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
• 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

Questions:
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

Questions:
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?