Advances in Time-to-Event Analyses in Clinical Trials University of Pennsylvania, 2023

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Congratulations to Devan, Lu, Zhenzhen and Fan!

This discussion:

- will focus on use of multiple endpoints in clinical trials.
- Comments mainly related to presentations of Devan Mehrotra and Lu Tian.

Lu Tian's work

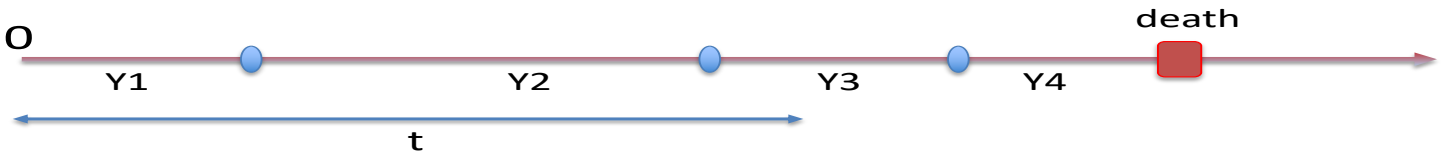
Analyzing duration of response (DOR)

Y_1: time to response; Y_2: DOR
If $Y_1 < T$ then $T = Y_1 + Y_2$. If $Y_1 \geq T$ then $Y_1 = \infty$.
T: time to endpoint
C: censoring time

- Induced informative censoring:
  The censoring time for Y_2 is $\max\{C - Y_1, 0\}$. If Y_1 is correlated with Y_2 then the observation of Y_2 is subject to informative censoring.
- Standard Kaplan-Meier estimation is biased. Lu Tian presented bias-corrected estimation of $S_{Y_2}(t)$ (same as Lin-Ying estimator.).
- Huang and Louis (1998, Biometrika): Joint estimation of a survival function and mark variables.
  - Mark variable could be DOR, medical cost, biomarker measurement, etc.

Devan Mehrotra's work

Analyzing composite or multiple endpoints



Y_j: the jth gap time

$T_j = Y_1 + ... + Y_j$: time to jth endpoint

t: time since 0

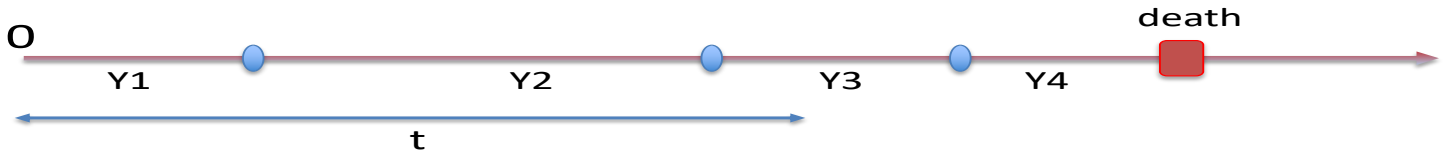
Data example: CV death, Non-fatal stroke, Non-fatal MI, Coronary revasc$\geq$30 days after randomization, Unstable angina

- Prentice, Williams & Peterson model (1981) assume the jth endpoint occurs with the hazard

$$\lambda_j(t - t_{j-1} \mid X, N^H(t^-)) = \lambda_{0j}(t - t_{j-1}) exp\{\beta_j' X + \phi(N^H(t^-))\}$$

$\lambda_{0j}(\cdot)$: baseline hazard function. $N^H(t^-)$: history of events prior to t

Can PWP Model be used in clinical trials?



Y_j: the jth gap time; $T_j = Y_1 + \ldots + Y_j$: time to jth endpoint

- For the purpose of testing, need simplification:
  $\lambda_j(t - t_{j-1} \mid X, N^H(t^-)) = \lambda_{0j}(t - t_{j-1})exp\{\beta_j' X + \phi(N^H(t^-))\}$ to
  $\boldsymbol{\lambda_j(t - t_{j-1} \mid X, N^H(t^-)) = \lambda_{0j}(t - t_{j-1})exp\{\beta_j' X\}}$
  – it requires that **each gap time carries NO memory from the event history!**
- PWP considered ordered endpoints so λ_j has concrete meaning; e.g., HIV - AIDS -Death
  What does λ_j mean if multiple endpoints have arbitrary order? (CV death, Non-fatal stroke, Non-fatal MI, etc.)
- Competing risks issues: Since 'death' must be part of censoring for other endpoints, what type of hazards is PWP model estimating? **- Cause-specific hazard**
- If PWP model estimates cause-specific hazards, does the hazard provide proper causal interpretation for clinical trials?

Statistical approaches

- **Anderson-Gill approach**: The AG model assumes constant intensity ratio; the multiple event process does not carry memory:
  $\lambda(t \mid N^H(t^-), X) = \lambda_0(t) exp\{\beta' X\}$
  - AG model is similar to a Poisson process; 'memoryless' is a very strong assumption!
  - Does not handle absorbing event such as death.

- **Wei-Lachin, Brown, Kost-McDermott, Stouffer, Lachin-Bebu approaches**: Cox PH model for each component, average resulting HR estimates with differential weights.
  - Conceptually, better than PWP and AG approaches.
  - In the presence of CV-death, the hazard for other multiple events (Non-fatal stroke, Non-fatal MI, etc.) are cause-specific hazards.
  - Are we comfortable with the use of cause-specific hazards to evaluate trial effects?

Statistical approaches

- **Win ratio statistic**: Aggregate pairwise subject-level between-treatment comparison of survival times based on sequential order of endpoint importance (Pocock et al., 2012).
  - The win ratio statistic is simple in its format but hard to understand.
  - Fortunately, in semi-competing risks setting, the aim of hypothesis testing has been clarified to test on the **observable part of the hazards of latent variables**; see Luo et al. (Biometrics, 2015) and Mao Lu (2021).
  - Analysis results possess causal interpretation!
- **Claggett et al. approach**: Quantify mean cumulative count of events over time using AUC to compare treatments. AUC is an overall summary measure of all the events.
  - Conceptually, this is an appropriate approach in the presence of multiple endpoints (including death).
  - Analysis results possess causal interpretation!
  - Why worst performance in simulation?