Statistical Issues in the Use of Composite Endpoints in Clinical Trials

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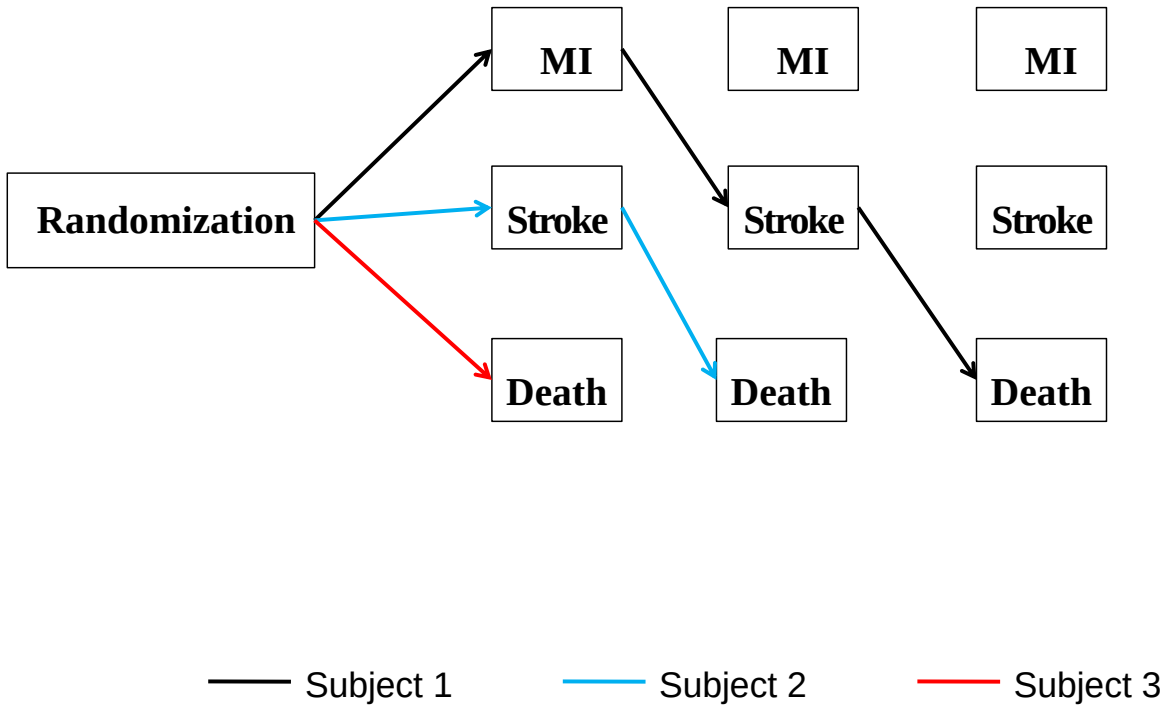
COMPOSITE ENDPOINTS

- Composite endpoints (CEP) in clinical trials:
  - CEP is defined as a group of endpoints that together form a single endpoint in a trial (Cannon, 1997).
  - Those individual endpoints are referred to as components of the CEP.
- The HOPE study (Yusuf *et al.*, 2000) investigated the effects of ramipril on cardiovascular events in high-risk patients with left ventricular dysfunction.
- CEP in HOPE:
  - myocardial infarction (MI)
  - stroke
  - cardiovascular death
- Patients who have any of these three events during the follow-up are considered to have experienced the CEP.

An Example of CEP



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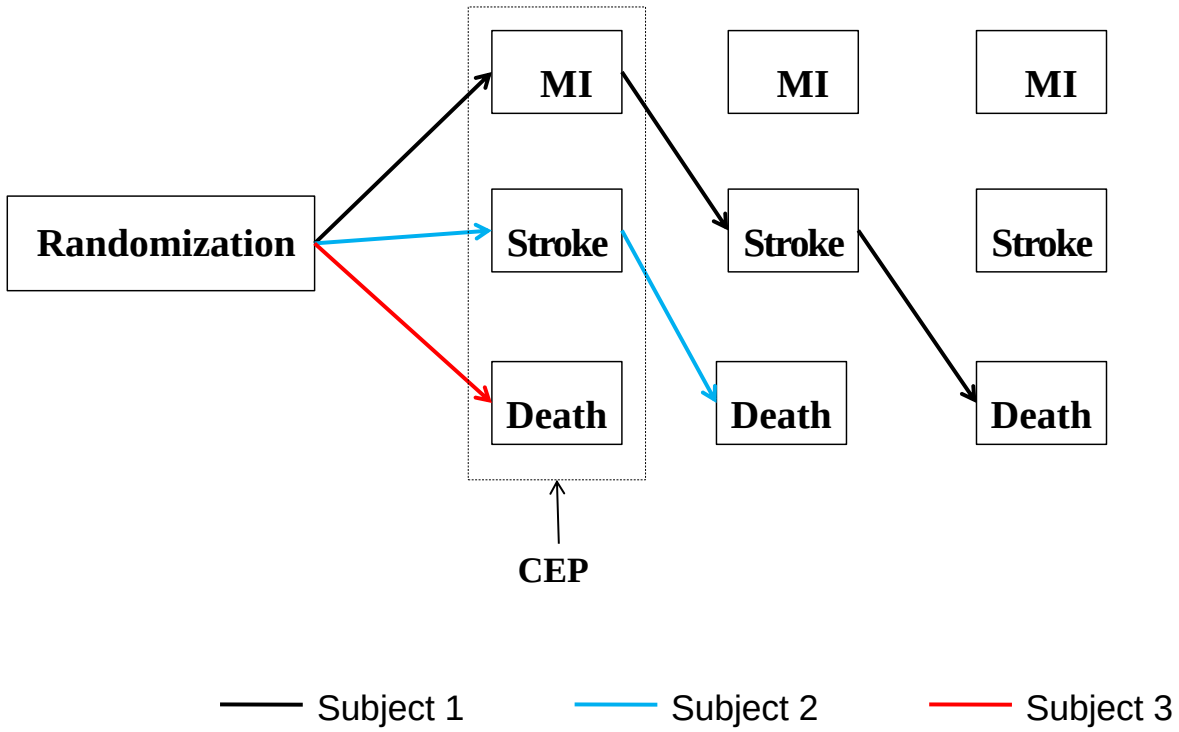

Our Present Objectives

- The focus of this study will be on CEP of time event data.
- We used models, asymptotic theory and empirical studies formally investigate the behaviour of estimation of treatment effects.
- Use simulations to study the implications of using CEP in the statistical power and sample size requirement.
- Investigate the validity of some of recommendations of CEP analysis.
- Study the effectiveness of alternative design and analysis

- Let T_i be the time to the CEP with $N_i(t) = I(T_i \leqslant t)$ and process history $\mathcal{H}_i(t) = \{N_i(u), Z_i, 0 < u < t\}$.
- Let $\Delta N_i(t) = N_i(t + \Delta t^-) - N_i(t^-)$ and $dN_i(t) = \lim_{\Delta t \downarrow 0} \Delta N_i(t)$.
- The hazard function for T_i is defined as

$$\lambda_i(t|\mathcal{H}_i(t)) = \mathscr{E}(dN_i(t)|\mathcal{H}_i(t)) = \lim_{\Delta t \downarrow 0} \frac{P(\Delta N_i(t) = 1|\mathcal{H}_i(t))}{\Delta t}$$

where $\mathscr{E}(\cdot)$ denotes the expectation operator with respect to the true process history.

Counting Process Notation: Review of Univariate Failure Times

- Let C_i denote censoring time and $X_i = \min(T_i, C_i)$.
- Let $Y_i(t) = I(X_i \geq t)$ be the at risk function.
- The observed counting process of T_i be $\bar{N}_i(t) = \int_0^t Y_i(u) dN_i(u)$
- Let $H_i(t) = \{N_i(u), Y_i(u), Z, 0 < u < t\}$ be the full history.
- Let $d\bar{N}_i(t) = \lim_{\Delta t \downarrow 0} \Delta \bar{N}_i(t)$.
- The hazard of the observed counting process of T_i is

$$\mathscr{E}(d\bar{N}_i(t) = 1 | H_i(t)) = Y_i(t)\lambda(t|Z_i)dt.$$

- The Cox model has the form

$$\lambda(t|Z_i) = \lambda_0(t)e^{\beta Z_i}$$

where $\lambda_0(t)$ is the baseline hazard function.

- The maximum partial likelihood estimation of β is obtained by solving:

$$U(\beta) = \sum_{i=1}^{n} \int_0^{\infty} \left(Z_i - \frac{S^{(1)}(\beta, t)}{S^{(0)}(\beta, t)} \right) d\bar{N}_i(t),$$

where $S^{(k)}(\beta, t) = \sum_{i=1}^{n} Y_i(t) Z_i^k \exp\{\beta Z_i\}, k = 0, 1.$

Composite Endpoint: Independent Case

- Let T_{i1} and T_{i2} be two independent failure times of subject i.
- T_{ik} has hazard functions $\lambda_k(t|Z_i)$, $k = 1, 2$.
- CEP analysis is based on $T_i = \min(T_{i1}, T_{i2})$ and $N_i(s) = I(s \leqslant T_i)$.
- The hazard function of CEP is

$$\mathscr{E}(dN_i(s)|H_i(s)) = \lambda_1(t|Z_i) + \lambda_2(t|Z_i).$$

- If $\lambda_{ik}(t|Z_i) = \lambda_{0k}(t)e^{\beta_k Z_i}$, $k = 1, 2$, then CEP has the hazard ratio

$$\frac{\lambda_{01}(t)e^{\beta_1} + \lambda_{02}(t)e^{\beta_2}}{\lambda_{01}(t) + \lambda_{02}(t)}.$$

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$$\frac{\lambda_{01}(t)e^{\beta_1} + \lambda_{02}(t)e^{\beta_2}}{\lambda_{01}(t) + \lambda_{02}(t)}.$$

Remarks:

1.The proportional hazard assumption holds for CEP, if

(A.1) $\beta_1 = \beta_2$: the same treatment effect across components, or

(A.2) $\lambda_{01}(t) = \lambda_{02}(t)$: the same frequency of occurrence.

2. Otherwise, PH does not hold for CEP analysis.

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2. Otherwise, PH does not hold for CEP analysis.

What are we estimating in this case?

Composite Endpoint: Events Are Associated

- Typically components of CEP are not independent.
- Consider a joint survivor function of T_{i1} and T_{i2} via a Clayton copula:

$$(\mathcal{F}(t_{i1}|Z_i;\beta_1)^{-\phi} + \mathcal{F}(t_{i2}|Z_i;\beta_2)^{-\phi} - 1)^{-1/\phi}.$$

  - $\mathcal{F}(\cdot\,|\cdot\,)$ is the survivor function.
  - ϕ is the association parameter.
  - Kendall's $\tau = \frac{\phi}{2+\phi}$ is a common measure of association for T_{i1} and T_{i2}.
  - $\Theta = (\beta_1, \beta_2, \phi)$.

- Assume $T_k \sim \text{Exp}(\lambda_k e^{\beta_k Z})$, $k = 1, 2$
- Using the Clayton copula, the joint survivor function of T_1 and T_2 is

$$[\exp(\lambda_1 e^{\beta_1 Z} \phi t_1) + \exp(\lambda_2 e^{\beta_2 Z} \phi t_2) - 1]^{-1/\phi}.$$

- If $T = \min(T_1, T_2)$, $P(T \geqslant t|Z; \Theta) = \mathcal{F}(t|Z; \Theta)$ is

$$[\exp(\lambda_1 e^{\beta_1 Z} \phi t) + \exp(\lambda_2 e^{\beta_2 Z} \phi t) - 1]^{-1/\phi}$$

with density

$$f(t|Z; \Theta) = -\frac{\partial \mathcal{F}(t|Z; \Theta)}{\partial t}.$$

The hazard function of T is

$$\lambda_T(t|Z;\Theta) = \frac{f(t|Z;\Theta)}{\mathcal{F}(t|Z;\Theta)}.$$

The hazard ratio is :

$$\frac{f(t|Z=1;\Theta)}{f(t|Z=0;\Theta)} \times \frac{\mathcal{F}(t|Z=0;\Theta)}{\mathcal{F}(t|Z=1;\Theta)},$$

which is NOT a constant even if (A.1) and (A.2) are true.

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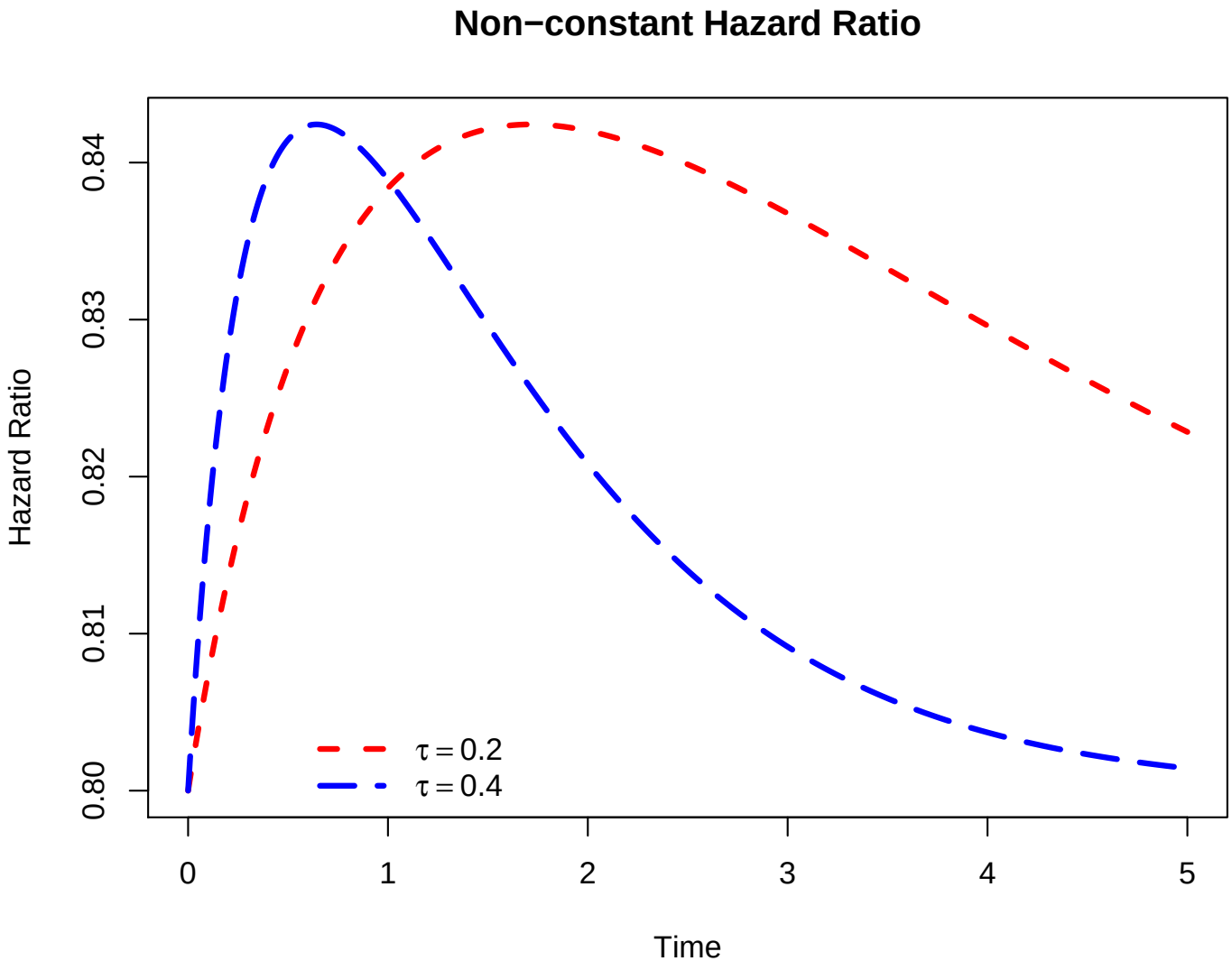
which is NOT a constant even if (A.1) and (A.2) are true.

Remark:
In general, proportional hazards assumption does not hold for CEP, even if this assumption holds for individual components!

Non-constant Hazard Ratio: Composite Endpoint



- Treatment effects: $\beta_1 = \beta_2 = \log(0.8)$ and equal frequency of occurrence: $\lambda_1 = \lambda_2 = 1$.

Misspecified Cox Model: The Limiting Value

In CEP analysis, the solution of β to the partial likelihood score function

$$U(\beta) = \sum_{i=1}^{n} \int_0^{\infty} \left(Z_i - \frac{S^{(1)}(\beta, t)}{S^{(0)}(\beta, t)} \right) d\bar{N}_i(t)$$

is a consistent estimate of β^*, the solution to limiting score function

$$U(\beta^*) = \int_0^{\infty} \left(\mathscr{E}(\sum_{i=1}^{n} Z_i d\bar{N}_i(t)) - \frac{\mathscr{E}(S^{(1)}(\beta, t))}{\mathscr{E}(S^{(0)}(\beta, t))} \mathscr{E}(\sum_{i=1}^{n} d\bar{N}_i(t)) \right),$$

where the expectation $\mathscr{E}$ is with respect to the true model (e.g. White 1982, Struthers and Kalbfleisch, 1986).

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where the expectation $\mathscr{E}$ is with respect to the true model (e.g. White 1982, Struthers and Kalbfleisch, 1986).

Remark: $\beta^* \neq \beta_0$.

Limiting Treatment Effect: The Independent Case

- Suppose $T_1 \perp T_2|Z$, and $T_k|Z \sim \text{Exp}(\lambda_k e^{\beta_k Z})$.
- If $T = \min(T_1, T_2)$ and $T|Z \sim \text{Exp}(\lambda_1 e^{\beta_1 Z} + \lambda_2 e^{\beta_2 Z})$.
- Random censoring: $C \perp T|Z$, $P(C \geqslant s|Z) = e^{-\rho s}$.
- This independent assumption gives

$$\begin{aligned}\mathscr{E}(Y_i(t)|Z_i) &= \mathscr{E}(Y_i^{\dagger}(t)|Z_i)\mathscr{E}(Y_i^{\ddagger}(t)|Z_i) \\ &= P(T > t|Z_i)P(C > t|Z_i) \\ &= \mathcal{F}(t|Z_i)G(t).\end{aligned}$$

- The expectations in the score equation for β^*, for example $\mathscr{E}(Z_i d\bar{N}_i(t))$, can be obtained as follows

$$\begin{aligned}\mathscr{E}(Z_i d\bar{N}_i(t)) &= \mathscr{E}(Z_i Y_i(t) dN_i(t)) \\ &= \mathscr{E}_{Z_i}\{\mathscr{E}_{Y_i(t)|Z_i}[\mathscr{E}_{dN_i(t)|Y_i(t),Z_i}(Z_i Y_i(t) dN_i(t))]\} \\ &= P(Z_i = 1) f(t|Z_i = 1) G(t) dt.\end{aligned}$$

- $\mathscr{E}(d\bar{N}_i(t))$, $\mathscr{E}(S^{(1)}(\beta, t))$, and $\mathscr{E}(S^{(0)})(\beta, t)$ can be obtained similarly.

- β^* solution is:

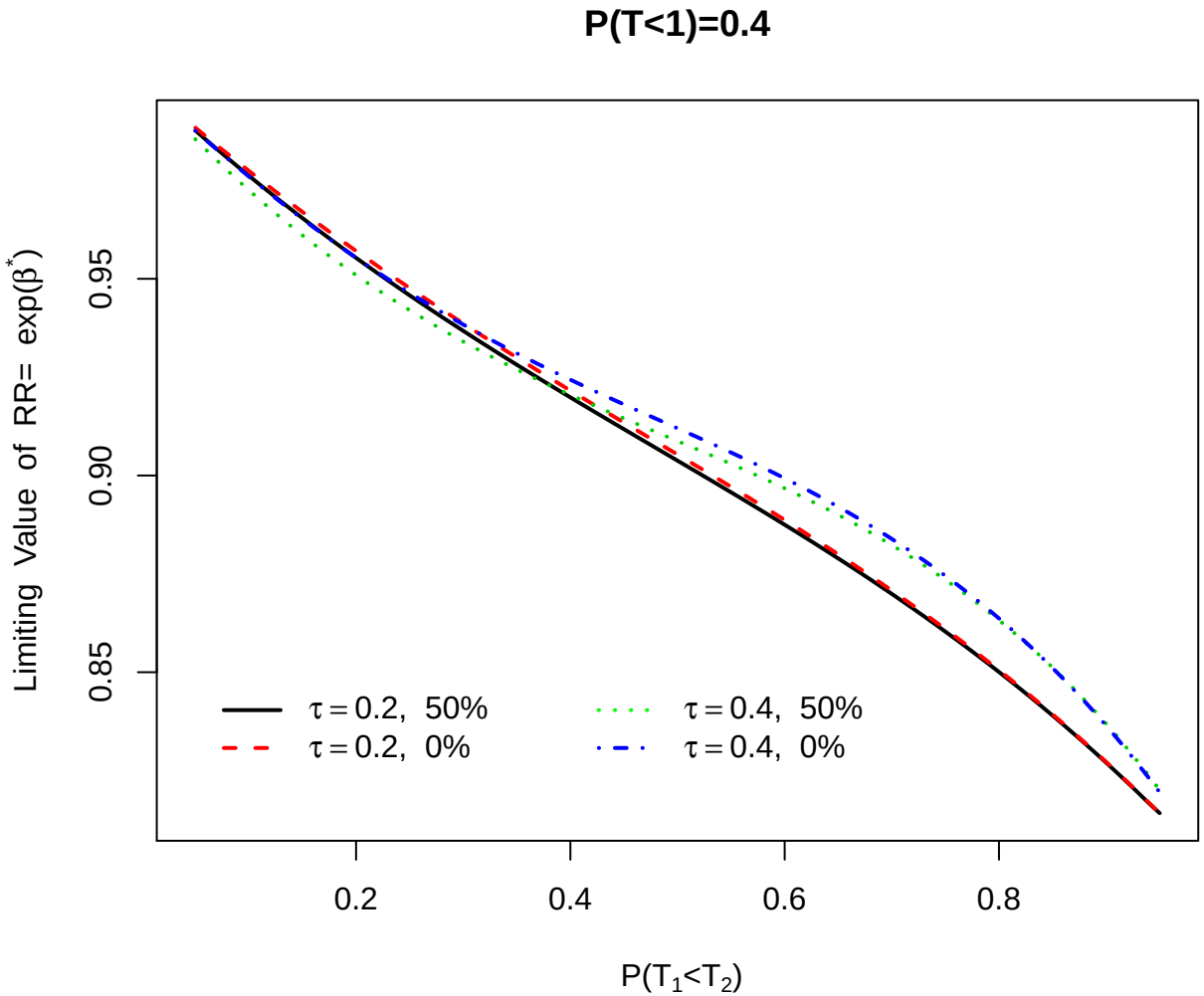
$$e^{\beta^*} = \frac{\lambda_1 e^{\beta_1} + \lambda_2 e^{\beta_2}}{\lambda_1 + \lambda_2}$$
$$= (\frac{\lambda_1}{\lambda_1 + \lambda_2})e^{\beta_1} + (\frac{\lambda_2}{\lambda_1 + \lambda_2})e^{\beta_2}$$

- The solution β^* is "weighted" average of β_1 and β_2.
- The "weights" are determined by λ_1 and λ_2, the frequencies of occurrence of the two type events.

Limiting treatment effect: Associated Components

- Use Clayton Copula to model the association.
- The solution of β^* is obtained by numerical integration.
- Some surprising observations on the relation between β^* and β_1, β_2, ϕ.

Limiting Value: Dependent Case with Unequal Treatment Effect



- 60% administrative censoring
- Different random censoring due to withdrawal
- Treatment effects: $\beta_1 = \log(0.8)$ and $\beta_2 = \log(1.0)$

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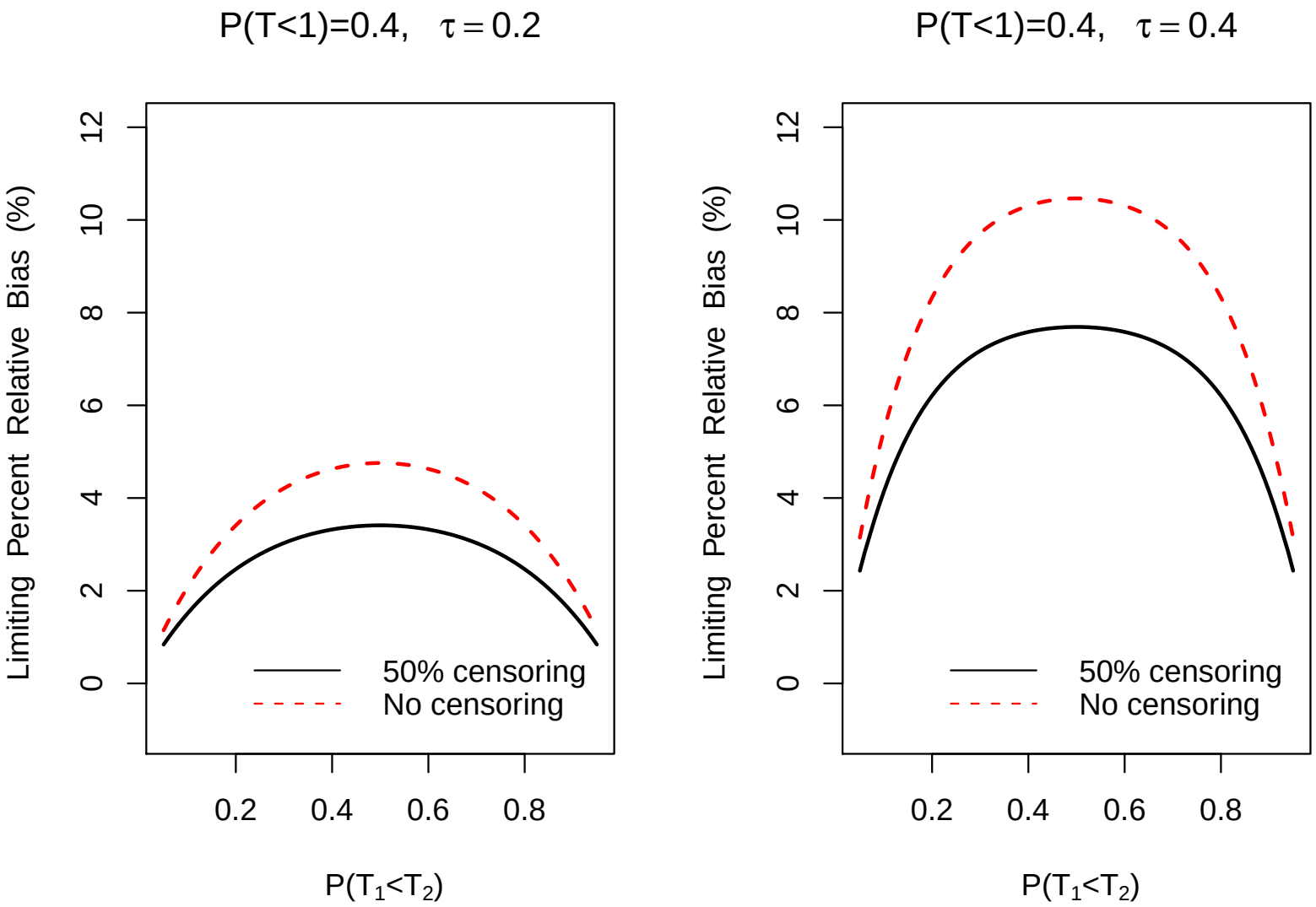

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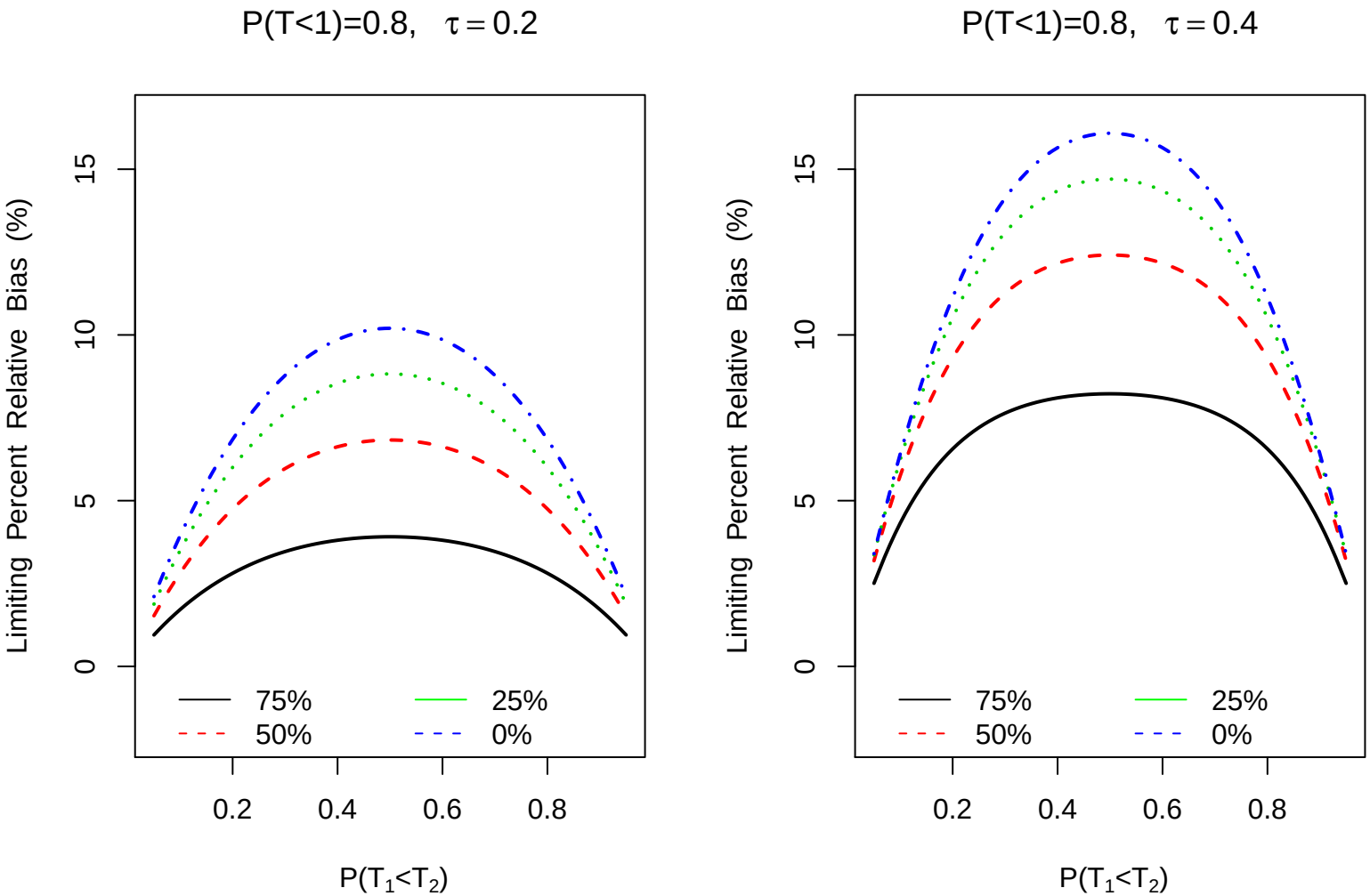


- 20% administrative censoring
- Different random censoring due to withdrawal
- Treatment effects: $\beta_1 = \beta_2 = \log(0.8)$

- Independent components: $T_1 \sim \text{Exp}(\lambda_1)$ and $T_2 \sim \text{Exp}(\lambda_2)$.
- Associated components: $\tau = 0.2, 0.4$.
- Consider both administrative censoring and random censoring.
- D is number of events required for CEP analysis:

$$D = \frac{4(z_{1-\alpha} + z_{1-\gamma})^2}{(\beta^*)^2},$$

  α is type I error for one-sided test;
  $1 - \gamma$ is power;
  β^* is the limiting value of treatment effect estimate;
- The number of subjects required is obtained based on the expected rate of CEP events during the follow-up.

Independent Components With Equal Treatment Effects

$$P(T_1 < T_2|Z = 0) = 0.25, \beta_1 = \log(0.8), \beta_2 = \log(0.8)$$

% admin. cens	% random cens	n	β^*	mean	ESE	AVE SE1	AVE SE2	95%CI	Power
60	60	3,410	-.223	-.223	.090	.090	.090	95—95	80—80
	40	2,265	-.223	-.224	.090	.090	.090	95—95	80—80
	20	1,694	-.223	-.224	.090	.090	.090	95—95	80—80
	0	1,353	-.223	-.224	.090	.090	.090	95—95	80—80
40	60	2,256	-.223	-.225	.090	.090	.090	95—95	81—81
	40	1,494	-.223	-.224	.090	.090	.090	95—95	81—81
	20	1,115	-.223	-.226	.090	.090	.090	95—95	81—81
	0	889	-.223	-.225	.090	.090	.089	95—95	80—80
20	60	1,678	-.223	-.226	.090	.090	.090	95—95	80—80
	40	1,106	-.223	-.227	.089	.090	.090	96—96	81—81
	20	822	-.223	-.224	.088	.090	.090	95—95	81—81
	0	653	-.223	-.223	.090	.090	.090	95—95	80—80

Independent Component With Unequal Treatment Effect

$$P(T_1 < T_2|Z = 0) = 0.25, \beta_1 = \log(0.8), \beta_2 = \log(1.0)$$

% admin cens	% random cens	n	β^*	mean	ESE	AVE SE1	AVE SE2	95%CI	Power
60	60	60,737	-.051	-.052	.020	.021	.021	96—96	82—82
	40	40,450	-.051	-.052	.021	.021	.021	95—95	81—81
	20	30,317	-.051	-.052	.021	.021	.021	95—95	81—81
	0	24,241	-.051	-.052	.021	.021	.021	95—95	82—82
40	60	40,411	-.051	-.052	.021	.021	.021	95—95	80—80
	40	26,892	-.051	-.052	.021	.021	.021	95—95	81—81
	20	20,143	-.051	-.052	.021	.021	.021	95—95	82—82
	0	16,099	-.051	-.052	.021	.021	.021	95—95	80—80
20	60	30,242	-.051	-.052	.021	.021	.021	95—95	80—80
	40	20,101	-.051	-.052	.021	.021	.021	95—95	82—82
	20	15,041	-.051	-.052	.021	.021	.021	94—94	81—81
	0	12,011	-.051	-.052	.021	.021	.021	94—94	81—81

Associated Component With Equal Treatment Effects

$\tau = 0.4$, $P(T_1 < T_2|Z = 0) = 0.25$, $\beta_1 = \log(0.8)$, $\beta_2 = \log(0.8)$

% admin. cens	% random cens	n	β^*	mean	ESE	AVE SE1	AVE SE2	95%CI	Power
60	60	3,825	-.210	-.210	.085	.085	.085	96—96	79—79
	40	2,611	-.207	-.207	.084	.084	.084	95—95	80—80
	20	2,009	-.204	-.204	.086	.082	.082	94—94	79—79
	0	1,619	-.203	-.203	.084	.082	.082	95—95	79—79
40	60	2,653	-.205	-.205	.083	.083	.083	94—94	80—80
	40	1,825	-.201	-.202	.081	.081	.081	95—95	80—80
	20	1,402	-.198	-.199	.079	.080	.080	95—95	81—81
	0	1,140	-.196	-.197	.079	.079	.079	95—95	80—80
20	60	2,033	-.202	-.203	.081	.082	.082	95—95	80—80
	40	1,393	-.198	-.199	.081	.080	.080	95—95	80—80
	20	1,056	-.196	-.197	.079	.079	.079	95—95	81—81
	0	857	-.194	-.194	.077	.078	.078	95—95	80—80

Associated Components With Unequal Treatment Effects

$\tau = 0.4$, $P(T_1 < T_2 | Z = 0) = 0.25$, $\beta_1 = \log(0.8)$, $\beta_2 = \log(1.0)$

% admin. cens	% random cens	n	β^*	mean	ESE	AVE SE1	AVE SE2	95%CI	Power
60	60	42,635	-.061	-.062	.025	.025	.025	96—96	82—82
	40	31,360	-.058	-.059	.024	.023	.023	95—95	81—81
	20	25,186	-.056	-.057	.023	.023	.023	95—95	80—80
	0	20,862	-.055	-.056	.022	.022	.022	95—95	81—81
40	60	32,419	-.057	-.057	.023	.023	.023	95—95	79—79
	40	25,866	-.052	-.052	.021	.021	.021	95—95	81—81
	20	21,787	-.049	-.049	.020	.020	.020	95—95	81—81
	0	18,906	-.047	-.047	.019	.019	.019	95—95	80—80
20	60	29,106	-.052	-.052	.021	.021	.021	95—95	80—80
	40	24,662	-.046	-.046	.018	.019	.019	95—95	79—79
	20	23,192	-.041	-.042	.016	.016	.016	96—96	81—81
	0	21,535	-.038	-.038	.015	.015	.015	96—96	80—80

The Marginal Model of Wei, Lin, and Weissfeld (1989):

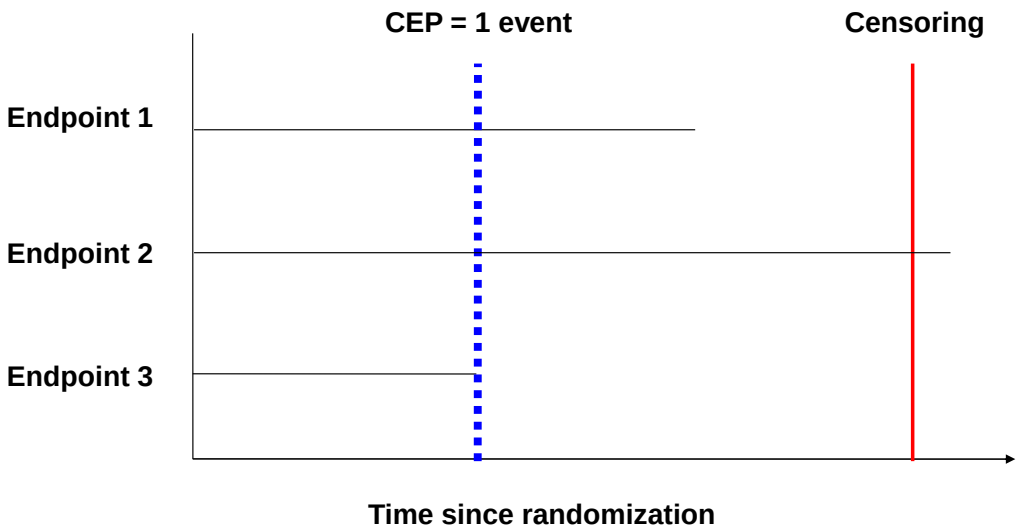
- Model-free to the dependence structure among the multivariate failure times, *i.e.*, components in CEP.
- Fit ordinary Cox model to each component and estimate the regression coefficients.
- Use robust variance estimate in inference to account for possible correlation in the data.

Advantages:

- Can be easily implemented in R or SAS.
- Affords great flexibility in formation of strata and risk sets.
- Well-developed variance estimator—Robust Variance Estimator.

Comparison of Multivariate Analysis and CEP

CEP analysis vs. Global Analysis



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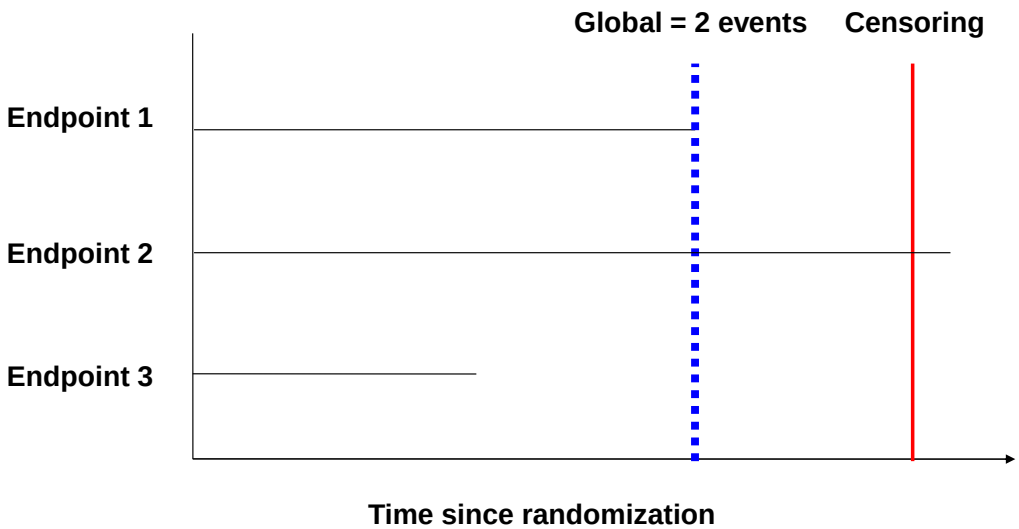


- Let $\lambda_{ki}(t) = \lambda_{k0}(t)e^{\beta_k Z}$ be the hazard function for kth event.
- The kth event-specific score function for β_k is

$$U_k(\beta_k) = \sum_{i=1}^{n} \int_0^{\infty} \left(Z_i - \frac{S_k^{(1)}(\beta_k, t)}{S_k^{(0)}(\beta_k, t)} \right) d\bar{N}_{ik}(t).$$

  $S_k^{(1)}(\beta, u) = \sum_{i=1}^{n} Y_{ik}(t) Z_i^r \exp\{\beta_k Z_i\}, r = 0, 1.$
- $\bar{N}_i(t) = \{\bar{N}_{ik}(t), k = 1, ..., K\}$ is observed multivariate counting process.
- $Y_{ik}(t)$ is the at risk indicator function for the kth event of subject i.
- Global estimate is weighted average of $\hat{\beta}_k$s.

Empirical Study II: Associated Components With Equal Treatment Effects

$\tau = 0.4$, $P(T_1 < T_2|Z = 0) = 0.25$, $\beta_1 = \log(0.8)$, $\beta_2 = \log(0.8)$

%admin. cens	% random cens	n	β^*	mean	ESE	AVE SE	95%CI	Power
60	60	3,387	-.223	-.224	.091	.09	95	80
	40	2,247	-.223	-.224	.089	.09	95	81
	20	1,679	-.223	-.225	.091	.09	94	81
	0	1,340	-.223	-.224	.09	.089	95	80
40	60	2,239	-.223	-.225	.091	.09	96	80
	40	1,481	-.223	-.224	.088	.089	95	81
	20	1,104	-.223	-.225	.086	.088	96	82
	0	879	-.223	-.225	.085	.088	96	82
20	60	1,666	-.223	-.225	.088	.089	96	82
	40	1,097	-.223	-.225	.088	.088	95	81
	20	815	-.223	-.224	.086	.087	95	83
	0	648	-.223	-.223	.086	.086	95	83

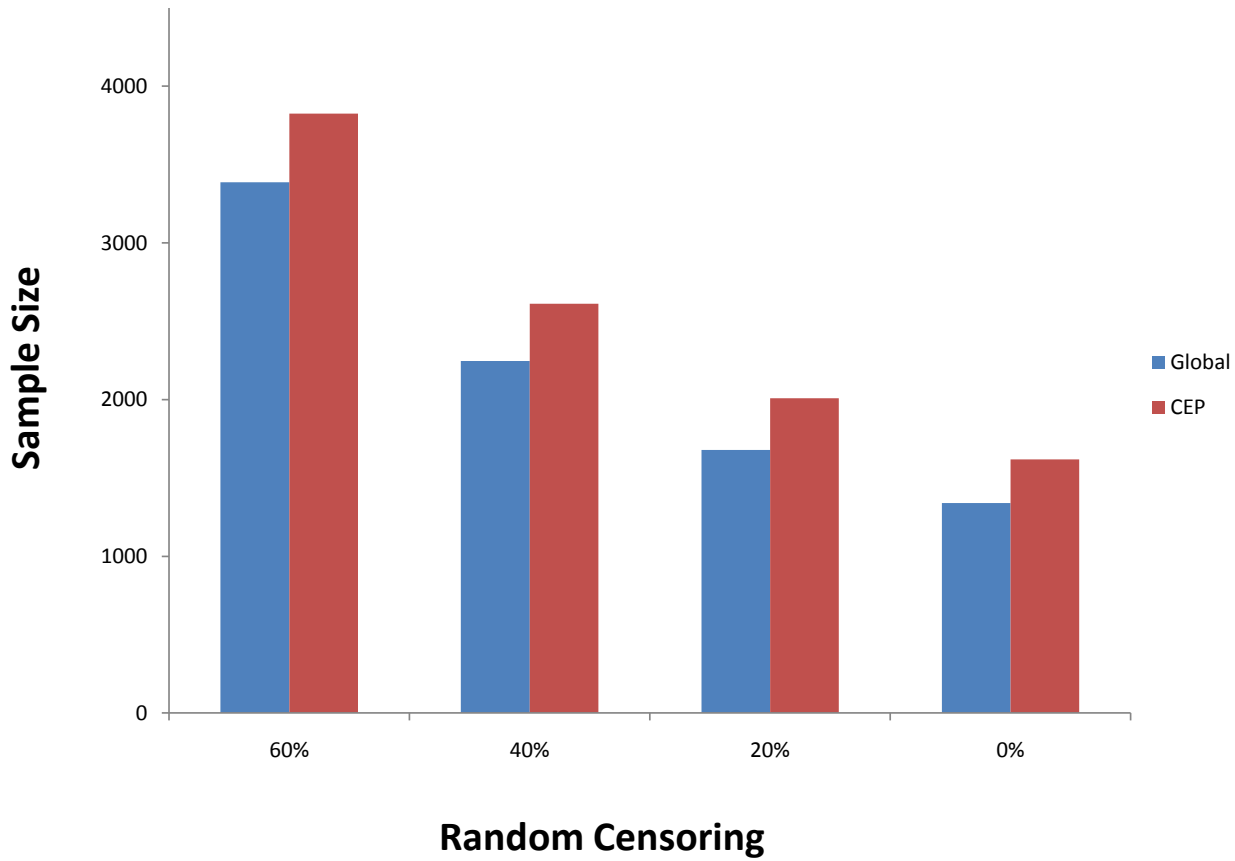
Empirical Study II: Associated Components With Unequal Treatment Effects

$\tau = 0.4$, $P(T_1 < T_2 | Z = 0) = 0.25$, $\beta_1 = \log(0.8)$, $\beta_2 = \log(1.0)$

% admin. cens	% random cens	n	β^*	mean	ESE	AVE SE	95%CI	Power
60	60	35,767	-.067	-.067	.026	.027	95	81
	40	24,218	-.066	-.067	.026	.026	96	81
	20	18,694	-.065	-.067	.026	.026	95	82
	0	14,937	-.065	-.066	.026	.026	94	82
40	60	24,327	-.066	-.066	.026	.026	96	81
	40	16,760	-.065	-.066	.025	.026	95	83
	20	12,771	-.064	-.065	.025	.025	94	83
	0	12,932	-.064	-.065	.025	.025	95	83
20	60	18,514	-.065	-.066	.026	.026	94	82
	40	12,367	-.065	-.066	.026	.025	94	83
	20	9,115	-.065	-.066	.025	.025	95	84
	0	7,182	-.066	-.067	.026	.025	95	84

Sample Size Requirement: Global vs CEP

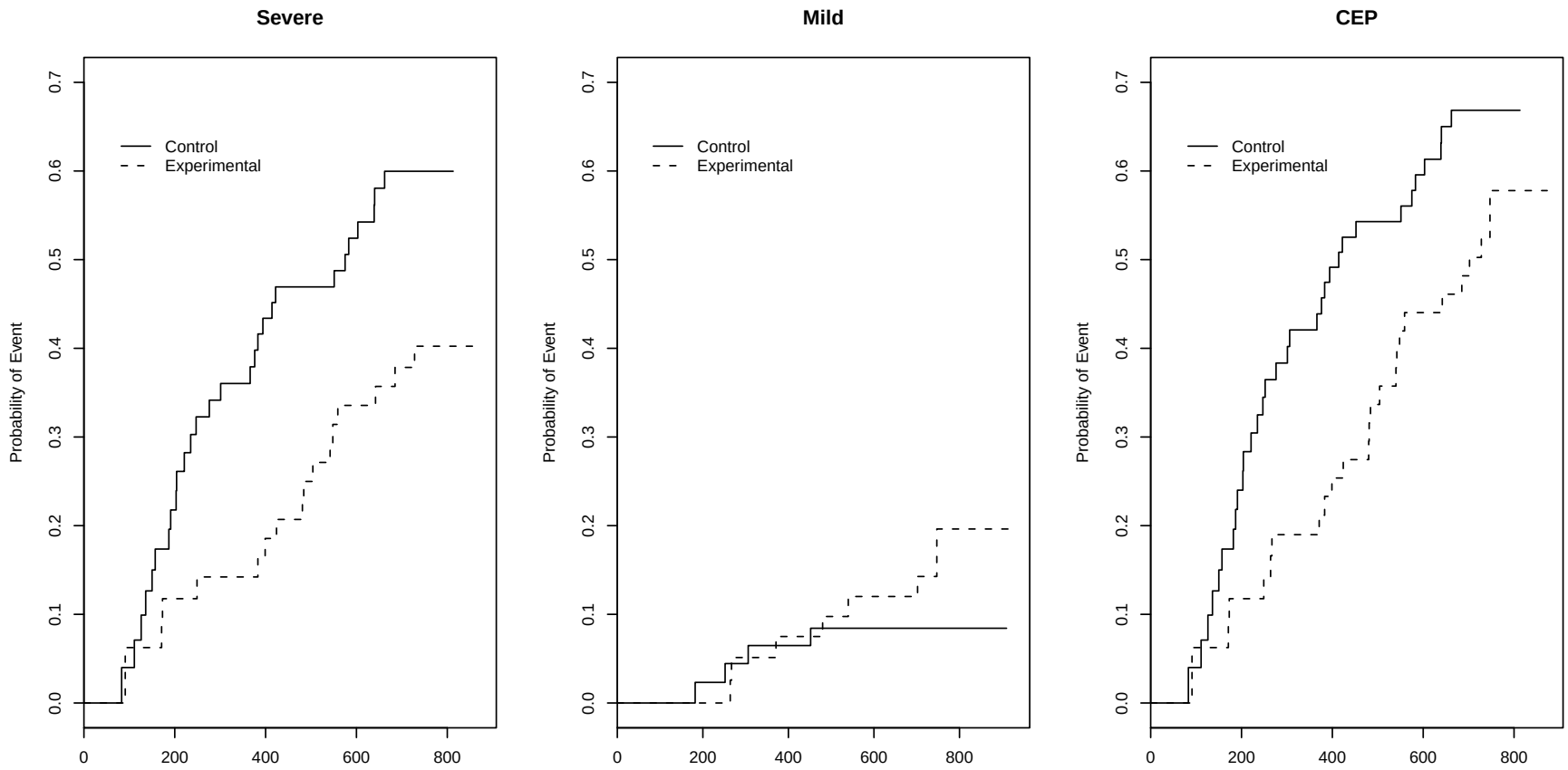
60% admin. cens., $\tau = 0.4$, $P(T_1 < T_2 | Z = 0) = 0.25$,
$\beta_1 = \log(0.8)$, $\beta_2 = \log(0.8)$



A Real Data Example

- An asthma management study—an experimental intervention was tested to delay the time to exacerbation.
- Two endpoints:
  - Endpoint I: severe exacerbation.
  - Endpoint II: mild exacerbation.
- CEP: time to the first event of endpoint I or II.

Probability of events: CEP and its components.



Real Data Analysis: Results

	RR	95%	p-value	p*
Severe	0.53	(0.285, 0.977)	0.042	0.22
Mild	2.14	(0.624, 7.310)	0.227	0.11
CEP	0.665	(0.388, 1.138)	0.137	0.063
Global (WLW)	0.702	(0.405, 1.219)	0.209	

p* is the p-value for testing the proportional hazards assumption.

References to CEP in the Literature

- Search Google Scholar:
  - Search “composite endpoint” and “clinical trial ” —about 2,940 hits since 2000.
  - Search “composite endpoint” and “clinical trial ” and “cardiovascular”— about 2,320 hits since 2000.
- PubMed —about 360 citations in the clinical trial category since 1993.
- Web of Science — about 530 citations:
  - Cardiovascular system and Cardiology (240)
  - Pharmacology and Pharmacy (170)
  - Surgery (81)
  - Hematology (72)
- Search “biostatistics” and “composite endpoint” in “statistics” in Google scholar—about 20 hits.

Some Key References for Composite Endpoints

1. Some uses of Composite Endpoints in clinical trials:
   - 1992. Braunwald *et al.* used a CEP in a cardiovascular trial;
   - 1997. Cannon outlined some rationale for CEP.

2. Critical thinking about CEP in medical literature:
   - 2003. Freemantle et al. raised several cautionary notes;
   - 2005. Montori *et al.*, Neaton *et al.*, and Chi further discussed potential pitfalls and recommendations.

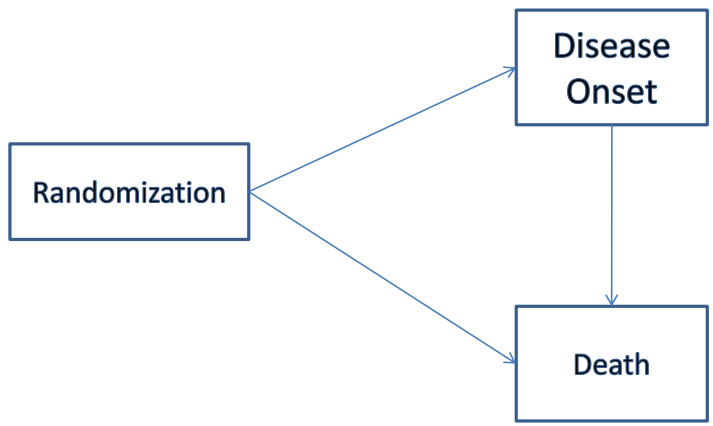
3. Meta-analysis and systematic reviews:
   - 2007-2008. Ignacio Ferreira-Gozalez *et al.*, Bethal *et al.*, Buzney *et al.*, Lim *et al.*, and more.

4. More discussions:
   - 2010. Tomlinson and Detsky; Sheehe.

Rationale Given for Composite Endpoints

- Due to increased event rate, CEP can increase statistical power, reduce sample size and required follow-up time.
- Handles multiplicity problem by using the time-to-first-event.
- Allows the measurement of "overall" benefit of the treatment.
- Useful when a single primary endpoint is hard to choose.
- Can avoid competing risk problem in time-to-event analysis.

Three-state Model



Cannon (1997), Freemantle et al, (2003), Chi (2005), Neaton et al., (2005), Freemantle and Calvert (2007).

Reported Limitations of Composite Endpoints

- Heterogeneity in the treatment effect across components:
  - Poor power for detecting heterogeneity.
  - Interpretation of treatment effect can be difficult.

- Importance of the components may not be equal at the patient level, *e.g.* TIA, stroke, MI, death.

Freemantle et al, (2003), Neaton et al., (2005), Montori et al., (2005), Freemantle and Calvert (2007).

Recommendations Regarding Composite Endpoints

- Individual components should have similar importance to patients;
- Individual components should have similar frequency of occurrence.
- Treatment should have similar effect on all components.

Freemantle et al, (2003), Chi (2005), Neaton et al., (2005), Montori et al., (2005), Freemantle and Calvert (2007), Tomlinson and Detsky (2010).

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Largest bias when components are associated!

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- Individual components should be analyzed separately as the secondary endpoints.

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Allow multivariate analysis and facilitate interpretation.

Freemantle et al, (2003), Chi (2005), Neaton et al., (2005), Montori et al., (2005), Freemantle and Calvert (2007), Tomlinson and Detsky (2010).

Discussion

- Cox model for analysis of CEP may not be appropriate: PH does not hold generally.
- Many factors jointly affect the treatment effect estimation:
  - the dependence structure in the individual components;
  - stochastic ordering and occurrence frequencies of individual components;
  - the amount of random censoring;
  - heterogeneity of the treatment effect across the individual components.
- "Equal treatment effect and equal frequency" of individual component may not be valid recommendation.
- The multivariate approach generally outperforms the CEP:
  - provides the average effect of treatment—facilitates the interpretation;
  - can achieve higher power and accuracy;
  - can claim treatment effect on individual components—permit intent-to-treat analysis.

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Thank you!