METHODS FOR ESTIMATING SURVIVAL BENEFITS IN THE PRESENCE OF TREATMENT CROSSOVER: A SIMULATION STUDY

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Objectives

Treatment crossover occurs when patients randomised to the control group of a clinical trial are permitted to switch onto the experimental treatment at some point during follow-up. It is common in oncology trials for a number of reasons, both practical and ethical, and can cause problems in estimating the true size of the efficacy gain provided by the experimental treatment. An intention to treat (ITT) analysis is likely to provide an underestimate of the "true" survival benefit associated with the new treatment – that is, the benefit that would have been observed had treatment crossover not been allowed.

Simple methods for adjusting for crossover, such as excluding or censoring crossover patients from the analysis, are highly prone to selection bias. More complex methods have been described in the literature, but a full comparison of these across a range of scenarios has not previously been undertaken.

We aimed to assess statistical methods for adjusting survival estimates in the presence of treatment crossover in order to identify which are the most appropriate in a range of scenarios.

Methods

We conducted a simulation study to assess the performance of crossover-adjustment methods in a range of scenarios. We purposefully ran scenarios that did not satisfy the specific assumptions made by the methods, in order to assess their sensitivities. A simulation study was required in order that the "truth" was known. We varied the treatment effect, crossover proportion, disease severity, time-dependency of the treatment effect and the crossover mechanism across 72 scenarios. The crossover adjustment methods assessed are listed in Table 1.

"Naive" methods were included alongside complex methods in order to understand their relative bias. The RPSFTM and IPE algorithm are randomisation-based methods, and are reliant on a "common treatment effect" assumption – that is, it is assumed that the relative treatment effect received by crossover patients is the same as that received by patients originally randomised to the experimental group. IPCW and SNM methods are observational-based and are reliant upon a "no unmeasured confounders" assumption – that is data must be available on any prognostic covariates.

Table 1: Methods included in simulation study

Naive Methods
Intention to treat analysis
Per protocol analyses (censor or exclude switchers)
Treatment as a time-dependent covariate
Complex Methods
Rank Preserving Structural Failure Time Model (RPSFTM)
Iterative Parameter Estimation (IPE) algorithm
Inverse Probability of Censoring Weights (IPCW)
Structural Nested Model (SNM) with g-estimation
Other Methods
Two-stage Weibull

Results

RPSFTM and IPE methods were unbiased only when the treatment effect was not time-dependent. Observational-based methods (IPCW and SNM with g-estimation) coped better with time-dependent treatment effects but are heavily data reliant, are sensitive to model misspecification and often produced high levels of bias in our simulations. Observational-based methods are particularly sensitive to the proportion of control group patients that crossover whereas randomisation-based methods are not. Naive methods performed particularly poorly and provided very high levels of bias.

Figure 1 shows the bias associated with selected methods in a range of scenarios in which the "common treatment effect" assumption held. In Scenarios 39, 40, 43 and 44 the treatment crossover proportion was very high (90-95%) and the observational-based methods produced extremely high levels of bias in these. Figure 2 shows the relative bias in a selection of scenarios in which the "common treatment effect" assumption did not hold. In these scenarios the randomisation-based methods performed much more poorly. This trend continued as the average treatment effect became increasingly different between crossover patients and patients originally randomised to the experimental group. In these scenarios, observational based methods represent a reasonable alternative to randomisation-based methods (unless crossover proportions are very high (as in Scenarios 37, 38, 41, 42).

Table of Outcomes Reported Across Studies

Figure 1: Bias in scenarios with common treatment effect

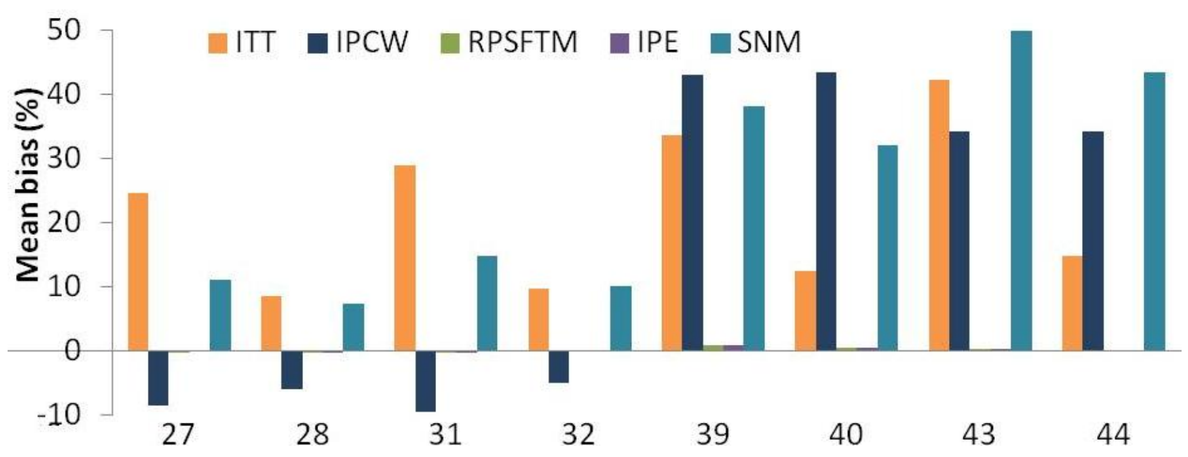
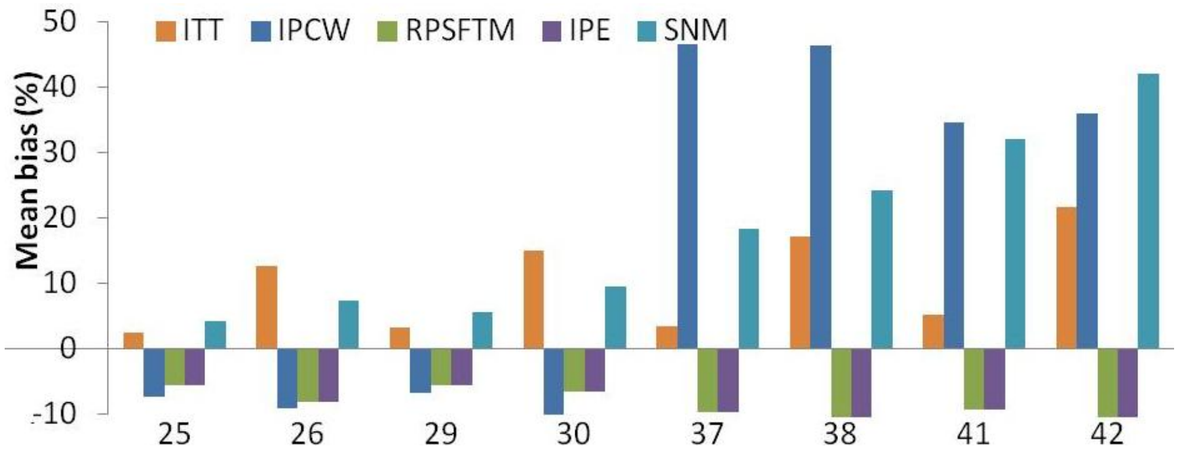


Figure 2: Bias in scenarios with a changing treatment effect



Conclusions

Currently available randomisation-based and observational-based methods for addressing treatment crossover have important limitations. However, in most circumstances they are likely to lead to lower bias than an ITT analysis, and they are always likely to be prefereble to "naive" adjustment methods. Observational-based methods are reliant on the availability of sufficient data to allow the crossover process to be modelled. This is problematic in the context of relatively small RCT datasets, and becomes almost impossible when extremely high proportions of control group patients cross over. Analysts should consider the treatment crossover mechanism, the control group crossover proportion, the treatment effect associated with different patient groups, and data availability when deciding which method to use to address treatment crossover.

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