Inference on Treatment Effects from a Randomized Clinical Trial in the Presence of Premature Treatment Discontinuation: The SYNERGY Trial

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Motivation: The SYNERGY trial

SYNERGY: The **S**uperior **Y**ield of the **N**ew strategy of **E**noxaparin, **R**evascularization, and **GI**Y**coprotein IIb/IIIa inhibitors trial

- Sponsored by *Sanofi-Aventis*, conducted by DCRI
- Randomized, open-label, multi-center trial with almost 10,000 high-risk patients with non-ST segment elevation acute coronary syndromes likely to undergo *PCI* (angioplasty) or *CABG* (bypass)
- Compare the *anticoagulants enoxaparin* (*Lovenox*, ENOX, by *injection* every 12 hours) and *unfractionated heparin* (UFH, by *IV bolus/continuous infusion*)
- *Outcome of interest*: All-cause *death* within 1 year

Motivation: The SYNERGY trial

SYNERGY protocol:

- Study drug to be *continued* until treating physician deemed *no further anticoagulation required* – "*treatment completion*"
- Study drug to be *mandatorily discontinued* if *bleeding*, other *adverse events*, *thrombocytopenia*, need for *CABG*, ...

Optional discontinuation: In the trial

- Some subjects *stopped* assigned study drug for reasons *not sanctioned by protocol* (e.g., MD or patient preference, etc)
- Some subjects *switched* (*crossed over*) to the other drug; *not sanctioned by protocol*

Motivation: The SYNERGY trial

Results: *Intent-to-treat* analyses

- *Analysis* of 1 year death: *hazard ratio* 1.06 (0.92–1.22)
- *Contradicts previous findings* showing ENOX *superior to* UFH
- *Higher risk*, more *aggressively managed* patient population?
- *Discontinuation*? 24.4% (13.2% *optional*, 11.3% *mandatory*) of ENOX subjects vs. 14.4% (7.5% *optional*, 6.9% *mandatory*) of UFH subjects

Question: "What would have been the difference in UFH and ENOX survival distributions *had no subject discontinued his/her assigned treatment*?"

Motivation: The SYNERGY trial

Proposed analyses:

- *Delete* all subjects discontinuing assigned study drug for any reason from the data set, do standard analysis
- *Artificially censor* outcomes for all subjects discontinuing assigned study drug for any reason *at the times of discontinuation*, do standard analysis
- Fit a *proportional hazards* (PH) model with *binary time-dependent on/off indicators* for each treatment

Question: "What would have been the difference in UFH and ENOX survival distributions *had no subject discontinued his/her assigned treatment*?"

- What is *really* meant by this?
- Do *any* of these analyses address it?

Motivation: The SYNERGY trial

Our objective: An instructive demonstration of how to *conceptualize* this problem

- *More precise* statement of the question
- *Statistical framework*
- $\Longrightarrow$ *Inverse probability risk set weighting* (Robins and Rotnitzky, 1992; Robins, 1993; Hernán et al., 2006)

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Conceptualization

Ideal goal: "Difference in survival distributions were all subjects in the population to *follow* each of the treatment regimens studied"

"**Following**" **a treatment regimen:**

- There are circumstances where *discontinuation* of regimen is *mandatory*, e.g., adverse event (*safety*, *ethical* reasons), CABG
- $\Longrightarrow$ *Mandatory discontinuation* is consistent with how treatment is *intended to or must be* administered
- $\Longrightarrow$ "*Following*" should acknowledge this

Optional discontinuation:

- Is *not consistent* with how treatment is intended to or must be administered
- Should thus be *distinguished from* mandatory discontinuation

Conceptualization

Question, better stated: "What would have been the difference in survival distributions corresponding to the *treatment regimes* for ENOX and UFH *had no subject discontinued his/her assigned treatment for optional reasons*?"

- Do the analyses mentioned previously address this?
- *Problem*: All are *ad hoc*, none arise *explicitly* from addressing this goal...

Better idea: Define a *statistical framework* in which the *treatment effect* of interest corresponding to this question can be *defined formally* $\Longrightarrow$ suggest valid *inferential methods*

Statistical framework

Situation: As in SYNERGY

- *Time-to-event* outcome up to $t_{\max}$ (e.g., 1 year)
- Outcomes *administratively censored* at $t_{\max}$

First step: Characterize the *ideal* situation with *no optional discontinuation* through $t_{\max}$

- *Treatment regimes* $z = 0$ (UFH) and 1 (ENOX)
- "Continue on z until completion or event meriting mandatory discontinuation"

Statistical framework

Ideal observed data: (POTENTIAL OUTCOMES) For a trial with n subjects and *no optional discontinuations*

$$W_i^* = \{Z_i, X_i, U_i^*, \Delta_i^*, S_i^*, E_i^*, V_i^H(S_i^*)\}, \quad i = 1, \ldots, n$$

- Z_i = observed (randomized) treatment assignment
- X_i= baseline covariates
- $U_i^* = \min\{T_i^*, C_i^*\}$ = time to failure or censoring
- $\Delta_i^* = I\{T_i^* \leq C_i^*\}$ = failure indicator
- $S_i^* = \min\{M_i^*, U_i^*\}$ = time to mandatory discontinuation, failure, or censoring
- $E_i^* = 1$ if $S_i^* = M_i^*$, $E_i^* = 0$ otherwise
- $V_i^H(u)$ = time-dependent covariate history through time u

Statistical framework

Effect of interest: Model for (net-specific) hazard for T^*

$$\lambda(t|Z) = \lim_{h \to 0} h^{-1} \mathsf{Pr}\{t \leq T^* < t + h | T^* \geq t, Z\} = \lambda_0(t) \exp(\beta Z)$$

- $\beta =$ *log hazard ratio* for regime 1 to regime 0

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Statistical framework

Inference on β: Assume $T^* \perp\!\!\!\perp C^* | Z$

- Solve for β the *partial likelihood score equation*

$$\sum_{i=1}^{n} \int \left\{ Z_i - \frac{\sum_{j=1}^{n} Z_j \exp(\beta Z_j) Y_j^*(u)}{\sum_{j=1}^{n} \exp(\beta Z_j) Y_j^*(u)} \right\} dN_i^*(u) = 0$$

- $dN_i^*(u)$ is the counting process increment $I(U_i^* = u, \Delta_i^* = 1)$
- $Y_i^*(u)$ is the at-risk process $I(U_i^* \geq u)$
- Note that S_i^*, E_i^*, $V^H(u), X_i$ *not needed*

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Statistical framework

Actual observed data: Some subjects *optionally discontinue*

$$W_i = \{Z_i, X_i, U_i, \Delta_i, S_i, E_i, V_i^H(S_i)\}$$

- Define O_i = time to *optional discontinuation* (if subject does); otherwise, set $O_i = \infty$
- Time to failure/censoring U_i; censoring indicator $\Delta_i = 1$ if failure, $= 0$ if censoring
- $S_i = \min\{O_i, M_i^*, U_i^*\}$, $E_i = 1, 2, 3$ if $S_i = O_i, M_i^*, U_i^*$ = time of "*first thing*" to happen
- Counting process increment $dN_i(u) = I(U_i = u, \Delta_i = 1)$
- At-risk process $Y_i(u) = I(U_i \geq u)$

Statistical framework

The problem:

- Assume $(U_i, \Delta_i) = (U_i^*, \Delta_i^*)$ if $O_i \geq S_i^* = \min\{M_i^*, U_i^*\}$; i.e., if $O_i = \infty$
- *Otherwise*, (U_i, Δ_i) *not necessarily* equal to (U_i^*, Δ_i^*)
- So, for some subjects, *only partial information* on hazard for T^*
- $\Longrightarrow$ Standard analysis using (U_i, Δ_i) in place of (U_i^*, Δ_i^*) for inference on β may *not apply*...

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Inference

Standard analysis: Solve in β

$$\sum_{i=1}^{n} \int \left\{ Z_i - \frac{\sum_{j=1}^{n} Z_j \exp(\beta Z_j) Y_j^*(u)}{\sum_{j=1}^{n} \exp(\beta Z_j) Y_j^*(u)} \right\} dN_i^*(u) = 0$$

Modification: *Weight* contributions of subjects in each *risk set* who have *not yet optionally discontinued* assigned treatment

Hazard rate for O at $u \geq 0$ given W_i^*:

- $$q(u, W^*) = \lim_{h \to 0} h^{-1} \Pr(u \leq O < u + h | O \geq u, W^*)$$

  for $u < S^*$, otherwise, $q(u, W^*) = 0$ because *no possibility* of being observed to *optionally discontinue* once mandatory discontinuation, censoring or failure has occurred

Inference

Critical assumption: For *consistent estimation* of β

- Similar to "*missing at random*"
- For $Q(u) = \{V^H(u), X\}$, *assume*

$$q(u, W^*) = q\{u, Z, Q(u)\} \text{ for } u \leq S^*$$

- I.e., the hazard at time u depends on (W^*) when $u < S^*$ *only* through the data $Z, Q(u)$ observed to time u
- *Plausible* – decision to optionally discontinue likely based on subject characteristics and experience up to time u
- *Issue* – Was all relevant information *captured* in the trial and hence available in $Q(u)$?

Inference

Define: $P(O \geq u|W) = K(u, W)$, where

$$K(u, W) = \exp\left[-\int_0^{u \vee S} q\{s, Z, Q(s)\}\, ds\right]$$

denotes the probability of not being optionally discontinued by time u or by time to mandatory discontinuation.

- "*Observed data*" counting process increment $dN_i(u) = I(U_i = u, \Delta_i = 1)$ and at risk process $Y_i(u) = I(U_i \geq u)$
- *Observe* $dN_i^*(u)$ and $Y_i^*(u)$ on i only if $O_i \geq u$, i.e.,

$$I(O_i \geq u)\, dN_i(u) = I(O_i \geq u)\, dN_i^*(u)$$

$$I(O_i \geq u) Y_i(u) = I(O_i \geq u) Y_i^*(u)$$

Weighting: *Replace* $dN_i^*(u)$ and $Y_i^*(u)$ in *ideal* estimating equations by

$$\frac{I(O_i \geq u) dN_i(u)}{K(u, W_i)} \quad \text{and} \quad \frac{I(O_i \geq u) Y_i(u)}{K(u, W_i)}$$

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Inference

Result: Solve in β

$$\sum_{i=1}^{n} \int \left\{ Z_i - \frac{\sum_{j=1}^{n} Z_j \exp(\beta Z_j) Y_j(u) \kappa(u, W_j)}{\sum_{j=1}^{n} \exp(\beta Z_j) Y_j(u) \kappa(u, W_j)} \right\} \kappa(u, W_i) dN_i(u) = 0$$

$$\kappa(u, W) = \frac{I(O \geq u)}{K(u, W)},$$

- *Must assume* $K(u, W) \geq \epsilon > 0$ for all $u \geq 0$
- *Can be shown*: Leads to *unbiased* estimating equation

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Implementation

1. Fit model for $q\{u, Z, Q(u)\}$, the hazard of optionally discontinuing *(e.g., proportional hazards model with time-dependent covariates)*

2. For each i and u equal to every *distinct event time*, estimate $K\{u, Z, Q(\cdot), S\}$; e.g., using Breslow's estimator

3. For each i, create *weights* at each *distinct event time* u equal to 0 if i *optionally discontinued* by u or using the estimates from step **2** if not

4. *Substitute* weights in the *modified score equations* and solve for β

Step 4: May be implemented in SAS `proc phreg`

- Counting process input format
- `weight` statement
- `cov(aggregate)` option
- "*Robust*" output *standard errors* will be *conservative* but work well

Application to SYNERGY

All-cause mortality within $t_{\max} = 365$ days (1 year):

- $n = 9784$ subjects, 4899 (4885) randomized to UFH (ENOX)

Discontinuation:

- *Overall*: 706 (14.4%) UFH, 1194 (24.4%) ENOX
- *Mandatory*: 337 (6.9%) UFH, 551 (11.3%) ENOX
- *Optional*: 369 (7.5%) UFH, 643 (13.2%) ENOX

Application to SYNERGY

Model for $K\{u, Z, Q(\cdot), S\}$: Numerous *baseline covariates* X, several *time-dependent covariates* $V^H(u)$ *post-randomization*

- $q\{u, Z, Q(u)\}$, $u > 0$: *Proportional hazards* model
  - Subset of X identified by *forward selection*
  - Included with Z and $V^H(u)$ in a final PH model
  - *Baseline*: Gender, height, troponin levels, smoking status, diabetes, Killip class, race, region, prior hypertension, prior CABG, prior ENOX, prior UFH, rales
  - *Time-dependent*: Transfusion status, creatine kinase (CK) levels, CK-MB levels

Application to SYNERGY

Hazard ratio, one year all-cause mortality

Method	Estimate	95% confidence interval	p-value
intent-to-treat	1.06	(0.92–1.22)	0.44
censor, all	1.03	(0.86–1.23)	0.77
censor, optional	1.08	(0.92–1.26)	0.33
time dependent	1.03	(0.86–1.23)	0.77
inverse weighted	1.08	(0.92–1.26)	0.36

- All results *similar*

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Application to SYNERGY

Possible explanations:

- %age of subjects who *optionally discontinued* either treatment = 9.8% overall; *not large*
- "*Important*" covariates may not have been measured $\Longrightarrow$ *ineffective* adjustment
- "*Important*" covariates in model for $K\{u \vee S, Q(u \vee S)\}$ and those retained in a *naive* PH model *ignoring discontinuation* do not *overlap*

Bottom line:

- Although all analyses do not find ENOX/UFH difference only the *weighted analysis* is designed to address the *well-formulated* question of interest
- Allows *confirmation* that the negative trial outcome was not an artifact of *differential rates* of discontinuation

Discussion

- *Sensible conceptualization* of "treatment effect had no subject discontinued his/her assigned treatment"
- *Critical*: *Distinguish* optional vs. mandatory discontinuation, focus on *treatment regimes*
- $\Longrightarrow$ Should collect *reasons* for discontinuation and *covariates* that may be associated with *decisions*
- Justification of *inverse probability risk set weighting*

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Discussion

- "The analysis that would have been done" under the standard assumption of *independent censoring* if there were *no optional discontinuation*
- *Key assumption*: Optional discontinuation depends on potential outcomes only through the observed data *"missing at random"*

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