}_0(X) = E\{\hat{\psi}_0\big(X, Z(0)\big)\|X\}$
4	*X* from the **treatment** group	$\hat{\phi}_0(X_j)$ for subjects with $T_j = 1$

Estimator for $E[Y(1) - Y(0)|S_{*+}]$ based on Method B

$$\frac{1}{n_{11}} \sum_{j \in \{j:T_j=1, A_j=1\}} Y_j - \frac{n_1}{n_{11} n_0} \sum_{j \in \{j:T_j=0, A_j=1\}} \frac{\hat{h}_1(X_j) Y_j}{\hat{g}(X_j, Z_j)}$$

Step	Data Used	Estimator for Parameter or Model
1	*X* and *Z* from the **experimental** treatment group	$\hat{F}_{Z(1)\|X}$: Conditional distribution of $Z(1)$ given X
2	*X*, *Z* and *Y* from the **BOTH** treatment groups	$\hat{g}(X, Z) \coloneqq \widehat{\Pr}(A = 1 \| X, Z)$
3	$\hat{F}_{Z(1)\|X}$ (Step 1) and $\hat{g}(X, Z)$ (Step 2)	$\hat{h}_1(X) \coloneqq E\left\{\hat{g}\left(X, \hat{Z}(1)\right) \middle\| \mathrm{X}\right\}$
4	*X* from the **control** group	$\hat{h}_1(X_j)$ for subjects with $T_j = 0$ $\hat{g}(X_j, Z_j)$ for subjects with $T_j = 0$

Estimator for $E[Y(1) - Y(0)|S_{++}]$ based on Method B

$$\frac{\sum_{j\in\{j:T_j=1,A_j=1\}} \hat{h}_0(X_j)Y_j}{\sum_{j\in\{j:T_j=1,A_j=1\}} \hat{h}_0(X_j)} - \frac{\sum_{j\in\{j:T_j=0,A_j=1\}} \hat{h}_1(X_j)Y_j}{\sum_{j\in\{j:T_j=0,A_j=1\}} \hat{h}_1(X_j)}$$

Probability of being adherent to the control treatment

$$h_i(X) \coloneqq E\{(g(X, Z(i))|X\}$$

Longitudinal repeated measurements

$A = \prod_{k=0}^{K-1} A^{(k)}$, and $A^{(k)}$ satisfies the Markov Property,

$$\Pr(A^{(k)} = 1 | A^{(k-1)} = 1, X, Z^{(1)}, Z^{(2)}, \cdots, Z^{(k)}) = \Pr(A^{(k)} = 1 | A^{(k-1)} = 1, X, Z^{(k)})$$

$$\Pr(A = 1) = g(X, Z, \beta) = \prod_{k=0}^{k-1} \Pr\left(A^{(k)} = 1 \middle| A^{(k-1)} = 1, X, Z^{(k)}\right)$$

$$= \prod_{k=0}^{K-1} g_k(X, Z^{(k)}, \beta^{(k)})$$

Implementing AdACE – “adace” R package

- https://cran.r-project.org/web/packages/adace/index.html
- est_S_Star_Plus_MethodA(X, A, Z, Y, TRT)

  est_S_Plus_Plus_MethodA(X, A, Z, Y, TRT)
  - X: a matrix, each row is a vector for baseline covariates for a subject
  - A: adherence status (A = 1 for adherence)
  - Z: a list of matrices, each list is the value for a set of intermediate outcome at each intermediate time point
  - Y: a vector for the value of the response variable
  - TRT: a vector for treatment indicator (1 for the experimental treatment and 0 for control)

Implementing AdACE – multiple imputation

TABLE 1 Illustration of MI to impute the potential outcome under treatment $T = t$ for patients assigned to treatment $T = 1 - t$

Subject	Randomized treatment	X	$Z^{(1)}$	$Z^{(2)}$	$Z^{(3)}$	$I^{(1)}$	$I^{(2)}$	$I^{(3)}$	Y
001	t	√	√	√	√	1	1	1	√
002	t	√	√	√	√	1	1	0	·
003	t	√	√	√	·	1	0	0	·
…									
101	$1 - t$	√	·	·	·	·	·	·	·
102	$1 - t$	√	·	·	·	·	·	·	·
103	$1 - t$	√	·	·	·	·	·	·	·

Abbreviations: MI, multiple imputation; "√", observed data; "·", unobserved data.

$I^{(1)}, I^{(2)}$, and $I^{(3)}$ are the indicators for adherence at the 3 post-baseline time points, respectively. The overall adherence status $A = I^{(1)}\ I^{(2)}\ I^{(3)}$

Repeat the above process using source data from patients randomized to 1-*t*.

Luo, J., Ruberg, S. J., & Qu, Y. (2022). Estimating the treatment effect for adherers using multiple imputation. Pharmaceutical Statistics, 21(3), 525-534.

Estimator for S_{*+}

Table 2: Estimators for the mean response on principal strata defined by treatment adherence

PS	Treatment	Patient	Estimator
S_{*+}	$T=0$	E_0	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}\left(A_{0j}Y_{0j}+(1-A_{0j})Y_{0j}(0)^{(m)}\right)}{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}}\right\}$
		E_1	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_1}A_{1j}Y_{1j}(0)^{(m)}}{\sum_{j=1}^{n_1}A_{1j}}\right\}$
		$E_0\cup E_1$	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}\left(A_{0j}Y_{0j}+(1-A_{0j})Y_{0j}(0)^{(m)}\right)+\sum_{j=1}^{n_1}A_{1j}Y_{1j}(0)^{(m)}}{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}+\sum_{j=1}^{n_1}A_{1j}}\right\}$
	$T=1$	E_0	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}Y_{0j}(1)^{(m)}}{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}}\right\}$
		E_1	$\frac{\sum_{j=1}^{n_1}A_{1j}Y_{1j}}{\sum_{j=1}^{n_1}A_{1j}}$
		$E_0\cup E_1$	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}Y_{0j}(1)^{(m)}+\sum_{j=1}^{n_1}A_{1j}Y_{1j}}{\sum_{j=1}^{n_0}A_{0j}(1)^{(m)}+\sum_{j=1}^{n_1}A_{1j}}\right\}$

E_0 is the set for patients randomized to the control group; E_1 is the set for patients randomized to the experimental treatment group

Estimator for S_{++}

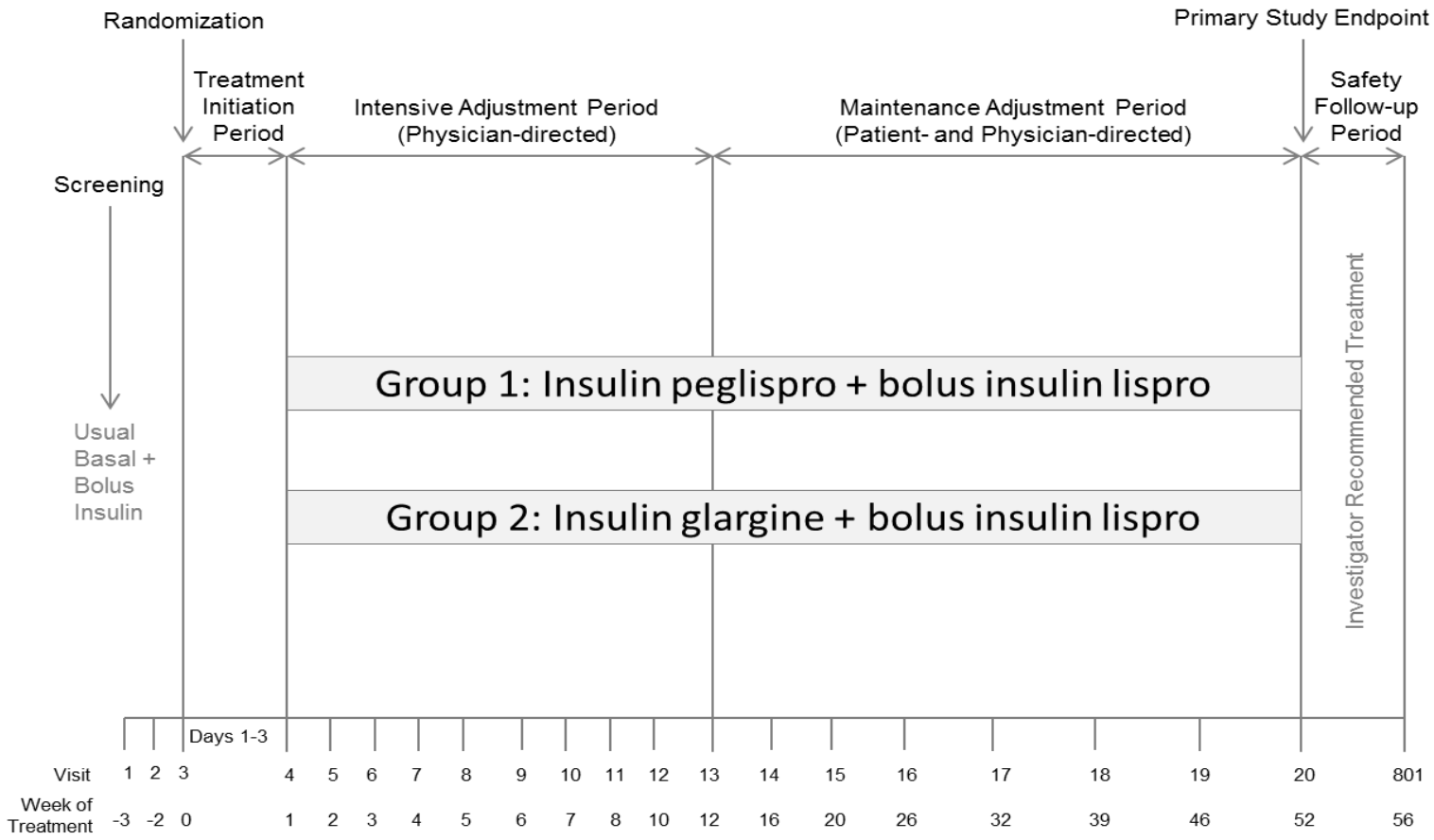
Table 2: Estimators for the mean response on principal strata defined by treatment adherence

S_{++}	$T=0$	E_0	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}Y_{0j}}{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}}\right\}$
		E_1	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}Y_{1j}(0)^{(m)}}{\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}}\right\}$
		$E_0 \cup E_1$	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}Y_{0j}+\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}Y_{1j}(0)^{(m)}}{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}+\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}}\right\}$
	$T=1$	E_0	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}Y_{0j}(1)^{(m)}}{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}}\right\}$
		E_1	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}Y_{1j}}{\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}}\right\}$
		$E_0 \cup E_1$	$\frac{1}{M}\sum_{m=1}^{M}\left\{\frac{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}Y_{0j}(1)^{(m)}+\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}Y_{1j}}{\sum_{j=1}^{n_0} A_{0j}A_{0j}(1)^{(m)}+\sum_{j=1}^{n_1} A_{1j}A_{1j}(0)^{(m)}}\right\}$

E_0 is the set for patients randomized to the control group; E_1 is the set for patients randomized to the experimental treatment group

Application

IMAGINE-3 Study



Primary Endpoint

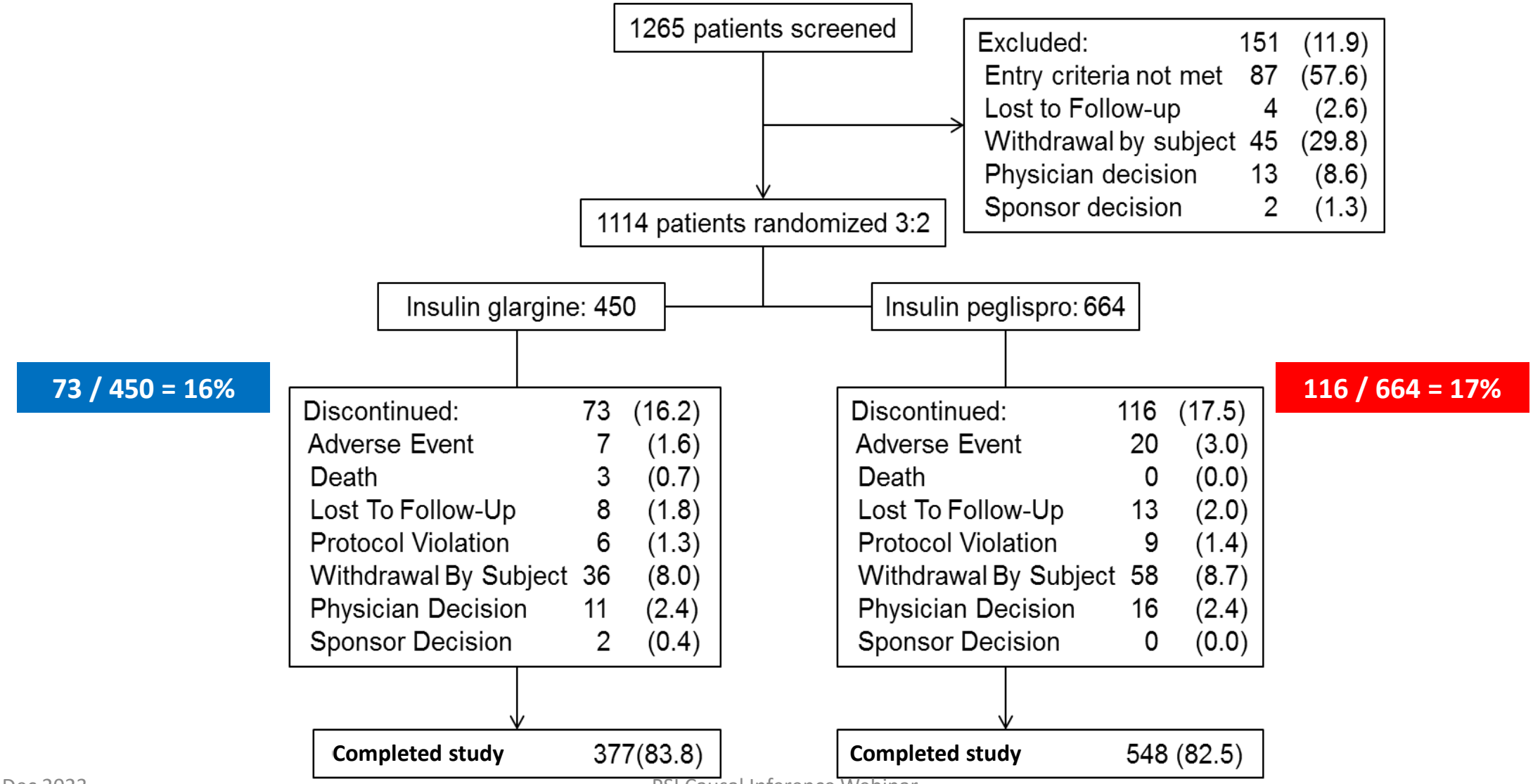
HbA1c at 52 weeks

Primary Analysis

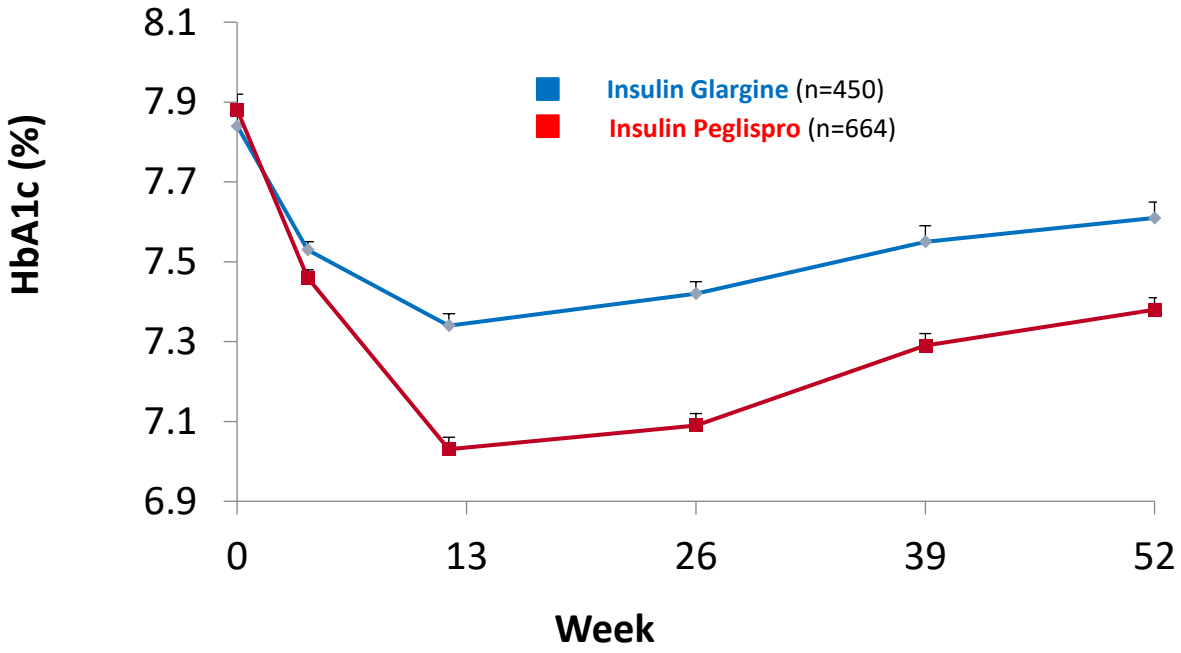
Non-Inferiority Margin = 0.4%

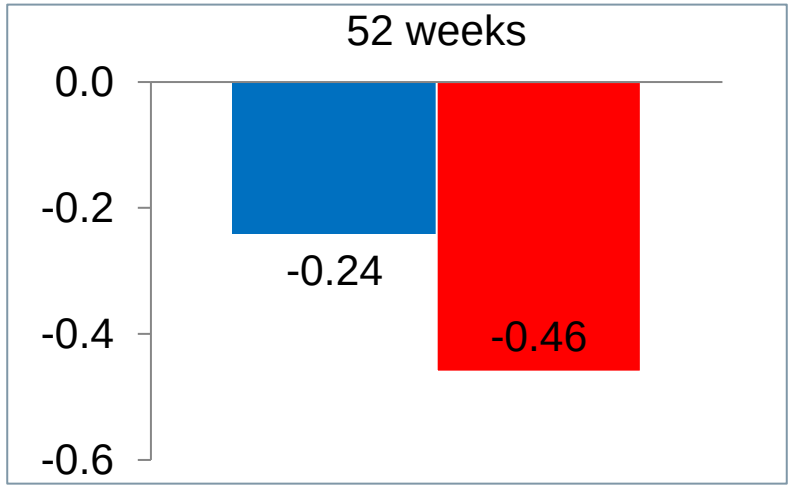
Bergenstal RM, Lunt H, Franek E, etc, Diabetes Obes Metab. 2016 Nov;18(11):1081-1088

Patients disposition



Primary result: HbA1c at 52 weeks





MMRM Analysis

LSM Diff = -0.22%, CI = (-0.32, -0.12)

Primary endpoint was met since the upper limit of CI is <0.4%

Superiority was also met

Classify the reasons for ICEs (treatment discontinuations)

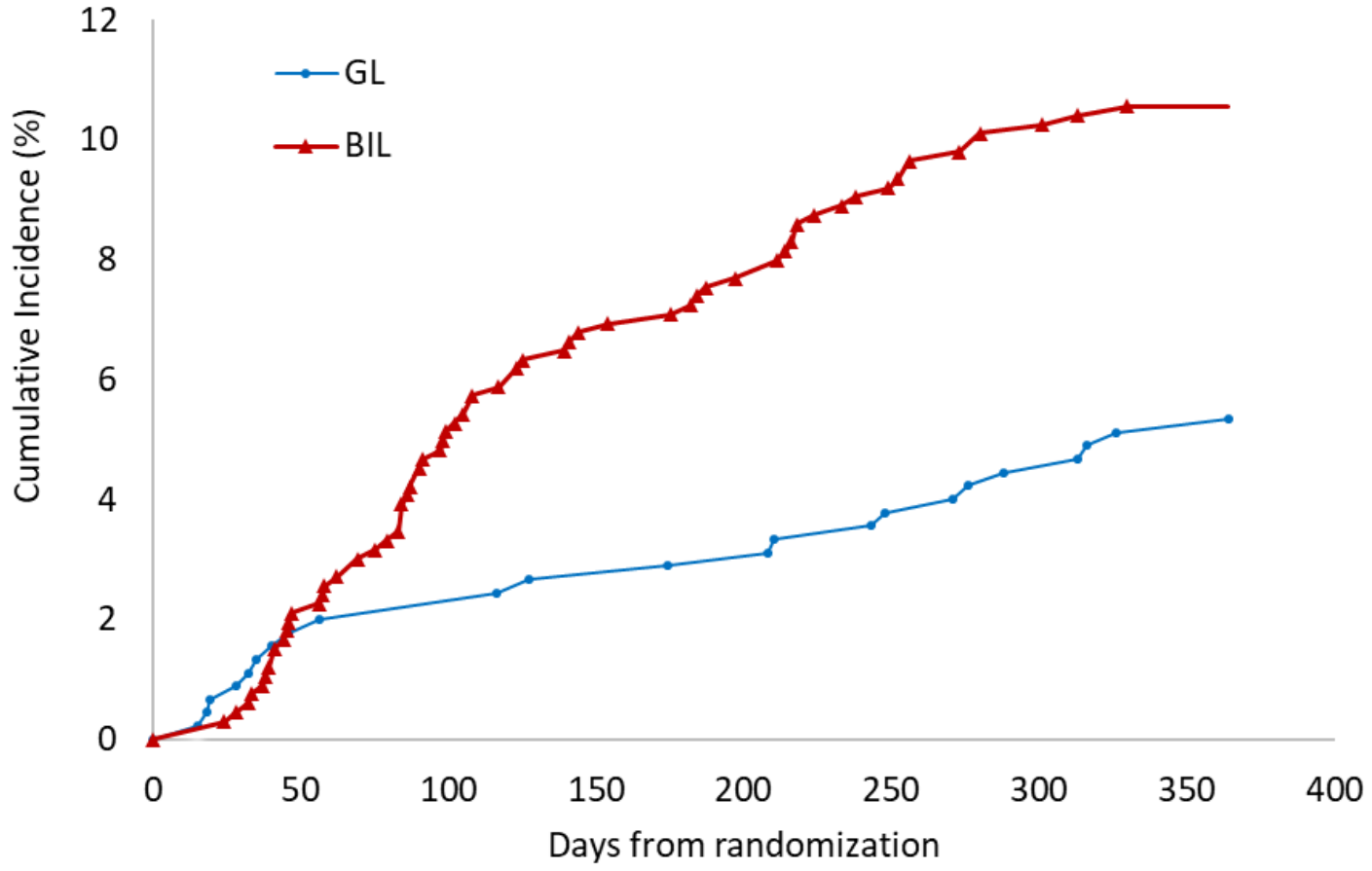
Reason for Treatment Discontinuation		Category of ICE	Classification Criteria
• Adverse Event • Death	→	Category I (Potentially Related to Safety)	With obvious AE or abnormal lab which could lead to discontinuation
• Lost To Follow-Up • Protocol Violation • Withdrawal By Subject • Physician Decision • Sponsor Decision	→	Category 2 (Potentially Due to LoE)	No obvious improvement in HbA1c or glucose at discontinuation as compared to baseline values
	→	Category 3 (Administrative)	No obvious safety or lack of efficacy reason leading to discontinuation

Patients Disposition After Reclassification

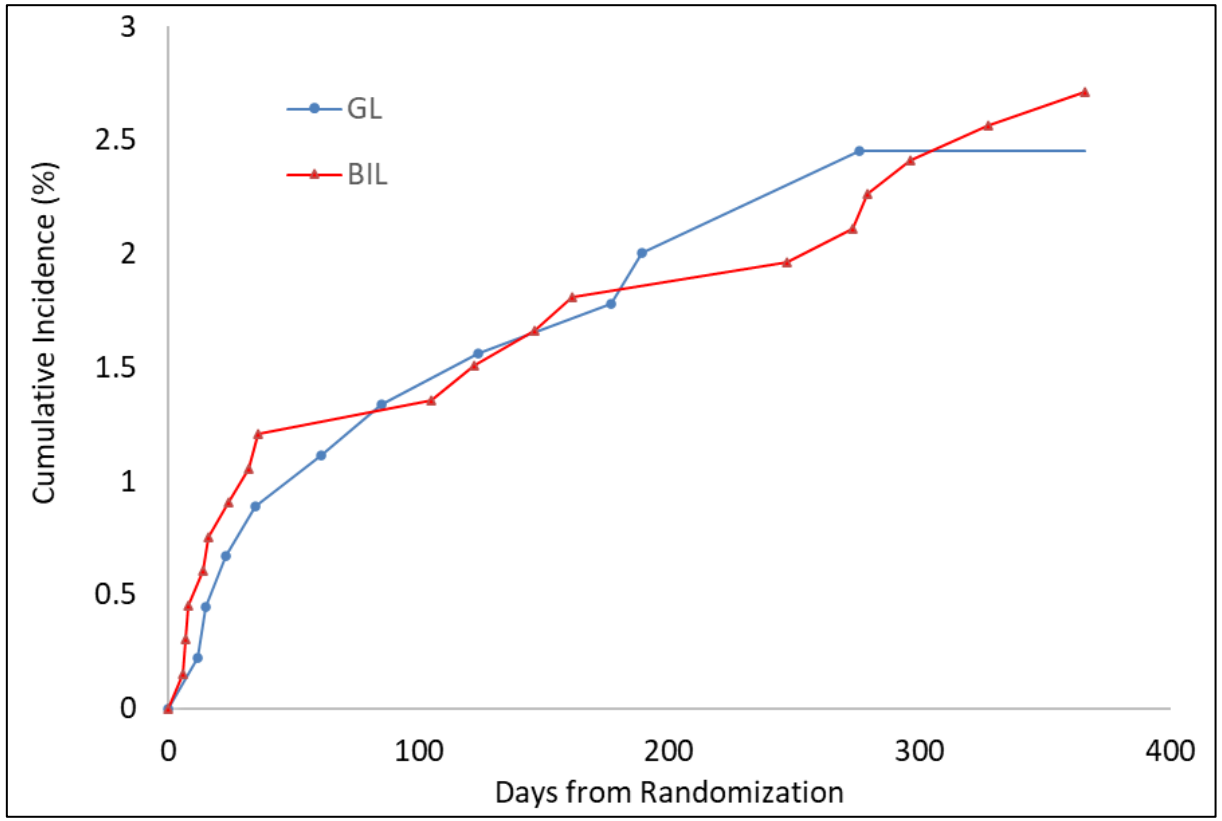
Adherence and ICE Status	Insulin Peglispro (N=663) n (%)	Insulin Glargine (N=449) n (%)
ICEs	154 (23.2)	81 (18.0)
Category 1 ICEs (Potentially Related to Safety)	70 (10.6)	24 (5.3)
Category 2 ICEs (Potentially Related to Efficacy)	18 (2.7)	11 (2.4)
Category 3 ICEs (Administrative Reasons)	70 (10.6)	50 (11.1)
Adherers	509 (76.8)	368 (82.0)

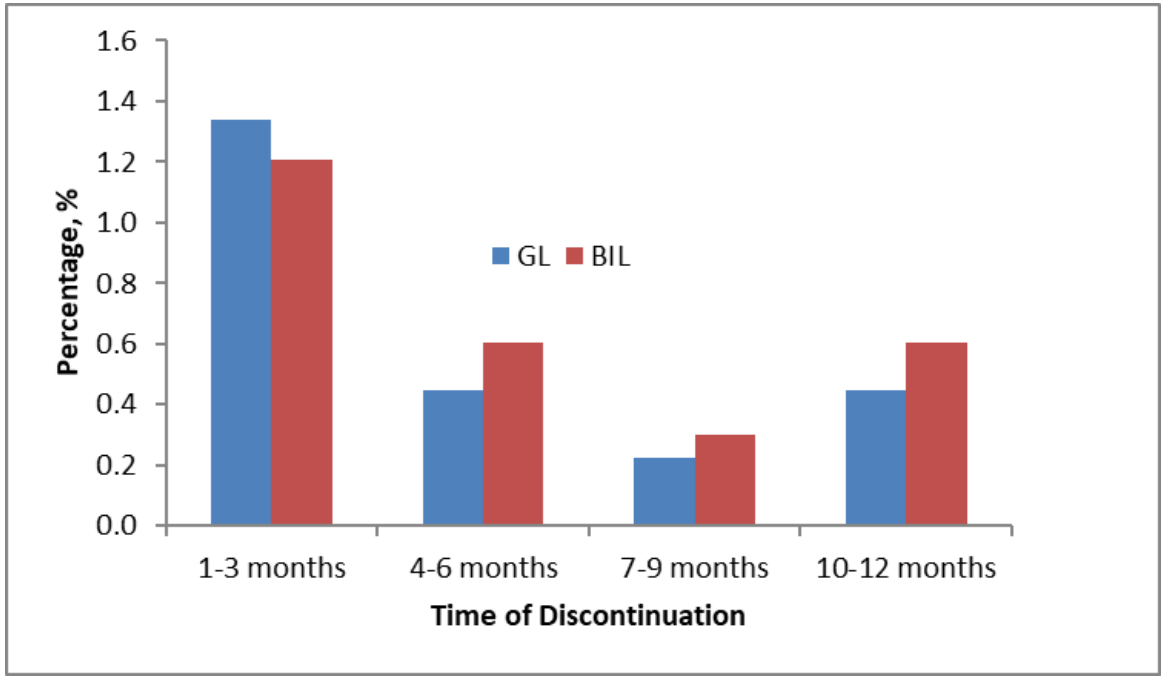
Abbreviations: ICE = Intercurrent Event

Cumulative incidence for treatment discontinuation potentially related to safety

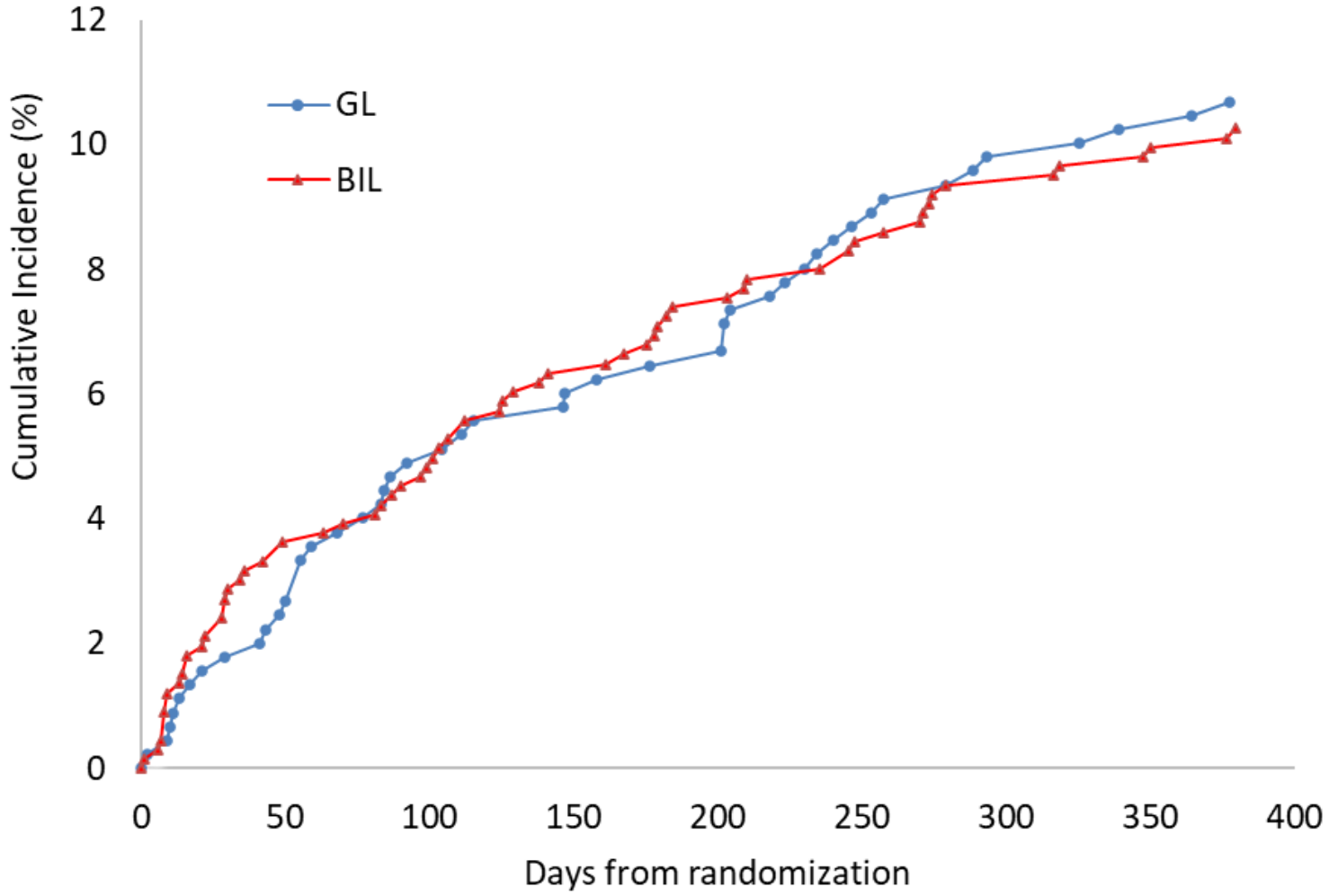


Treatment discontinuation potentially related to efficacy





Cumulative incidence for treatment discontinuation due to administrative reasons



Estimation models

- Seven baseline covariates (X): *age*, *gender*, *HbA1c*, *low density lipoprotein cholesterol* (*LDL-C*), *triglyceride* (*TG*), *fasting serum glucose* (*FSG*), and *alanine aminotransferase* (*ALT*).
- Intermediate outcomes
  - Z_1: a vector of 6 variables: *HbA1c*, *LDL-C*, *TG*, *FSG*, and *ALT* at Week 12 and whether experiencing the *injection site reaction* in the first 12 weeks
  - Z_2 : a vector of 6 variables: *HbA1c*, *LDL-C*, *TG*, *FSG*, and *ALT* at Week 12 and whether experiencing the *injection site reaction* between 12 and 26 weeks

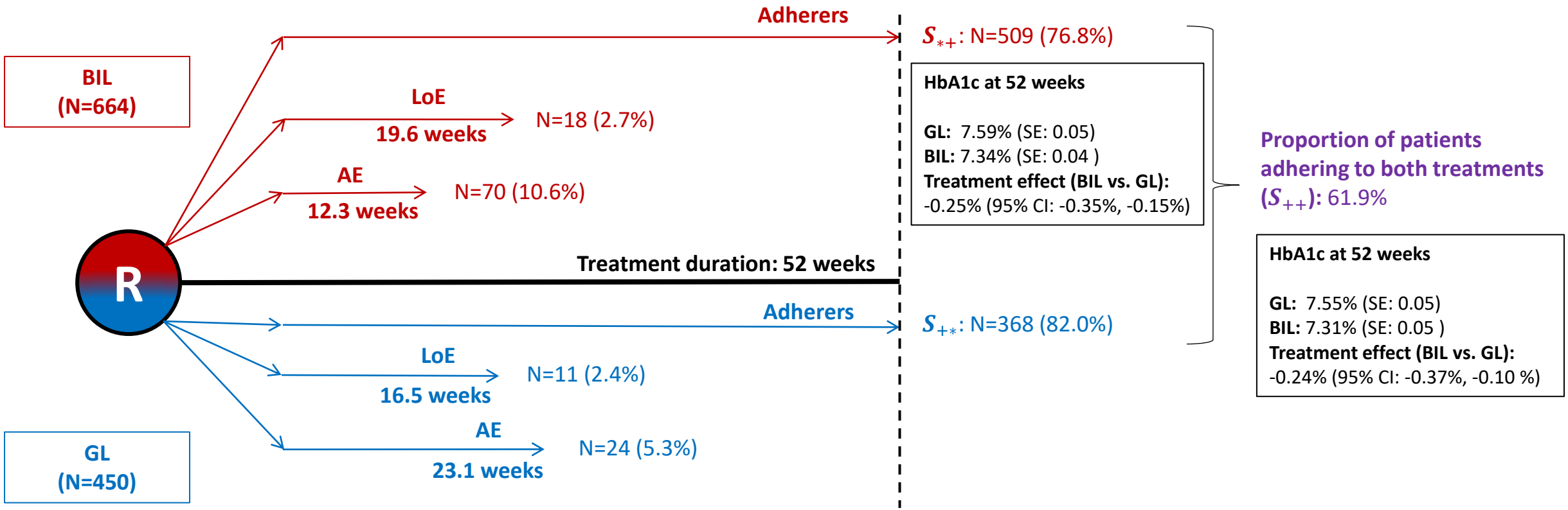
Results on adherers … and more

Method	GL (LS mean ± SE)	BIL (LS mean ± SE)	Treatment difference for BIL vs GL (95% confidence interval)
Naïve adherers estimator	7.57 ± 0.04	7.34 ± 0.03	-0.23 (-0.33, -0.14)
ACE on S_{*+}	7.59 ± 0.05	7.34 ± 0.04	-0.25 (-0.35, -0.15)
ACE on S_{++}	7.55 ± 0.05	7.31 ± 0.05	-0.24 (-0.37, -0.10)
MMRM on S_{**}	7.61 ± 0.04	7.38 ± 0.03	-0.22 (-0.32, -0.12)
MMRM after J2R imputations on S_{**}	7.62 ± 0.04	7.41 ± 0.03	-0.21 (-0.30, -0.11)

Abbreviations: ACE, adherers causal estimator; BIL, basal insulin lispro; GL, insulin glargine; J2R, jump to reference; LS, least squares; MMRM, mixed model with repeated measures; SE, standard error.

Bootstrap method was used to construct the 95% confidence interval

Visualize the estimation for the tripartite estimands



Discontinuation due to administrative reasons occurred in ~11% of each treatment group.

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