Hypothetical Strategies: 
Current Challenges

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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 lose 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

<table>
<thead>
<tr>
<th>Tolerate control</th>
<th>Tolerate treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>$S_{TC}$</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>$S_{T\overline{C}}$</td>
</tr>
</tbody>
</table>

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

Patients who tolerate control: $S_{TC}$ plus $S_{T\overline{C}}$
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?
  - May require strong assumptions
  - Different from comparing outcomes in patients who tolerate treatment ($S_{TC}$ and $S_{TC}$) and patients who tolerate control ($S_{TC}$ and $S_{TC}$) in the trial
Revision 2 of Treatment Effect
in Treatment Tolerators

What is the treatment effect in patients who can tolerate the treatment \((S_{TC} \text{ and } S_{TC^-})\)?

• 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.
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Thank you!