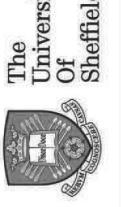


Adjusting for Treatment Switching in Oncology clinical trials with correlated survival outcomes

Iain Bennett (September 2016)

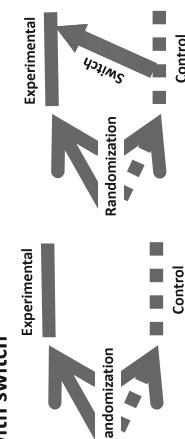


1) Introduction

Late phase oncology clinical trials are often confounded by treatment switching, which is the practice whereby patients randomized to the control arm switch to an experimental treatment (1). This is illustrated in Figure 1. An intent to treat (ITT) analysis of an endpoint such as overall survival measured after this switch is no longer a comparison of the groups as randomized.

Typically this switch is for ethical reasons, either once the treatment has shown to be effective on a surrogate endpoint or because no alternative treatments exist (1). A common point to allow switch is at the progression of disease (a potential surrogate endpoint). It is believed that the time until this progression of disease and the overall survival time maybe correlated with the amount of correlation varied by disease (2).

Figure 1: Illustration of trial without and with switch



2) Methods

Several methods have been proposed to analyse data contaminated by switch (1), however, in this poster only a selection are presented:

- Censoring at switch (PP-CENS) – patients who switch are censored at the time of switch.
- Treatment as a time varying covariate (TVC) – switch treatment is included as a time varying covariate in a Cox proportional hazards model.
- Rank-preserving structural failure time models (RPSFT) as described in the next box.

Use of simulation studies

Prior simulation studies have been performed (1, 3) which compared the performance of these methods against simulated data, however, they have not explicitly considered correlation between time to progression and overall survival when simulating the underlying survival times.

3) The RPSFT model

This model proposed by Robins and Tsiatis (4) considers 2 different survival times for a patient i with notation:

T_i – the observed survival time

U_i – the latent survival time with no treatment

An accelerated failure time model is then proposed to relate these such as :

$$U_i(\varphi) = T_{ci} + T_{Ei} e^{\varphi}$$

Where T_{Ei} is the observed time on experimental therapy and T_{ci} is defined as $T_{ci} = T_i - T_{Ei}$. When T_{Ei} is defined as actual exposure time this is called ‘‘on-treatment’’ RPSFT, while when T_{Ei} is defined as time from first exposure to death this is called ‘‘treatment group’’ RPSFT. For both models φ is an unknown parameter with true value φ_0 . It can be seen that $e^{\varphi} < 1$ or equivalently $\varphi < 0$ implies the treatment is beneficial and extends life. It can also be seen that only one treatment effect is assumed for switch and randomized exposure.

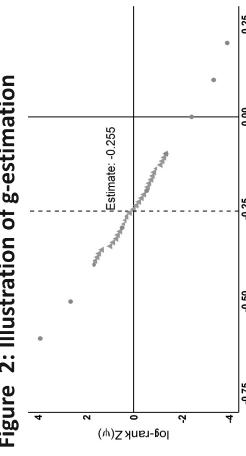
Estimation of $\widehat{\varphi}_0$

As U_i (latent survival time) is a baseline characteristic it can be assumed to be balanced by randomization between the two randomized treatment groups. This fact is used to estimate φ_0 using g-estimation as follows:

- Define a grid of candidate values for φ
- Derive latent survival times $U_i(\varphi)$ for each candidate value for φ
- Compare the latent survival times as randomized using a test of difference in survival such as a log-rank test to derive a normally distributed test statistic $Z(\varphi)$ where $Z(\varphi) = 0$ means no difference in U_i
- Select $\widehat{\varphi}_0$ as the value of φ where $Z(\varphi) \approx 0$

This estimation procedure is shown in Figure 2.

Figure 2: Illustration of g-estimation



Search step (decreasing grid size with second pass) • Pass: 1: Pass: 2
 $\log\text{-rank } Z(\varphi)$
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 ρ
ITT = Intent-to-treat analysis
PP-CENS = Censoring at switch
TVC = Treatment as time varying covariate

4) Novel simulation study design

In order to test the different proposed methods a simulation study was conducted where by clinical trial datasets were simulated where patients who progressed could switch treatment at progression time. Across these the following parameters were varied:

- Correlation between time to progression (TP) and overall survival (OS)
- Proportion of control arm patients who switched
- Duration of treatment effect of experimental therapy (whether it only reduced the risk of death while on treatment or also after treatment)
- Magnitude of treatment effect for control arm patients who switch (common or a reduced effect).

5) Results

The percentage bias for a selection of methods and scenarios investigated is shown in Figure 3 and Figure 4.

- The ITT analysis underestimates the true treatment effect with a lower bias when TTP and OS is correlated (when OS and TTP is correlated patients with shorter OS more likely to be observed to switch as have shorter TTP)

- Simple methods censoring at crossover (PP-CENS) and Treatment as a time varying covariate (TVC) exhibit considerable bias when a correlation between TTP and OS exists (as switch is related to prognosis)
- both ‘‘treatment group’’ and ‘‘on treatment’’ applications of RPSFT have similar bias regardless of the data generation procedure when there is a common treatment effect for switch and randomized therapy
- Bias for RPSFT is dramatically increased when switch treatment is less effective than randomized treatment

Figure 3: Results for simple methods

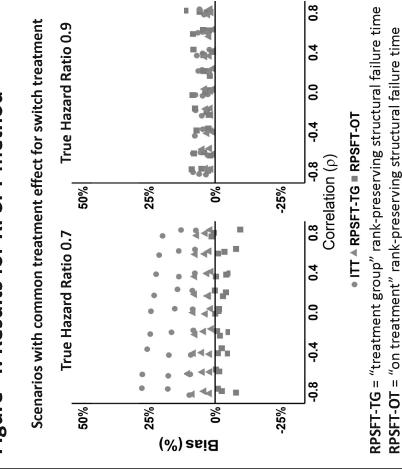


RPSFT-TG = ‘‘Treatment group’’ rank-preserving structural failure time RPSFT-OT = ‘‘on treatment’’ rank-preserving structural failure time

References

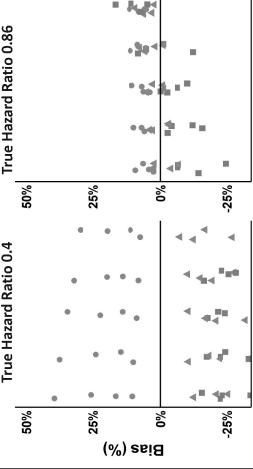
- 1) Latimer, N.R. et al (2014) Adjusting survival time estimates to account for treatment switching in randomized controlled trials. *Medical Decision Making*, 34, 387–402.
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- 3) Morden et al (2011) Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. *BMC Medical Research Methodology*, 11, 1–20.
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Figure 4: Results for RPSFT method



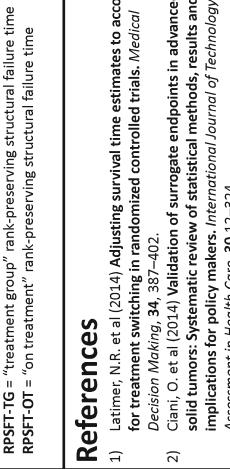
RPSFT-TG = ‘‘Treatment group’’ rank-preserving structural failure time RPSFT-OT = ‘‘on treatment’’ rank-preserving structural failure time

Scenarios with reduced effect for switch treatment



RPSFT-TG = ‘‘Treatment group’’ rank-preserving structural failure time RPSFT-OT = ‘‘on treatment’’ rank-preserving structural failure time

Scenarios with common treatment effect for switch treatment



RPSFT-TG = ‘‘Treatment group’’ rank-preserving structural failure time RPSFT-OT = ‘‘on treatment’’ rank-preserving structural failure time

Scenarios with common treatment effect for switch treatment

Adjusting for Treatment Switching in Oncology clinical trials with correlated survival outcomes

Iain Bennett (September 2016)

Switching in Oncology



1) Introduction

Late phase oncology clinical trials are often confounded by treatment switching which is the practice whereby patients randomized to the control arm switch to the experimental treatment (1). This is illustrated in Figure 1. An intent-to-treat (ITT) analysis of an endpoint such as overall survival measured after this switch is no longer a comparison of the groups as randomized.

3) The RPSFT model

This model proposes different survival times for a patient i with notation: T_i – the observed survival time; T_{EI} – the latent survival time with no treatment. An accelerated failure time model is then proposed to relate these such as:

$$U_i(\varphi) = T_{EI} + T_{FI} e^{\varphi}$$

Where T_{EI} is defined as the observed time on experimental therapy and T_{FI} is defined as the exposure time this is called ‘on-treatment’ RPSFT, while at time from first exposure to death this is called ‘off-group’ RPSFT. For both models φ is an unknown parameter with true value φ_0 . It can be seen that $\varphi < \varphi_0$ implies the treatment is less effective. It can also be seen that only one is assumed for switch and randomized exposure.

Estimation of θ_{RPSFT}

- As U_i (latent survival) to be assumed to be two randomized trials estimate φ using grid of
- Define a grid of
- Derive latent survival times $U_i(\varphi)$ for each candidate value
- Compare the latent survival times as randomized using a test statistic such as a log-rank test to derive a normal distribution $Z(\varphi)$ where $Z(\varphi) = U_i(\varphi) - U_i(\varphi_0)$
- Select $\hat{\varphi}_0$ as the best estimate. This estimation procedure is shown in Figure 2.

2) Methods

Proposed adjustment methods

Several methods have been proposed to analyse data contaminated by switch (1), however, in this poster only a selection are presented:

- Censoring switch (PP-CENS) – patients who switch are censored at the time of switch.
- Treatment as a time varying covariate (TVC) – switch treatment is included as a time varying covariate in a Cox proportional hazards model.
- Rank-preserving structural failure time models (RPSFT) as described in the next box.

Use of simulation studies
Prior simulation studies have been performed (1, 3) which compared the performance of these methods against censored data, however, they have not explicitly considered correlation between time to progression and overall survival when simulating the underlying survival times.

4) Novel simulation study design

In order to test the different proposed methods a study was conducted where by clinical trial data simulated where patients who progressed could treatment at progression. Across these the following parameters were varied:

- Correlation between time to progression (TPP) and overall survival (OS)
- Proportion of control arm patients who switch
- Duration of treatment effect of experimental therapy (whether it only reduced the risk of death while on treatment or also after treatment)
- Magnitude of treatment effect for control arm who switch (common or a reduced effect).

5) Results

The percentage bias for a selection of methods are investigated is shown in Figure 3 and Figure 4.

- The ITT analysis underestimates the true treatment effect with a lower bias when TPP and OS is correlated and TPP is correlated with shorter OS to be observed to switch as have shorter TPP
- Simple methods censoring at crossover (PP-CENS) treatment as a time varying covariate (TVC) exist considerable bias when a correlation between TPP and OS exists (as switch is related to prognosis)
- both ‘treatment group’ and ‘on treatment’ RPSFT have similar bias regardless of the generation procedure when there is a common effect for switch and randomized therapy
- RPSFT is unadjusted increases with increased treatment is less effective than randomized treatment

Figure 1: Illustration of trial without and with switch

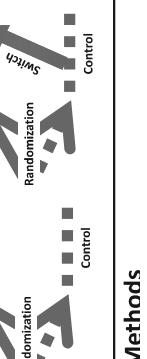


Figure 2: Illustration of g-estimation

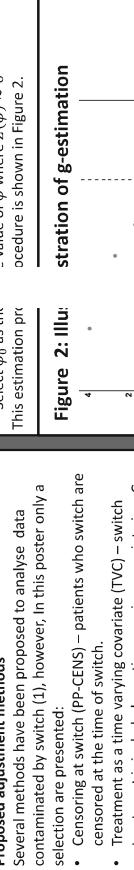
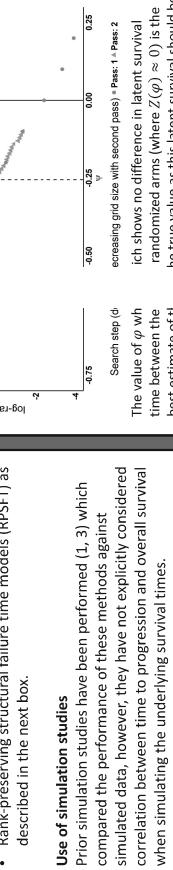
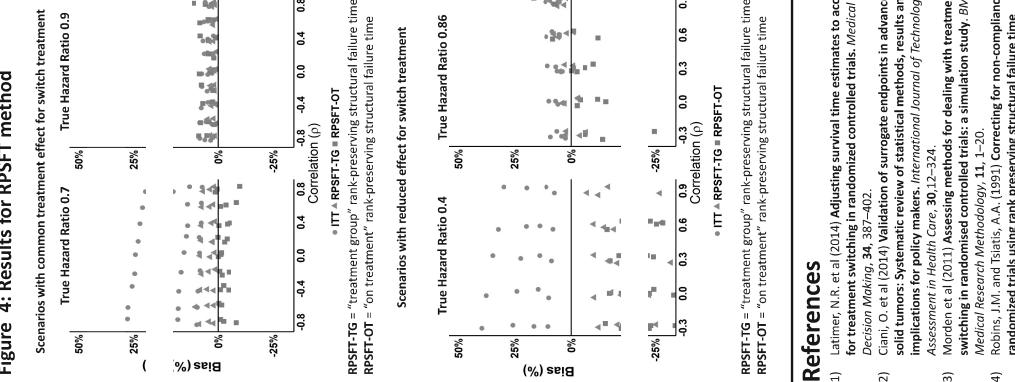


Figure 3: Results for simple methods



ITT = intent-to-treat analysis
PP-CENS = Censoring at switch
TVC = Treatment as time varying covariate

Figure 4: Results for RPSFT method



ITT = “treatment group” rank-preserving structural failure time
RPSFT-OT = “on treatment” rank-preserving structural failure time

References

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Adjusting for Treatment : clinical trials with correlation

Iain Bennett (September 2016)

1) Introduction

Late phase oncology clinical trials are often confounded by treatment switching which is the practice whereby patients randomized to the control arm switch to the experimental treatment (1). This is illustrated in Figure 1. An Intent to treat (ITT) analysis of an endpoint such as overall survival measured after this switch is no longer a comparison of the groups as randomized.

3) The RPSI

This model proposes different survival times:
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Switching in Oncology inted survival outcomes

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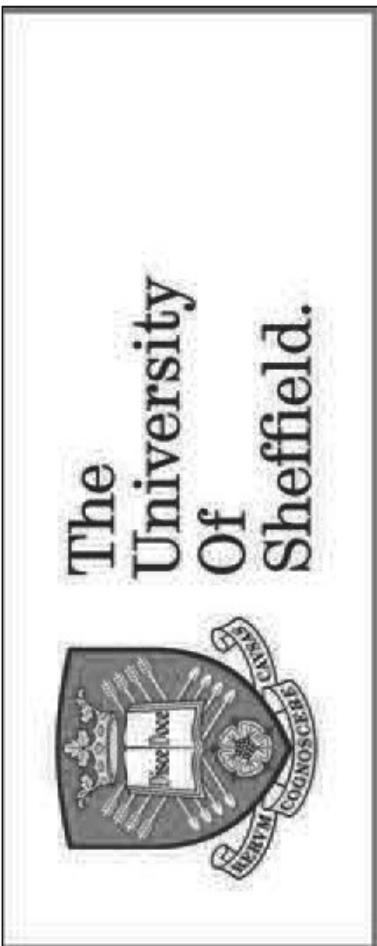
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4) Novel simulation study des

In order to test the different proposed methods a study was conducted where by clinical trial dataset simulated where patients who progressed could receive treatment at progression. Across these the following parameters were varied:

- Correlation between time to progression (TTP), survival (OS)

$$U_i(\phi) = T_{r_i} + T_{F_i} e^\phi$$



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Figure 4: Results for RPSFT method

Scenarios with common treatment effect for switch treatment



Typically this switch is for ethical reasons, either once the treatment has shown to be effective on a surrogate endpoint or because no alternative treatments exist (1). A common point to allow switch is at the progression of disease (a potential surrogate endpoint). It is believed that the time until this progression of disease and the overall survival time maybe correlated with the amount of correlation varied by disease (2).

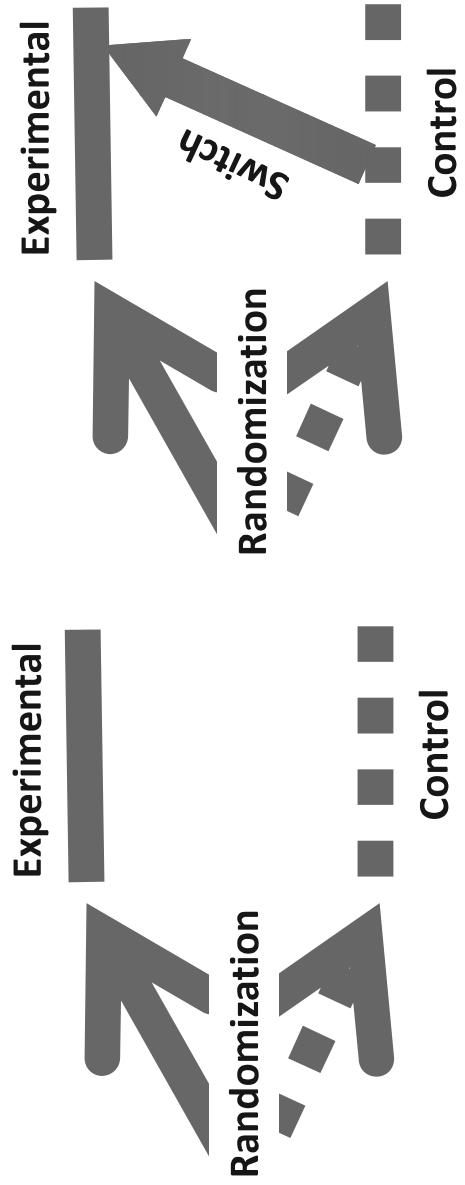
Where T_{Ei} is the observed time, T_{Ci} is defined as T_{Ei} exposure time this when T_{Ei} is defined is called ``treatment`` unknown parameter $\varphi < 1$ or equivalent beneficial and extent treatment effect is exposure.

Estimation of $\widehat{\varphi}_0$

As U_i (latent survival) be assumed to be two randomized trials estimate φ_0 using

- Define a grid of
- Derive latent survival for φ
- Compare the latent test of different φ derive a normal distribution $Z(\varphi) = 0$ mean

Figure 1: Illustration of trial without and with switch



2) Methods

- Proportion of control arm patients who switch
- Duration of treatment effect of experimental treatment (whether it only reduced the risk of death while on treatment or also after treatment)
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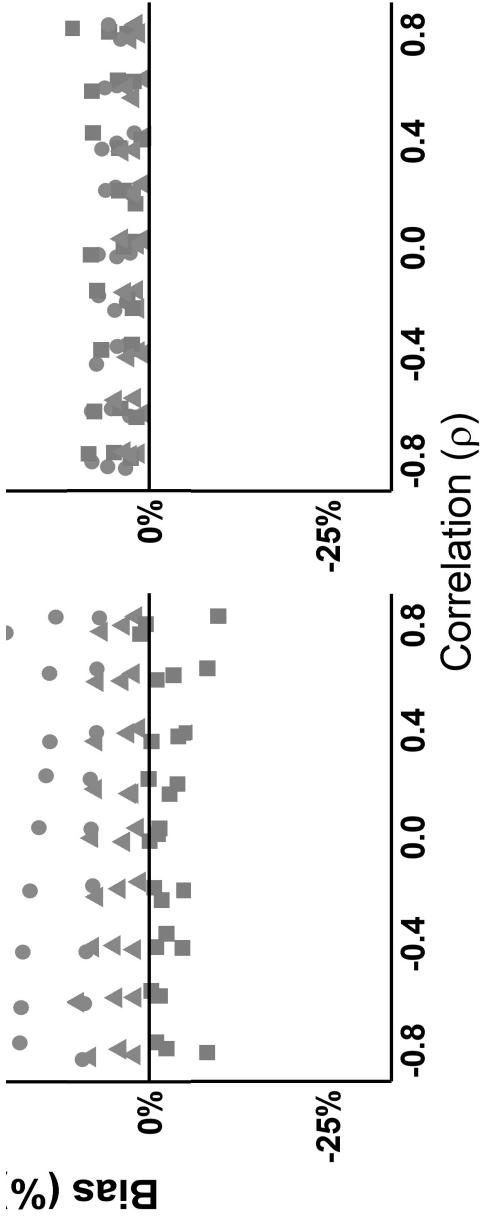
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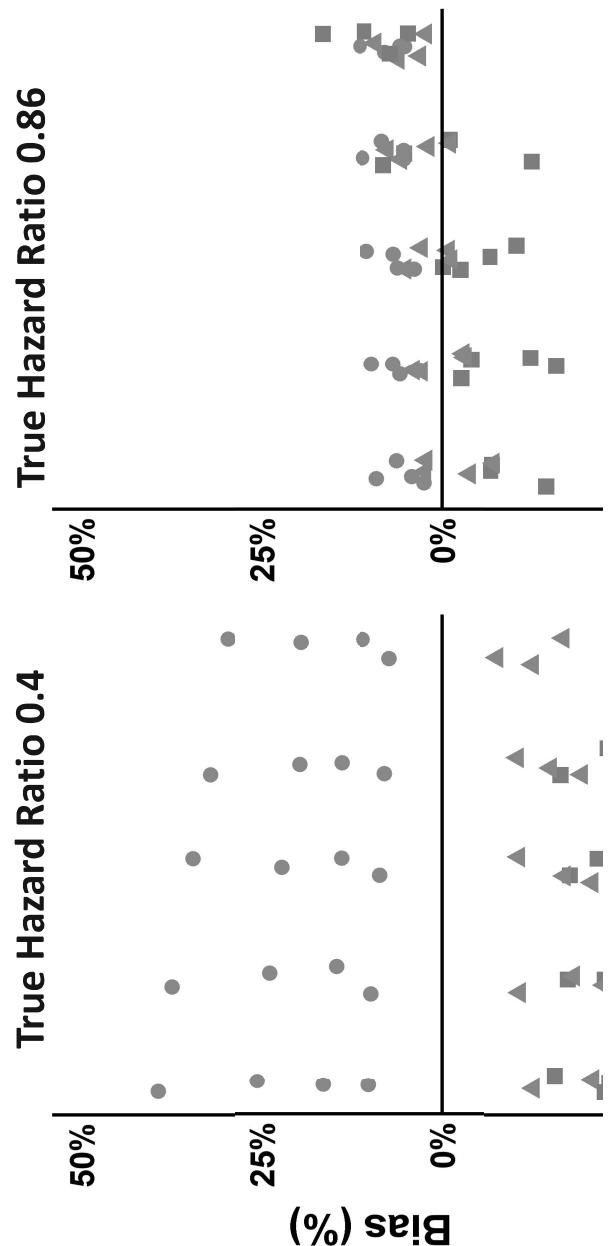
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RPSFT-TG = "treatment group" rank-preserving structural failure time
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Scenarios with reduced effect for switch treatment



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Proposed adjustment methods

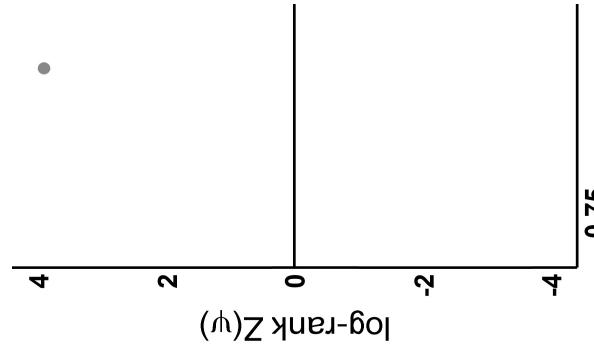
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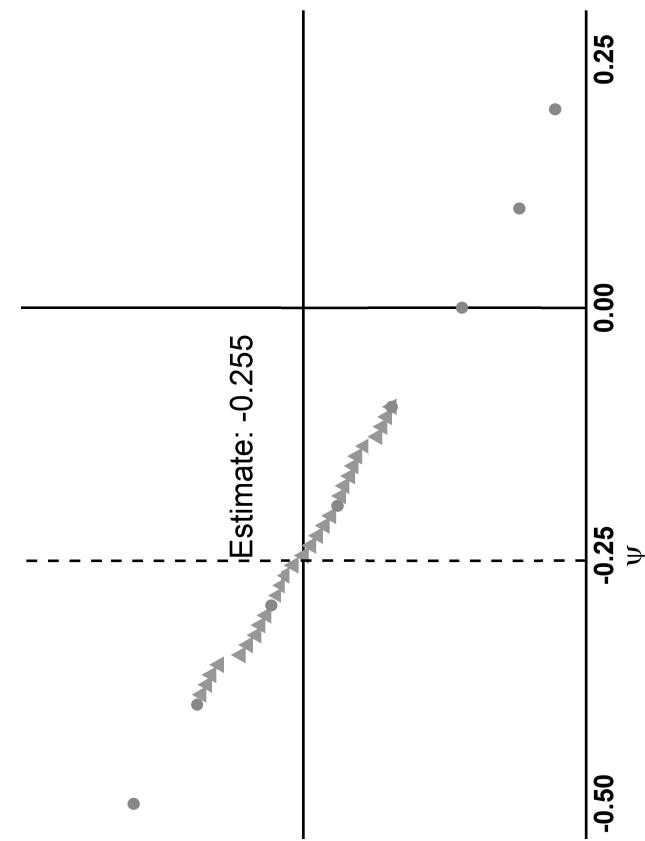
Figure 2: Illustration



Search step (d)
The value of φ when the time between the best estimate of the balanced by random

value of φ where $Z(\varphi) \approx 0$
procedure is shown in Figure 2.

stratification of g-estimation

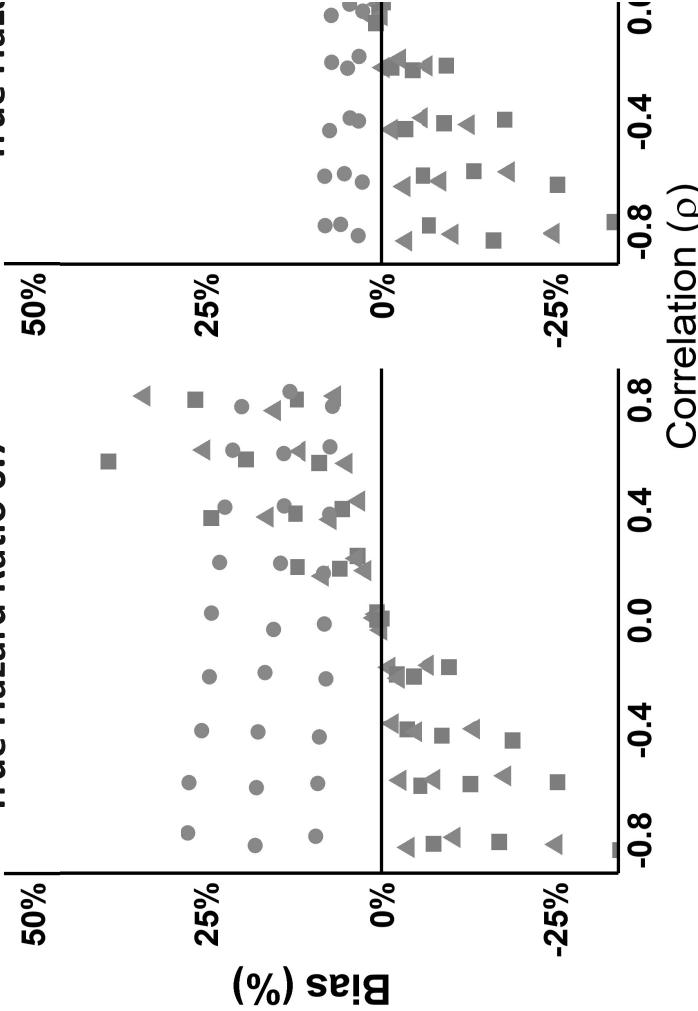


increasing grid size with second pass) • Pass: 1 ▲ Pass: 2
which shows no difference in latent survival
randomized arms (where $Z(\varphi) \approx 0$) is the
true value as this latent survival should be
optimized.

Figure 3: Results for simple method:

Scenarios where treatment effect applied at all

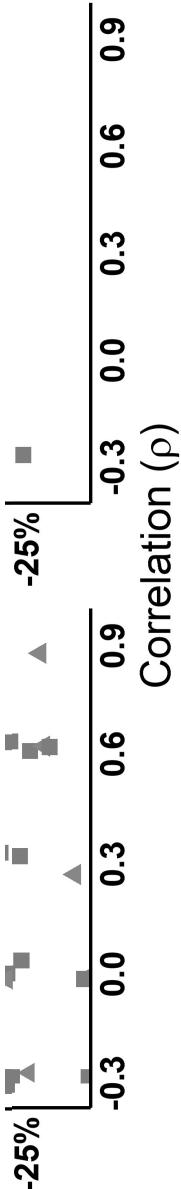
True Hazard Ratio 0.7



• ITT ▲ PP-CENS ■ TVC

ITT = Intent-to-treat analysis
PP-CENS = Censoring at switch
TVC = Treatment as time varying covariate

Treatment
time



RPSFT-TG = "treatment group" rank-preserving structural failure time
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References

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