Session 9 : Advances in Sample Size Methods
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Sample size considerations for clinical trials with two primary time-to-event outcomes

Toshimitsu Hamasaki, PhD, pstat®
National Cerebral and Cardiovascular Center

Tomoyuki Sugimoto, PhD
Hirosaki University School of Sciences and Technology

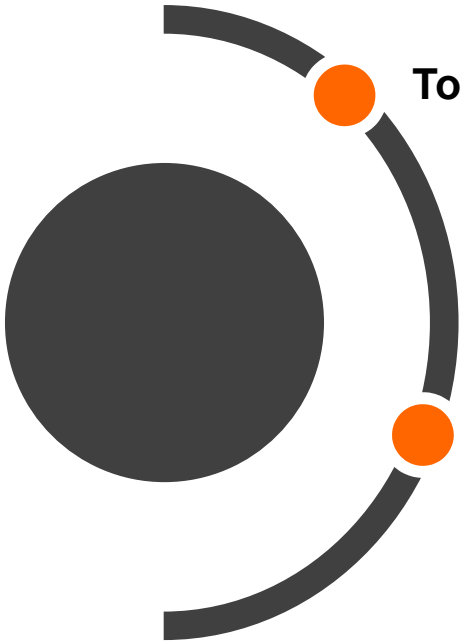
Koko Asakura, PhD
National Cerebral and Cardiovascular Center

Scott R. Evans, PhD
Harvard School of Public Health

Mayumi Fukuda, MD
National Cerebral and Cardiovascular Center

Haruko Yamamoto, MD, PhD
National Cerebral and Cardiovascular Center

Goals and outlines



To discuss sample size determination when using two time-to-event outcomes for comparing two interventions in superiority clinical trials as co-primary or primary contrasts

- A use of two primary or co-primary time-to-event endpoints has become common in clinical trials evaluating interventions in many disease areas such as infectious disease, oncology, or cardiovascular disease.

Structure of presentation

1. Design issues in clinical trials with two time-to-event outcomes
2. Study designs, hypothesis testing and powers
3. Time dependency association and censoring scheme
4. Behavior of sample size
5. Summary

Examples: clinical trials with two time-to-event outcomes

Disease area	Outcomes	
HIV (Kaposi's sarcoma in HIV-infected)	◆ Kaposi's sarcoma (KS) progression ◆ HIV virologic failure	◆ Both events are not fatal and each event is not censored by other event. ◆ Subjects who do not experience both events yet are censored at the same time (e.g., by the end of the study or patient drop-out) in the end of follow-up period.
Oncology	◆ Overall survival (OS) ◆ Time to progression (TTP) or Progression-fee survival (PFS)	◆ OS requires long follow-up periods after disease progression, which leads to quite long and also expensive studies. ◆ PFS is often included as a short-term primary endpoint, defined as the time from randomization until **tumor progression** or **death** from any cause, whichever may occurs earlier than OS.
Cardiovascular	◆ Major cardiac adverse event (MACE) ◆ Death	◆ MACE is a composite endpoints, including multiple types of clinical events of varying degrees of relatedness. ◆ Death is included as a component of MACE and it is the most important event

Design Issues: sample size

(i) Inferential goal for multiple outcomes

- To evaluate a joint statistical significance on **BOTH** outcomes
  "**Multiple Co-Primary Endpoints**"
- To evaluate a statistical significance on **AT LEAST ONE** outcome
  "**Multiple Primary Endpoints**"

Sample sizing for two time-to-event outcomes could be more complex compared with other scale outcomes such as continuous or binary outcomes- the following aspects should carefully be considered in sample size determination in clinical trials with two time-to-event outcomes

(ii) Censoring scheme between two outcomes

- Whether an event of interest is **FATAL** or **NON-FATAL**
- A non-fatal event could be censored by the fatal event (**DEPENDENT censoring**)

(iii) Time dependent association between two outcomes

- Whether the association between the two time-to-event outcomes could be changed with the time

Superiority clinical trials with two time-to-event outcomes

Endpoint (**EP1**): (T_{i1}^*, C_{i1})

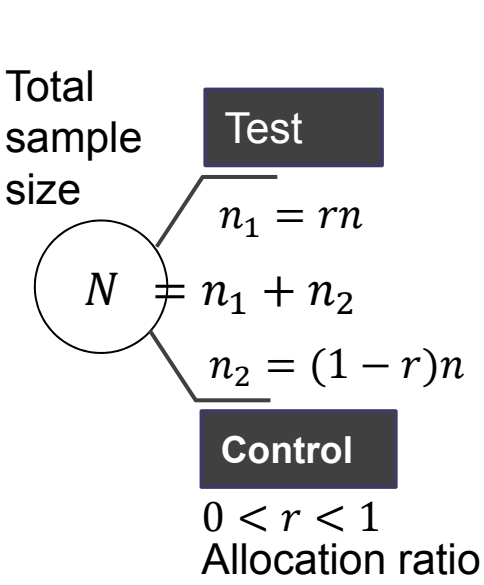
"**Positively**" correlated

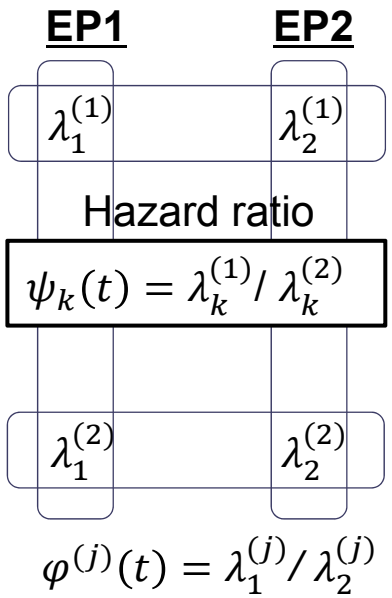
Endpoint (**EP2**): (T_{i2}^*, C_{i2})

$(T_{ik}^*, C_{ik})(k = 1,2: i = 1, \ldots, n_j)$
Underlying continuous survival time and potential censoring time for the kth outcome for the ith subject

Study end C Censored

$0 \rightarrow\rightarrow\rightarrow T_a$: accrual duration $\rightarrow\rightarrow\rightarrow T_f$: follow-up duration





- **Observed bivariate survival data**
  $\{(T_{i1}, T_{i2}, \Delta_{i1}, \Delta_{i2}, g_i)\}_{i=1}^n$
  $T_{ik} = \min(T_{ik}^*, C_{ik})$
  $\Delta_{ik} = \mathbf{1}(T_{ik}^*, C_{ik})$
  $\mathbf{1}(\cdot)$ is the index function
  $g_i = 1 \rightarrow i$th subject to test
  $g_i = 2 \rightarrow i$th subject to control
- **Hazard function**

$$\lambda_k^{(j)}(t) = \lim_{dt \to 0} \frac{\Pr\left(t \le T_{ij}^* < t + dt \mid t \le T_{ij}^*, g_i = j\right)}{dt}$$

$j = 1$(test); 2 (control)

Logrank test statistics for each endpoint

Hypothesis for each endpoint

$$\begin{cases} \mathrm{H}_{0k}: \psi_k(t) \geq 1, & \text{for all } t \\ \mathrm{H}_{1k}: \psi_k(t) < 1, & \text{at some } t \end{cases}$$

logrank test statistics

$$Z_k = -\widehat{U}_k(\tau) \Big/ \sqrt{\widehat{V}_{kk}(\tau)}$$

For large sample, each Z_k is approximately normally distributed $Z_k \sim \mathrm{N}(0,1)$ under H_{0k}

$\widehat{U}_k(t) = \sqrt{n} \int_0^t \widehat{H}_k(s)\{d\hat{\Lambda}_k^{(2)}(s) - d\hat{\Lambda}_k^{(1)}(s)\}$ ⋯Bivariate (weighted) logrank statistics process

$\Lambda_k^{(j)}$: Cumulative hazard function $\Lambda_k^{(j)} = \int_0^t \lambda_k^{(j)}(s)ds$

$\hat{\Lambda}_k^{(j)}(t)$: Nelson-Aalen estimator of $\Lambda_k^{(j)}$

$y_k^{(j)}$: "At risk" process in group j $y_k^{(j)} = \sum_{i=1}^N \mathbf{1}(g_i = j, T_{ik} \geq t)$

$\widehat{H}_k(s) = n^{-1}\widehat{W}_k(t) y_k^{(1)} y_k^{(2)} / \{y_k^{(1)} + y_k^{(2)}\}$

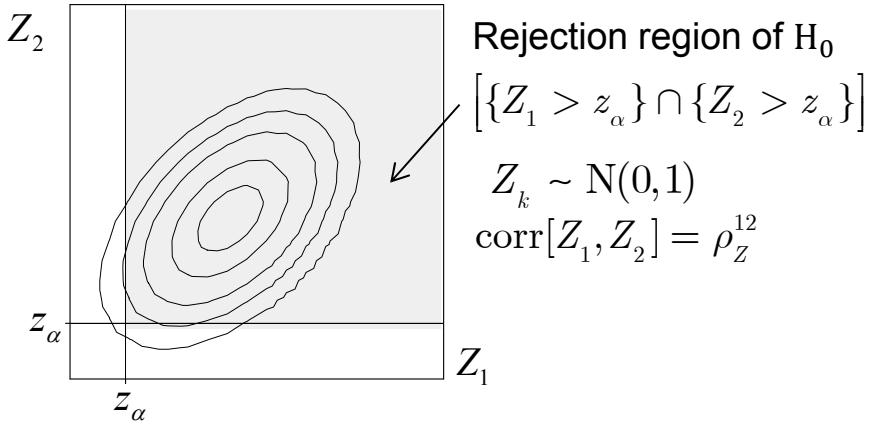
$\widehat{V}_{kk}(\tau)$ ⋯Well-known conditional variance of $U_k(\tau)$

Superiority hypothesis testing for both or at least one endpoint

Co-Primary

$$\begin{cases} \mathrm{H}_0: \psi_1(t) \geq 1 \text{ or } \psi_2(t) \geq 1, & \text{for all } t \\ \mathrm{H}_1: \psi_1(t) < 1 \text{ and } \psi_2(t) < 1, & \text{at some } t \end{cases}$$

Intersection-union test



Rejection region of H_0

$$\left[\{Z_1 > z_\alpha\} \cap \{Z_2 > z_\alpha\}\right]$$

$$Z_k \sim \mathrm{N}(0,1)$$

$$\mathrm{corr}[Z_1, Z_2] = \rho_Z^{12}$$

$\alpha \cdots$ significant level for hypothesis testing

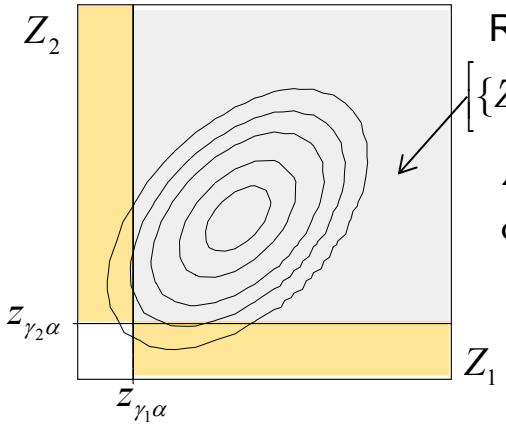
$z_a \cdots$ a upper α th percent point of the standard normal distribution

Primary

$$\begin{cases} \mathrm{H}_0: \psi_1(t) < 1 \text{ or } \psi_2(t) < 1, & \text{for all } t \\ \mathrm{H}_1: \psi_1(t) \geq 1 \text{ and } \psi_2(t) \geq 1, & \text{at some } t \end{cases}$$

Union intersection test

Weighted Bonferroni adjustment



Rejection region of H_0

$$\left[\{Z_1 > z_{\gamma_1\alpha}\} \cup \{Z_2 > z_{\gamma_2\alpha}\}\right]$$

$$Z_k \sim \mathrm{N}(0,1)$$

$$\mathrm{corr}[Z_1, Z_2] = \rho_Z^{12}$$

$\gamma_k \cdots$ weight $\gamma_1 + \gamma_2 = 1$

$z_{\gamma_k a} \cdots$ a upper $\gamma_k \alpha$ th percent point of the standard normal distribution

Power for detecting the effect on both or at least one endpoint

Co-Primary

$$1-\beta = \Pr\left[\bigcap_{k=1}^{2}\{Z_k > z_\alpha\}\,|\mathrm{H}_1\right]$$

Conjunctive power

Primary

$$1-\beta = \Pr\left[\bigcup_{k=1}^{2}\{Z_k > z_{\gamma_k\alpha}\}\,|\mathrm{H}_1\right]$$

Disjunctive power
Weighted Bonferroni adjustment

- The power is calculated by the cumulative distribution function of bivariate standardized normal distribution with correlation $\boldsymbol{\rho}_Z$

$$1-\beta = \Pr\left[\bigcap_{j=1}^{2}\left\{Z_k > z_\alpha\right\}\right] \approx \int_{z_\alpha-\sqrt{n}\mu_1/\sqrt{V_{11}}}^{\infty}\int_{z_\alpha-\sqrt{n}\mu_2/\sqrt{V_{22}}}^{\infty} f(z_1^*, z_2^*; \boldsymbol{\rho}_Z)\,\mathrm{d}z_1\,\mathrm{d}z_2$$

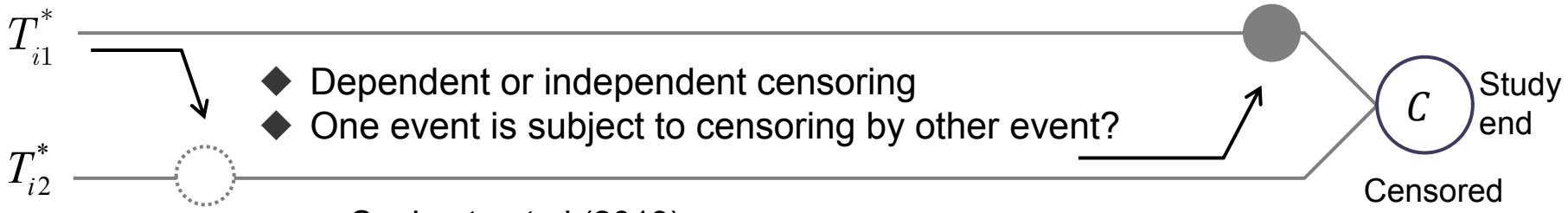
bivariate normal density function

$$z_k^* = \left(U_k - \sqrt{n}\mu_k\right)\Big/\sqrt{V_{kk}}$$

$$\boldsymbol{\rho}_Z = \begin{pmatrix} 1 & \rho_Z^{12} \\ \rho_Z^{21} & 1 \end{pmatrix}$$

$f(\cdot,\cdot;\boldsymbol{\rho})$ is the bivariate normal density function with zero mean vector and correlation matrix $\boldsymbol{\rho}_Z$

Censoring scheme: dependent or independent censoring



Sugimoto et al (2013)

1. Both non-fatal

HIV trial

E1: $T_{i1} < C$ ··· Time to virologic failure
E2: $T_{i2} < C$ ··· Discontinuation due to toxicity

Semi-competing risk (Fine et al, 2001)

2. One fatal

Cardiovascular Trial/ Oncology

E1: $T_{i1} < \min(T_{i2}, C)$ ··· Hospitalization TTS
E2: $T_{i2} < C$ ··· Death OS

4. Composite

E1': $T_{i1} = \min(T_{i1}, T_{i2})$
E2': T_{i1} or T_{i2}

Composite and its component
◆ MACE and Death
◆ PFS and OS

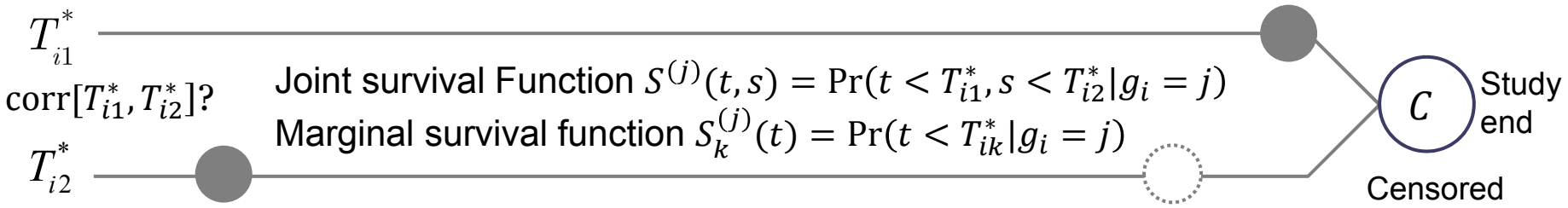
3. Both fatal

Oncology Trial

E1: $T_{i1} < \min(T_{i2}, C)$ ··· Disease-specific mortality
E2: $T_{i2} < \min(T_{i1}, C)$ ··· Other cause- specific mortality

Fine JPH et al. *Biometrika* 2001; **88**:907-919: Sugimoto et al. Biostatistics 2013; **14**:409-421

Modeling time-dependent association



- **Correlation between the two cumulative hazard variates** (Hsu, Prentice, 1996)

$$\rho_{\Lambda}^{(j)} = \mathrm{corr}\left[\Lambda_1^{(j)}(T_{i1}^*), \Lambda_2^{(j)}(T_{i2}^*)\right] = \int_0^{\infty}\int_0^{\infty} S^{(j)}(t,s)\, d\Lambda_1^{(j)}(t)\, d\Lambda_2^{(j)}(s) - 1 > 0$$

In absence of censoring, $\rho_{\Lambda}^{(j)}$ can be estimated replacing functions $\Lambda_k^{(j)}(t)$ with Nelson-Aalen estimators . If each marginal is exponential distribution, $\rho_{\Lambda}^{(j)} = \mathrm{corr}[T_{i1}^*, T_{i2}^*]$

- **Correlation between the two test statistics**

$$V_{12} = \int_0^{\tau}\int_0^{\tau} H_1(t) H_2(s) C(t,s) G(t,s) \left\{ \frac{d\Lambda^{(1)}(t,s)}{a^{(1)} y_1^{(1)}(t) y_2^{(1)}(s)} + \frac{d\Lambda^{(2)}(t,s)}{a^{(2)} y_1^{(2)}(t) y_2^{(2)}(s)} \right\}$$

$$\rho_Z^{12} = \frac{V_{12}}{\sqrt{V_{11} V_{22}}}$$

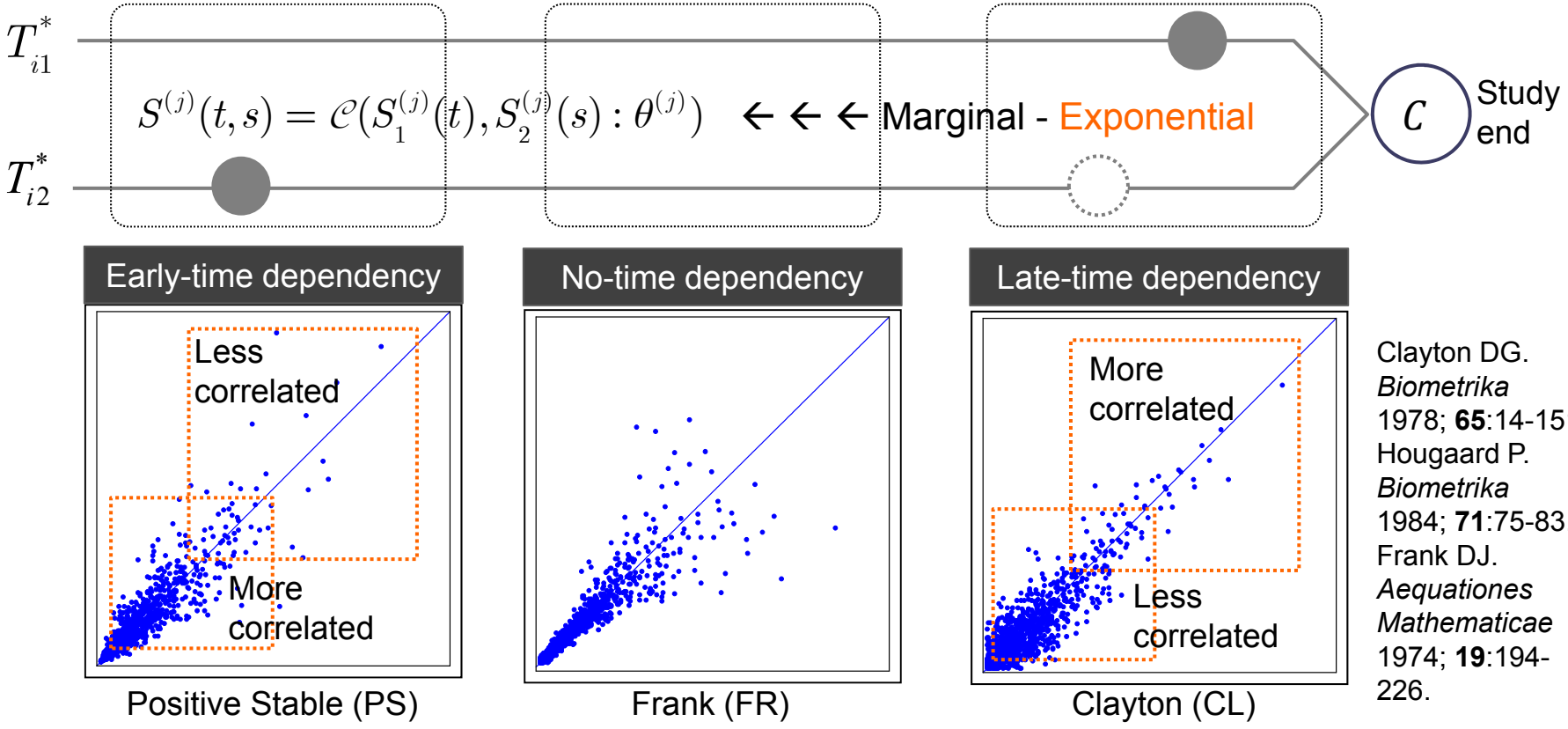
$$V_{kk} = \int_0^{\tau} H_k(t)^2 \left\{ \frac{d\Lambda_k^{(1)}(t)}{a^{(1)} y_k^{(1)}(t)} + \frac{d\Lambda_k^{(2)}(t)}{a^{(2)} y_k^{(2)}(t)} \right\}$$

$$\Lambda^{(j)}(t,s) = \int_0^t \int_0^s \lambda^{(j)}(x,y)\, dy\, dx$$

$$a^{(k)} = n_k / N$$

$$y_i^{(j)}(t) = \mathrm{E}[\bar{Y}_i^{(j)}] / n^{(j)}$$

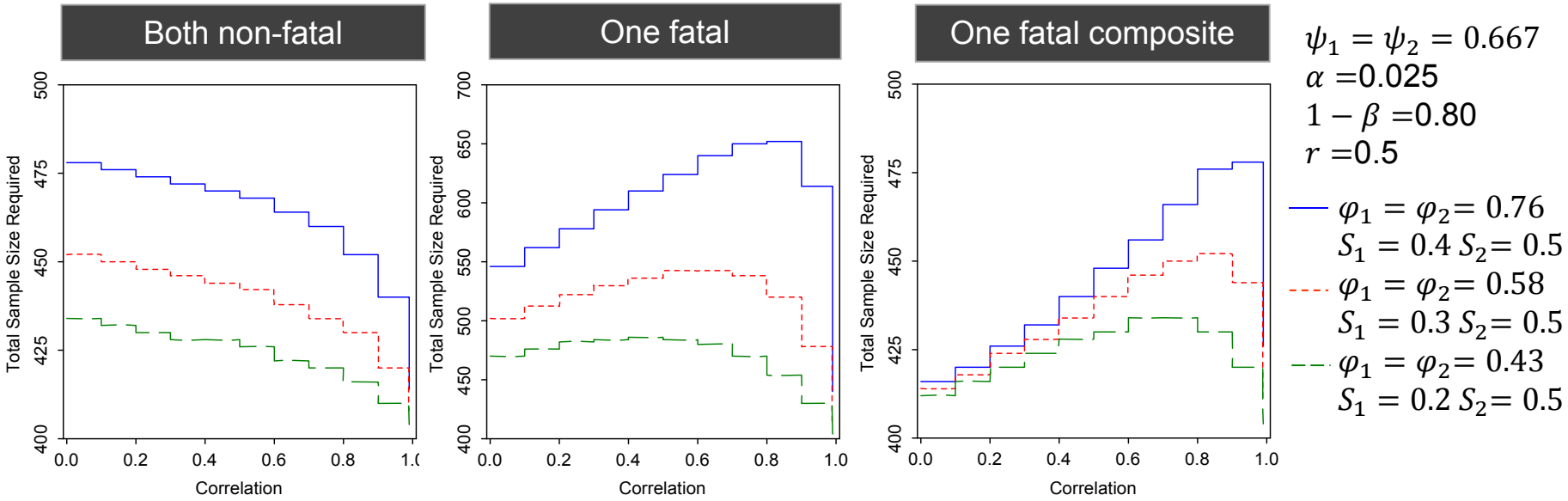
Modeling time-dependent association by copulas



Clayton DG. *Biometrika* 1978; **65**:14-151.
Hougaard P. *Biometrika* 1984; **71**:75-83.
Frank DJ. *Aequationes Mathematicae* 1974; **19**:194-226.

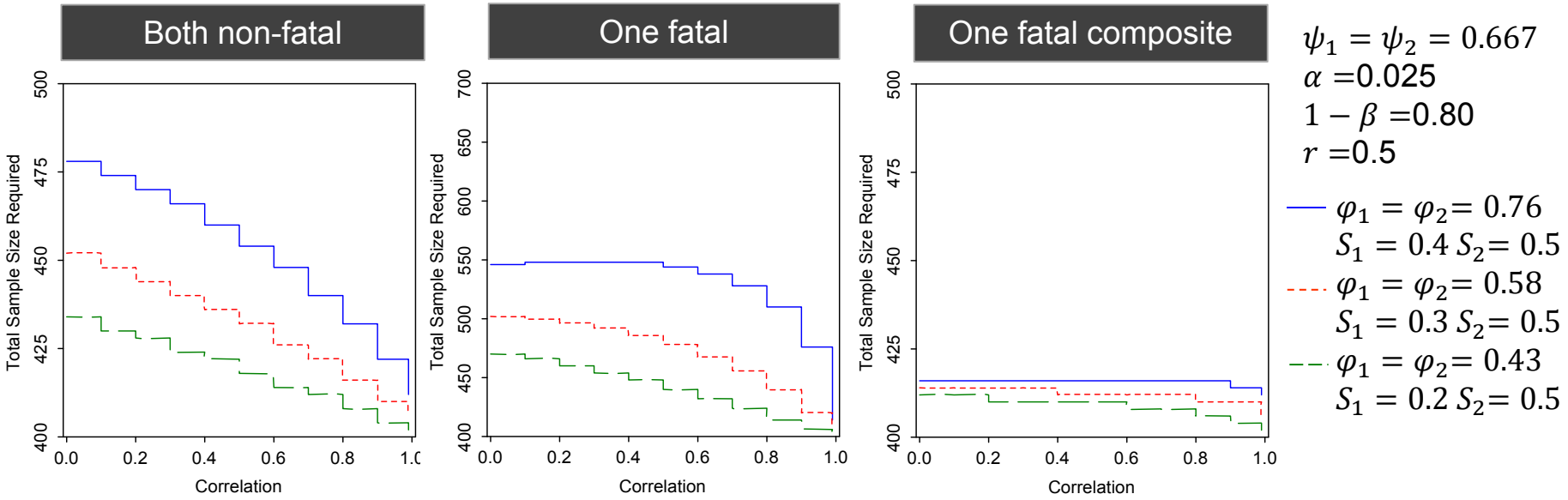
C be a function which generates the joint survival functions $S^{(j)}(t,s)$ from the two marginal $S_1^{(j)}(t)$ and $S_2^{(j)}(t)$ with association parameter $\theta^{(j)}$

Total sample size for "co-primary" endpoints: "late-time" dependency



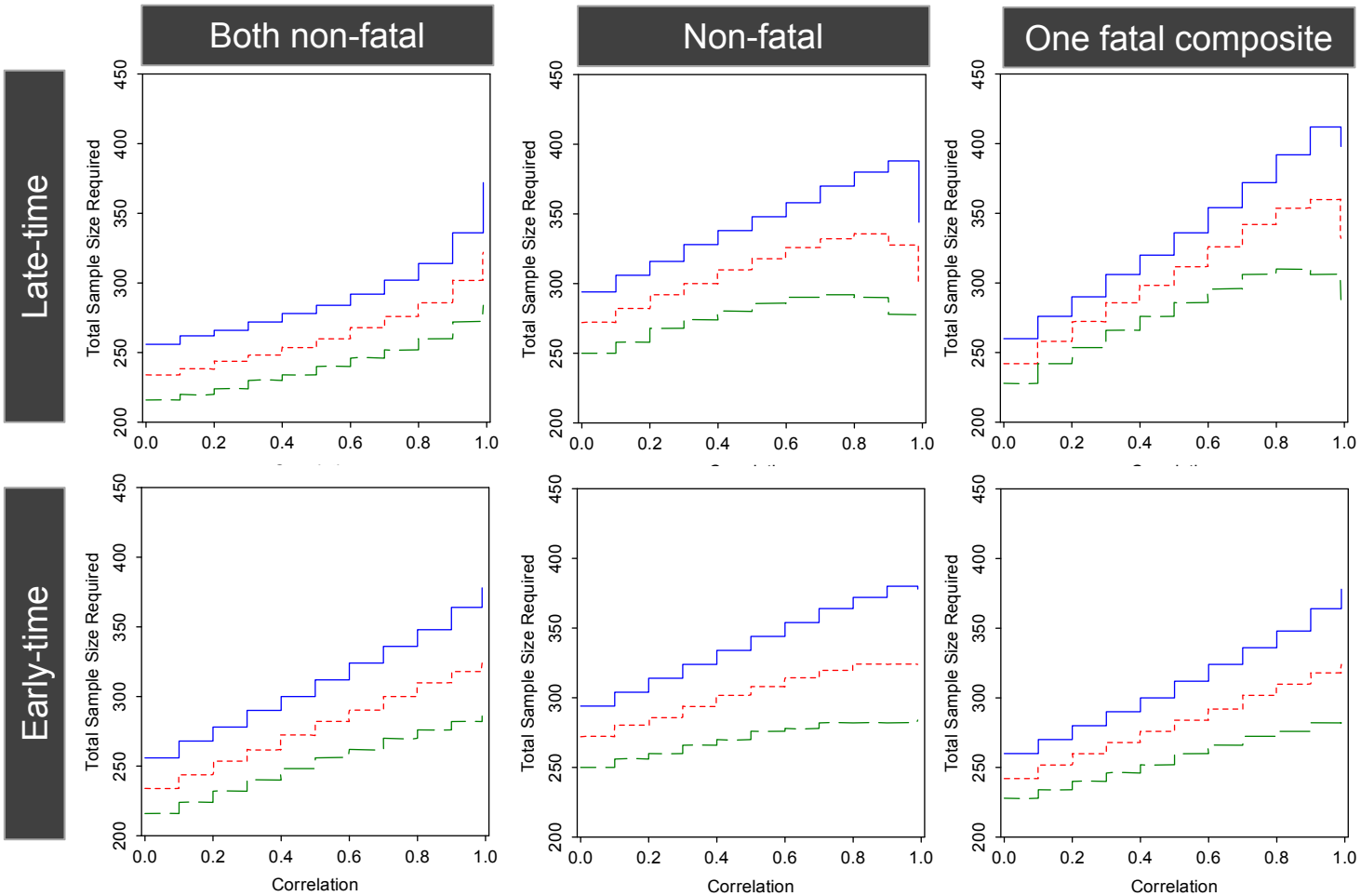
- For **both nonfatal**, the sample size decreases as correlation goes toward one, maximum is given when the correaltion is zero
- For **one fatal** and **one fatal composite**, the sample size increases until some point and then decreases as correaltion goes toward one, maximum depends on hazard ratios- For is significant effect of censoring by other event on sample size behavior.

Total sample size for "co-primary" endpoints: "early-time" dependency



- For **both nonfatal**, **one fatal** and **one fatal composite**, the sample size decreases as correaltion goes toward one, maximum is given when the correaltion is zero
- For **one fatal** and **one fatal composite,** there is no significant effect of censoring by other event on sample size behavior.

Total sample size for “primary” endpoints: un-weighted Bonferroni



$\psi_1 = \psi_2 = 0.667$
$\alpha_1 = \alpha_2$=0.0125
$1 - \beta$ =0.80
r =0.5

$\varphi_1 = \varphi_2$= 0.76
$S_1 = 0.4\ S_2$= 0.5

$\varphi_1 = \varphi_2$= 0.58
$S_1 = 0.3\ S_2$= 0.5

$\varphi_1 = \varphi_2$= 0.43
$S_1 = 0.2\ S_2$= 0.5

Summary

Focus

- Methods for power and sample size determination for comparing the effect of two interventions in superiority clinical trials with two time-to-event outcomes, when the aim is (i) to evaluate a joint effect on both outcomes, or (ii) to evaluate an effect on at least one outcome

Findings

- Sample sizing in clinical trials with two time-to-event outcome is more complex compared with other scale endpoints such as continuous or binary outcomes- many aspects to be considered in sample size determination in clinical trials.
  - **Co-primary**: Assuming zero correlation is not conservative when one event is fatal and the association between the two time-to-event is late-time dependency
  - **Primary**: Assuming one correlation is not conservative when one event is fatal and the association between the two time-to-event is late-time dependency
- The relationship between two time-to-event outcomes including censoring scheme and time dependency associations should be carefully evaluated when sample size is determined

Thank you for your kind attention

If you have any questions, please **e-mail to**

toshi.hamasaki@ncvc.go.jp