2023 UPenn Conference on Statistical Issues in Clinical Trials

Rebecca A. Betensky

April 17, 2023

General themes

- Multi-state modeling more informative than simple hazard modeling
- Estimands should remove censoring and be applicable to real-world settings and account for intercurrent events

FDA Guidance May 2021 E9(R1)

- Statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials
- Purpose: need for clarity in descriptions of risks and benefits of a treatment
- Precision in describing a treatment effect facilitated by constructing *estimand* corresponding to clinical question of interest
- Clarity requires ”thoughtful envisioning” of *intercurrent events* (e.g., discontinuations, switchings)
- Statistical analysis of clinical trial data should be aligned to the estimand.

Estimand

- Precise description of the treatment effect reflecting the clinical question posed by a clinical trial objective
- Summarizes at a population level what the outcomes would be in the same patients under different treatment conditions
- Developed in light of intercurrent events, which should be considered explicitly
- Sets the stage for multi-state models and removal of censoring from estimation

Multi-state models for trial data:
Terry Therneau

- Multi-state models are more informative than simple hazard models (regarding causal process).
- Many estimands of interest; provide insights into disease process.
- Software will make these accessible.

Question:

1. What about at design stage?

Non- and semi-parametric analysis of composite endpoints: Lu Mao

- General pairwise comparisons (GPC) allow ranking of events (e.g., win ratio, proportion in favor, win odds)
- Estimands depend on censoring distributions; do not generalize
- Solutions:
  - Non-parametric: restricted estimands
  - Semi-parametric: assume model (e.g., time invariant win ratio)
  - Estimation with censored data via IPCW or restricted mean via survival estimates of component events

<u>Questions:</u>

1. This removes censoring. What about confounder imbalance (due to chance)?
2. Different censoring for different components?

Statistical Approaches for Component-Wise Censored Endpoints: Anne Eaton

- Problem: different censoring for component endpoints of composite
- FDA approach: ignore interval censored nature of non-fatal event
- Decompose probability of composite into two pieces: KM for death, Kernel estimator for non-fatal event among those alive
- Parametric modeling via illness death model, constant intensities

<u>Questions:</u>

1. Can this accommodate dependent censoring (i.e., informative visit process) for the non-fatal event (plausible)?
2. This does require independence between censoring for death and non-fatal event (reasonable?).
3. Does this allow for death to be ascertained separately from a study visit?

Estimands in clinical trials with complex life history processes: Richard Cook

- Distinction between marginal and causal interpretation: clinical trials suited for former.
- Marginal analyses are not sufficient to reveal treatment effects; need intensity-based insights, for causal interpretation.
- Estimand should target a marginal process feature with clear scientific relevance.
- Features should be interpretable in the real world.
- Estimands should not be sensitive to unobservable assumptions.
- Incorporate intercurrent event into response process.
- Multi-state models complex but useful.

Questions

- How are meaningful estimands determined when a trial is being designed?
- How do you meaningfully design a trial that uses multi-state modeling to obtain estimands?
- How do you meaningfully design a trial with complex censoring that your estimator will handle but you may not be able to characterize?