Evaluating bias associated with inadequate variable selection when using inverse probability of censoring weights to adjust for treatment switches in clinical trials

Jingyi Xuan[1], Shahrul Mt-Isa[2], Nicholas R Latimer[3], Victoria Yorke-Edwards[1], Kristel Vandormael[4], William Malbecq[5*], Ian R White[1]

[1]MRC Clinical Trials Unit, University College London, London, UK, [2]BARDS HTA Statistics, MSD, Zurich, Switzerland, [3]Sheffield centre for Health and related Research, School of Medicine and Population Health, University of Sheffield, Sheffield, UK, [4]BARDS HTA Statistics, MSD, Brussels, Belgium, [5]Department of Mathematics, University of Brussels, *Previous employee of MSD Brussels

Introduction

Participants switch between randomised treatments, or onto other treatments is common in clinical trials. When treatment switches do not represent treatment pathways that would be observed in clinical practice, adjustment analyses may be used to estimate counterfactual outcomes to inform healthcare decision making.

Inverse probability of censoring weights (IPCW) is a common method used to correct for the selection bias induced by per-protocol (PP) analysis by giving extra weight to uncensored individuals who had similar prognostic characteristics to censored individuals. Such weights are computed by modelling selected covariates. IPCW relies on the no unmeasured confounding (NUC) assumption, and selecting variables can be challenging.

In this study, we aim to explore the behaviour of IPCW under conditions where too few, too many, and mis-specified covariates are included in the weighting models.

Methods

We performed a **simulation study** in realistic trial settings.

- **Data-generating mechanism (DGM):** Models for time-varying covariates (TVCs), treatment switching and outcome were designed to generate data. Scenarios were designed to vary treatment switching and outcome mechanism, correlation between two confounders, and sample size. Figure 1 (right part) describes the scenarios explored.
- **Estimand**: The risk difference between randomised groups at week 96.
- **Analysis methods**: Intention to treat (ITT), PP and potential IPCW implementations with different TVCs selected (Table 1).

  We follow these steps to implement IPCW:

  1. Censor at treatment switching
  2. With identified TVCs, we model:

  $$logit\ P(C_{iv} = 1 \mid C_{i(v-1)} = 0, \boldsymbol{K_{iv}}) = \boldsymbol{\zeta K_{iv}} + \iota f(v),$$

  where C_{iv} denotes censoring and $\boldsymbol{K_{iv}}$ is the set of measurements of identified TVCs for participant i at visit v.

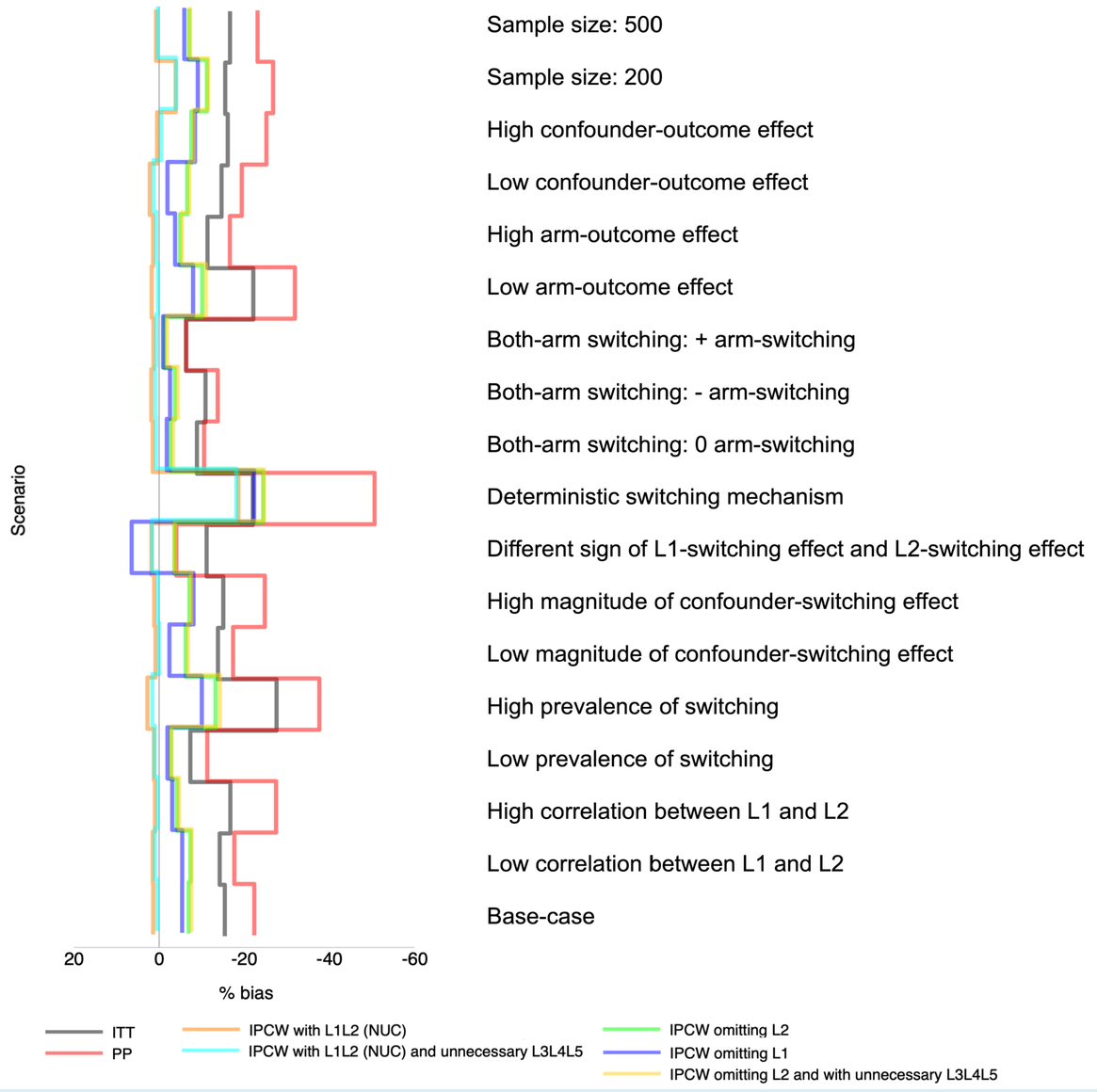
  3. Compute the inverse probability weight (IPW).
  4. Finally we perform the outcome model with the calculated IPW.

Table 1: IPCW implementations explored.

Implementation situations	Methods explored
Correct	**IPCW with L1L2 (NUC)**
Too few TVCs	**IPCW omitting L1** **IPCW omitting L2**
Mis-specified TVCs	IPCW omitting L2 and with unnecessary L3 IPCW omitting L2 and with unnecessary L4 IPCW omitting L2 and with unnecessary L5 **IPCW omitting L2 and with unnecessary L3L4L5**
Too many TVCs	IPCW with L1L2 (NUC) and unnecessary L3 IPCW with L1L2 (NUC) and unnecessary L4 **IPCW with L1L2 (NUC) and unnecessary L3L4L5**

Note: L1 and L2 are time-varying confounders that are associated with both the treatment switching and the counterfactual outcome; L3 is an outcome risk factor that does not predict treatment switching; L4 and L5 are treatment switching factor that do not predict counterfactual outcome. Performance of methods in bold are shown in Figure 1.

Figure 1: % bias from methods in Scenario 1-18.



Results

- IPCW provided unbiased estimates when NUC and positivity assumptions were satisfied. (—— in scenarios except 9&17)
- IPCW with too many covariates but satisfied NUC performed well considering both bias and standard errors. (——)
- IPCW with too few or mis-specified confounders gave biased estimates. (——)
- All (even suboptimal) IPCW implementations outperforms PP in most scenarios except for the less usual case where selection bias caused by two confounders is in different direction and cancels out.

Conclusions

- Including variables in weighting models that are not confounders is sub-optimal but is preferable to excluding confounding variables.
  → It is important to ensure complete data collection on all potential confounders for IPCW.
- In the presence of treatment switching, IPCW is a safer choice than PP to estimate the effect of receiving the treatment as assigned.
  → When important confounders are collected in a clinical trial, use IPCW as an analysis method instead of PP.

References

1. Hernan MA and Robins JM. Per-Protocol Analyses of Pragmatic Trials. The New England Journal of Medicine 2017; 377(14): 1391–1398.
2. Cole SR and Hernan MA. Constructing Inverse Probability Weights for Marginal Structural Models. American Journal of Epidemiology 2008; 168(6): 656–664.
3. Howe CJ, Cole SR, Chmiel JS et al. Limitation of Inverse Probability-of-Censoring Weights in Estimating Survival in the Presence of Strong Selection Bias. American Journal of Epidemiology 2011; 173(5): 569577.
4. Turkova A, White E, Mujuru HA et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. The New England Journal of Medicine 2021; 385(27): 2531–2543.

Acknowledgement

- This research is funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
- We thank ODYSSEY trial team for their help.

Smarter Studies
Global Impact
Better Health