Selection bias and correlation in seamless phase II/III clinical trials with survival data

Josephine N. Khan

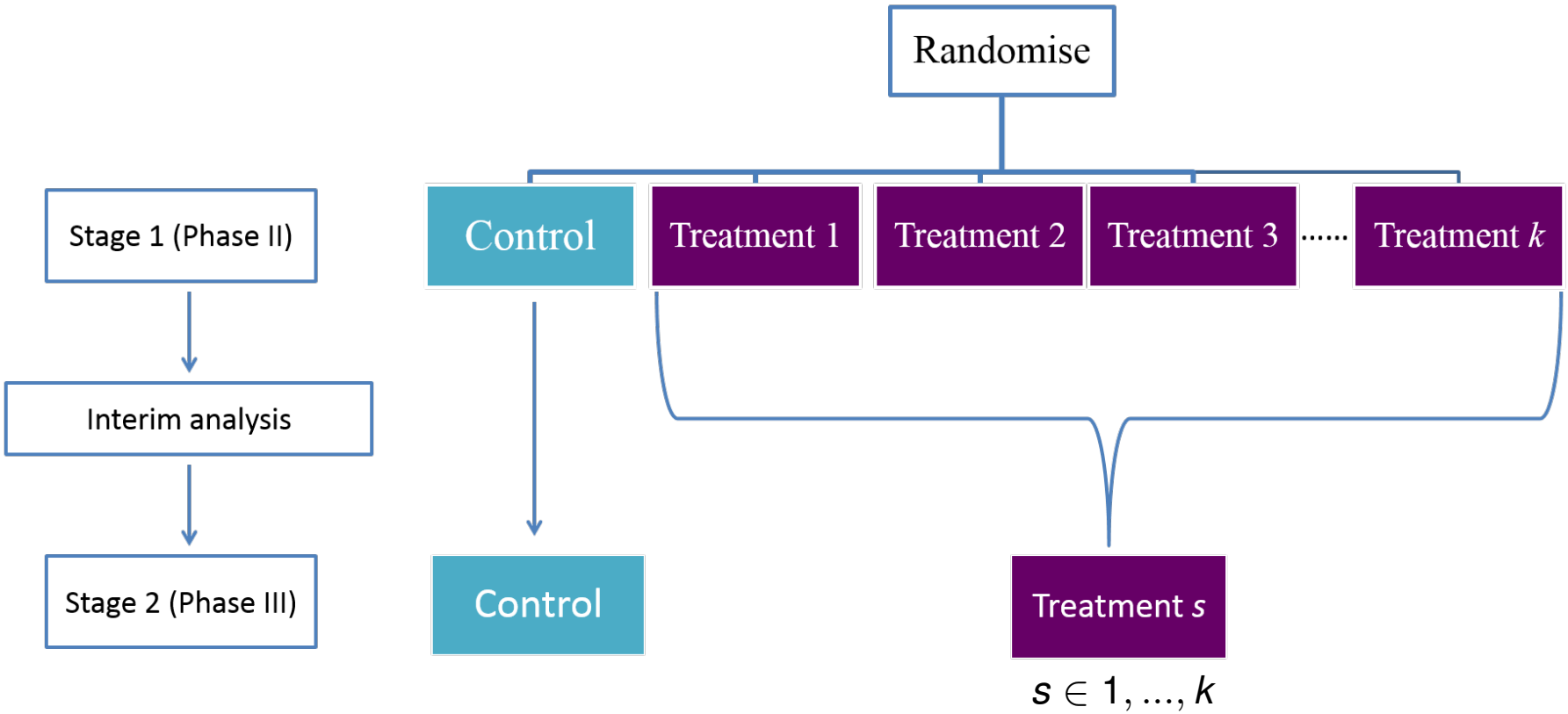
j.n.khan@warwick.ac.uk

Supervisors:

Dr. Peter Kimani, Prof. Nigel Stallard and Dr. Ekkehard Glimm

Outline

Seamless phase II/III clinical trial



Interim analysis allows design modifications including:
- Sample size re-estimation
- Stopping early for futility/efficacy
- Treatment selection

Bias

- At the end of the trial, interest is to estimate, θ_s, the treatment effect in the selected group.
- Bias is introduced at the interim analysis due to early treatment selection, therefore we seek to find an unbiased estimator for θ_s.
- Unbiased estimation was introduced by [Cohen and Sackrowitz, 1989] where they derived a Uniformly Minimum Variance Conditionally Unbiased Estimator in a two-stage trial setting assuming independent stage 1 statistics.
- Treatment comparison with a common control violates the assumption of independence.

Treatment selection bias - normally distributed outcomes

Notation

Consider a trial with k experimental treatment arms plus a control arm.
Assume outcomes for treatment i, $i = 0, 1, ..., k$, are $N(\mu_i, \sigma^2)$, where $i = 0$ corresponds to the control treatment.

Stage 1

- n_1 patients per arm
- Sample means $\bar{X}_i \sim N(\mu_i, \sigma_1^2)$ for treatment i, where $\sigma_1^2 = \sigma^2/n_1$
- Treatment $s \in \{1, ..., k\}$ selected at interim analysis; $\bar{X}_s = max\{\bar{X}_1, ..., \bar{X}_k\}$

Stage 2

- n_2 patients per arm
- Sample means $\bar{Y}_j \sim N(\mu_j, \sigma_2^2)$ for $j \in \{0, s\}$, where $\sigma_2^2 = \sigma^2/n_2$

Naive estimator

- Aim is to estimate the mean treatment difference θ_s.
- The MLE treatment j is the weighted average of stage 1 and 2 data given by:

$$\hat{\mu}_j = \frac{\sigma_2^2 X_j + \sigma_1^2 Y_j}{\sigma_1^2 + \sigma_2^2}$$

- This is biased as it does not take into account selection at the interim analysis.
- Stage 2 data alone is unbiased however inefficient.

Selection bias and MSE

Scenario with 3 experimental treatments with treatment selection at the end of the trial where $\mu_1 = 0$.

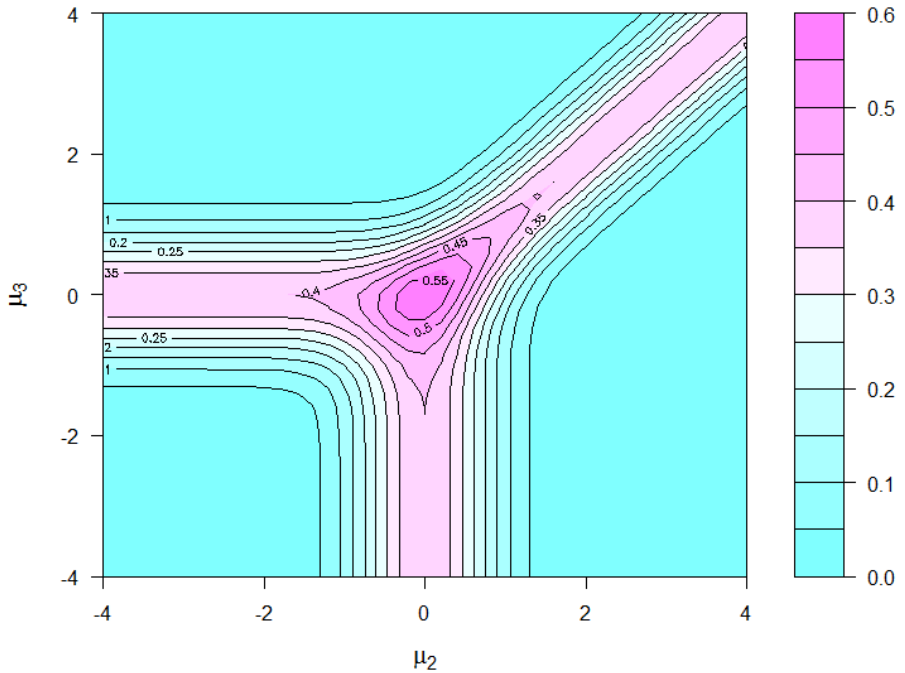


Figure 2.1: Selection bias in units of $\sigma\sqrt{2/n}$

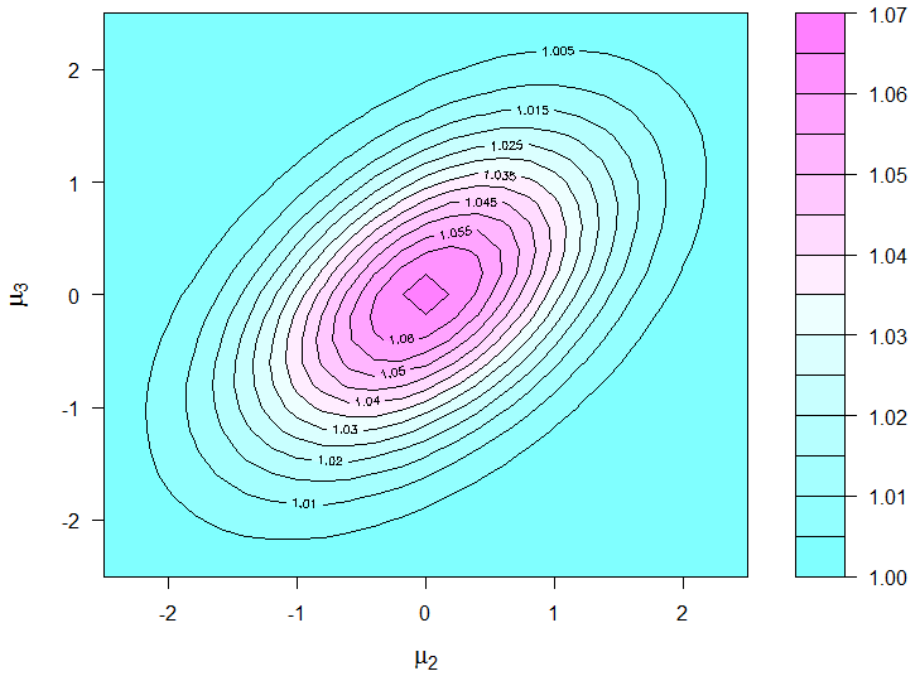


Figure 2.2: $\sqrt{MSE}$ in units of $\sigma\sqrt{2/n}$

UMVCUE for normal data

- Stage 2 data provides a sufficient and complete estimate for the selected treatment μ_s.
- Conditional on stage 1 data and selection rules, a UMVCUE can be found by the method of Rao-Blackwellization.
- The UMVCUE for μ_s is given by [Kimani et al., 2013]:

$$\tilde{\mu}_s = \hat{\mu}_s - \frac{\sigma_2^2}{\sqrt{\sigma_1^2 + \sigma_2^2}} \frac{\phi(W_B(1,2))}{\Phi(W_B(1,2))}$$

where, $W_B(1,2) = \left(\sqrt{\sigma_1^2 + \sigma_2^2}/\sigma_1^2\right)(\hat{\mu}_s - \bar{x}_{(2)})$

- So the unbiased estimator is:

$$\tilde{\theta}_s = \tilde{\mu}_s - \hat{\mu}_0$$

Bias and MSE of $\hat{\theta}_s$ and $\tilde{\theta}_s$

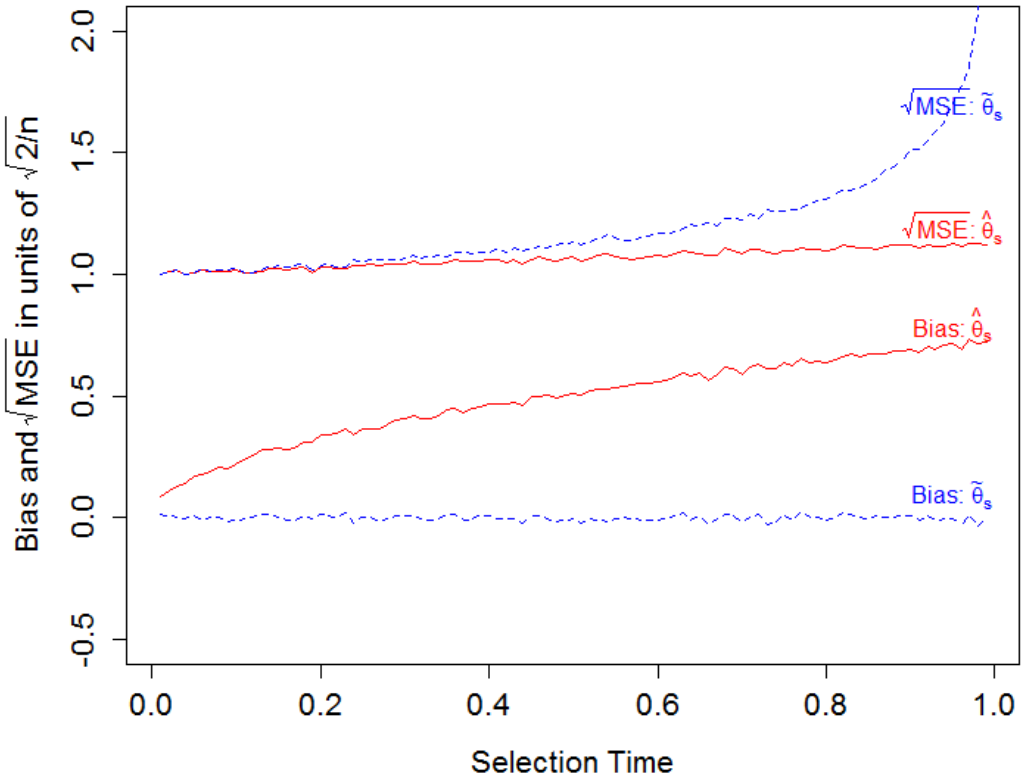
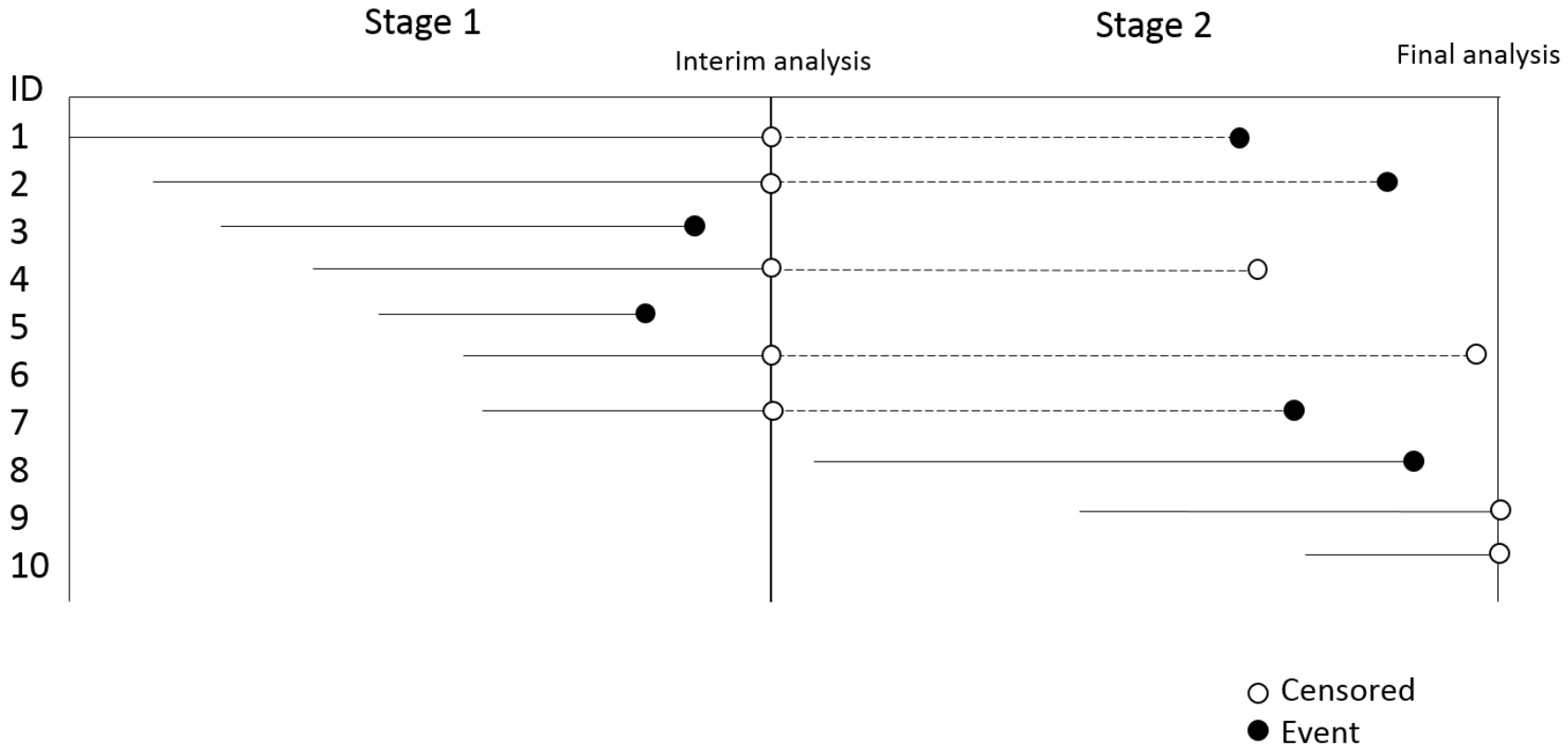


Figure 2.3: Selection bias and $\sqrt{MSE}$ of $\hat{\theta}_s$ and $\tilde{\theta}_s$ for $k = 4$

Treatment selection bias - survival outcomes

Example of survival data



Asymptotic normality of the log-rank statistic

- The score statistic for experimental treatment $k = 1, 2$ is

$$S_k = \sum_{j=1}^{r} (d_{jk} - e_{jk}) \sim N(\theta_k v_k, v_k).$$

- The log hazard ratio of interest, θ_k, is thus estimated by:

$$\hat{\theta}_{ik} = \frac{S_{ik}}{v_{ik}} \sim N\left(\theta_{ik}, \frac{1}{v_{ik}}\right)$$

where, $v_{ik} = \sum_{j=1}^{d_i} n_{jk}(1 - n_{jk})$ and n_{jk} is the number of patients at risk at time t_j in group k.

- Assume treatment 1 is selected at the interim analysis, i.e. $\hat{\theta}_{11} < \hat{\theta}_{12}$ then joint asymptotic distribution of $(\hat{\theta}_{11}, \hat{\theta}_{12}, \hat{\theta}_{21})$ is:

$$\begin{pmatrix} \hat{\theta}_{11} \\ \hat{\theta}_{12} \\ \hat{\theta}_{21} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_1 \\ \theta_2 \\ \theta_1 \end{pmatrix}, \begin{pmatrix} \frac{1}{v_{11}} & \frac{v_{11,12}}{\sqrt{v_{11} v_{12}}} & \frac{v_{11}}{\sqrt{v_{11} v_{21}}} \\ \frac{v_{11,12}}{\sqrt{v_{11} v_{12}}} & \frac{1}{v_{12}} & \frac{v_{12,21}}{\sqrt{v_{12} v_{21}}} \\ \frac{v_{11}}{\sqrt{v_{11} v_{21}}} & \frac{v_{12,21}}{\sqrt{v_{12} v_{21}}} & \frac{1}{v_{22}} \end{pmatrix} \right)$$

where,

$$\begin{aligned} v_{i1,i2} &= \frac{\sum_{j=1}^{d_i} \phi_j}{\sqrt{\sum_{j=1}^{d_i} n_{j1}(1-n_{j1}) \cdot \sum_{j=1}^{d_i} n_{j2}(1-n_{j2})}} \\ \phi_j &= n_{j1} n_{j2}. \end{aligned}$$

- Define independent increments to de-correlate stage 1 and stage 2 [DiScala and Glimm, 2011].

$$\tilde{\theta}_{2k} = \frac{S_{2k} - S_{1k}}{v_{2k} - v_{1k}} \sim N\left(\theta_{2k}, \frac{1}{v_{2k} - v_{1k}}\right).$$

- Then the joint asymptotic distribution of $(\hat{\theta}_{11}, \hat{\theta}_{12}, \tilde{\theta}_{21})$ is:

$$\begin{pmatrix} \hat{\theta}_{11} \\ \hat{\theta}_{12} \\ \tilde{\theta}_{21} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_1 \\ \theta_2 \\ \theta_1 \end{pmatrix}, \begin{pmatrix} \frac{1}{v_{11}} & \frac{v_{11,12}}{\sqrt{v_{11} v_{12}}} & 0 \\ \frac{v_{11,12}}{\sqrt{v_{11} v_{12}}} & \frac{1}{v_{12}} & 0 \\ 0 & 0 & \frac{1}{v_{21} - v_{11}} \end{pmatrix} \right).$$

UMVCUE for survival data

Seperate Controls

- We extend the methods from [Kimani et al., 2013], however in order to maintain independence between stage 1 statistics we first consider separate controls for each experimental treatment.
- W.L.O.G let Q denote the condition such that $Q = I(\hat{\theta}_{11} < \hat{\theta}_{12})$.
- Let $\sigma^2_{1k} = \frac{1}{V_{1k}}$ and $\sigma^2_{21} = \frac{1}{V_{21} - V_{11}}$.
- Let $\tilde{\theta}^*_1 = \frac{\sigma_{21}}{\sigma_{11}}\hat{\theta}_{11} + \frac{\sigma_{11}}{\sigma_{21}}\tilde{\theta}_{21}$

UMVCUE for survival data

Seperate Controls

- Conditional on Q, $\tilde{\theta}_1^*$ and $\hat{\theta}_{12}$ are sufficient and complete statistics for θ_1
- Thus by the Rao-Blackwell Theorem the UMVCUE is

$$\tilde{\theta}_s = E[\tilde{\theta}_{21}|\hat{\theta}_{12}, \tilde{\theta}_1^*, Q] = \hat{\theta}_{s,mle} + \frac{\sigma_{21}^2}{\sqrt{\sigma_{11}^2 + \sigma_{21}^2}} \frac{\phi(W_{(1,2)})}{\Phi(W_{(1,2)})} \tag{1}$$

where, $W_{(1,2)} = \frac{\sqrt{\sigma_{11}^2 + \sigma_{21}^2}}{\sigma_{11}^2}(\hat{\theta}_{12} - \hat{\theta}_{s,mle})$

Simulation studies

- A total of 1500 patients randomised to two experimental treatment groups and control.
- Simulate survival times from Weibull distribution with log(HR), $\theta_s \in [-1.61, 0]$.
- Interim analysis is conducted after a total of 450 events with final analysis after 900 events. The log hazard ratio for the selected treatment is estimated θ_s

Simulation Study

Estimators considered for θ_s:

- $\hat{\theta}_2$ - stage 2 data
- $\hat{\theta}_{s,mle}$ - MLE (weighted average of stage 1 and 2 data ignoring selection
- $\tilde{\theta}_s$ - UMVCUE (accounts for selection and correlation between stages)
- $\tilde{\theta}_{s,new}$ - UMVCUE (stage 2 data includes new patients only)

Simulation Results

Mean log(HR) and bias from 1000 simulations with final analysis after a total of 900 events.

	True log HR (θ_s)				
	0	-0.22	-0.51	-0.92	-1.61
$\hat{\theta}_2$	-0.00272	-0.225	-0.5209	-0.920	-1.685
bias($\hat{\theta}_2$)	-0.00272	-0.00216	-0.0101	-0.00451	-0.0761
$\hat{\theta}_{MLE}$	-0.0226	-0.2422	-0.544	-0.984	-1.792
bias($\hat{\theta}_{MLE}$)	-0.0226	-0.0191	-0.0338	-0.0676	-0.183
$\tilde{\theta}_{s,new}$	0.0165	-0.188	-0.495	-0.883	-1.633
bias($\tilde{\theta}_{s,new}$)	0.0165	0.0349	0.0152	0.0330	-0.0239
$\tilde{\theta}_s$	0.00816	-0.211	-0.511	-0.948	-1.750
bias($\tilde{\theta}_s$)	0.00816	0.0119	-0.000571	-0.0326	-0.141

Simulation Results - Bias and MSE

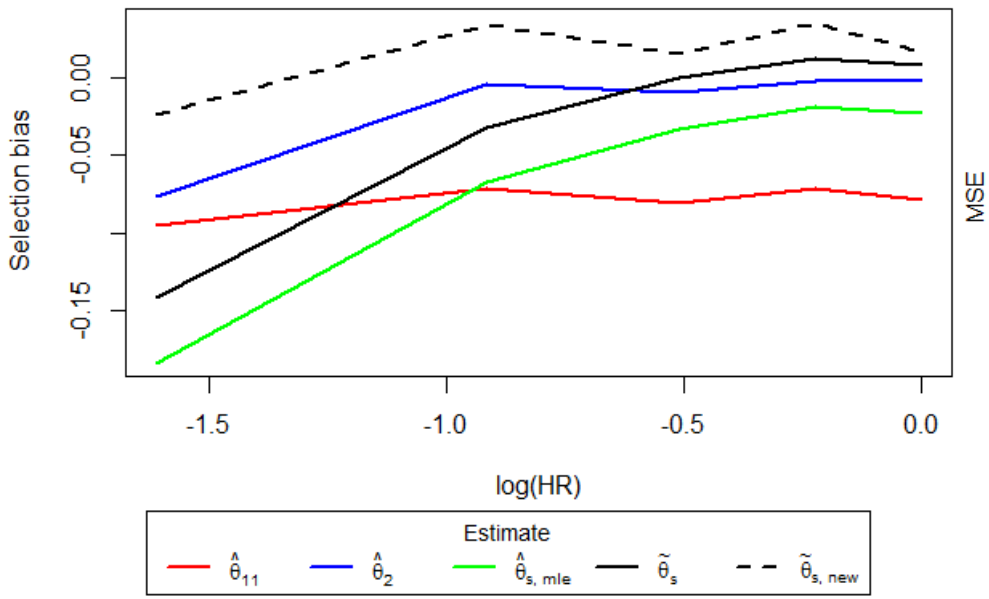


Figure 3.1: Selection Bias, k=4

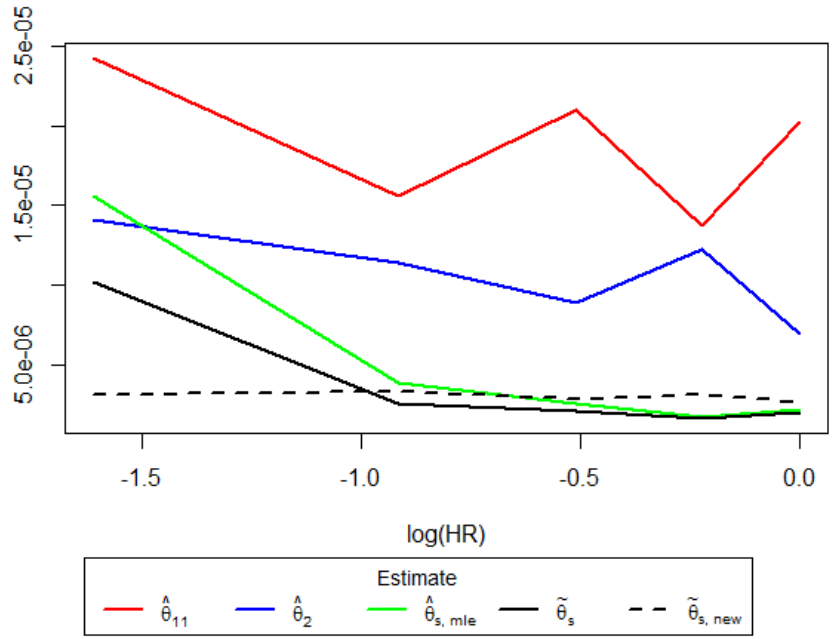


Figure 3.2: $\sqrt{MSE}$, k=4

UMVCUE for survival data

Common Control

- Now we consider a common control for each experimental treatment
- This introduces correlation between interim statistics
- [Robertson et al., 2016] derive a UMVCUE that accounts for correlation between stage 1 statistics in a multivariate normal setting.
- We now estimate the inverse log(HR) and select the treatment with maximum observed efficacy at the interim analysis.

UMVCUE

- Let $Z_1 = \hat{\theta} + 11 + \frac{\sigma_{11}^2}{\sigma_{21}^2}\tilde{\theta}_{21}$ and $Z_2 = \hat{\theta}_{12} + \frac{\rho\sigma_{11}\sigma_{12}}{\sigma_{21}^2}\tilde{\theta}_{21}$
- Then the UMVCUE is given by [Robertson et al., 2016]:

$$\tilde{\theta}_s = \begin{cases} \frac{\sigma_{21}^2 Z_1}{\sigma_{11}^2+\sigma_{21}^2} - \frac{\sigma_{21}^2}{\sqrt{\sigma_{11}^2+\sigma_{21}^2}}\frac{\phi(W)}{\Phi(W)}, & \text{if } \frac{\sigma_{11}^2}{\sigma_{21}^2} > \rho. \\ \frac{\sigma_{21}^2 Z_1}{\sigma_{11}^2+\sigma_{21}^2} + \frac{\sigma_{21}^2}{\sqrt{\sigma_{11}^2+\sigma_{21}^2}}\frac{\phi(W)}{\Phi(W)}, & \text{if } \frac{\sigma_{11}^2}{\sigma_{21}^2} > \rho. \\ \frac{\sigma_{21}^2 Z_1}{\sigma_{11}^2+\sigma_{21}^2}, & \text{if } \frac{\sigma_{11}^2}{\sigma_{21}^2} = \rho. \end{cases}$$

Where,

$$W = \frac{(Z_1 - Z_2)\sqrt{\sigma_{11}^2+\sigma_{21}^2}}{\sigma_{11}^2 - \rho\sigma_{11}\sigma_{21}} - \frac{Z_1}{\sqrt{\sigma_{11}^2+\sigma_{21}^2}}$$

Simulation Results - Bias and MSE

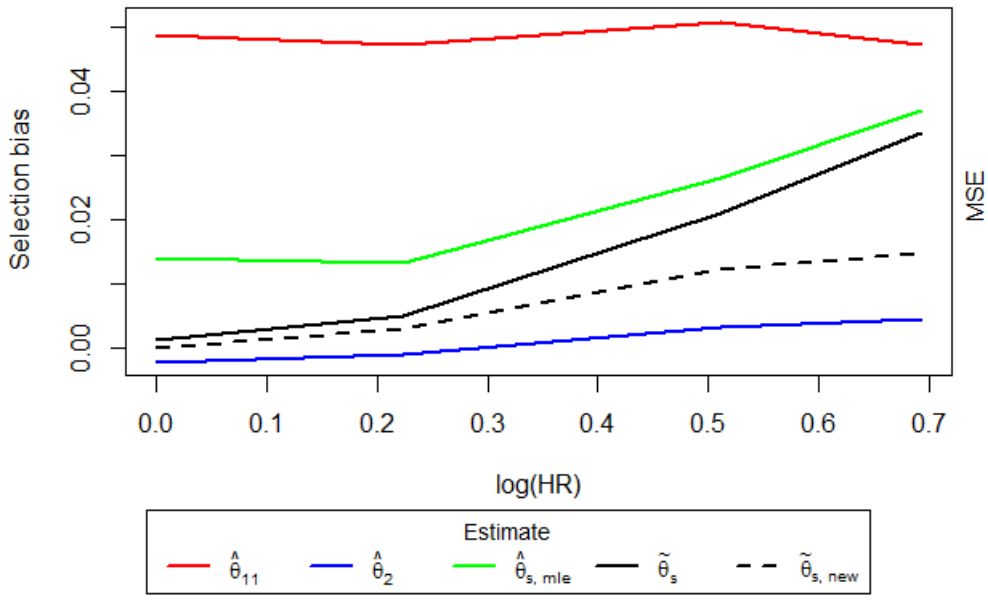


Figure 3.3: Selection Bias, k=4

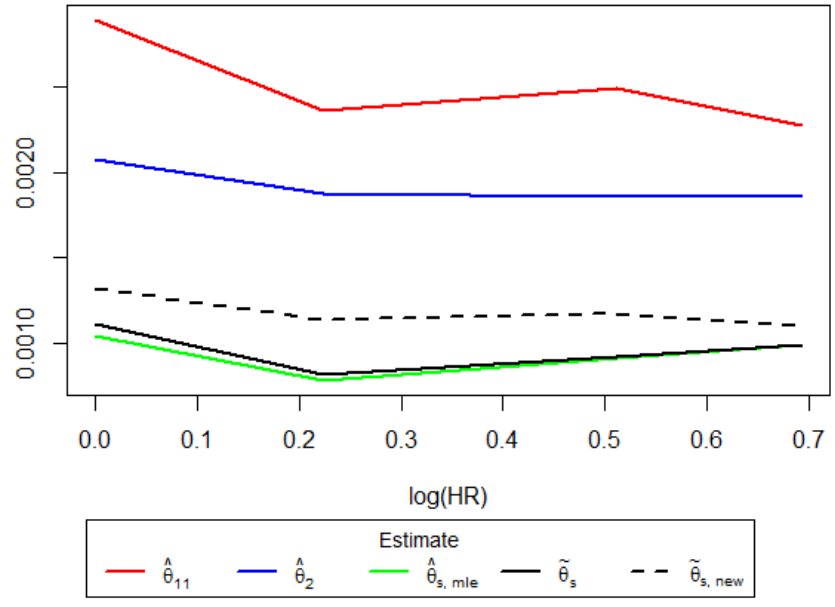


Figure 3.4: $\sqrt{MSE}$, k=4

	True log HR (θ_s)			
	0	0.22	0.51	0.69
$\tilde{\theta}_s$	0.0019	0.225	0.528	0.73
bias($\tilde{\theta}_s$)	0.0019	0.0019	0.018	0.035
$\sqrt{\text{MSE}}(\tilde{\theta}_s)$	0.0011	0.00081	0.00096	0.0010
$\tilde{\theta}_{s,new}$	0.0037	0.225	0.523	0.708
bias($\tilde{\theta}_{s,new}$)	0.0037	0.0022	0.013	0.015
$\sqrt{\text{MSE}}(\tilde{\theta}_{s,new})$	0.00134	0.00113	0.00116	0.00113

Further work

- Adapt UMVCUE from [Robertson et al., 2016] to rank treatments by smallest HR in order to directly apply to time-to-event data.
- Apply methods to real data in the setting of sub-population selection.

References

Cohen, A. and Sackrowitz, H. B. (1989).
Two stage conditionally unbiased estimators of the selected mean.
Statistics and Probability Letters, **8**:273 – 278.

DiScala, L. and Glimm, E. (2011).
Time-to-event analysis with treatment arm selection at interim.
Statistics in Medicine, **30**:3067–3081.

Kimani, P. K., Todd, S., and Stallard, N. (2013).
Conditionally unbiased estimation in phase II/III clinical trials with early stopping for futility.
Statistics in Medicine, 32(17):2893–2910.

Robertson, D. S., Prevost, A. T., and Bowden, J. (2016).
Accounting for selection and correlation in the analysis of two-stage genome-wide association studies.
Biostatistics, 0(0):1–27.

Thank-you for listening.

Any questions?