What is the Question?

The Importance of Estimand Thinking in Clinical Trials: Alzheimer's Disease Example

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Jen Murphy Disclosures

- Employee of Biogen
- No content about products from Biogen or competing companies
- No content about data from Biogen or competing companies
- All content is publicly available

Steve

Steve Ruberg Disclosures

- Self-employed
- Consult with various pharma/biotech companies
- All content is publicly available
- Lilly stockholder
- Nothing in this talk represents a conflict of interest

Steve

What is the Question?

How long is the hike on Mt. Kilimanjaro?

19,341 feet

On day 6, hikers take on average 4.65 hours.

Steve

What is the Question?

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

Steve

What is the Question?

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?

Jen

Outline

1. Some Axioms

2. Review of First Principles
   - Cause-and-Effect and Causal Inference

3. The Need for Estimand Thinking
   - Defining a Treatment
   - Defining a Treatment Effect Question

4. Alzheimer's Disease Example

Jen

Outline

1. **Some Axioms**

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4. Alzheimer's Disease Example

Steve

We hold these truths to be self-evident …

Science is about understanding the true **cause-and-effect** relationships in Nature.

What is the nature of Nature?

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

We rarely KNOW the truth.

There is uncertainty and variability.

Steve

We hold these truths to be self-evident …

Drug Development is about answering the question:

Does this treatment *cause* that outcome?

The **outcomes** includes a range of **benefits** (efficacy) and **risks** (adverse events).

Clinical trials are scientific experiments to elucidate the effects of the treatment being studied.

Statistics is used to **quantify the likelihood of the *causal* relationship** between the treatment and the outcomes.

Jen

We hold these truths to be self-evident …

Stakeholders have different priorities

Sponsor
- What treatment do we want to study (for ultimate approval)?
- What do we want the label to say?

Regulators
- Should this treatment be approved under this label?

HTA/Insurer
- Does the benefit-risk-cost justify reimbursement for the treatment?

Physician/HCP
- Should I prescribe this treatment to THIS patient?

Patient
- What can I expect when I take THIS treatment as prescribed?

Jen

We hold these truths to be self-evident …

ICH E9(R1) Addendum

A.3.1 ESTIMANDS 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)."

Jen

We hold these truths to be self-evident …

If we want "**to quantify a Treatment Effect"** (on any outcome), then we should be **absolutely clear and precise** as to what we mean by

1. **Treatment,** and
2. **Effect***

***Keeping in mind "effect" has multiple outcomes.**

Steve

Definition of "Treatment" (New)

Distinction between

Experimental Medication (ExM)

and

Estimand-Defined Study Treatment (EDST)

Experimental Medication
Placebo
Adabatemab*

Estimand-Defined Study Treatment
ExM alone
ExM + symptomatic medications

***Fictitious**

Jen

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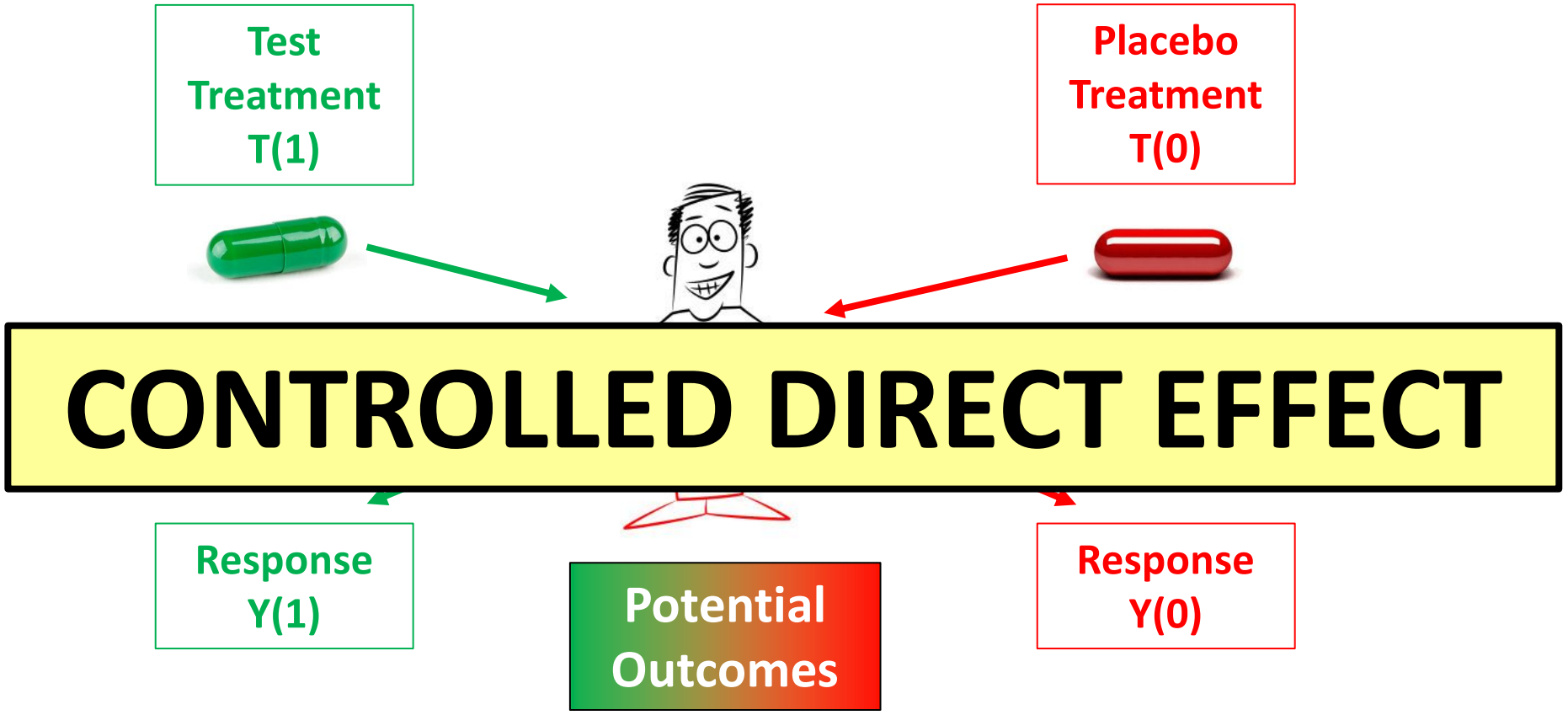
4. Alzheimer's Disease Example

Steve

Cause-and-Effect

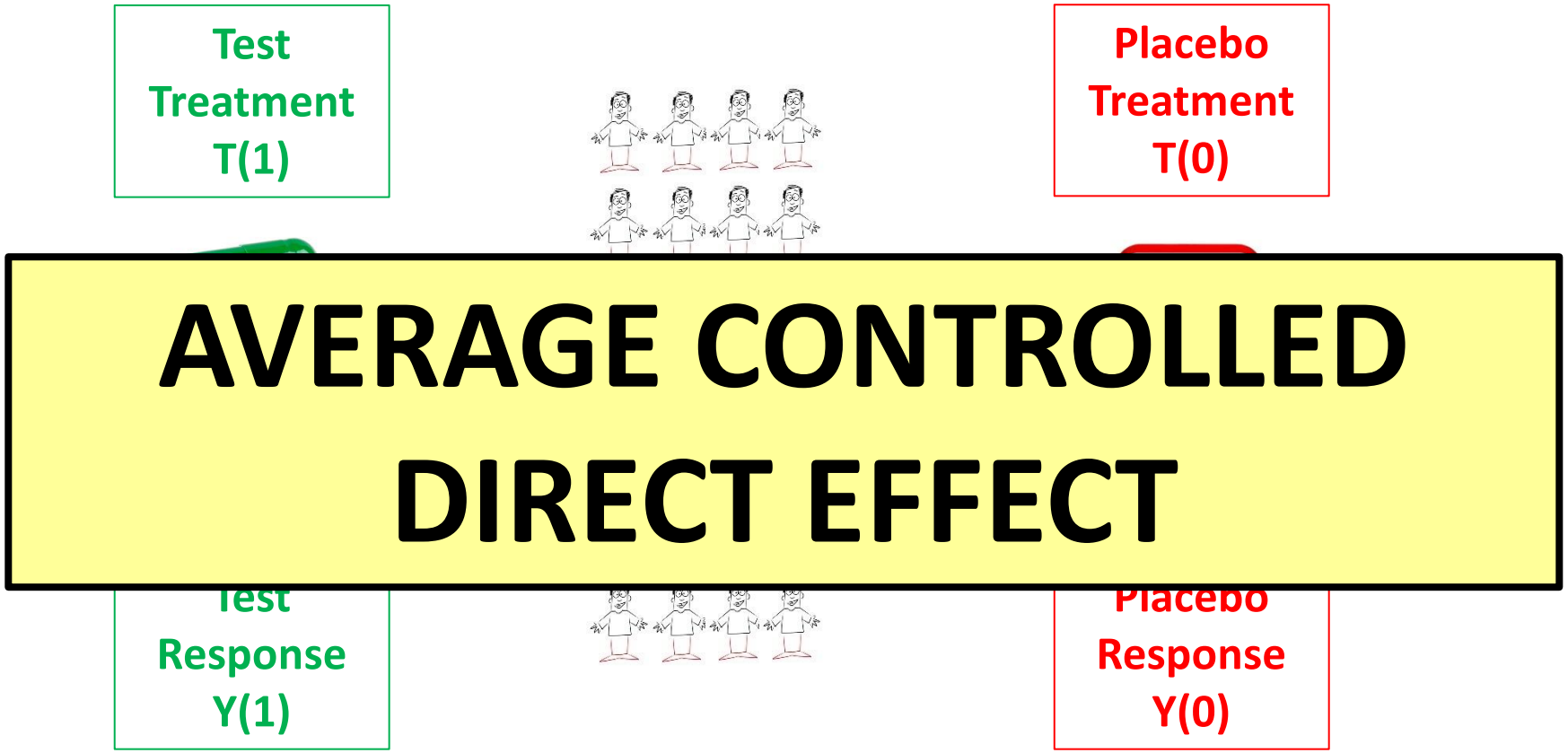


Treatment Effect = Y(1) – Y(0)

"how the outcome of treatment compares to what would have happened to the same subjects under different treatment conditions"

Steve

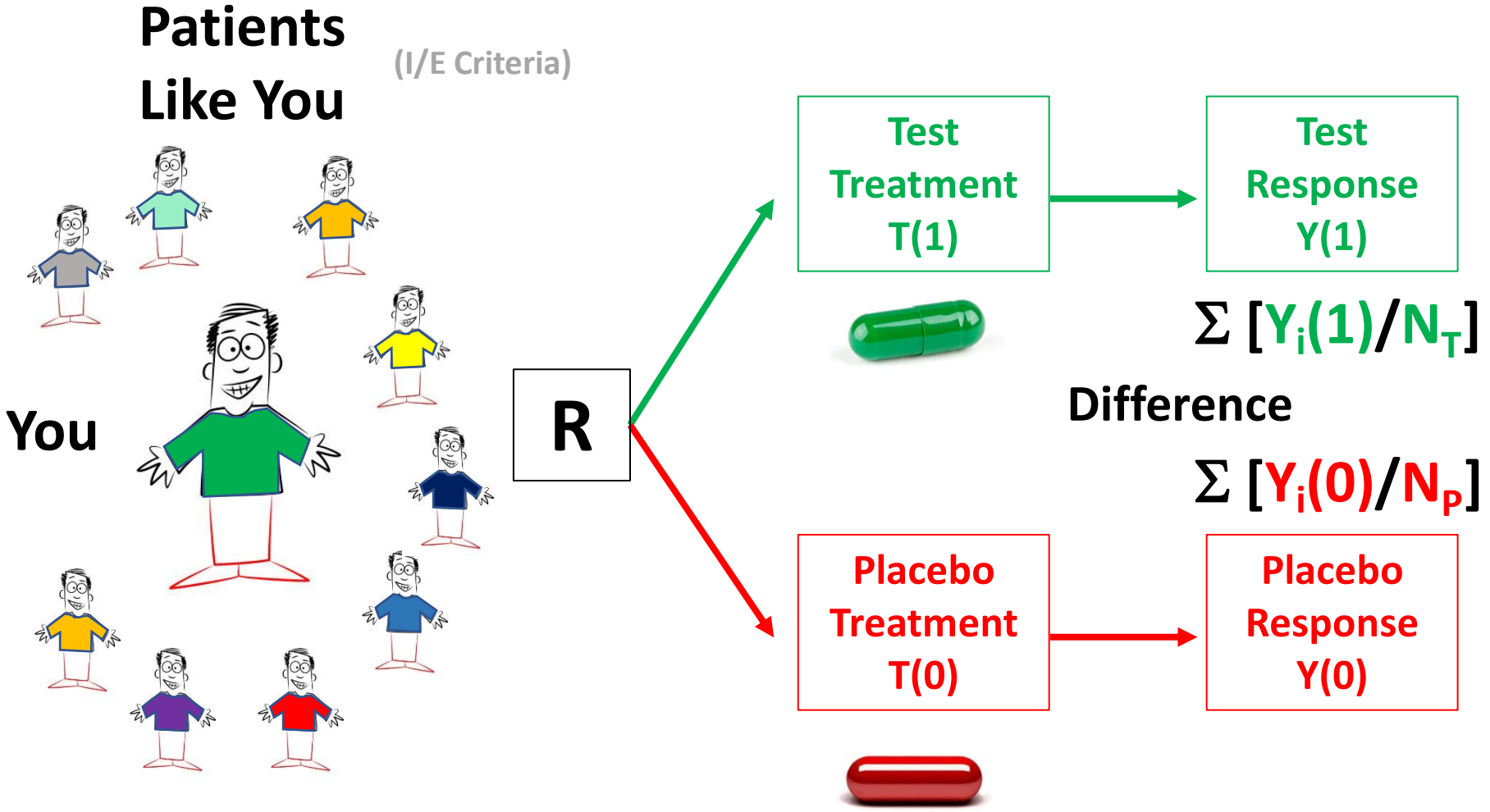
Cause-and-Effect



Estimator = $\Sigma\ [Y_i(1) - Y_i(0)] / N$

Steve

Cause-and-Effect



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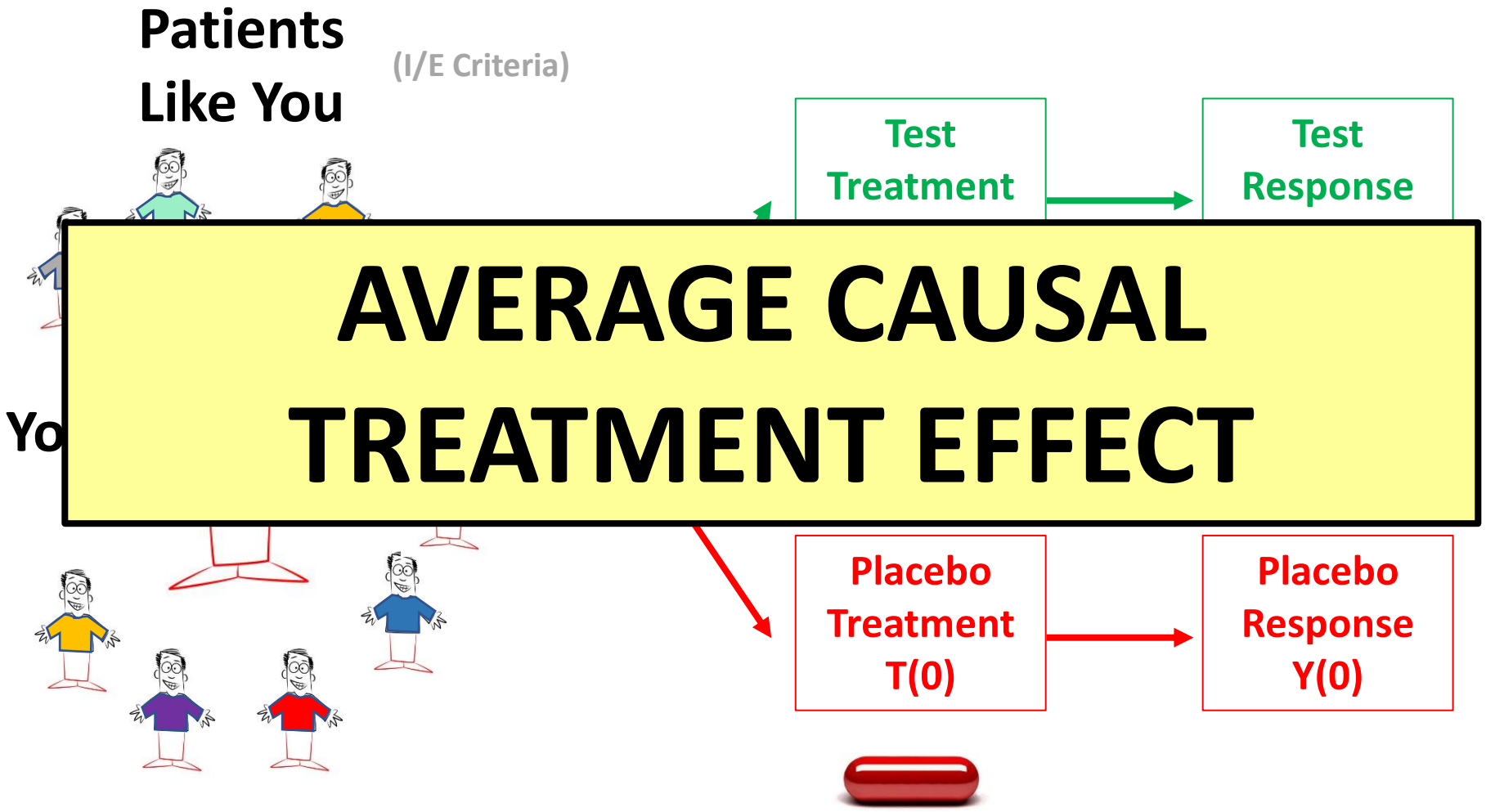
Cause-and-Effect



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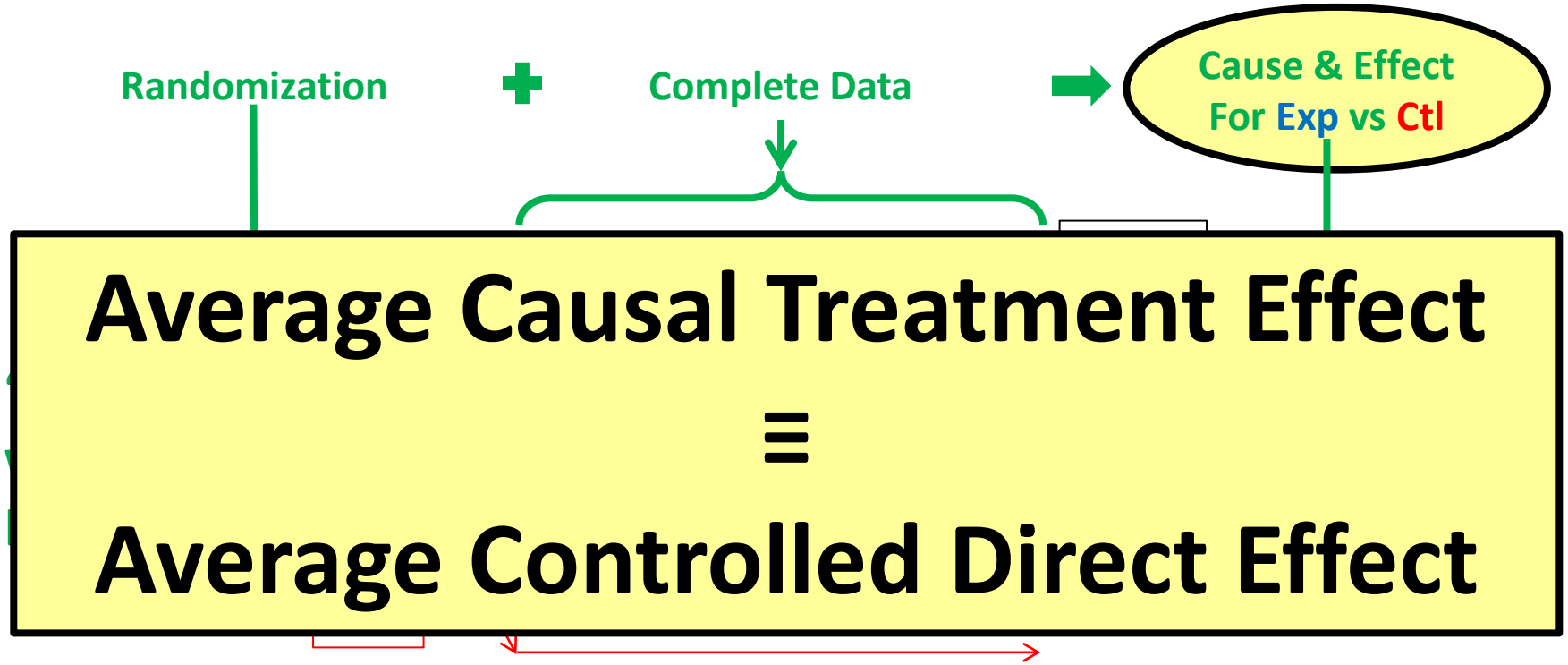
Cause-and-Effect



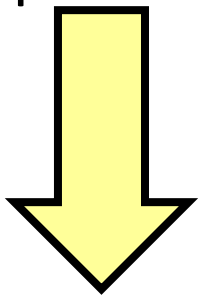
Charles Sanders Peirce & Joseph Jastrow (1885). On Small Differences in Sensation. First published in Memoirs of the National Academy of Sciences, 3, 73-83. (Presented 17 October 1884)

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

Steve

Cause-and-Effect

- **Goal**: Estimate the Controlled Direct Effect (CDE) for the **experimental medication**
  - The basis for cause and effect
- Randomization is **THE TOOL** for estimating CDE
  - **Requires** complete data
  - **Requires** adherence to the experimental medication



Average Causal Treatment Effect ≡ Average Controlled Direct Effect

Steve

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Jen

Alzheimer's Disease

Neurological Heterogeneity

Neurological mechanism of AD is multifactorial

Comorbid neurodegenerative diseases exist in AD brains

Comorbid non-neuro medical conditions exist

- Disease of aging

Normal individual neuro-variation

Jen

Alzheimer's Disease

Clinical Heterogeneity

Individual variation in the 3 primary cognitive symptoms

Memory loss *Language changes* *Visuospatial decline*

Individual variation in expression of behavioral and neuropsychiatric symptoms

Functional ADLs *Anxiety/agitation/apathy*

Individual variation in pace of disease progression

Jen

Estimand Thinking

We design a trial with the hopes that everyone adheres to the protocol to estimate the ***controlled direct effect***

- Patients remain on their ***experimental medication***
- Patients follow the protocol to the end of the study

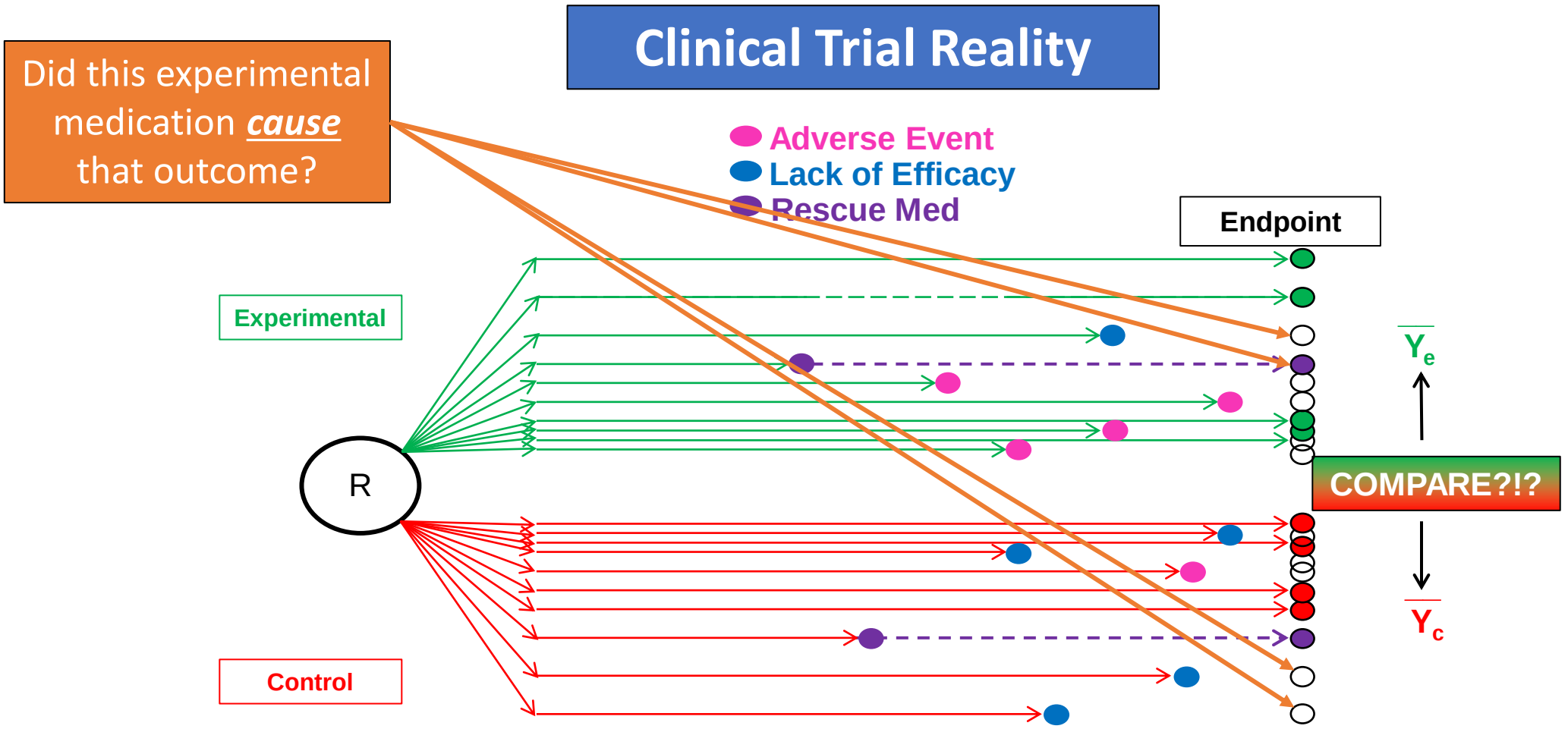
Yet patients stop taking their ***experimental medication***

- Clinical trial reality and ethical patient care intervene
- Study discontinuation/LTFU ≡ discontinuation of their ***ExM***

This breaks the logical basis for causal inference.

Jen

Estimand Thinking



Jen

Estimand Thinking

How am I supposed to make causal inference? Somethin's gotta give!

Steve

Estimand Thinking

If we want "**to quantify a Treatment Effect"** (on any outcome), then we should be **absolutely clear and precise** as to what we mean by

1. **Treatment,** and
2. **Effect***

***Keeping in mind "effect" has multiple outcomes.**

Steve

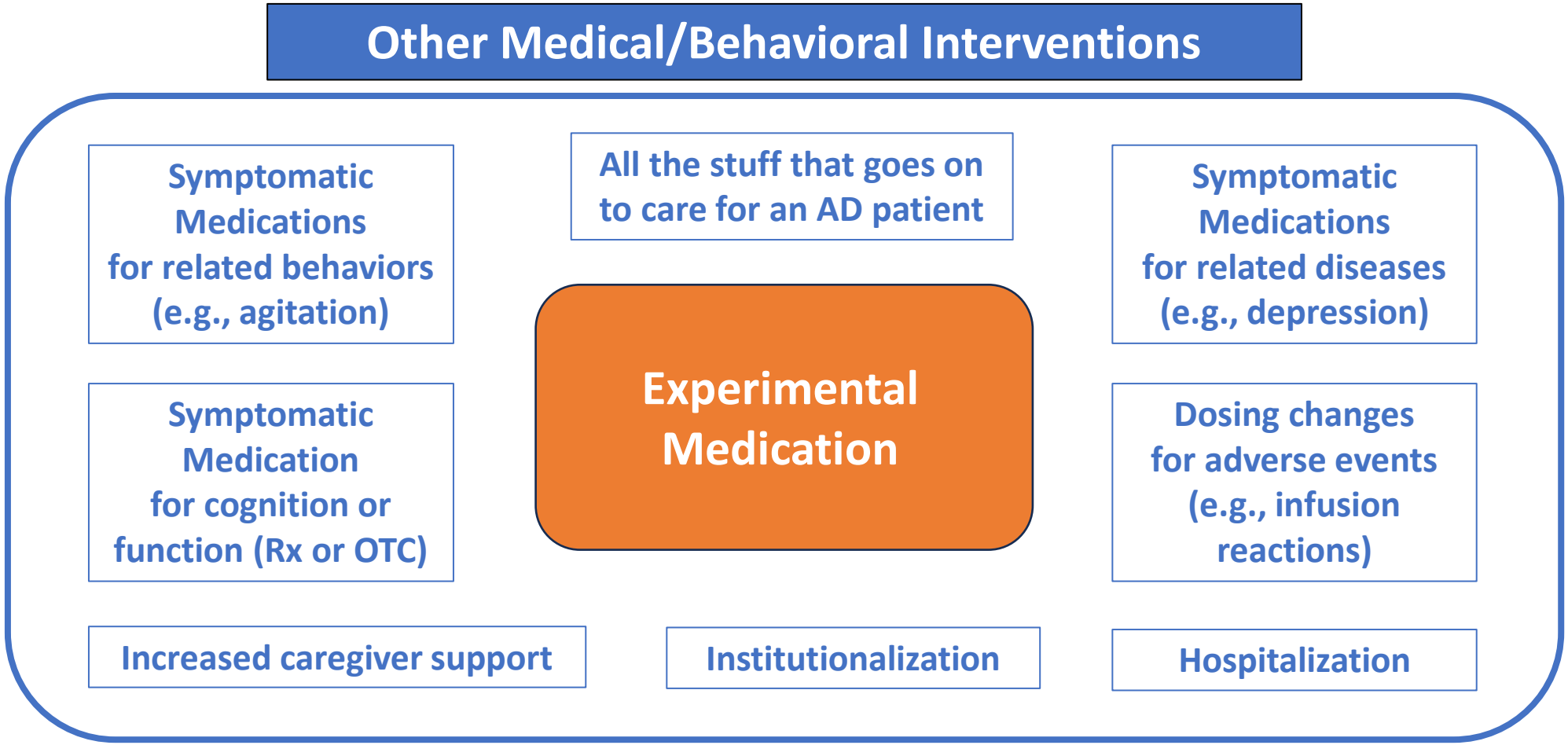
Estimand Defined Study Treatment

Define the treatment *precisely* for the estimand (EDST).

- Experimental Medication (ExM) alone
- ExM with titration scheme
- ExM with diet and exercise
- First-line ExM followed by second-line therapy for patients with well-defined disease progression
- ExM on top of fixed background medication
- ExM on top of flexible background medication
- ExM with addition of rescue medication for well-defined disease progression
- ExM with (or without) another clinical intervention (e.g., surgery, ventilation, hospitalization)

Jen

Estimand-Defined Study Treatment



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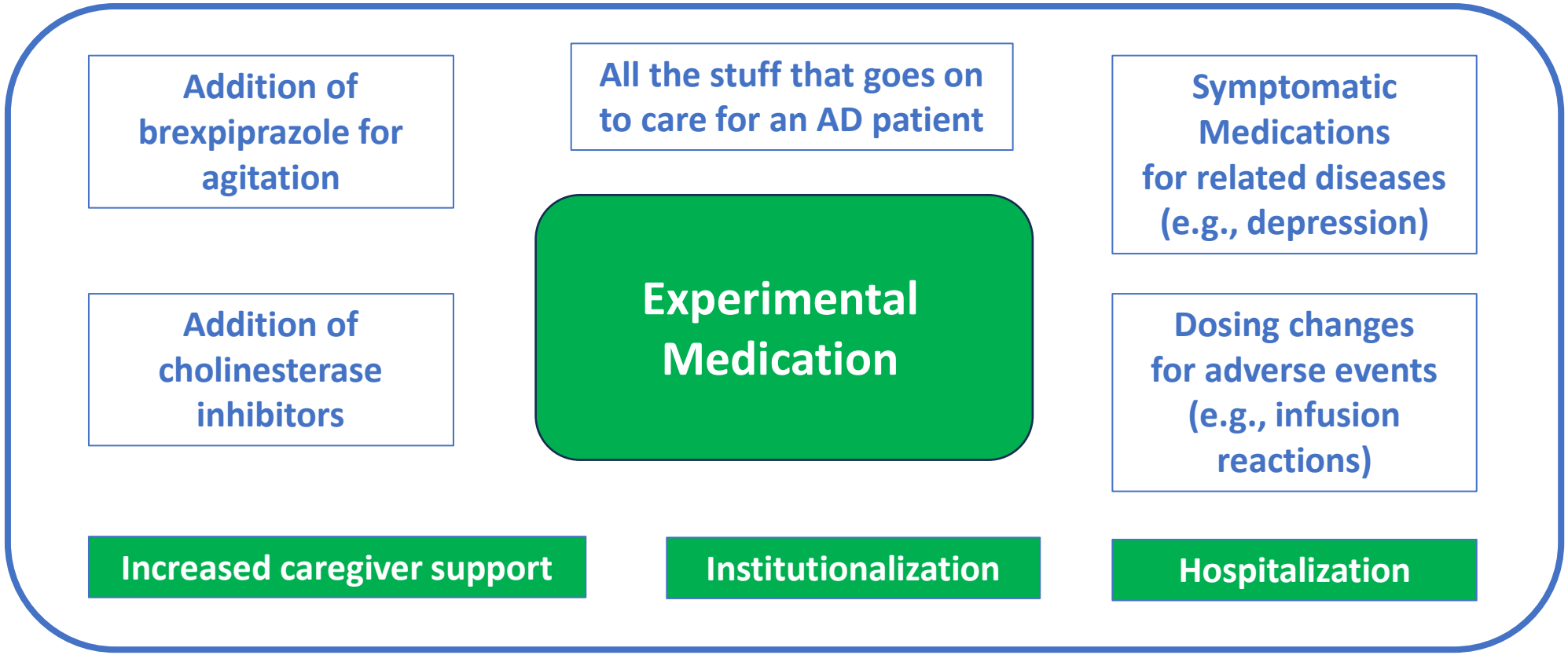
Estimand-Defined Study Treatment



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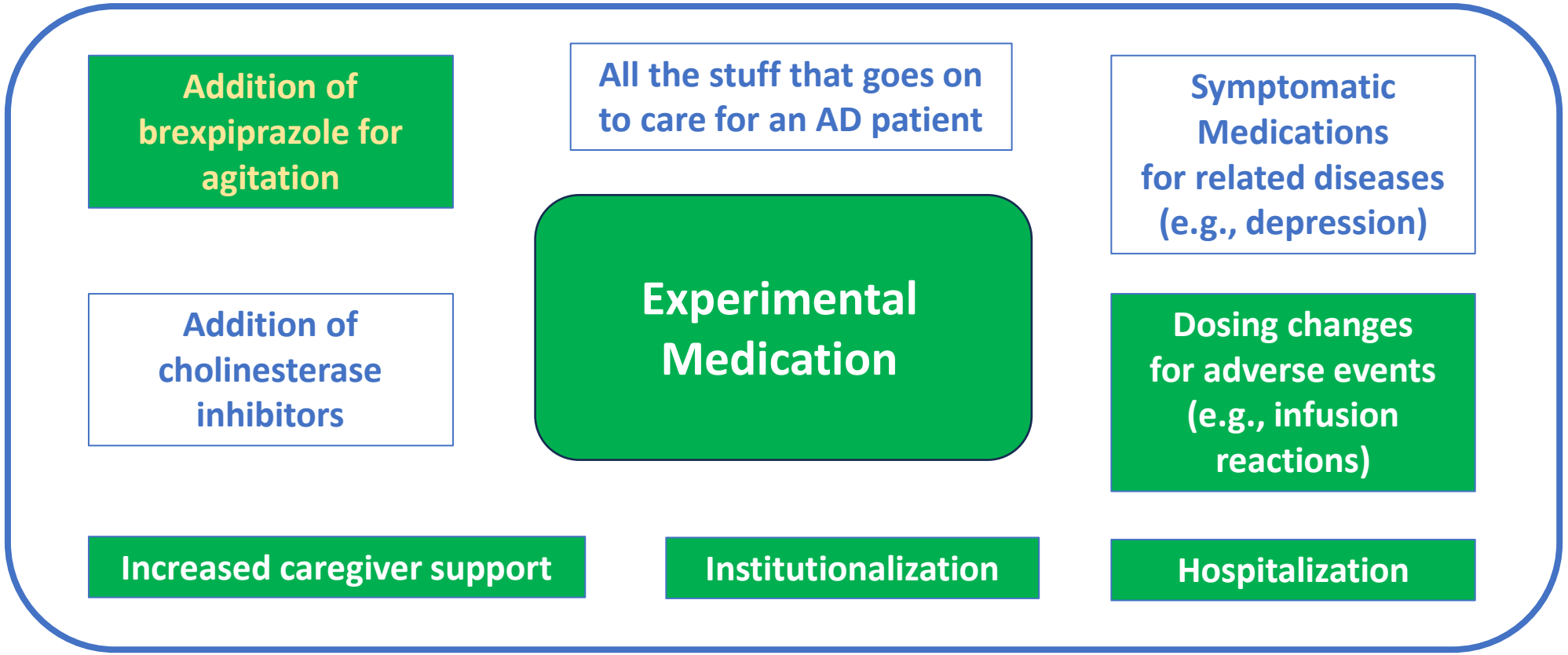
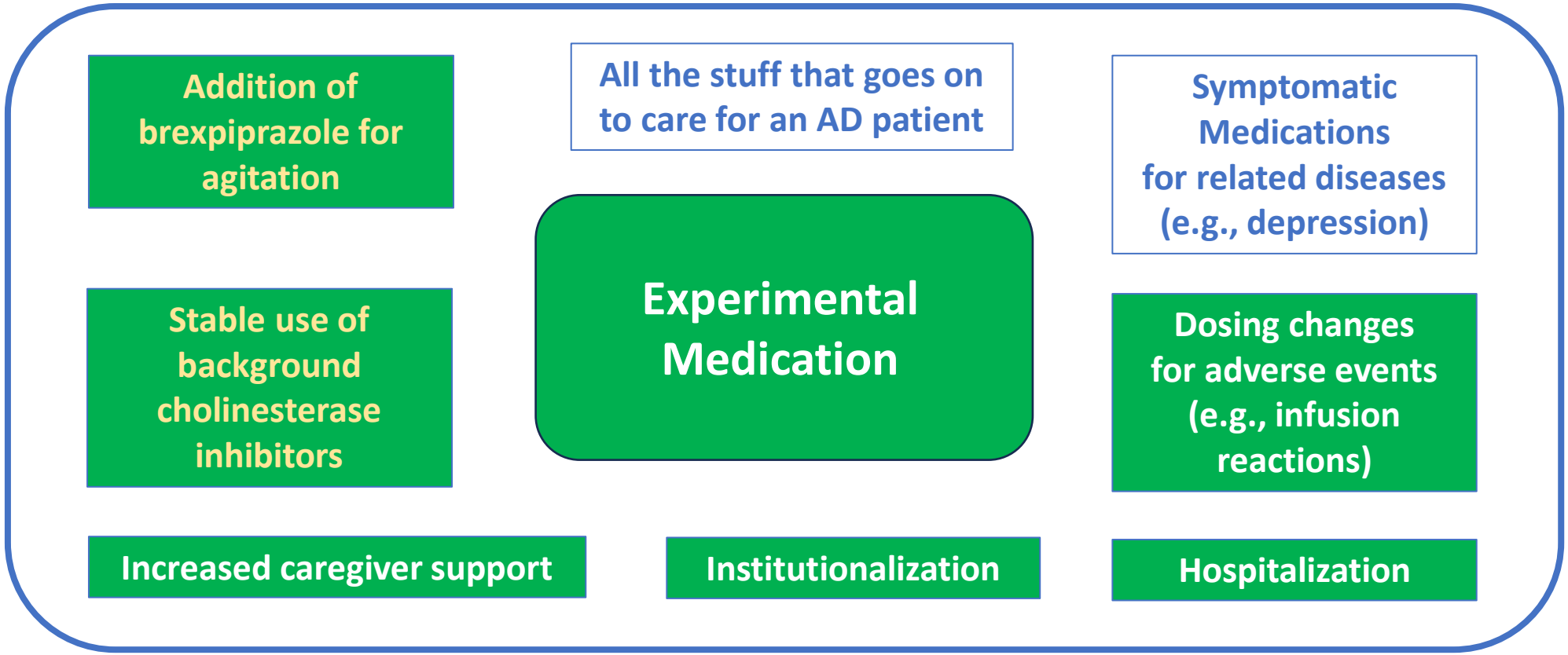
Estimand-Defined Study Treatment



Jen

Estimand-Defined Study Treatment



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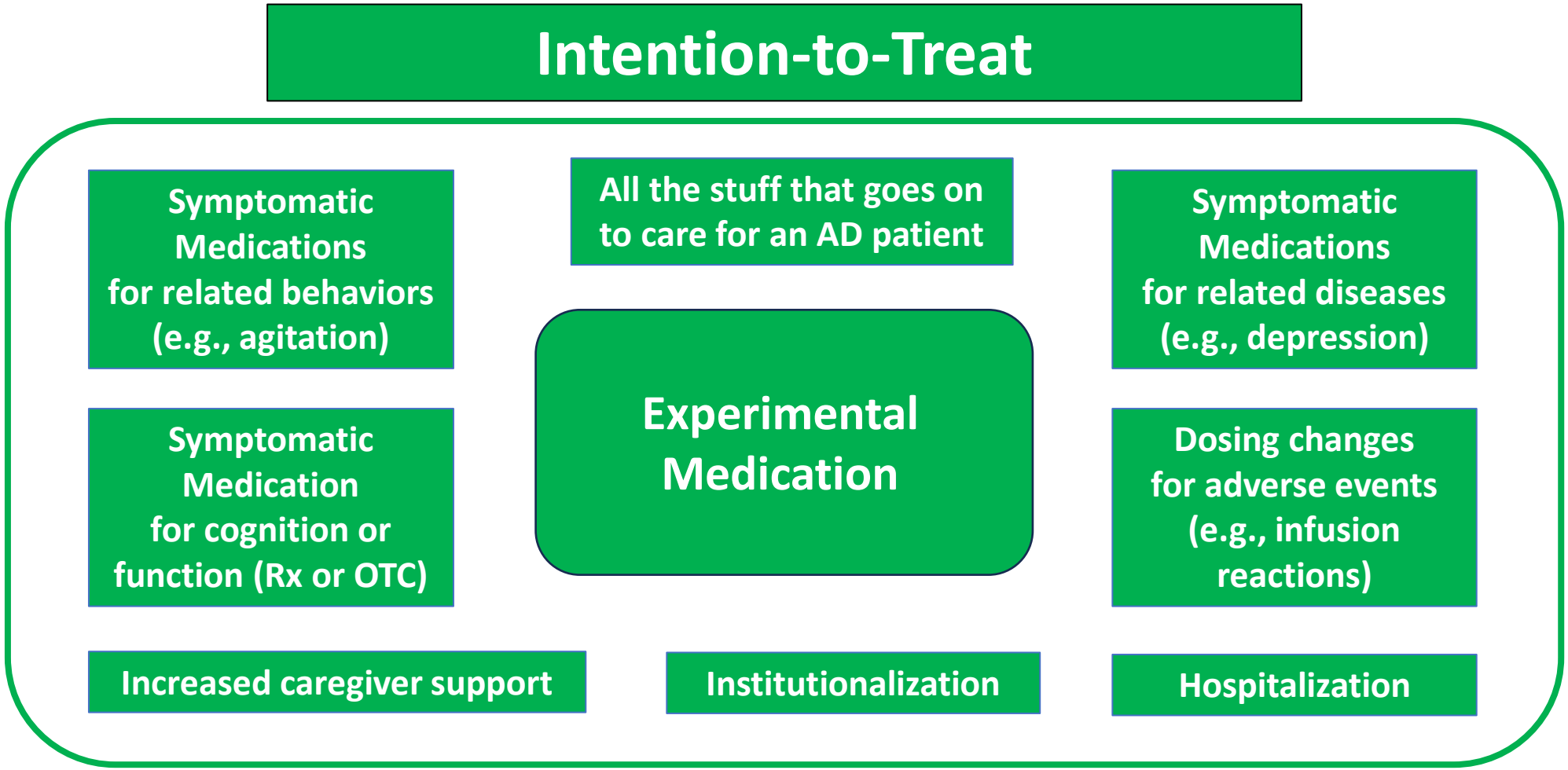
Estimand-Defined Study Treatment



Steve

Estimand-Defined Study Treatment (EDST)

Bold Proclamation #1

Discontinuation of the EDST breaks the logic of cause-and-effect. Therefore, …

the only Intercurrent Event of interest is discontinuation of the EDST.

There are multiple reasons for DC of the randomized study treatment, …
Adverse events, lack of efficacy, administrative reasons, …
but the central issue is DC of the estimand defined study treatment.

Jen

Estimand-Defined Study Treatment (EDST)

If you want to study a treatment policy, then define what it is *precisely*.

- Initiate **ExM** but allow for use of symptomatic treatments as needed
  - Define what "as needed" means? Are there any guidelines/rules for their use?
  - Which symptomatic treatments? (Any? All? Some?)
- **ExM** on top of stable use of symptomatic treatments
  - What's constitutes "stable"? Same medication but different dose?
  - Allow different medications but in the same class (e.g., cholinesterase inhibitors)?

Once the "treatment policy" is *precisely* specified,

THAT DEFINES THE TREATMENT UNDER STUDY.

"Estimand Defined Study Treatment (EDST)"

Steve

Estimand Defined Study Treatment

Bold Proclamation #2

With an “estimand-defined study treatment” clearly specified …

There is no such thing as a treatment policy.

Jen

Estimand Thinking

Choosing the Clinical Question (1)

What are the patients' outcomes ***at the end of the study***? (i.e., regardless of how they got there; non-adherence to study medication or use of other interventions)

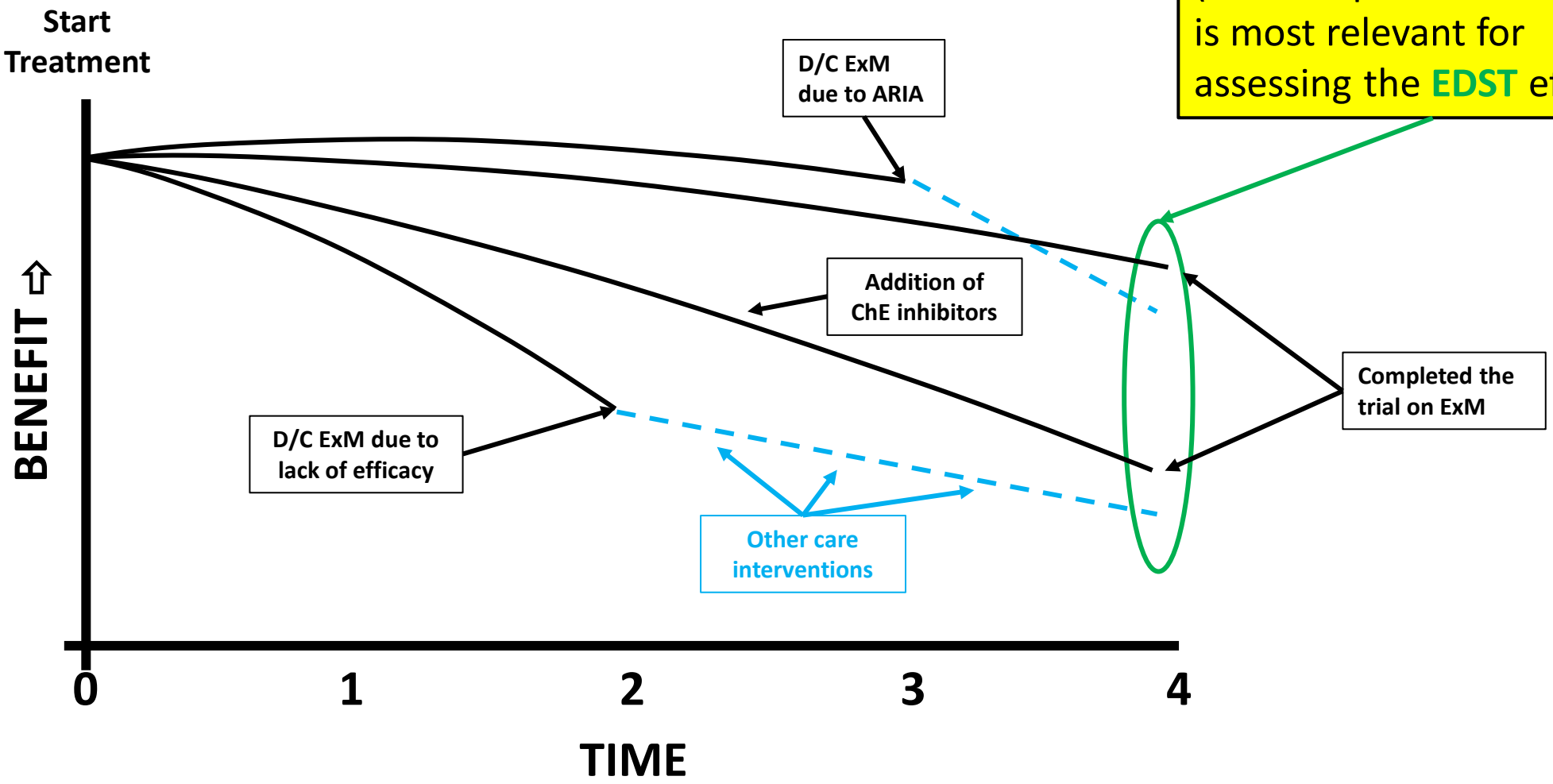
- Some patients take their EDST to the end of the trial.
- Some appear to have benefit of the EDST, but D/C due to adverse events. What is their outcome at the end of the trial?
- Some D/C their EDST for other reasons (e.g., lack of efficacy, loss of caregiver). What happens to their outcomes?

Jen

Estimand Thinking

Choosing the Clinical Question (1)

The outcome for each patients at the end of study (the timepoint of interest) is most relevant for assessing the **EDST** effect.



Steve

Estimand Thinking

Defining Estimand Attributes (1)

Attributes

- Treatment
- Population
- Primary Outcome Variable
- Summary Measure for Comparing Treatments

Strategies for Intercurrent Events

Treatment policy, hypothetical, composite, while on treatment, principal stratification

Steve

Estimand Thinking

Defining Estimand Attributes (1)

Estimand Defined Study Treatment (implied by clinical question)

- The initiation of ExM + whatever else is done to care for the patients throughout the study

Population

- All patients meeting I/E criteria

Primary Outcome Variable

- Change in AD Score from baseline (e.g., CDR-SB, iADRS, …)

Steve

Estimand Thinking

Defining Estimand Attributes (1)

Population-level Summary (implied by clinical question)

- Difference in mean changes from baseline to endpoint of trial

Strategy for ICEs

- *There are no ICEs**
- Capture outcome variable on all patients at the end of the trial
- Analysis considerations: If patients are lost-to-follow-up or death occurs, some assumptions must be made to impute their response at the endpoint

Implied by definition of Treatment: randomized *study medication + whatever else

Jen

Steve

Estimand Thinking

Defining Estimand Attributes

First WHAT

WHAT is the clinical question?

WHAT do we mean by treatment under study?

- What constitutes an ICE?

WHAT do we mean by treatment effect?

WHAT defines a successfully treated patient?

Then HOW

Define the strategy for **HOW** to analyze the data.

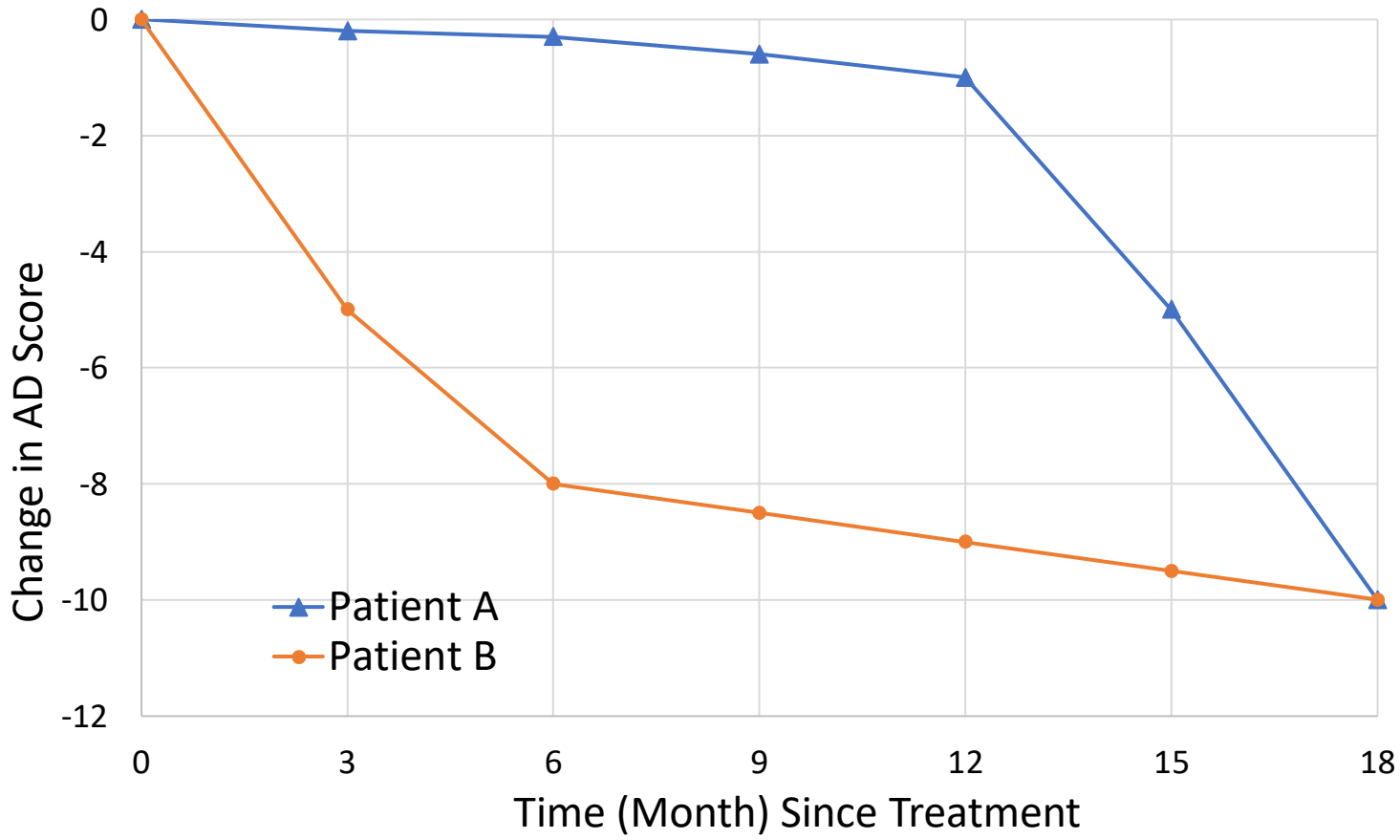
- **HOW** to handle ICEs (if any).
- Which data is used in the analysis and **HOW** it will be used.

HOW to interpret an estimate.

Jen

Estimand Thinking

Defining Estimand Attributes



- **Patients A and B had the same change from baseline to 18 months in iADRS**
- **Patient A should have overall better quality of life**

Jen

Estimand Thinking
Choosing the Clinical Question (2)

What are the patients' outcomes ***during the course of the study***? (i.e., regardless of how they got there; discontinue EDST for any reason or any other interventions)?

- Some patients take their EDST to the end of the trial.
- Some appear to have benefit of the EDST, but D/C due to adverse events. What is their outcome at the end of the trial?
- Some D/C their EDST for other reasons (e.g., lack of efficacy, loss of caregiver). What happens to their outcomes?

Steve

Estimand Thinking
Choosing the Clinical Question (2)

SAME

Estimand Defined Study Treatment

- The initiation of **study medication + whatever** else is done to care for the patients throughout the study

Population

- All patients meeting I/E criteria

Primary Outcome Variable

- Change from baseline in AD Score (e.g., CDR-SB, iADRS, …)

Steve

Estimand Thinking
Choosing the Clinical Question (2)

Population-level Summary (implied by clinical question)

- Other options

Strategy for ICEs

SAME

- There are no ICEs*
- Capture outcome variable on all patients at the end of the trial
- Analysis considerations: If patients are lost-to-follow-up, some assumptions must be made to impute their response at the endpoint

*Implied by definition of Treatment: *study medication + whatever else*

Steve

Estimand Thinking
Choosing the Clinical Question (2)

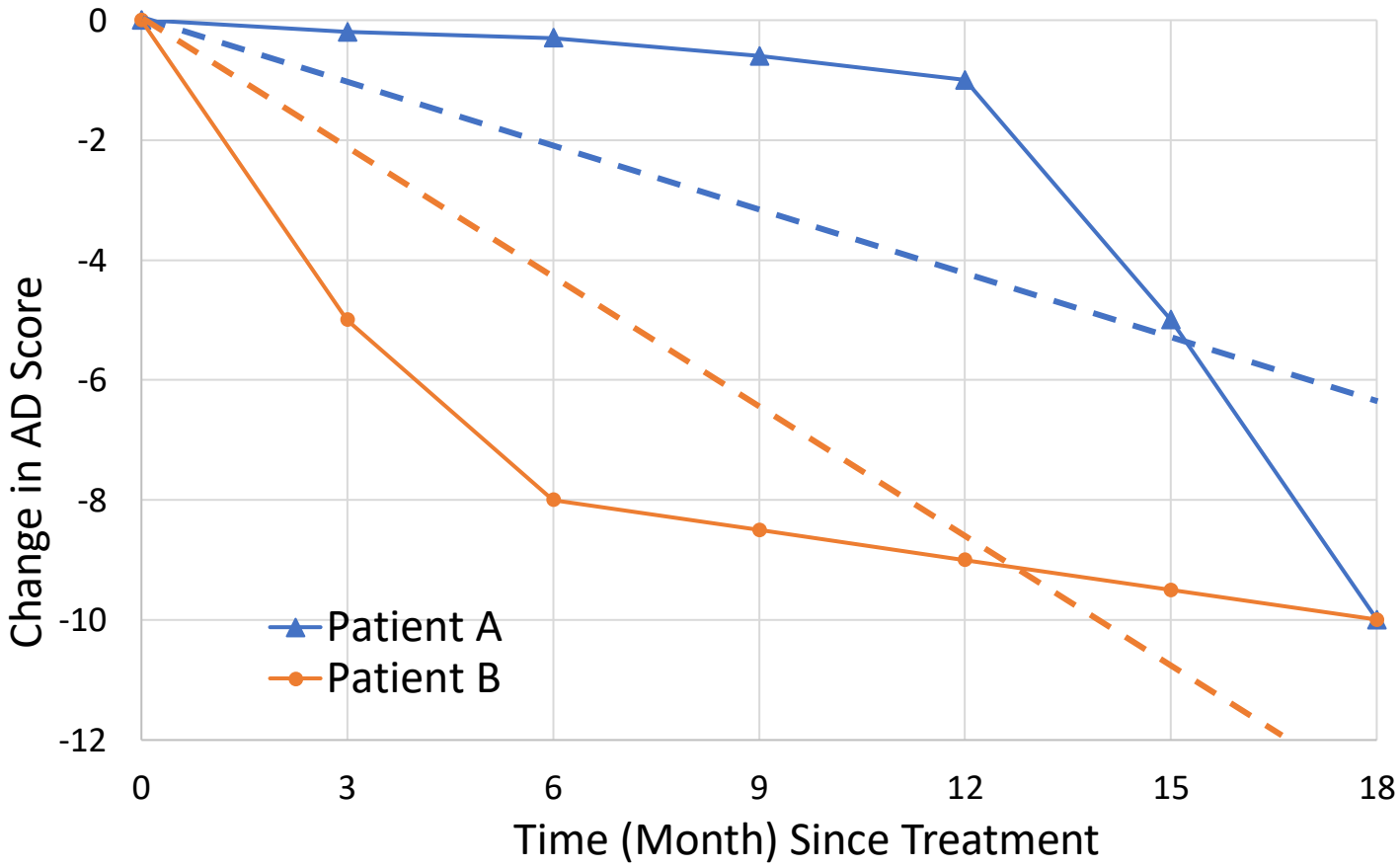
Population-level Summary (implied by clinical question)

- Difference in mean changes from baseline to endpoint of trial
- Difference in average slopes of individual patients' response curves
- Difference (or ratio) of disease progression model parameter(s)

Steve

Estimand Thinking

Choosing the Clinical Question (2)



- **Patients A and B had the same change from baseline to 18 months in iADRS**
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Steve

Estimand Thinking
Choosing the Clinical Question (2)

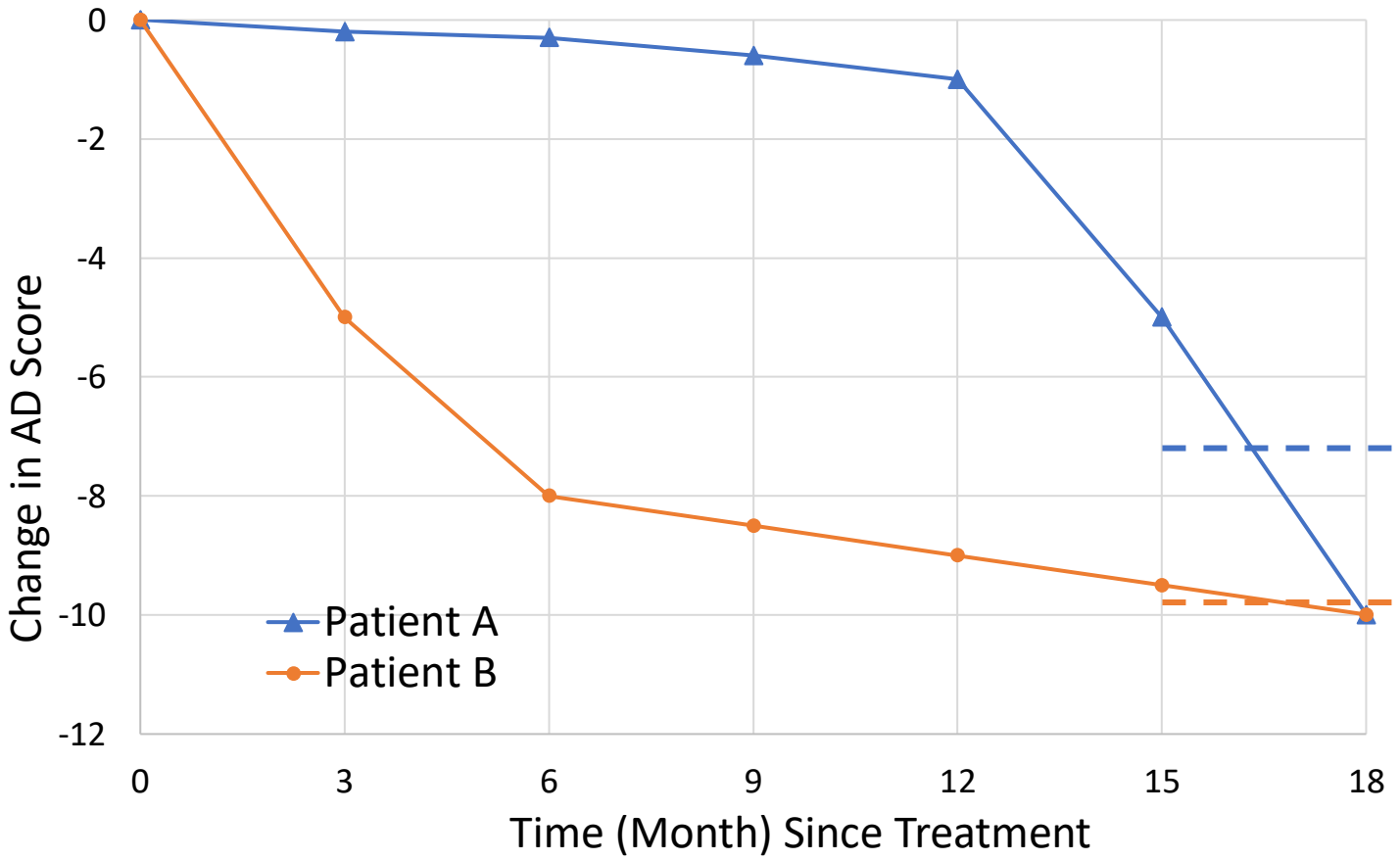
Population-level Summary (implied by clinical question)

- Difference in mean changes from baseline to endpoint of trial
- Difference in average slopes of individual patients' response curves
- Difference (or ratio) of disease progression model parameter(s)
- Average of change in last two measurements

Steve

Estimand Thinking

Choosing the Clinical Question (2)



- **Patients A and B had the same change from baseline to 18 months in iADRS**
- **Patient A should have overall better quality of life**

Steve

Estimand Thinking
Choosing the Clinical Question (2)

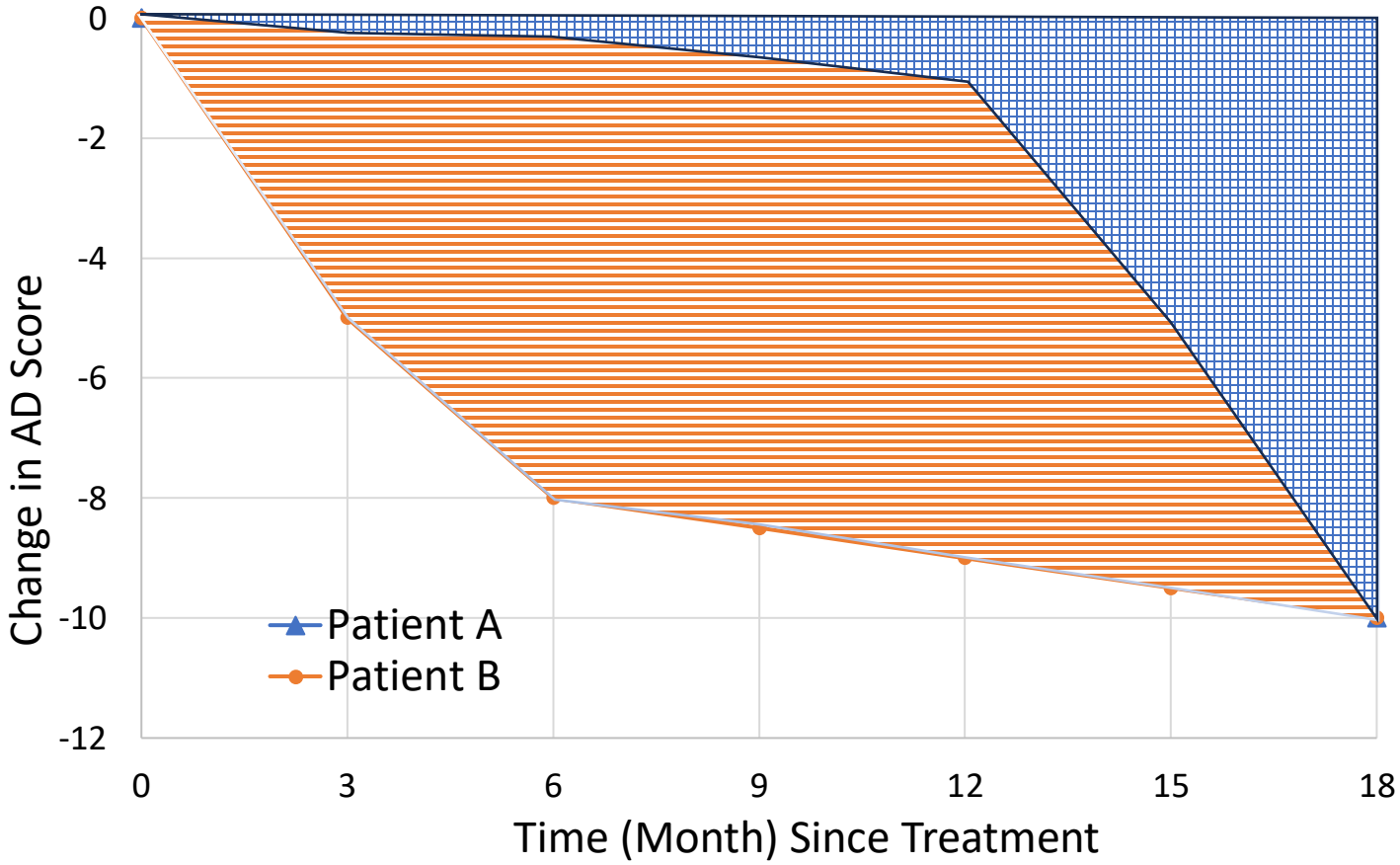
Summary Measure

- Difference in mean changes from baseline to endpoint of trial
- Difference in average slopes of individual patients' response curves
- Difference (or ratio) of disease progression model parameter(s)
- Average of change in last two measurements
- Area under the curve

Steve

Estimand Thinking

Choosing the Clinical Question (2)

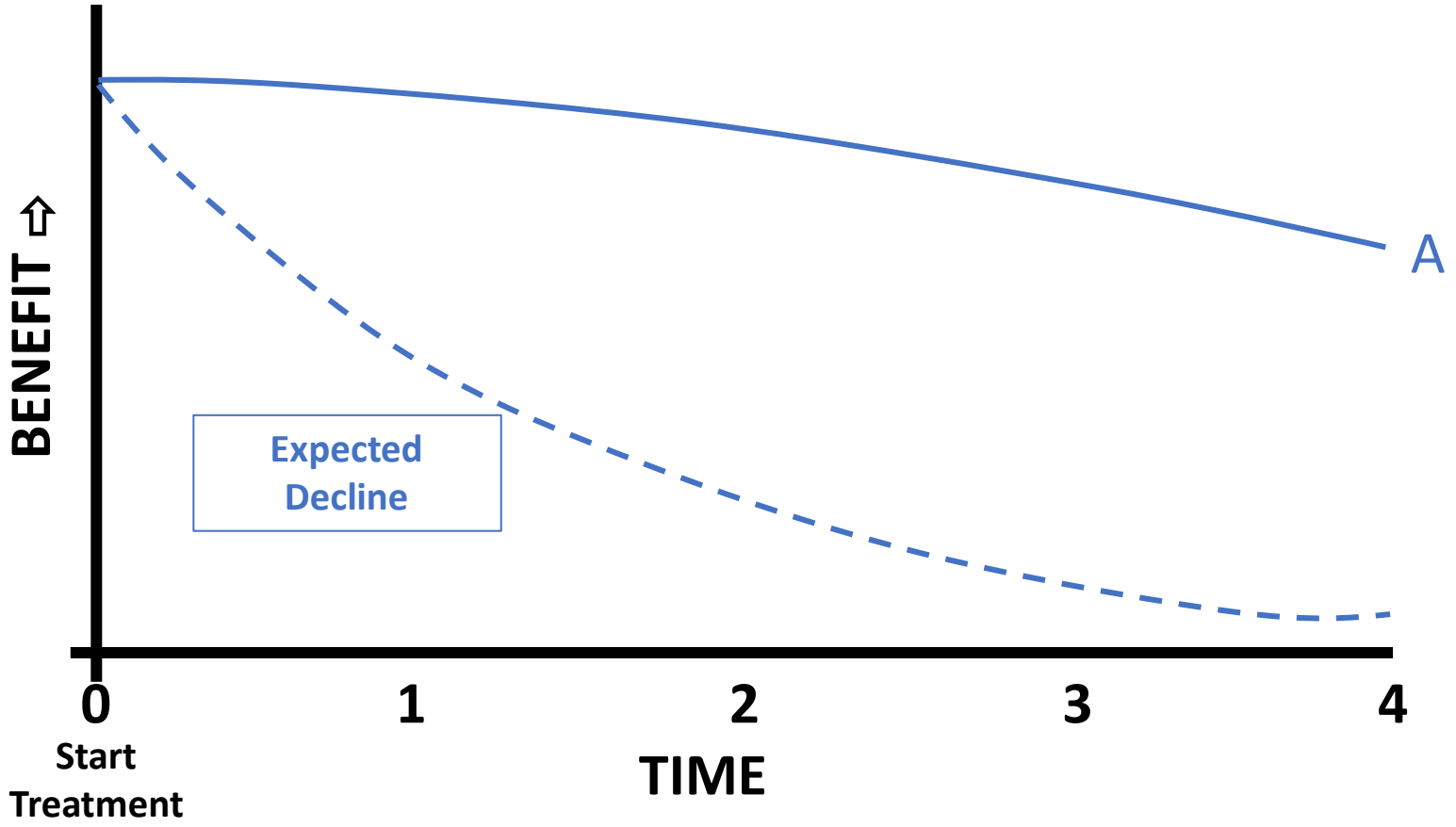


- **Patients A and B had the same change from baseline to 18 months in iADRS**
- **Patient A should have overall better quality of life**

Jen

Estimand Thinking

Choosing the Clinical Question (3)

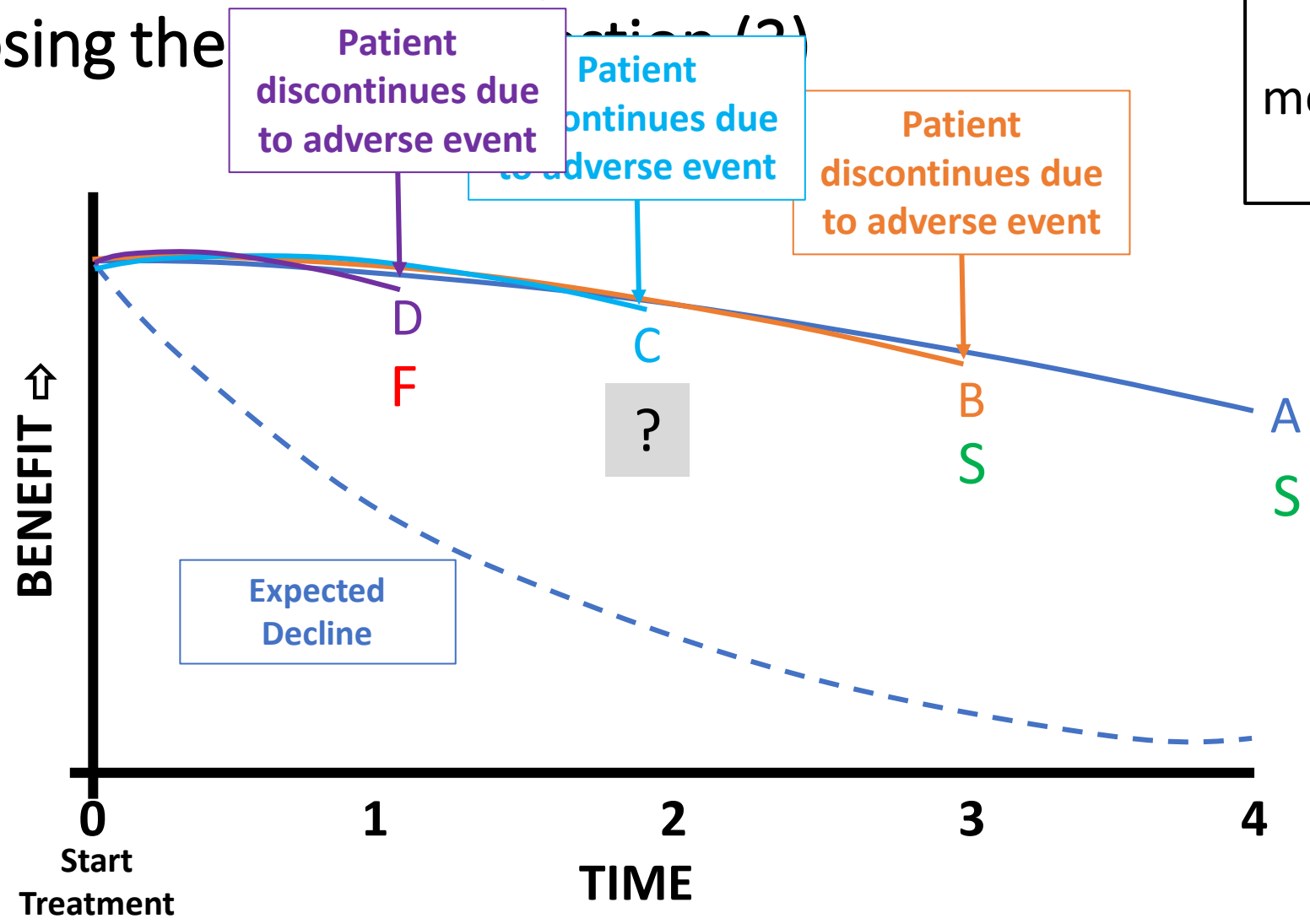


This patient is a **SUCCESS.**

Estimand Thinking

Choosing the [illegible]ction (2)

How do you capture theses clinically meaningful and relevant considerations?



Jen

Estimand Thinking

Choosing the Clinical Question (3)

What is the question?

What proportion of patients have a ***successful outcome while on the Experimental Medication***? (i.e., where 'success' is defined as achieving an acceptable level of response for at least M months)

Steve

Estimand Thinking
Choosing the Clinical Question (3)

SAME

Estimand Defined Study Treatment

- The use of **experimental medication (+ other defined interventions)** to care for the patients while on the **ExM**

Population

- All patients meeting I/E criteria

Steve

Estimand Thinking
Choosing the Clinical Question (3)

Primary Outcome Variable

Define an acceptable level of beneficial response

- Small decrease in score from baseline
  - Last measurement or average of last two measurement
- Shallow slope of response profile
- Less area under the curve
- PLUS at least M months on the EDST

Steve

Estimand Thinking
Choosing the Clinical Question (3)

Population-level Summary (implied by clinical question)

- Proportion of positive responders
- Duration of acceptable response
- Time to progressing to an unacceptable response

Strategy for ICEs

- ICE = discontinuation of ExM
- Analysis considerations: Minimal … classify all patients as a treatment success or failure

Steve

Estimand Thinking

Choosing the Clinical Question

Estimand Defined Study Treatment *Effect* Questions

What is the EDST effect …

Regardless of whether/how the EDST is taken

If the EDST is taken as directed

When the patient takes the EDST

While the patient is taking the EDST

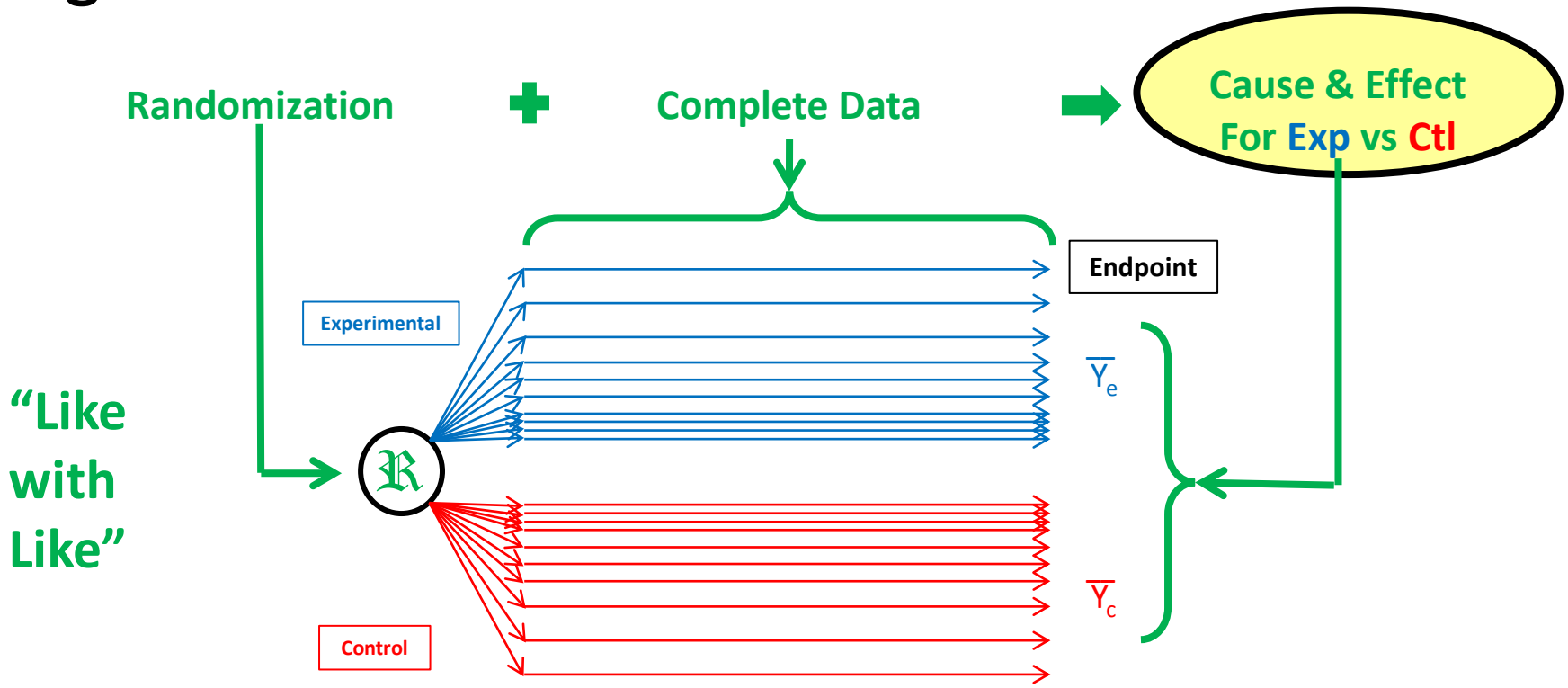
For patients who *adhere* to the EDST as prescribed

…

Steve

Estimand Thinking

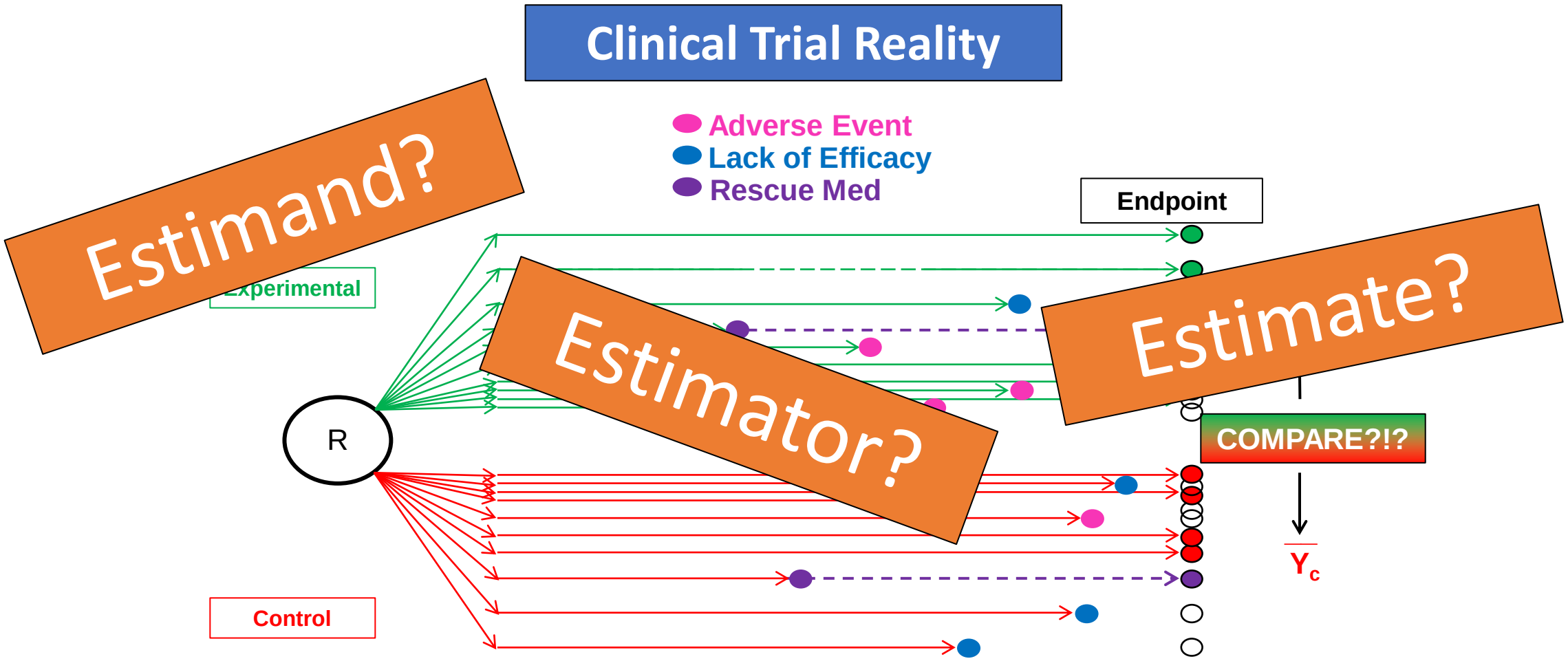
Choosing the Clinical Question



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

Jen

Estimand Thinking

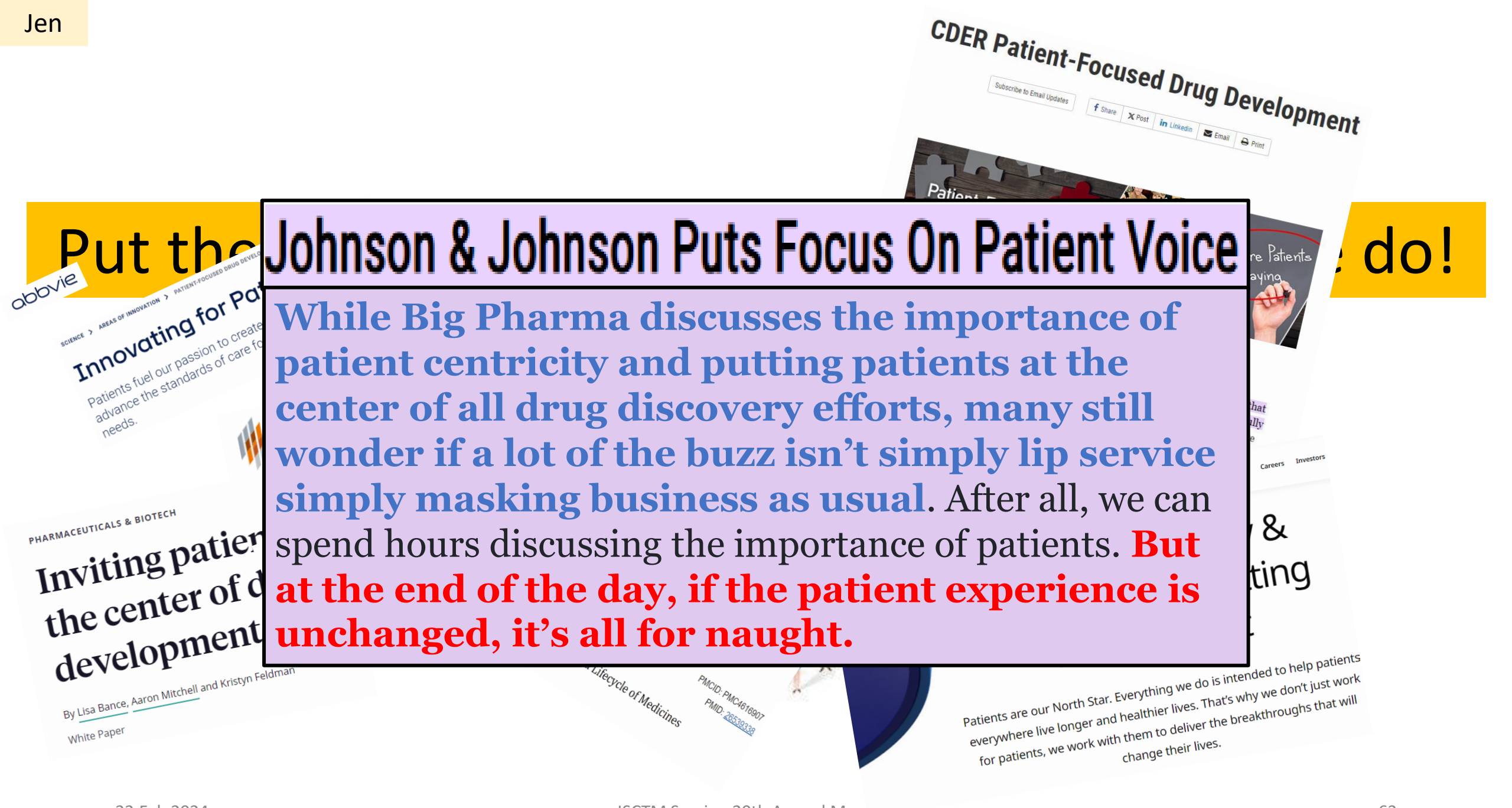


Jen

Put the … do!

Johnson & Johnson Puts Focus On Patient Voice

While Big Pharma discusses the importance of patient centricity and putting patients at the center of all drug discovery efforts, many still wonder if a lot of the buzz isn't simply lip service simply masking business as usual. After all, we can spend hours discussing the importance of patients. **But at the end of the day, if the patient experience is unchanged, it's all for naught.**



Jen

Estimand Thinking

Choosing the Clinical Question (4)

Steve

Estimand Thinking
Choosing the Clinical Question (4)

Conducted informal interviews with …

Family
Friends
Doctors and other healthcare providers

Asked open ended question

If you had unlimited time with your doctor and could ask any question about a treatment being prescribed to you …

Took copious notes

Reviewed and synthesized them

Result

Amazingly consistent !!!!

Steve

Estimand Thinking
Choosing the Clinical Question (4)

The Tripartite Estimand Approach (TEA)*

Three Clinically Meaningful (and causal) Estimands

1. The difference in proportion of patients that **D/C ExM due to AEs**
   - Can also assess time to discontinuation
2. The difference in proportion of patients that **D/C ExM due to LoE**
   - Need to assess time to discontinuation
3. For **those who could adhere to the ExM**, the difference for the primary efficacy response outcomes
   - 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.**

Jen

Estimand Thinking

Choosing the Clinical Question (4)

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 23% chance that you could have an adverse reaction that will prevent you from taking this medication.
{explain adverse reactions and their characteristics: 2% death; ARIA, siderosis, infusion site reactions}

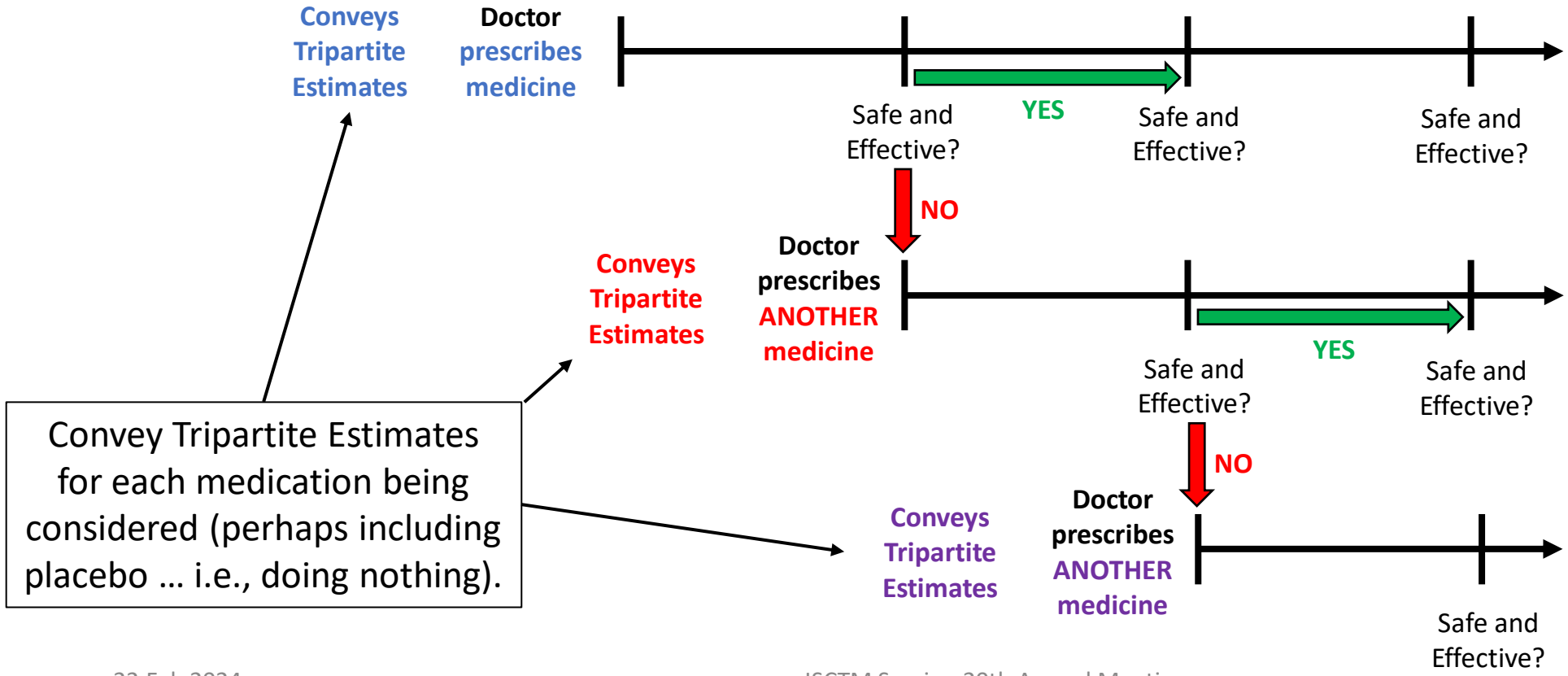
Second, this drug does not work for everyone, and there is about a 8% chance that you or I might choose to try something else. But, let's give it at least 6 months to see how it works.

Third, 69% of patients can 'stick with this treatment' and do quite well. On average, those patients experienced a 40% slowing of disease progression versus doing nothing (i.e., placebo) and a 15% improvement over Drug X."
{explain long-term adverse reactions and their characteristics}

Jen

Estimand Thinking

Choosing the Clinical Question (4)



Steve

Estimand Thinking
Choosing the Clinical Question (4)

Important Points

These three questions are very relevant and important to all stakeholders.

> "I wish I had those three pieces of information that I could tell all my patients."

Current methods for handling ICEs produce conservative estimates of the treatment effect.

- Need for increased sample size
- Less significant results – Type 2 Errors?

Steve

Estimand Thinking

Choosing the Clinical Question (4)

Bold Proclamation #3

Why should patients who cannot adhere to the experimental treatment prevent those who can from having access to that treatment?

Steve

Has this presentation produced a scientifically meaningful effect on your estimand thinking?

We hope so!

THANK YOU.