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.

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.
• TSEest was less sensitive to changes in the proportion of switchers than TSEsimp. TSEest separate produced higher standard errors in scenarios with 5 treatments.

Conclusions:
• IPCW, TSEsimp and TSEest 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.


Table 1: Simulation Scenario Parameters

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Sample size</th>
<th>Number of treatments available to switch only</th>
<th>Proportion of control group patients that switch</th>
<th>Proportion of switchers that switch to treatment 1</th>
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<tr>
<td>1</td>
<td>500</td>
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<td>80%</td>
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<tr>
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<td>80%</td>
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<td>4</td>
<td>1000</td>
<td>5</td>
<td>50%</td>
<td>10%*</td>
</tr>
</tbody>
</table>

Note*: in the scenarios with 5 treatments, 10% of switchers switched to treatment 2, 20% of switchers switched to control treatment 1 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.

Figure 1: Percentage bias in control group RMST

Figure 2: Estimated standard mean time (RMST) in the control group, in the absence of treatment switching

Figure 3: 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.
• Weights applied in outcome model

TSE – treatments combined (TSE1)
• Calculated separate 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].