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The TSEipcw Method as an Alternative Solution to the Problem of Treatment Switching

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Introduction

Statistical adjustment of overall survival (OS) times for treatment switching is a common health technology assessment requirement. In randomised clinical trials, control-arm patients may switch to active treatment during follow-up, e.g. following disease progression.

The two-stage estimation (TSE) method predicts counterfactual survival times for patients who switch treatments (i.e. to estimate survival had no switching occurred). However, this can induce informative censoring because the counterfactual survival model only adjusts survival times for non-switchers. Re-censoring adresses this but can significantly reduce long-term information, which can be problematic. NICE DSU TSD 16[1] recommends presenting analyses both with and without re-censoring.

The inverse probability of censoring weights (IPCW) method aims to address informative censoring by weighting uncensored patients using baseline and time-dependent covariates[2].

TSE combined with IPCW (TSEipcw), has been proposed [3] to address the issues associated with re-censoring.

Assumptions of IPCW

IPCW requires that the 'no unmeasured confounders' assumption is approximately true. This means that censoring must be independent of the outcome (i.e switching). Further, to be unbiased, data must have been collected up to the point of switch for switchers and over the whole trial period for non-switchers[4].

Assumptions of TSE

The estimation of the treatment effect using the TSE method should be accurate providing the following holds; the accelerated failure time (AFT) model used fits the data well, there are 'no unmeasured confounders' at the point of the secondary baseline and switching occurs soon after the secondary baseline[5].

The TSEipcw Method

Stages one and two of the TSE method are used to create a counterfactual survival dataset. Then, a model predicting the probability of remaining uncensored is fitted to obtain patient weights which can be used in weighted survival models[3].

We used both SAS[6] and R[7] for a sensitivity analysis investigating this method, making best use of the functionalities of the respective programs.

1. The TSE method was conducted by modelling the time from progression to death dependent on switching via AFT models, using 'PROC LIFEREG' in SAS. The following parametric models were explored: exponential, gamma, generalised gamma, gompertz, log-logistic, log-normal and Weibull. Using the model with the lowest AIC an acceleration factor (AF) was obtained.

2. The shrinkage factor (1/AF) was used to adjust the survival times to provide counterfactual survival times (without re-censoring). Then, counterfactual start and stop times were calculated for each patient period. A period was defined on a patient level basis where all the time-varying covariates remained the same. When a time-varying covariate changed, a new period (row) was assigned with start and stop times.

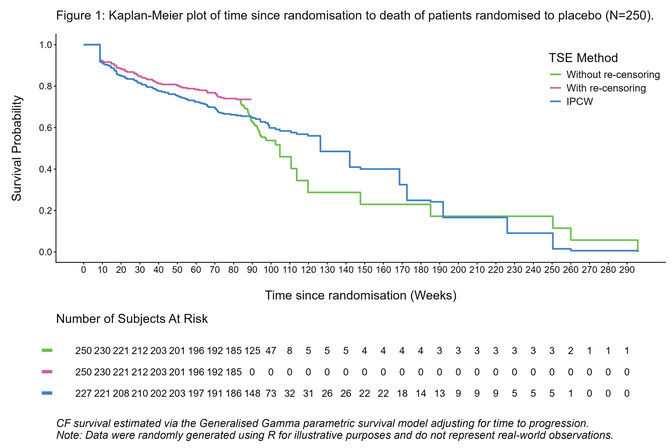
3. Stabilised IPCW were estimated as the ratio of two time-varying Cox regression models, making use of the coxph() function from the 'survival' package in R[8]. Each model predicted the probability of remaining uncensored at the end of each period. The numerator of the stabilised weight calculation adjusted for baseline covariates. The denominator adjusted for baseline covariates, treatment history and time-varying covariates.

4. The calculated patient-time weights were then used in the estimation of parametric survival extrapolations of counterfactual OS data. This process was completed using the 'flexsurv' package in R[9].

Results

The TSEipcw counterfactual OS times resided between the 'with' and 'without' re-censoring counterfactual times, whilst also preserving long term-data. This enabled more reliable estimates of the long-term survival benefit of the treatment. Figure one has been created, using randomly generated data, to depict this.

Figure 1: Kaplan-Meier plot of time since randomisation to death of patients randomised to placebo (N=250).



CF survival estimated via the Generalised Gamma parametric survival model adjusting for time to progression.
Note: Data were randomly generated using R for illustrative purposes and do not represent real-world observations.

Conclusion

No single treatment-switching method will be optimal in all circumstances. Considerations should therefore be made as to which methods are most appropriate given the study design and data availability. There were clear limitations with the typical treatment-switching adjustment methods in this long-term survival analysis. The TSEipcw method is a useful alternative when estimating counterfactual survival times in the presence of treatment switching.

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