Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study

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Methods for adjusting for treatment switches in late-stage cancer trials Workshop. 20th February 2012

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Contents

- Project aim
- Design of the simulation study
- Methods considered
- Results
- Conclusions and limitations

Project aim

- To identify methods proposed to adjust for treatment switching in RCTs
- Apply the methods to a real life data from an RCT with treatment switching
- Undertake a simulation study to compare methods across different scenarios

Study design (1)

Data simulated to reflect a two-arm RCT with a known benefit of experimental treatment over control treatment

Patients assumed to have been recruited over a one-year period. All patient censored at 3 years after first patient recruited

Initial survival times generated for all patients from a Weibull distribution with parameters γ=0.5 and λ such that 90% patients dead after 3 years

Study design (2)

All patients assumed to either be good prognosis or poor prognosis. Survival times of those in the good prognosis group inflated by a certain factor

Certain proportion of patients are treatment switchers – poor prognosis patients more likely to switch

Switching time for these patients generated randomly from a uniform distribution between time zero and time of death

Study design (3)

Survival times adjusted depending on the amount of time each patient was on experimental or control treatment.

Each patient's survival time made up of their time on control T_c and time on experimental T_E. Patients in the control arm who don't switch have $T_E = 0$. Patients in the experimental arm all have $T_C = 0$ (only considering one-way switching)

Adjusted survival time $T^* = T_C + e^{\Psi}T_E$

(where e^{Ψ} is the true acceleration factor)

16 Scenarios considered

Variable	Scenarios	Details
Sample size	1	**500** patients, 250 in each arm
Weibull shape parameter γ	1	**0.5**, to represent mortality decreasing over time
Weibull scale parameter λ	1	**1.33**, chosen such that 90% of patients have died after 3 years of follow-up
Prob of patient having a good:poor prog	2	**30%:70%** vs. **75%:25%**
Difference in survival between good and poor prog groups	2	Survival times of good prog group inflated by a factor of **1.2** vs. **3**
Prob of patient switching dependent on prog group	2	**Good = 10%** and **Poor = 25%** vs. **Good = 50%** and **Poor = 75%**
Switching time	1	From a **uniform** distribution
True treatment effect	2	Hazard ratio of **0.9** vs. **0.7** (equivalent to acceleration factors of **1.23** vs. **2.04**)

Methods considered (1)

“Naïve” methods

- **ITT analysis – patients included in randomised group regardless of switching**
- **Exclude patients who switch treatments**
- **Censor patients at the point at which they switch treatments**
- **Consider treatment as a time-varying covariate**

Can be subject to selection bias if patients who switch are not representative of the whole population

Methods considered (2)

Adjusted hazard ratio methods

Causal proportional hazards estimator - Loeys and Goetghebeur[1]

- Assumes “all-or-nothing” compliance, i.e. patients switch at time zero or not at all. Often unlikely to be appropriate in this setting.

- K-M estimates used to adjust HR
- Applied using “*stcomply”* in Stata

Adjusted Cox model - Law and Kaldor[2]

- An extension to the time-varying covariate method
- Patients divided into groups depending on their switching pattern i.e. if two treatment A and B, all patients are AA, BB, AB or BA
- Assumes hazard rates between groups are multiplicative – not true as conditioning on future events, i.e. patients in AB or BA group have a hazard of zero until they switch

Methods considered (3)

Accelerated failure time model methods – give adjusted estimate of acceleration factor (AF)

Rank preserving structural failure time models (RPSFTM) – Robins and Tsiatis[3]

- Applied using *strbee* in Stata
- Considered with log-rank, Cox, Exponential and Weibull tests

Iterative parameter estimation (IPE) algorithm – Branson and Whitehead[4]

- Replaces test based estimation of AF above with an iterative algorithm
- Parametric model fitted – Weibull used here
- Works by adjusting the survival time of switching patients based on the current estimate of AF, introducing issue of recensoring if survival time increased beyond administrative censoring time
- Available as an option on *strbee* in Stata

Methods considered (4)

Parametric randomisation-based methods – Walker et al[5]

- Involves full parametric modelling of the relationship between survival time and treatment received
- Estimating equations approach used – said to be less sensitive to model misspecification
- Applied using *gparmee* in Stata

Methods considered (5)

In total, 12 methods considered:

Method	Estimate produced
Intention to treat (ITT)	HR or AF
Exclude switchers	HR or AF
Censor at switch	HR or AF
Treatment as time-varying covariate	HR
Loeys & Goetghebeur method	HR
Law & Kaldor method	HR
RPSFTM with logrank test	AF
RPSFTM with Cox test	AF
RPSFTM with exponential test	AF
RPSFTM with Weibull test	AF
IPE algorithm	AF
Walker parametric method	AF

Performance measures

For each scenario, 1000 independent datasets generated and all methods applied to each. Performance of each method in that scenario assessed using the following:

1) **Bias:** The difference between the mean adjusted treatment effect across all simulated datasets compared to the true treatment effect for that scenario

2) **% Successful estimation:** The proportion of simulated datasets for which the method gave an estimate of the adjusted treatment effect

3) **Coverage** and **mean square error**

Results

Focus on two particular scenarios of interest. In both cases:

- **30%** patients in good prognosis group, **70%** in poor prognosis group
- True treatment effect is **HR=0.7 (AF = 2.04)**

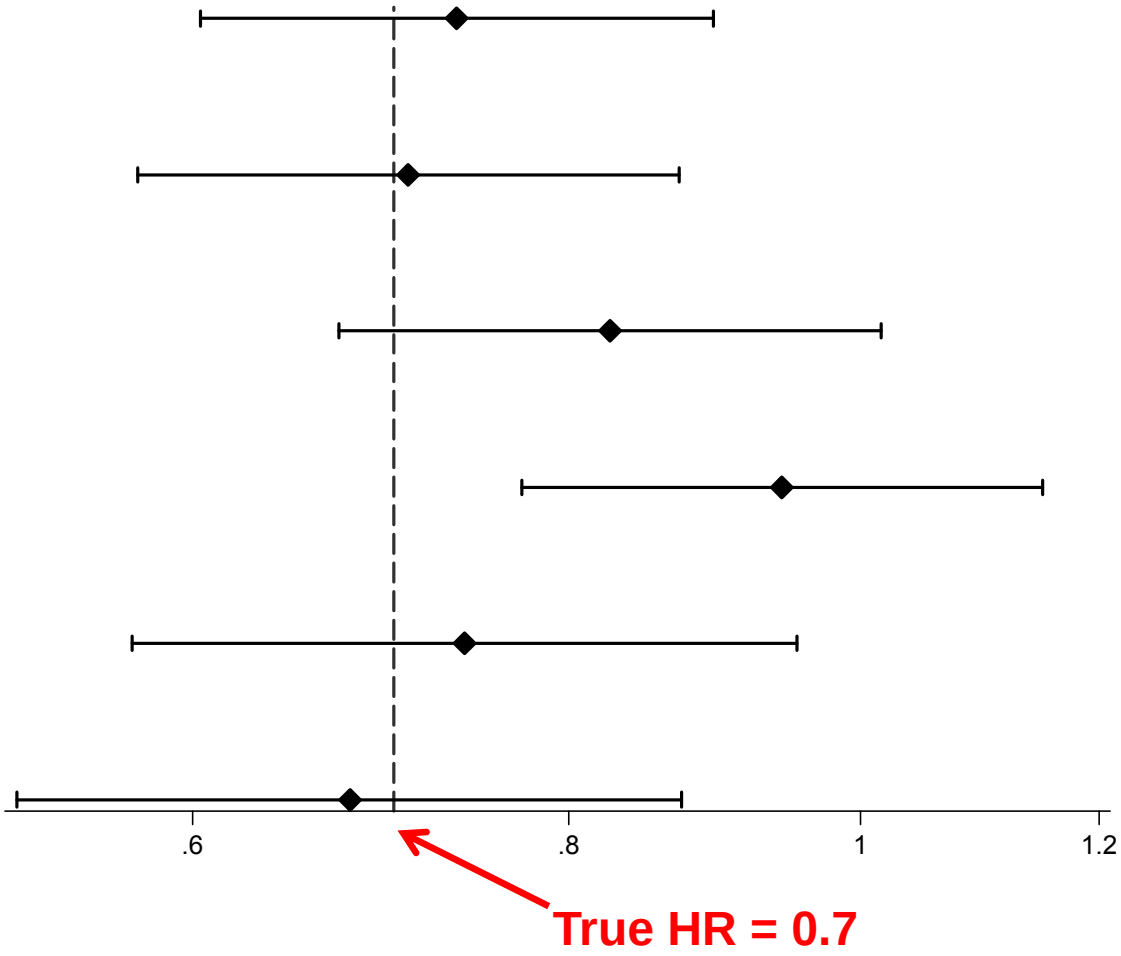
Scenarios differ by the proportion of patients switching:

A) **10%** of good prognosis patients, **25%** of poor prognosis patients.
Survival of good prognosis patients inflated by a factor of **1.2**.

B) **50%** of good prognosis patients, **75%** of poor prognosis patients
Survival of good prognosis patients inflated by a factor of **3**.

Results – Scenario A

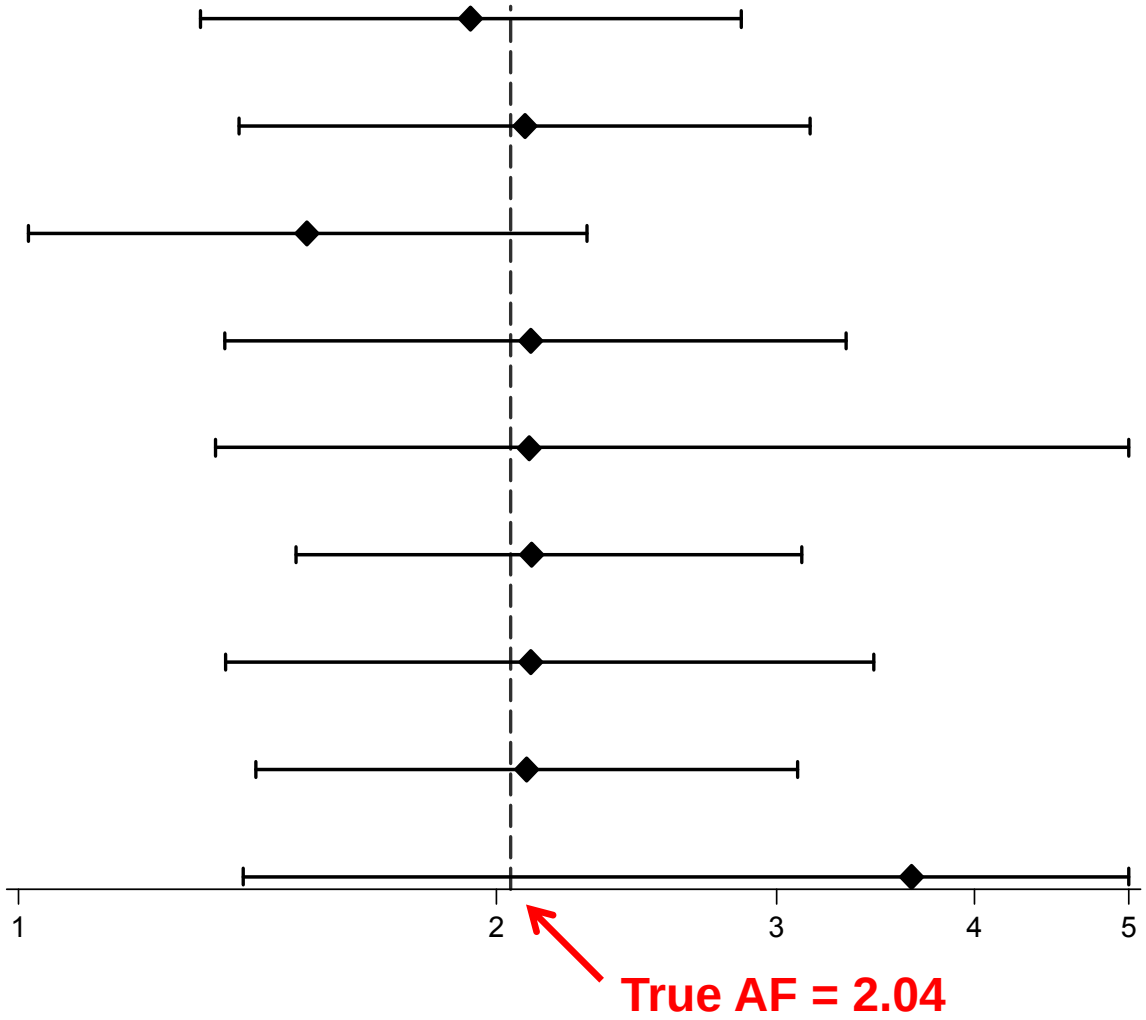
Adjusted hazard ratio methods



	Bias
ITT	0.03
Exclude switchers	0.005
Censor at switch	0.12
Time-varying covariate	0.24
Law & Kaldor	0.04
Loeys & Goetghebeur	-0.03

Results – Scenario A

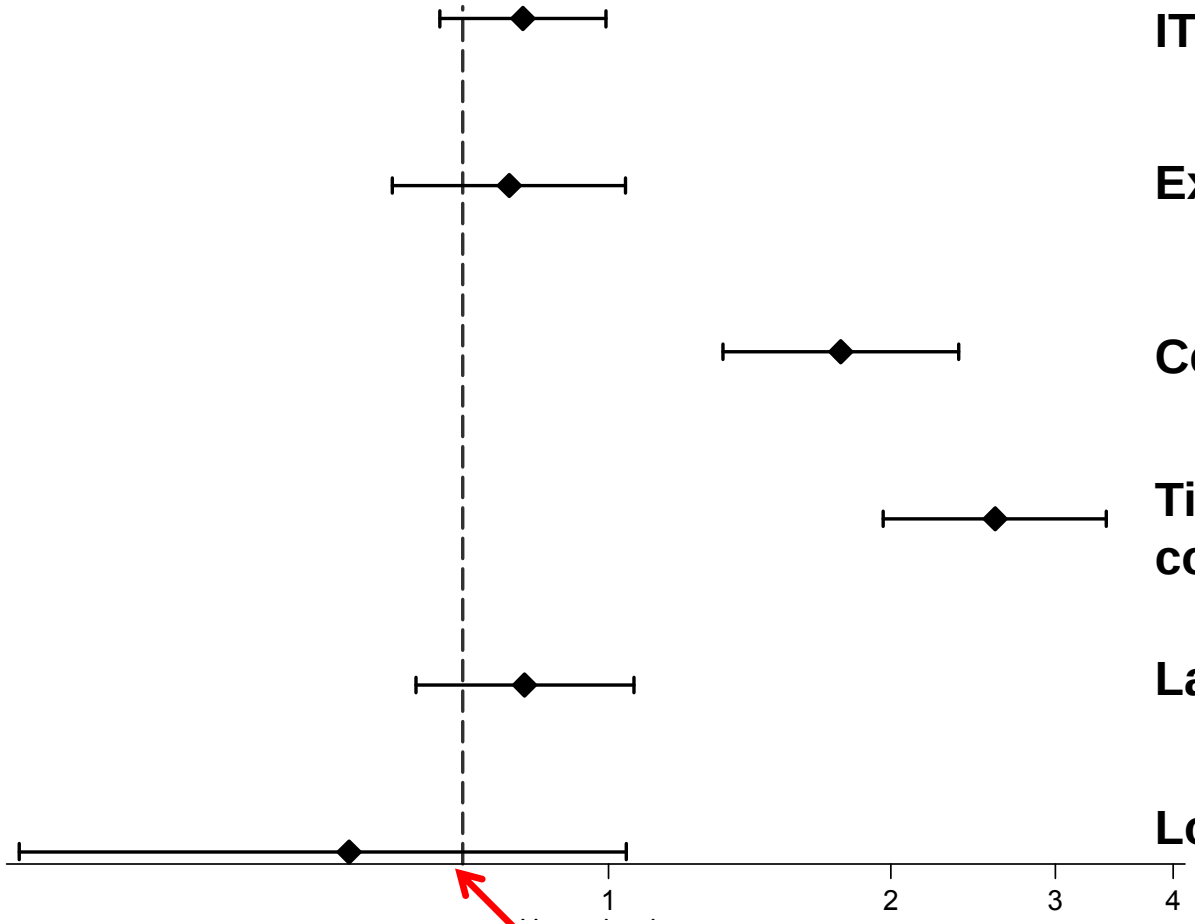
Adjusted acceleration factor methods



	Bias
ITT	-0.12
Exclude switchers	0.04
Censor at switch	-0.52
RPSFTM - Logrank	0.06
RPSFTM - Cox	0.06
RPSFTM - Expo	0.06
RPSFTM - Weibull	0.06
IPE algorithm	0.05
Walker parametric	1.61

Results – Scenario B

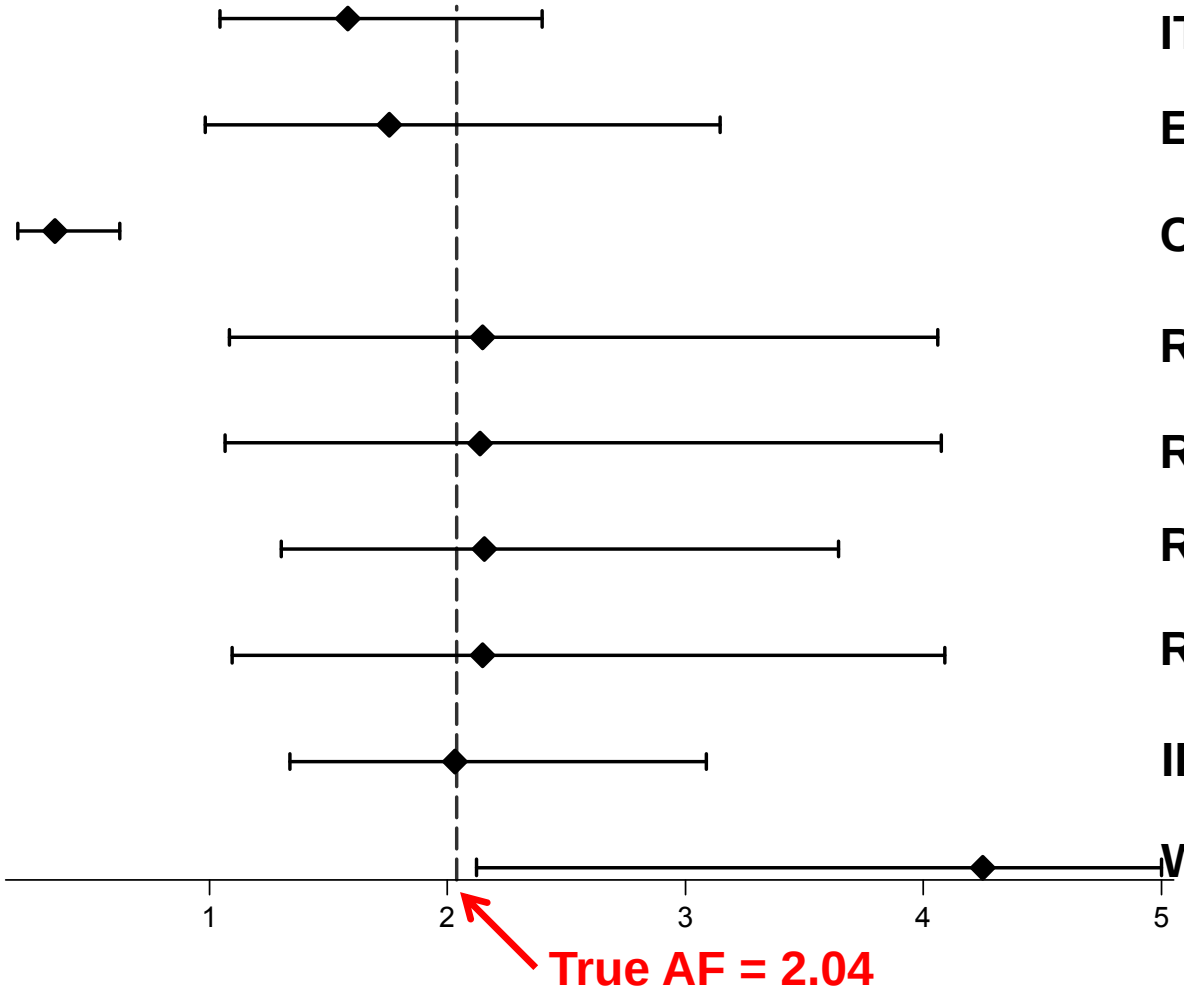
Adjusted hazard ratio methods



	Bias
ITT	0.11
Exclude switchers	0.08
Censor at switch	1.07
Time-varying covariate	1.88
Law & Kaldor	0.11
Loeys & Goetghebeur	-0.17

Results – Scenario B

Adjusted acceleration factor methods



	Bias
ITT	-0.46
Exclude switchers	-0.28
Censor at switch	-1.69
RPSFTM - Logrank	0.11
RPSFTM - Cox	0.10
RPSFTM - Expo	0.11
RPSFTM - Weibull	0.11
IPE algorithm	-0.01
Walker parametric	2.21

% successful estimation

Method	Successful estimation	
	Scenario A	Scenario B
Intention to treat (ITT)	100%	100%
Exclude switchers	100%	100%
Censor at switch	100%	100%
Treatment as time-varying covariate	100%	100%
Law & Kaldor method	100%	100%
Loeys & Goetghebeur method	100%	**96.9%**
RPSFTM with logrank test	100%	100%
RPSFTM with Cox test	**92.2%**	**92.4%**
RPSFTM with exponential test	100%	100%
RPSFTM with Weibull test	100%	100%
IPE algorithm	100%	100%
Walker parametric method	**75.4%**	**88.3%**

Conclusions and limitations (1)

- ITT analysis dilutes treatment effect in the presence of treatment switching
- Naïve methods often inappropriate, particularly when high proportion of switchers or big difference in prognosis between those who do and do not switch
- Censoring at switching time and considering treatment as a time-varying covariate particularly poor
- RPSFTM methods give good estimates of the true treatment effect

Conclusions and limitations (2)

- Consider different scenarios: larger treatment effect, larger difference in prognosis between those who do and do not switch etc.
- Methods assume one treatment effect i.e. its just as effective whether the patient is on it from the start or switches onto it – fair assumption?
- Extensions to trials with switching in both directions
- Adjusting for other patient characteristics

References

[1] Loeys T, Goetghebeur E. “A causal proportional hazards estimator for the effect of treatment actually received in a randomized trial with all-or-nothing compppliance”. *Biometrics 2003, 59:100-105*

[2] Law MG, Kaldor JM. “Survival analyses of randomized clinical trials adjusted for patients who switch treatments”. *Statistics in Medicine 1996, 15:2069-2076*

[3] Robins JM, Tsiatis AA. “Correcting for non-compliance in randomized trials using rank preserving structural failure time models”. *Communications in Statistics-Theory and Methods 1991, 20(8):2609-2631*

[4] Branson M, Whitehead J: “Estimating a treatment effect in survival studies in which patients switch treatments”. *Statistics in Medicine 2002, 21:2449-2463*

[5] Walker AS, White IR, Babiker AG: “Parametric randomization-based methods for correcting for treatment changes in the assessment of the causal effect of treatment.” *Statistics in Medicine 2004, 23(4):571-590*

[6] Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ: “Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study.” *BMC Med Res Methodol. 2011 Jan 11;11:4*