MSR9

# Adjusting For Switches to Multiple Treatments in Randomised Controlled Trials (RCTs): A Comparison of Inverse Probability Weighting (IPCW) and Two-Stage Estimation (TSE) Methods

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**Background:** Treatment switching describes the situation where patients in a randomised control trial (RCT) diverge from the treatment pathway that they were randomised to receive.[1-4] It causes difficulty in assessing the effectiveness and cost effectiveness of treatments. Statistical methods can be applied to adjust for treatment switching. Previous studies have focused on switches between randomised treatments (typically switches from the control group onto the experimental treatment), but in practice patients may switch onto a variety of different treatments.[4] This simulation study assesses the performance of inverse probability of censoring weights (IPCW) and Two-stage estimation (TSE) applied to scenarios where patients in the control group could switch to multiple subsequent treatments.[4-6] The adjustment methods can be applied by (i) combining together all switches and making one adjustment or (ii) adjusting for switches to each treatment separately.

## Methods:

**Simulation study**

- Design based on Latimer et al (2020)[6]
- RCT with 1:1 randomisation.
- Switching permitted in the control group
- Switchers can switch to one of 2 treatments in Scenarios 1-16, and one of 5 treatments in 17-20

**Data generating mechanism (DGM)**

1. **Underlying survival times** –
   - Generated using survsim[7]
   - Binary prognosis variable created.
   - Divided into time periods of 21 days.

**2. Time to disease progression** – Overall survival time multiplied by random number with beta distribution, scale 5 and shape 10.

**3. Time dependent confounding -** Metastatic event variable *M* was created. *M* depended on treatment received and baseline prognosis, and reduced survival times

**4. Switching mechanism (i) -** Switch was permitted after disease progression, with a maximum of one switch per patient

**5. Switching mechanism (ii) -** Switchers were allocated to receive a subsequent treatment based on baseline prognosis

**6. Effect of switching -** Impacted occurrence of post-switch metastatic event. Influenced survival times through treatment effect and metastatic event

**7. Censoring times**

Censoring was applied at 730 days for scenarios 1-20. Additional simulation scenarios were run with censoring at 500 and 300 days.

**Table 1: Simulation Scenario Parameters**

| Scenario | Sample size | Number of treatments available to switch onto | Proportion of control group patients that switch | Proportion of switchers that switch to treatment 1 | Treatment effects |
|---|---|---|---|---|---|
| 1 | 500 | 2 | 20% | 80% | T1 1.5; T2 1.2 |
| 2 | | | | | T1 1.2; T2 1.7 |
| 3 | | | | 60% | T1 1.5; T2 1.2 |
| 4 | | | | | T1 1.2; T2 1.7 |
| 5 | | | 50% | 80% | T1 1.5; T2 1.2 |
| 6 | | | | | T1 1.2; T2 1.7 |
| 7 | | | | 60% | T1 1.5; T2 1.2 |
| 8 | | | | | T1 1.2; T2 1.7 |
| 9 | 1000 | | 20% | 80% | T1 1.5; T2 1.2 |
| 10 | | | | | T1 1.2; T2 1.7 |
| 11 | | | | 60% | T1 1.5; T2 1.2 |
| 12 | | | | | T1 1.2; T2 1.7 |
| 13 | | | 50% | 80% | T1 1.5; T2 1.2 |
| 14 | | | | | T1 1.2; T2 1.7 |
| 15 | | | | 60% | T1 1.5; T2 1.2 |
| 16 | | | | | T1 1.2; T2 1.7 |
| 17 | 500 | 5 | 20% | 10%* | T1 1.2, T2 1.3, T3 1.4, T4 1.6, T5 1.8 |
| 18 | | | 50% | | T1 1.2, T2 1.3, T3 1.4, T4 1.6, T5 1.8 |
| 19 | 1000 | | 20% | | T1 1.2, T2 1.3, T3 1.4, T4 1.6, T5 1.8 |
| 20 | | | 50% | | T1 1.2, T2 1.3, T3 1.4, T4 1.6, T5 1.8 |

Footnotes: * In the scenarios with 5 treatments, 10% of switchers switched to treatment 2, 20% of switchers switched to treatment 3 and 25% of switchers switched to treatment 4. Treatment effects represent the time ratio treatment effects for treatment 1 (T1) and Treatment 2 (T2). Scenarios 1-20 were censored at 730 days, scenarios 1-16 were repeated with censoring at 500 days and scenarios 9-16 were repeated with censoring at 300 days.

**Estimand** Restricted mean survival time (RMST) in the control group, in the absence of treatment switching

**Treatment switching adjustment methods**

**IPCW – treatments combined (IPCW1)**
- Censored at time of switch
- Switching weights estimated using binary logistic model
- Weights applied in outcome model

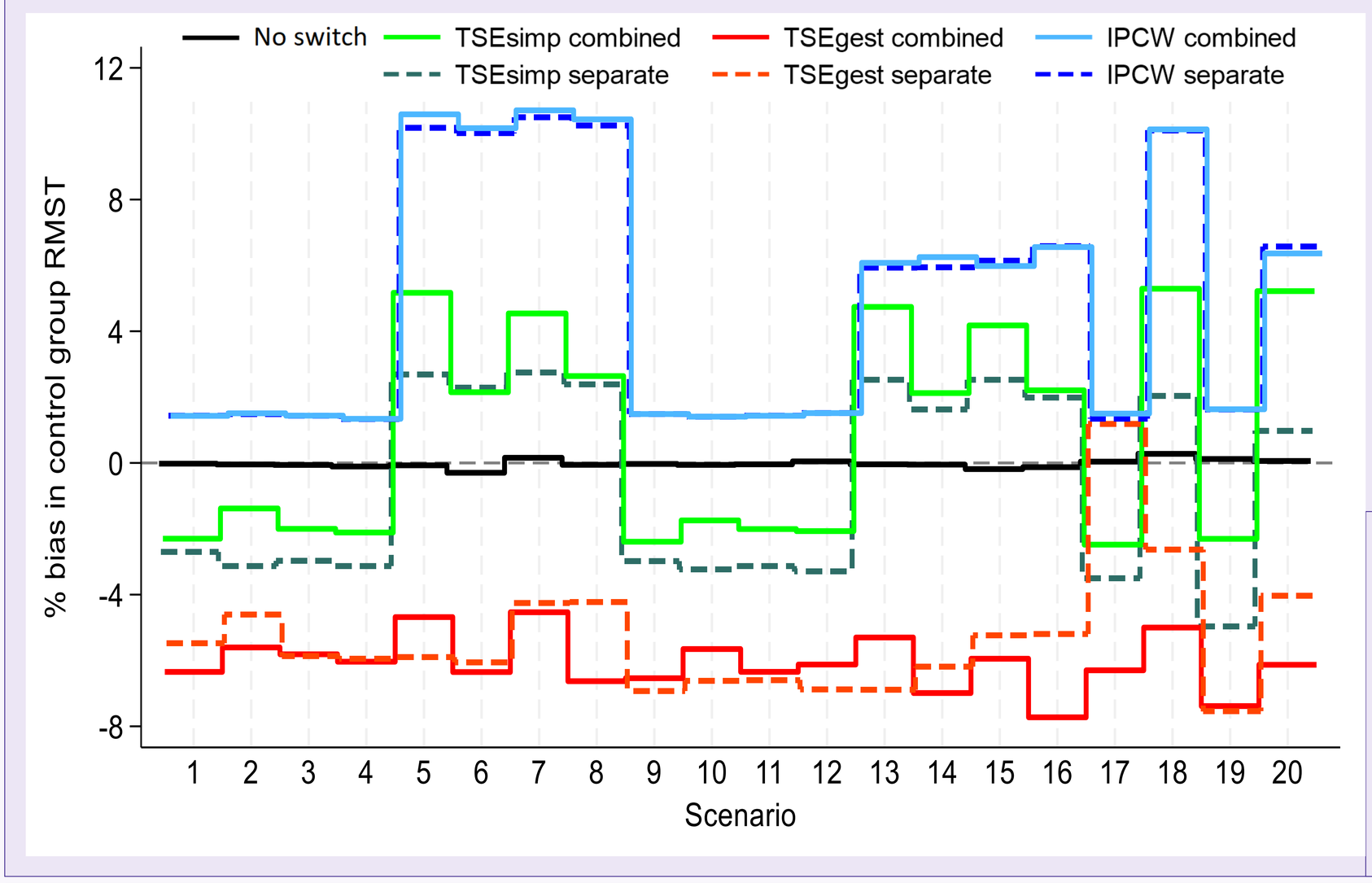
**IPCW – treatments separate (IPCW2)**
- Censored at time of switch
- Switching weights estimated using multinomial logistic model
- Weights applied in outcome model

**TSE – treatments combined (TSE1)**
- Calculated combined post-progression treatment effect (TE) for all switchers vs no-switchers in control group
- Use TE to adjust the survival time data
- Apply outcome model to adjusted data

**TSE – treatments separate (TSE2)**
- Calculated separate post-progression TEs for each type of switcher vs no-switchers in control group
- Use TE to adjust the survival time data
- Apply outcome model to adjusted data

**TSE applied using standard regression (TSEsimp) and using g-estimation (TSEgest) (**see Latimer et al (2020) for further details on these methods)[4,6]

**Figure 1: Percentage bias in control group RMST**




## Results:

- There was little difference between applications of adjustment methods that combined switchers or dealt with switchers to different treatments separately.
- IPCW performed well in scenarios with low proportions of switching, but produced high bias in scenarios with higher proportions of switching.
- TSEsimp produced negative bias when switching proportions were low and positive bias when switching proportions were high. TSEsimp combined was more sensitive to changes in treatment effect than TSEsimp separate.
- TSEsimp separate performs better than TSEsimp combined with higher proportions of switchers.
- TSEgest was less sensitive to changes in the proportion of switchers than TSEsimp. TSEgest separate produced higher standard errors in scenarios with 5 treatments.

## Conclusions:

- IPCW, TSEsimp and TSEgest are all capable of adjusting for treatment switching to multiple treatments.
- There is no clear advantage associated with using applications of treatment switching adjustment methods that distinguish between switches to different treatments, over applications which combine switchers.
- Applications that dealt with switches to different treatments separately were prone to higher standard errors and convergence issues.

**References:** 1. Latimer, N.R., et al., Adjusting survival time estimates to account for treatment switching in randomized controlled trials—an economic evaluation context: methods, limitations, and recommendations. Medical Decision Making, 2014. 34(3): p. 387-402. 2. Latimer, N.R. and K.R. Abrams, NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment switching. Report by the Decision Support Unit, 2014. 3. Bell Gorrod, H., N.R. Latimer, and K.R. Abrams, NICE DSU Technical Support Document 24 Adjusting survival time estimates in the presence of treatment switching: An update. Report by the Decision Support Unit, forthcoming. 4. Latimer, N.R., et al., Adjusting for treatment switching in randomised controlled trials–a simulation study and a simplified two-stage method. Statistical methods in medical research, 2017. 26(2): p. 724-751. 5. Robins, J.M. and D.M. Finkelstein, Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics, 2000. 56(3): p. 779-788. 6. Latimer, N., I. White, K. Tilling, and U. Siebert, Improved two-stage estimation to adjust for treatment switching in randomised trials: g-estimation to address time-dependent confounding. Statistical methods in medical research, 2020. **29**(10): p. 2900-2918. 7. Crowther, M.J. and P.C. Lambert, *Simulating complex survival data.* The Stata Journal, 2012. **12**(4): p. 674-687. **Acknowledgment:** This research is funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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