Biost 572 Presentation 1

Introduction, Motivation

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Chapter 20

Application of Time-to-Event Methods in the Assessment of Safety in Clinical Trials

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Adapted from the book:

Design and Analysis of **Clinical Trials** with **Time-to-Event Endpoints**

Edited by Karl E . Peace

Chapman and Hall/CRC 2009

Beta-Blocker Heart Attack Trial

- Group et al. (1982)
- Propranolol vs Placebo
- Primary endpoint: All cause mortality
  - Propranolol 7% mortality (135 deaths)
  - Placebo showed 9.5% mortality (183 deaths).
- Crude incidences of various AEs was observed to be higher in Propranolol arm
- Time-to-event analysis suggested evidence of shorter time to first AE i.e bronchospasm/fatigue (Davis et al., 1987)

Literature Review: Moore and van der Laan (2009)

Parametric framework

- Covariate adjustment in linear models can provide gains in precision over unadjusted estimate (Biost 514/515/570)
- Adjusting in logistic regression often does not buy you improvements in precision (Robinson and Jewell, 1991; Hernández et al., 2006)

Estimating equations framework

- Estimation of nuisance parameters
- "Lack of criterion for selecting candidate solutions when there are multiple roots in parameter of interest"

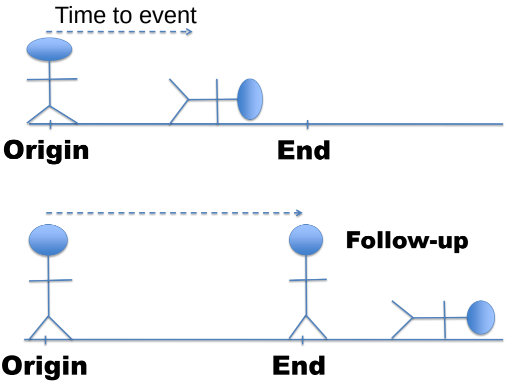
Focus of the paper: Discrete failure time

Objectives

- Estimation of treatment specific survival at a fixed end point
- Exploits important (**pre-specified**) covariates to improve efficiency in treatment specific survival at fixed end point
- Provide a consistent estimator in the presence of informative censoring

"**Ultimate**" goal: Difference in survival probabilities between treatments adjusting for pre-specified covariates of interest.

Introduction to Time-to-event outcomes



Event of Interest: Death/Infection/AE

Right censored data: Non-ignorable missing data.

Informative censoring

Brief Review: Survivor/Hazard function

$$S(t) = Pr(T > t) = 1 - F(t)$$

- $F(t)$ is the fraction of the population whose event time has been observed by time t.

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{\mathrm{Pr}[t \leq T < t + \Delta t | T \geq t]}{\Delta t}$$

- Conditional probability per unit time (Hazard rate).

Brief Review: Survival Analysis

Cox (1972) Proportional Hazards Regression

$$\lambda(t|A, \mathbf{W}) = \lambda_0(t) \exp(\beta_1 A + \boldsymbol{\beta}_W^T \mathbf{W})$$

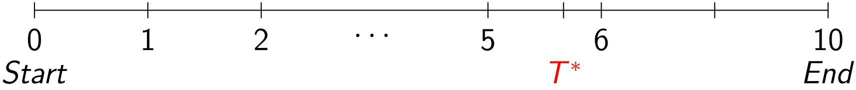
Cox PH allows us to adjust for baseline covariates with **W**

Assumptions of Cox-PH

- Non-informative censoring
- Proportional hazards (odds) assumptions
- Large sample size*

Solution: Biost 515/537 Cox-PH with robust standard errors.

Setup: Discrete Version (Zhang and Gilbert, 2010)



$$\lambda(t_j) = \Pr(T = t_j | T > t_{j-1})$$

T^*: "True" failure time (Unobserved due to discrete follow-up)

$T = t_j$ if $T^* \in [t_{j-1}, t_j)$ with t_j for $j = 1, \cdots, 10$.

$\widetilde{T} = min(T, C)$: where C is our censoring time.

$\Delta = I(T \leq C)$: Indicator of subject **not** being censored

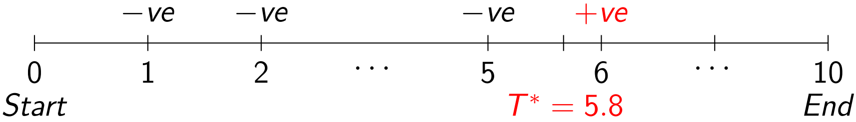
$A \in \{0, 1\}$: Treatment indicator

$\mathbf{W}$: Observed covariates

Discrete failure time

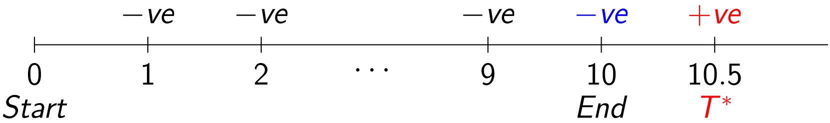
If someone develops an infection during the study

$\cdots \quad \widetilde{T} = min(6, +\infty) = 6$ with $\Delta = 1$



If someone develops an infection after the study ended

$\cdots \quad \widetilde{T} = min(11.5, 10) = 10$ with $\Delta = 0$



Scientific questions: Setup based on the paper

Having observed the data $O = (\mathbf{W}, A, \widetilde{T}, \Delta) \sim P_O$ where P_O is the data generating mechanism.

$$P_O \rightarrow \Psi_1(p_O)(t_k) = \Pr(T_1 > t_k) = E_0(S_0(t_k|A = 1, \mathbf{W}))$$

$$P_O \rightarrow \Psi_0(p_O)(t_k) = \Pr(T_0 > t_k) = E_1(S_0(t_k|A = 0, \mathbf{W}))$$

We might be interested in the following treatment effect at t_k

$$\mathbf{P_O} \rightarrow \boldsymbol{\Psi}_{\mathbf{AD}}(\mathbf{p_O})(\mathbf{t_k}) = \Pr(\mathbf{T_1} > \mathbf{t_k}) - \Pr(\mathbf{T_0} > \mathbf{t_k})$$

Proposed method & Author's claims

$$\mathbf{P_O} \rightarrow \mathbf{\Psi_{AD}}(\mathbf{p_O})(\mathbf{t_k}) = \Pr(\mathbf{T_1} > \mathbf{t_k}) - \Pr(\mathbf{T_0} > \mathbf{t_k})$$

- "Target" the parameter of interest directly
- Targeted MLE: borrow useful information from parametric models and overcome drawbacks of estimating equations.
- "**Doubly robust**"
  - Robust to model mis-specification
  - Overcomes the problem of informative censoring
- Simulations on weak/strong covariate in combination with random censoring and informative censoring.

What is to come

- Introduction to targeted MLE for survival outcomes
- Estimation algorithm
- Test the coded algorithm on a “toy” dataset
- Test with the proposed simulation in the paper

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