Estimand Considerations for Time-to-Event Analysis of Patient-Reported-Outcomes

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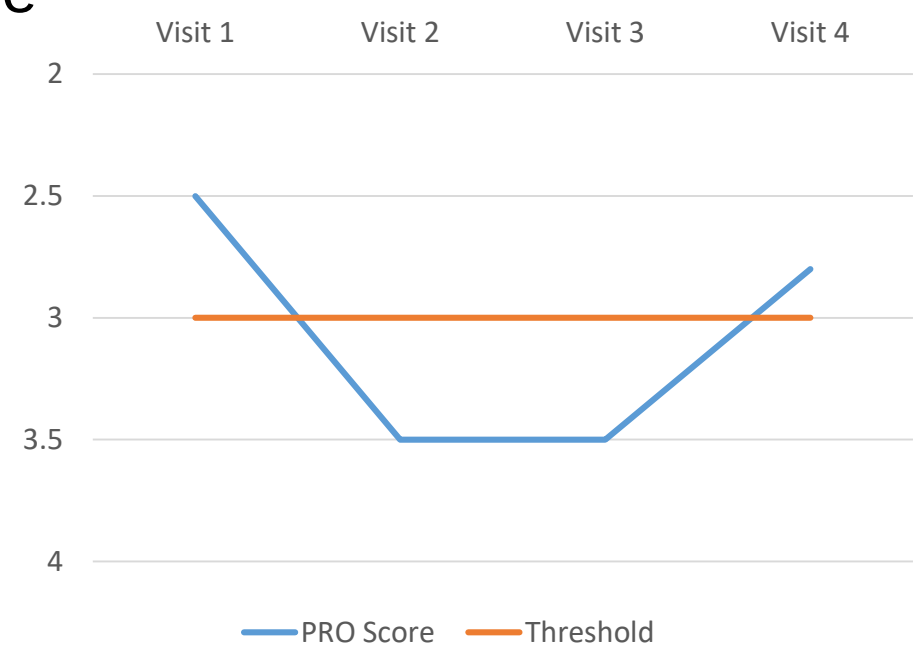
Introduction

- Evaluating the patient experience to compare treatments can be complicated, especially in oncology, where patients are assessed repeatedly for long periods of time.
- Complicating factors include discontinuation of treatment, crossing over treatment arms, disease progression and death. Data may or may not be collected after these events.
- Time-to-meaningful-deterioration is often an important patient-reported outcome (PRO).
- Lack of clear PRO research objectives and inconsistency in how PRO data are analyzed makes it difficult to interpret results both within and across trials.
- The estimand framework provides a structure to align a research question with study design, conduct, and statistical analysis.

Objective: To highlight considerations when applying the estimand framework for time-to-event analyses of PRO data.

Time to Deterioration

- Definition of event:
  - Threshold for deterioration– not focus here
  - Different definitions for deterioration used
    - Time to first deterioration
    - Time to confirmed deterioration
    - Time to definitive deterioration
- Censoring rules:
  - Consideration of estimand strategies
  - Not always clear



Estimands

Estimand Attributes:

1. Treatments
2. Target population
3. Endpoint of interest
4. Intercurrent events (ICEs)
5. Population level summary

Estimand Strategies for Intercurrent Events (ICEs):

- Treatment Policy strategy
- Composite strategy
- Hypothetical strategy
- Principal Stratum strategy
- While on Treatment strategy

Research question:
Does Treatment A delay PRO deterioration, disease progression, discontinuation, or death, longer than the Treatment B?

Attribute	
Treatments	Treatment A Treatment B
Target Population	All participants, according to the inclusion/exclusion criteria
Endpoint	Time to PRO deterioration, disease progression, discontinuation, crossover, or death
Event definition	First deterioration in PRO endpoint, disease progression, discontinuation, crossover, or death (occurring after no more than 3 missing assessments, for example)
ICEs	Disease progression: Composite strategy (define as an event) Death: Composite strategy (define as an event) Discontinuation: Composite strategy (define as an event) Crossover: *Composite strategy (define as an event)*
	Missing for unknown reasons/withdrawal: Hypothetical, censor

Considerations

- Must be careful in the interpretation because a simply stating research question may not make clear the handling of the all ICEs.
- Composite strategy for progression: may mirror progression-free survival
  - Interpretation may be difficult for other strategies, eg, hypothetical
  - Data would need to be collected post progression to use treatment policy
- Assumption: Censored participants have the same probability of experiencing deterioration, progression, crossover or death as those who are not censored
  - Is that reasonable here?

Research question:
Does Treatment A delay PRO deterioration or death, longer than the Treatment B?

Attribute	
Treatments	Investigational Treatment Comparator Treatment
Target Population	All participants, according to the inclusion/exclusion criteria
Endpoint	Time to PRO deterioration, or death
Event definition	First deterioration in PRO endpoint or death
ICEs	Disease progression: **Hypothetical, censor** Death: Composite strategy (define as an event) Discontinuation: **Hypothetical, censor** Crossover: **Hypothetical, censor**
	Missing for unknown reasons/withdrawal: Hypothetical, censor

Considerations

- This estimand focuses on PRO deterioration
  - Assuming PRO data not collected after progression, crossover, discon’t
- Death should not be censored, but what about disease progression?
- Assumption: Censored participants (those who have progressed) have the same probability of experiencing deterioration, as those who are not censored
  - Is this reasonable?
  - What if data post-progression, crossover or discontinuation are collected?

However…

- Are there settings where assumptions more likely to hold?

Key Messages

- Estimands for time-to-deterioration of PROs can vary widely.
- Event definitions should be relevant to the trial setting.
- Careful consideration is needed for appropriate interpretation.

Thank you for listening!

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