Appendix: Proofs

Paper: Assessing clinical utility of treatment effects using repeated outcome measurements in comparative trials with application to cardiovascular diseases

Authors: Zachary R. McCaw, PhD; Lu Tian, ScD; Stephanie Armbruster, MSc; Brian L. Claggett, PhD; Garrett Fitzmaurice, ScD; Alberto Foa, MD; Marc A. Pfeffer, MD, PhD; Lee-Jen Wei, PhD

A. 1. Consistency

By the uniform law of large numbers, and uniform consistency of the Kaplan-Meier $\hat{S}(t)$(1),

$$\hat{\theta} = \int_0^\tau \bar{Z}(t)\hat{S}(t)dt = \int_0^\tau \frac{n^{-1}\sum_{i=1}^n Z_i(t)I(X_i \geq t)}{n^{-1}\sum_{i=1}^n I(X_i \geq t)}\hat{S}(t)dt$$

converges to:

$$\int_0^\tau \frac{E\{Z(t)I(X \geq t)\}}{P(X \geq t)}S(t)dt,$$

where $S(t)$ is the survival function of T at time point t.

Since C is independent of Z(t) and T, the above quantity can be simplified as

$$\int_0^\tau \frac{E\{Z(t)I(X \geq t)\}}{Pr(T \geq t)P(C \geq t)}Pr(T \geq t)dt = \int_0^\tau \frac{E\{Z(t)I(X \geq t)\}}{P(C \geq t)}dt.$$

The numerator in the integrand is

$$Pr(C \geq t)E\{Z(t \wedge T)\}.$$

Thus, $\hat{\theta}$ is consistent.

A. 2. Asymptotic normality

$$\sqrt{n}\big(\hat{\theta} - \theta\big) = \sqrt{n}\int_0^\tau \left\{\frac{n^{-1}\sum_{i=1}^n Z_i(t)I(X_i \geq t)}{n^{-1}\sum_{i=1}^n I(X_i \geq t)}\hat{S}(t) - \frac{E\{Z(t)I(X \geq t)\}}{P(X \geq t)}S(t)\right\} dt.$$

Let

$$\bar{D}(t) = \frac{1}{n}\sum_{i=1}^n Z_i(t)I(X_i \geq t)\,, \qquad d(t) = E\{Z(t)I(X \geq t)\}$$

$$\bar{Y}(t) = \frac{1}{n}\sum_{i=1}^{n} I(X_i \geq t)\,, \text{and } \; y(t) = P(X \geq t).$$

Then,

$$\sqrt{n}\big(\hat{\theta} - \theta\big) = \sqrt{n}\int_0^{\tau} \left\{\frac{\bar{D}(t)}{\bar{Y}(t)}\hat{S}(t) - \frac{d(t)}{y(t)}S(t)\right\} dt = I_d + I_y + I_s + o_p(1),$$

where

$$I_d = \int_0^{\tau} \frac{S(t)}{y(t)} \cdot \sqrt{n}\{\bar{D}(t) - d(t)\}\, dt$$

$$I_y = -\int_0^{\tau} \frac{d(t)S(t)}{y^2(t)} \cdot \sqrt{n}\{\bar{Y}(t) - y(t)\}\, dt,$$

and

$$I_s = \int_0^{\tau} \frac{d(t)}{y(t)} \cdot \sqrt{n}\big\{\hat{S}(t) - S(t)\big\} dt.$$

Now, using the asymptotic martingale representation theorem(1),

$$I_s = -\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\int_0^{\tau} \mu(t;\tau)\frac{dM_i(t)}{y(t)} + o_p(1)$$

where $dM_i(t) = dN_i(t) - Y_i(t)dA(t)$, $N_i(t) = I(X_i \leq t, \delta_i = 1)$, $Y_i(t) = I(X_i \geq t)$, $A(t)$ is the cumulative hazard function of *T*, that is $A(t) = -\ln\{S(t)\}$, and

$$\mu(t;\tau) = \int_t^{\tau} \frac{d(u)S(u)}{y(u)} du.$$

Moreover,

$$I_d = \frac{1}{\sqrt{n}}\sum_{i=1}^{n}\int_0^{\tau} \frac{S(t)}{y(t)}\{D_i(t) - d(t)\}dt,$$

$$I_y = -\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\int_0^{\tau} \frac{d(t)S(t)}{y^2(t)}\{Y_i(t) - y(t)\}dt,$$

where $D_i(t) = Z_i(t)I(X_i \geq t)$. It follows that

$$\sqrt{n}\big(\hat{\theta} - \theta\big) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n}\psi_i(\tau) + o_p(1),$$

where

$$\psi_i(\tau) = \int_0^\tau \frac{S(t)}{y(t)}\{D_i(t) - d(t)\}dt - \int_0^\tau \frac{d(t)S(t)}{y^2(t)}\{Y_i(t) - y(t)\}dt - \int_0^\tau \frac{\mu(t;\tau)dM_i(t)}{y(t)}.$$

By the central limit theorem

$$\sqrt{n}(\hat{\theta} - \theta) \to N(0, \sigma^2)$$

with $\sigma^2 = E\{\psi_i^2(\tau)\}$. We can estimate σ^2 by plugging in consistent estimators for those unknown parameters to obtain $\hat{\psi}_i(\tau)$. A consistent estimator for the variance is

$$\hat{\sigma}^2 = n^{-1}\sum_{i=1}^{n}\hat{\psi}_i^2(\tau). \tag{A-1}$$

References

1. Fleming TR, Harrington DP. Counting Processes and Survival Analysis. John Wiley & Sons; 2011. 454 p.