Hypothetical Strategies: Current Challenges

Lei Nie, Ph.D.

Associate Director, DB2/OB/OTS/CDER/FDA

July 23, 2020

Acknowledgements

- Jinglin Zhong and many others in OB/OTS/CDER
- Frank Bretz and others
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

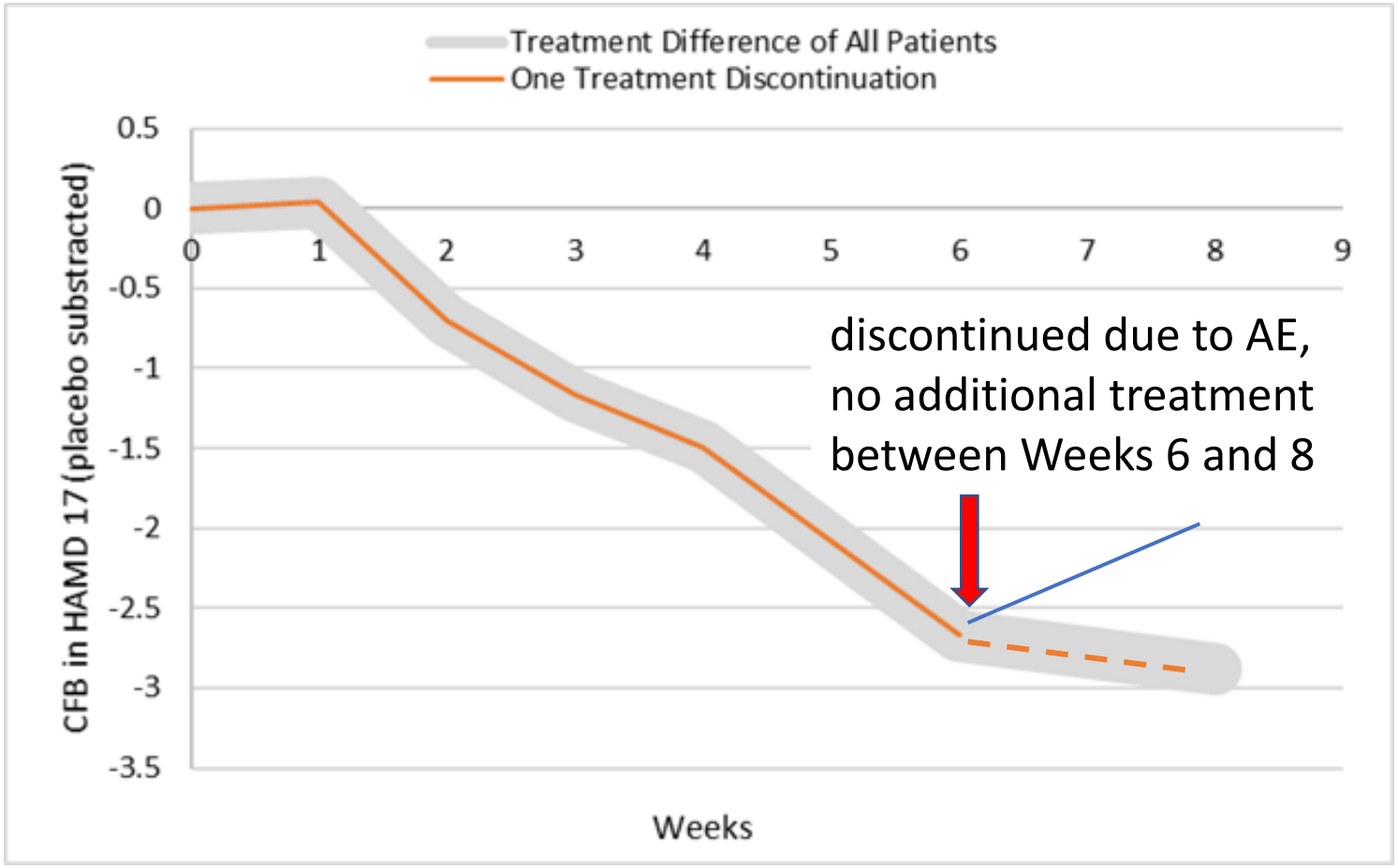
- Categories of Intercurrent events (ICEs)
- Clinical questions regarding treatment effects
- Clinical questions targeted by hypothetical strategies and related challenges
- Alternative strategies and their own challenges
- Gaps between clinical questions and available strategies provided by ICH E9 (R1)

Categories of Intercurrent Events

- E9(R1) introduced a categorization of intercurrent events
  - Affect interpretation of the measurements
  - Affect the existence of the measurements
  - Manifest as intermediate clinical events

- For the purpose of defining treatment effect, we use the following:
  - Category 1: Intercurrent events are direct consequences of the treatments, e.g., treatment discontinuation due to AE, LOE, treatment-related death
  - Category 2: Intercurrent events are interventions, e.g., additional medicine, surgery
  - Category 3: Intercurrent events are consequence of a temporary environmental change, e.g., temporary noncompliance due to COVID-19

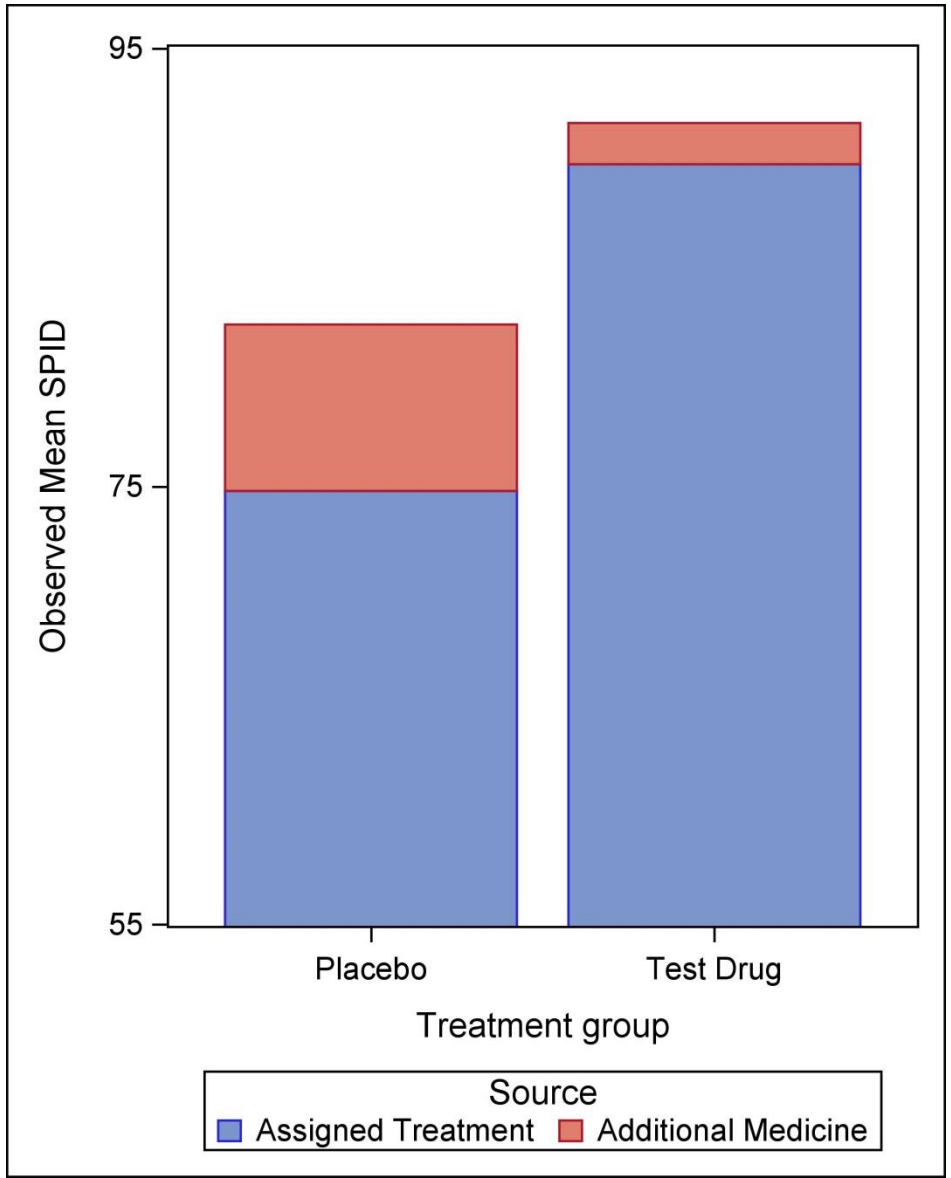
Clinical Questions Related to Category 1 ICE



Clinical questions:

- What is the observed treatment effect for the patient at Week 8?
- If the patient did not experience AE discontinue the treatment, what is the expected treatment effect at Week 8? (problematic)

Clinical Questions Related to Category 2 ICEs



The observed effect is a combined effect of treatment and Intervention.

Clinical questions:

- What is the combined effect of treatment and Intervention?

- What is the effect due to the treatment?
  - Do we have to ask "what is the treatment effect **had the intervention not occurred**?"
  - In nonrandomized studies, we ask "what is the average treatment effect (ATE)?"; we do not ask ""what is ATE had the confounding not occurred?"

Hypothetical Strategies

- Answer questions
  - What is the treatment effect if patients did not experience category 1 ICEs (which are direct consequences of the treatment)
  - What is the effect of treatment (separated from the intervention) when some patients experience category 2 ICEs (interventions)?

- Challenges in clinical justification
  - The hypothetical scenario of “if all patients can tolerate the treatments” is clearly problematic because tolerability is an intrinsic characteristic of the treatment
  - All hypothetical scenarios of “intercurrent event would not occur” can be challenging too

- Challenges in providing estimation: not all data observable

Alternative Strategy 1: Treatment Policy Strategy

- The occurrence of the intercurrent event is considered irrelevant
- The treatment effect is not the same one that is aimed by hypothetical strategies
- Data not collected after ICE are missing; Can be problematic in NI trials if used to address Category 2 ICEs.

Example: Oncology trials continue to follow patients for PFS/OS after patients discontinue treatments due to AE

- If patients‘ data are not collected, we need to imagine the outcome under the hypothetical scenarios if they were followed

Alternative Strategy 2: Composite Variable Strategies

- Intercurrent event is incorporated into the definition of the endpoint.
- Could be good alternatives to hypothetical strategies for category 2 ICEs and answer the question “what is the effect due to the treatment”?
- Change endpoint: different components may be of different importance

Example: In HIV trials, treatment discontinuations due to AEs are considered virologic failures.

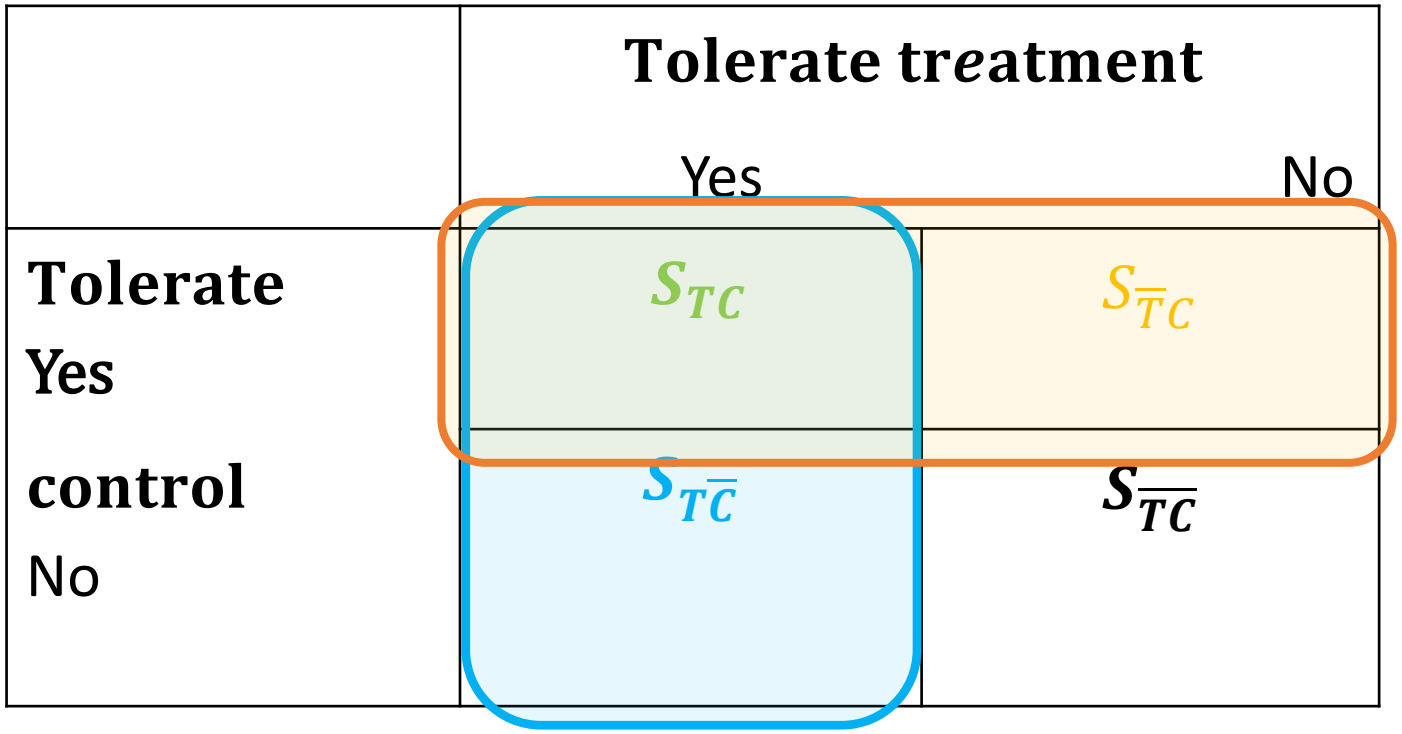
- Because we assume that patients will loss control of viral loads after the treatment discontinuation if they do not take additional treatments.

Other Alternative Strategies for Modified Questions

- Problematic: What is the treatment effect if all patients can tolerate the treatments?

- Revised: What is the treatment effect in patients who can tolerate the treatments?
  - This is the treatment effect for “tolerators”
  - The subpopulation “who can tolerate the treatments” is not clearly defined, as it depends on treatment and control
  - Potential solutions to target two different ‘tolerators’:
    - Principal stratum strategies
    - Randomized withdrawal trial design

Defining Populations of "Who Can Tolerate the Treatments": Principal Stratum



Patients who tolerate treatment: S_{TC} plus $S_{T\overline{C}}$

Patients who tolerate control: S_{TC} plus $S_{\overline{T}C}$

Revision 1 of Treatment Effect in Always Tolerators

What is the treatment effect in patients who can tolerate both the treatment and the control S_{TC}

- Design: Randomize all eligible patients to treatment and control
- Strategy: principal stratum strategy
- Challenges.
  - How do we identify S_{TC}? How do we label the treatment effect?
  - <u>May require strong assumptions</u>
  - Different from comparing outcomes in patients who tolerate treatment (S_{TC} and $S_{T\overline{C}}$) and patients who tolerate control (S_{TC} and $S_{\overline{T}C}$) in the trial

Revision 2 of Treatment Effect in Treatment Tolerators

What is the treatment effect in patients who can tolerate the treatment (S_{TC} and $S_{T\bar{C}}$)?

- Design: Enroll patients who can tolerate the treatment and randomized these patients into the treatment or the control.

- Challenge: how do we define patients who can tolerate the treatment in the indication? examples:
  - Zelnorm (for irritable bowel syndrome with constipation) is contraindicated for patients with high CV risk (post-hoc)
  - Xarelto: prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding (post-hoc)

An Example of Randomized Withdrawal Designs

- Drug: Rifaximin
- Indication: Treatment of irritable bowel syndrome with diarrhea
- Two typical randomized placebo-controlled short-term (14 days) trials
- One additional randomized-withdrawal trial to study long-term effect

Reference:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021361s025lbl.pdf

Estimation

- A hypothetical scenario in which the intercurrent event would not occur: the value of the variable is the value which the variable would have taken in the hypothetical scenario

- Determining the “unobservable” value needs assumptions:
  - Is the assumption realistic?
  - Are the results sensitive to the assumption?

Drug-Specific Guidance on the Importance of Reliable Estimation

- EMA Guideline on treatment of Alzheimer's disease
  - "providing that reliable methods of estimation can be identified; an appropriate target of estimation could be based on a hypothetical scenario in which the new concomitant medication or modifications in the dose of concomitant medications had not been introduced."
- EMA Guideline treatment or prevention of diabetes
  - "treatment effect can be estimated under the assumption that rescue medication or use of other medications that will influence HbA1c values, was not introduced, provided that a reliable estimate of that effect can be obtained."
- FDA Guidance for Industry. Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment.
  - hypothetical strategy was currently not recommended for the primary analysis to address the influence of hematopoietic stem cell transplantation because it may not be possible to design a clinical trial to estimate the treatment effect defined by the hypothetical strategy

Examples on Estimation Methods Handling Treatment Switch

- In oncology trials, patients may switch treatment after disease progression. Estimation of effect in OS relies on strong assumptions
  - Rank Preserving Structural Failure Time Model, assuming that treatment effect is equal for all patients regardless the time when the treatment is received
  - Inverse Probability of Censoring Weights: no unmeasured confounders
  - EMA “Question and answer on adjustment for cross-over in estimating effects in oncology trials”. recommends against those hypothetical strategy causal inference methods that rely on very strong assumptions

Criteria to Select Estimand Strategies

- Whether clinical questions are of clinical and regulatory importance or interest;
- Whether a reliable estimator can be provided with appropriate sensitivity analyses

Question to consider: Does ICH E9 (R1) really anticipate we can only select among the 5 strategies?

Gaps between Clinical Questions of Interest and Estimand Strategies

- Gaps: Some clinical questions are of interest. But it is hard to addressed them by any of the 5 estimand strategies as defined.
  - Some question we discussed earlier
  - Question about a maintenance therapy, recognizing that patients who discontinued the therapy would not have long term effect (e.g. long term health condition will be like the condition at baseline)?
- How do we close these gaps?
  - Should we describe the treatment effect without creating the hypothetical scenarios if possible?
  - Should we expand the definition of hypothetical strategies?
  - Should we explore additional estimand strategies?

Summary

- Hypothetical strategies
  - Aim to estimate drug effects
  - Challenges in clinical justification and in estimation with the current definition
- Alternatives:
  - Composite variable strategies: endpoints are changed
  - Treatment policy strategy: clinical questions are changed
  - Randomized withdrawal design: challenging to interpret and label the treatment effect
  - Principal stratum strategies challenging to interpret and label the treatment effect
- Gaps and challenges remain, collaboration
  - to close the gaps between clinical questions of interest and estimand strategies
  - to address estimation problems including sensitivity analyses through innovations.

Summary

- Hypothetical strategies
  - Aim to estimate drug effects
  - Challenges in clinical justification and in estimation with the current definition
- Alternatives:
  - Composite variable strategies: endpoints are changed
  - Treatment policy strategy: clinical questions are changed
  - Randomized withdrawal design: challenging to interpret and label the treatment effect
  - Principal stratum strategies challenging to interpret and label the treatment effect
- Gaps and challenges remain, collaboration
  - to close the gaps between clinical questions of interest and estimand strategies
  - to address estimation problems including sensitivity analyses through innovations.

Thank you!