Evaluation of methods that adjust for treatment switching in clinical trials

Richard Fox [a], Lucinda Billingham [a b], Keith Abrams [c]

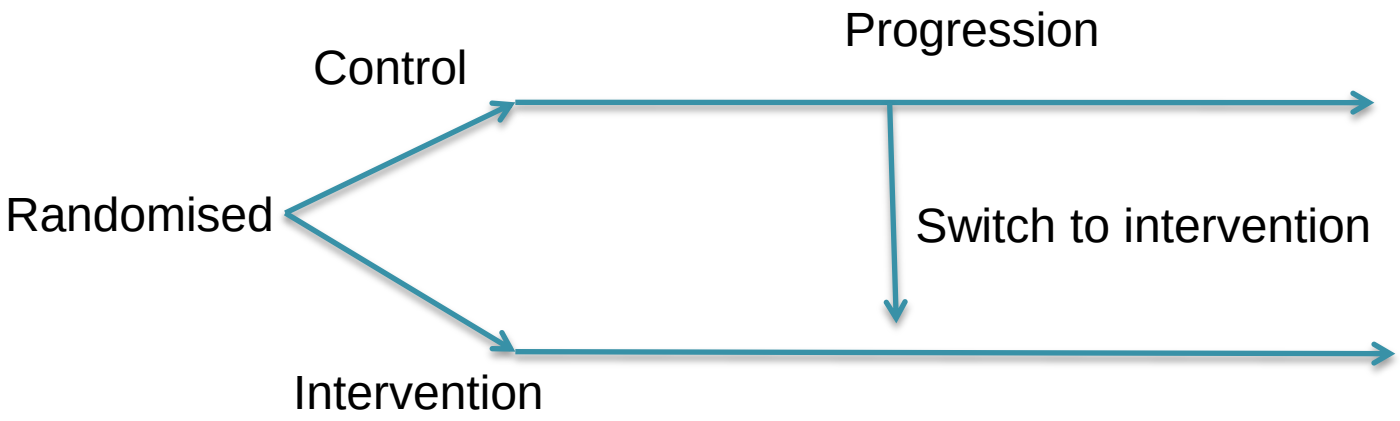
[a] Cancer Research UK Clinical Trials Unit, University of Birmingham, UK
[b] MRC Midland Hub for Trials Methodology Research, University of Birmingham, UK
[c] Centre for Biostatistics and Genetic Epidemiology, University of Leicester, UK

Cancer Research UK Clinical Trials Unit
@CRCTU

UNIVERSITY OF BIRMINGHAM

Introduction

- Patients in RCTs may switch treatments for reasons associated with their illness
- Treatment switching dilutes estimates of treatment efficacy
- From a review of trials featuring treatment switching we observed 84% switching in one trial



- We investigate this scenario (switch control to intervention)

Methods

- 9 methods identified
- Hazard (6) and Time Ratio (3) scales
  - Time ratios
    - Measure of treatment effect
    - Extent survival time is modified by treatment
    - e.g. TR=2 implies survival time doubled on average
- Some methods have numerous test / assumptions

Methods - Hazard Ratio scale

1. Intention to treat (ITT)
2. Per-protocol
   i. Delete patients that switch (PPD)
   ii. or Censor at time of switch (PPC)
3. Time varying covariate (TVC)
4. Adjusted Cox Model (AdjCox) — *Law & Kaldor 1996* [1]
5. Causal PH estimator (CaPH) — *Loeys & Goetghebeur 2003* [2]
6. Inverse Probability Treatment Weighting (IPTW) — *Hernan et al 2000* [3]

Methods - Time Ratio scale

1. Rank preserving structural failure time model (RPSFT)
    i. Multiple tests (*4) — *Robins & Tsiatis 1991* [4]
2. Iterative parameter estimation (IPE) — *Branson & Whitehead 2002* [5]
3. Parametric randomisation based method (PRB) — *Walker et al 2004* [6]

SIMULATING SURVIVAL DATA

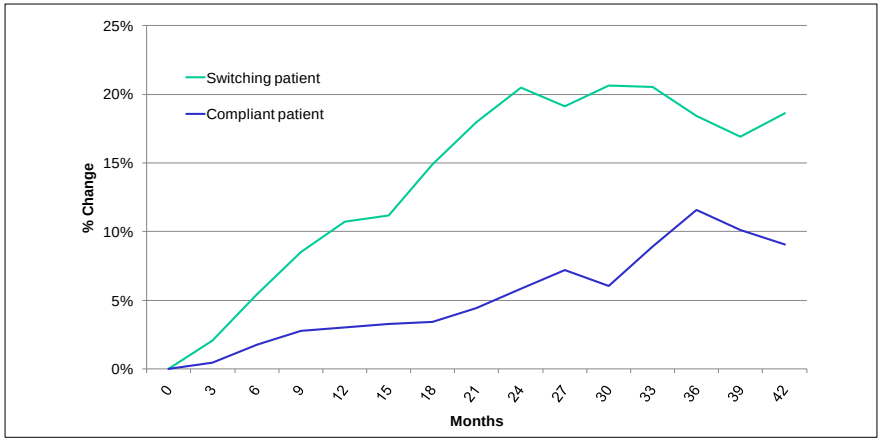
- Survival data has Weibull distribution (λ=1.01, γ=0.5)
  - AFT property: dividing log HR by shape parameter (γ) returns acceleration parameter (TR) [7]

    e.g. $\exp(-\ln(HR)/\gamma) = \exp(-\ln(0.7)/0.5) = 2.04$

- Patients randomised to control or intervention (1:1)
  - Controlled parameters creating 24 scenarios
    - Treatment effect
    - % good vs bad prognosis within arm
    - P(switching | prognosis)
    - Survival / Switching times scaled by prognosis
    - Censoring %
  - Review of NICE technology appraisals informed the above

SWITCHING TRIGGER

- IPTW method requires a time dependent covariate related to treatment switching / compliance
- Designed biomarker level
  - $\Delta \geq 20\%$triggers a switch (from baseline)
  - Beyond switching time level fluctuates around $\Delta = 20\%$level
  - Non-switching patients $\Delta < 20\%$



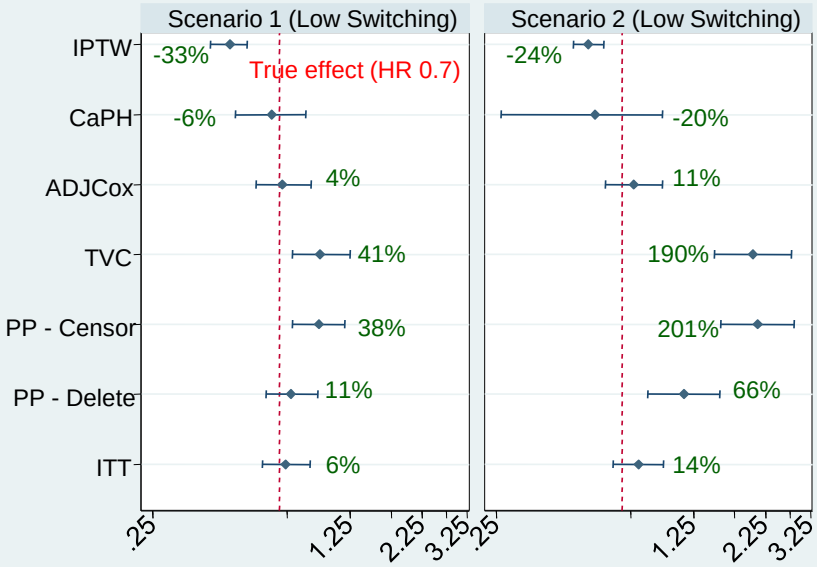
Assessing methods

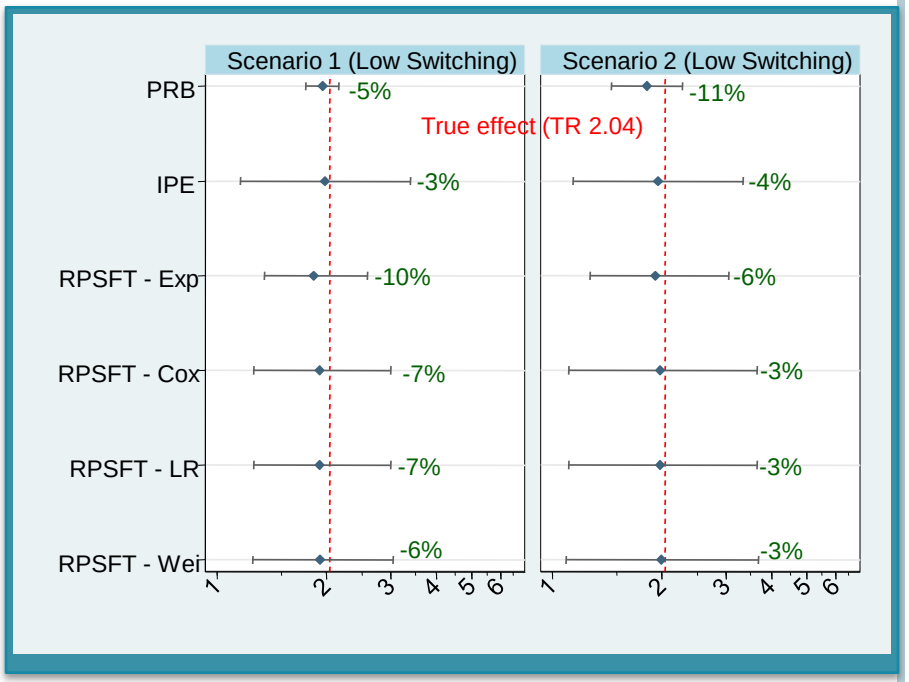
- % Bias $$\frac{(\hat{\beta}_i - \beta)}{\beta} * 100$$
- Standard-error of the effect-size $$SE(\hat{\beta}_i)$$
- Mean Square Error (combines above) $$(\hat{\beta}_i - \beta)^2 + SE(\hat{\beta}_i)^2$$
- Coverage
  - % estimates where 95% CI includes true effect size
- % successful estimates
- Averaged over 1000 simulated datasets for each scenario

Results – Low Bias Scenarios

Scenario (Switching)	% Good prognosis within treatment group	P(switch|prognosis)		Effect size (HR / TR)
		Poor prognosis	Good prognosis	
1 (Low)	75%	0.5	0.25	0.7 /2.04
2 (Low)	50%	0.5	0.25	0.7 /2.04

Hazard Ratio Scale



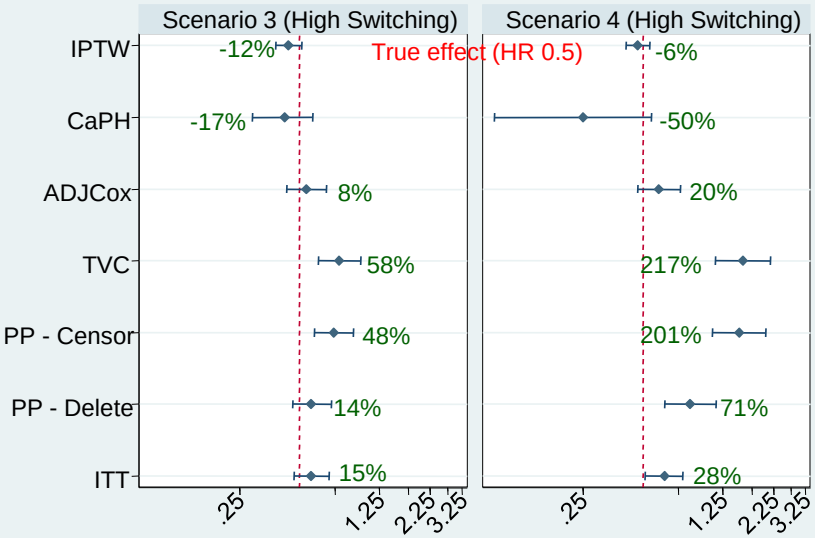


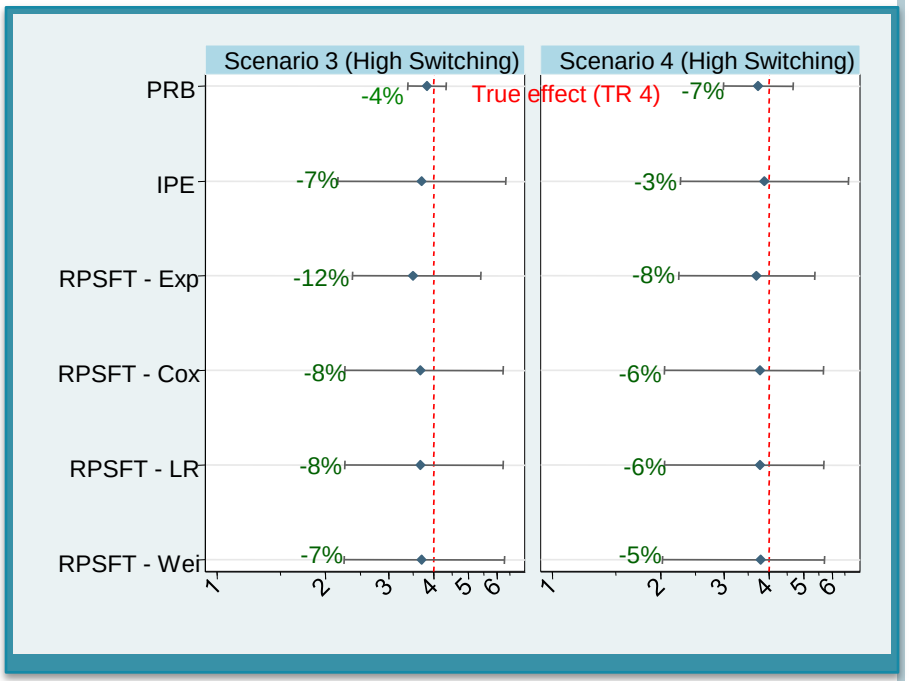
Time Ratio Scale

Results – High Bias Scenarios

Scenario (Switching)	% Good prognosis within treatment group	P(switch|prognosis)		Effect size (HR / TR)
		Poor prognosis	Good prognosis	
3 (High)	50%	0.85	0.25	0.5 / 4
4 (High)	75%	0.85	0.5	0.5 / 4

Hazard Ratio Scale

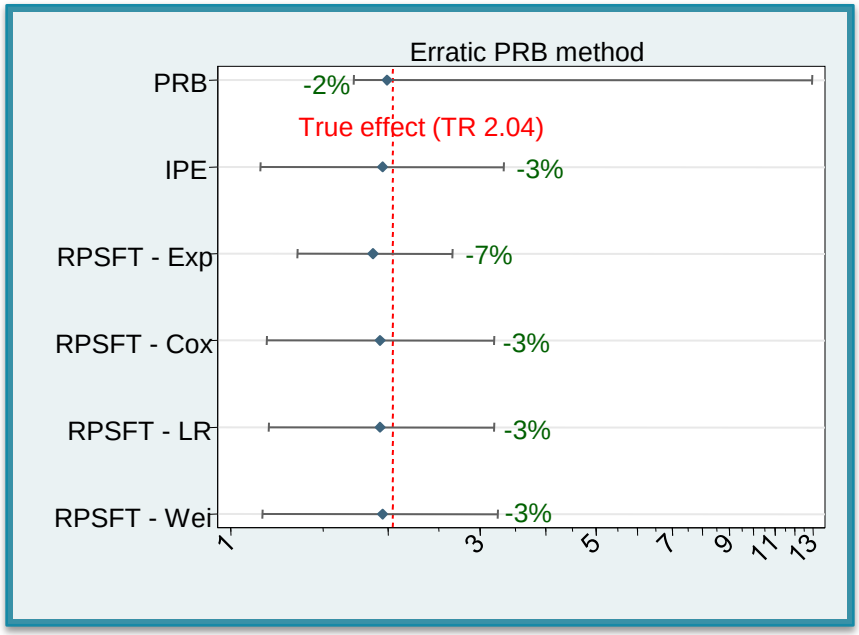




Time Ratio Scale

Results – Erratic Results

- PRB can return erratic results
  - Sensitive to specification of frailty



Scenario	% Good prognosis within treatment group	P(switch|prognosis)		Effect size (HR / TR)
		Poor prognosis	Good prognosis	
Morden[8] - Sc 6	30%	0.75	0.5	0.7 / 2.04

Results – Key Findings

- Switching is common in clinical trials
- ITT results can be heavily biased
- Per-protocol is not appropriate where switching occurs
- Adjustment not routinely applied
  - Some of the methods available (Stata)
- RPSFT and IPE consistent under these conditions
  - IPE has 100% successful estimation
  - IPE also returns estimates of the Weibull parameters
  - Results robust to additional censoring

Conclusion

We recommend that the IPE method of Branson & Whitehead be utilised in the analysis of clinical trials that feature treatment switching.

Available from Ian White's software page:

http://www.mrc-bsu.cam.ac.uk/Software/stata.html#Software_IW

My email:

foxrp@bham.ac.uk

Extensions

- Simulate alternative survival distributions
- Additional covariates
- Multiple switching directions
- Dependent censoring
- Other methods
  - Meta / Bayes analysis
  - Structural nested mean models
- Statistical analysis plan – sensitivity

References

1. Law and J Kaldor. Survival analyses of randomised clinical trials adjusted for patients who switch treatment. *Stat Med, 15:2069-2076, 1996.*
2. T Loeys and E Goetghebeur. A causal proportional hazards estimator for the effect of treatment actually received in a randomised trial with all-or-nothing compliance. *Biometrics, 59(1):100-105, 2003.*
3. M Hernan, B Brumback, and J Robins. Marginal structural models to estimate the causal effect of zidovudine on the survival of hiv-positive men. *Epidemiology, 11(5):561-570, September 2000.*
4. J Robins and A Tsiatis. Correcting for non-compliance in randomised trials using rank preserving structural failure time models. *Communication in Statistics-Theory and Methods, 20(8):2609-2631, 1991.*
5. M Branson and J Whitehead. Estimating a treatment effect in survival studies in which patients switch treatment. *Stat Med, 21:2449-2463, 2002.*
6. S Walker, I White, and A Babiker. Parametric randomization-based methods for correcting for treatment changes in the assessment of the causal effect of treatment. *Stat Med, 23:571-590, 2004.*
7. Collett, D. (2003), *Modelling Survival Data in Medical Research* (2nd ed.)
8. J Morden et al. Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. *BMC Med Res Methodol. 2011 Jan 11;11:4.*