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Accounting for Uncertainty in Decision Analytic Models Using Rank Preserving Structural Failure Time Modeling: Application to Parametric Survival Models

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ABSTRACT

Objectives: Rank Preserving Structural Failure Time models are one of the most commonly used statistical methods to adjust for treatment switching in oncology clinical trials. The method is often applied in a decision analytic model without appropriately accounting for additional uncertainty when determining the allocation of health care resources. The aim of the study is to describe novel approaches to adequately account for uncertainty when using a Rank Preserving Structural Failure Time model in a decision analytic model. **Methods:** Using two examples, we tested and compared the performance of the novel Test-based method with the resampling bootstrap method and with the conventional approach of no adjustment. In the first example, we simulated life expectancy using a simple decision analytic model based on a hypothetical oncology trial with treatment switching. In the second example, we applied the adjustment method on published data when no individual patient data were available. **Results:** Mean estimates of overall and incremental life expectancy were similar across methods. However, the bootstrapped and test-based estimates consistently produced greater estimates of uncertainty compared with the estimate without any adjustment applied. Similar results were observed when using the test based approach on a published data showing that failing to adjust for uncertainty led to smaller confidence intervals. **Conclusions:** Both the bootstrapping and test-based approaches provide a solution to appropriately incorporate uncertainty, with the benefit that the latter can implemented by researchers in the absence of individual patient data.

Modern randomized controlled trials (RCTs), which remain the gold standard in terms of evaluating the efficacy and safety of new interventions, often accommodate treatment switching from the control group to the experimental treatment group at some point during the trial. Treatment switching is primarily driven by ethical considerations; for instance, it would be unethical to disallow treatment switching for patients randomly allocated to therapy shown to be inferior in an interim analysis, particularly in cases where no other nonpalliative therapy options exist. Moreover, treatment switching can be used to boost trial recruitment, for example, by allowing switching after a primary endpoint has been observed (commonly, progression-free survival) [1]. It has been reported that over half the recent health technology assessments (HTAs) in oncology performed by the National Institute for Health and Care Excellence (NICE) in England and Wales and the Pharmaceutical Benefits Advisory in Australia have involved trials that included treatment switching [2].

Standard statistical approaches used in the analysis of RCTs are designed to compare groups based on the intention-to-treat (ITT) principle, which means that patients are analyzed according to their randomized treatment assignment and that all patients who were enrolled and received treatment are included in the analysis [3]. When patients in both groups receive the investigational intervention in a trial, such conventional analyses may not provide an accurate estimate of the comparative effectiveness of the two therapies, particularly for endpoints, such as overall survival (OS), which is critical for cost-effectiveness analysis, even though it is often not the primary endpoint of the trial. Although it is ethically justifiable to allow patients to switch to an experimental therapy after reaching the primary endpoint (e.g., progression-free survival), which may be the key endpoint for regulatory approval, methods are required to adjust for the effects of treatment switching on other endpoints (e.g., OS) that are crucial for health economic analysis and HTA decision making.

Simple methods of adjusting for treatment switching have been historically used in HTAs, such as those excluding switchers from the analysis or censoring their data at the time of switch, but these can create selection bias because treatment switching is often related to prognosis [4]. Recent recommendations indicate that these simple approaches should be avoided for the

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estimation of OS and replaced with methodologies that preserve randomization and are designed to address the issue of bias instead [5]. The Rank Preserving Structural Failure Time (RPSFT) model, inverse probability of censoring weights and two-stage adjustment estimation methods have all been shown to produce unbiased adjustments, provided the assumptions underpinning them hold true [6–8]. The RPSFT method, introduced by Robins and Tsiatis, provides an estimate of the OS time for the control group had treatment switching not occurred [6]. It estimates OS measured from the time of treatment switching by applying an estimate of the benefit of the experimental treatment (derived iteratively and referred to as the *inverse of the acceleration factor*). This method assumes that the benefit of the experimental treatment is the same whether it was received from the time of randomization or only received later as a switch treatment (referred to as the "constant treatment effect" assumption).

Given the potential confounding caused by treatment switching, it is important that appropriate adjustment methods are used for health economic analyses based on treatment switching trials and for informing HTAs. For example, in a 2012 NICE appraisal of vemurafenib for the treatment of melanoma the incremental cost-effectiveness ratio was decreased from over £75,000 per quality-adjusted life year gained to approximately £52,000 after adjusting for treatment switching [9]. This evidence suggests that failure to appropriately adjust for treatment switching has the potential to lead to misinformed HTA decision making. Although the use of adjustment methods in HTA submissions is beginning to be accepted in some countries, there is paucity of data on the role of adjustment methods in probabilistic sensitivity analysis (PSA), which is used to capture uncertainty and inform decision making in the HTA process [2,10]. PSA can be defined, in terms of a health economic modeling analysis, as the process in which "all input parameters are considered as random quantities and therefore are associated with a probability distribution that describes the state of science" [11]. The most commonly used adjustment method (RPSFT model) is known to introduce additional uncertainty when estimating (adjusted) hazard ratios (HRs) in treatment switching trials, an effect which also has the potential to influence HTA decision making [6]. When survival times are adjusted for treatment switching within decision analytic models, these adjusted HRs are rarely used explicitly. Instead, more commonly parametric survival curves are generated based on the adjusted patient survival.

The aim of the present study was to describe novel approaches to adequately adjust for uncertainty when using an RPSFT model, by (1) simulating life expectancy using a straightforward decision analytic model based on a hypothetical oncology trial with treatment switching, and (2) applying one of the approaches on published data to demonstrate the value of adjusting for uncertainty when using RPSFT models.

Methods

In a standard application of RPSFT model proposed by Robins and Tsiatis [6], two different survival times for a patient, i, are considered with notation:

- T_i– the observed survival time
- U_i– the latent survival time with no treatment

An accelerated failure time model is proposed to relate these, such as:

$$U_i(\varphi) = T_{Ci} + T_{Ei}e^{\varphi}$$

where T_{Ei} is the observed time on experimental therapy, and T_{Ci} is defined as $T_{Ci} = T_i - T_{Ei}$. The treatment parameter theta (φ) is an unknown with true value φ_0. By assuming the latent survival times will be balanced through randomization a g-estimation procedure can be used to estimate φ_0. This g-estimation proceeds by proposing a candidate set of values for the unknown parameter φ; estimating the latent survival time $U_i(\varphi)$ for both arms and then comparing as randomized using a suitable test. The candidate value of φ which leads to no difference in the comparison of the latent survival time as randomized is then taken as the estimate for φ_0. Using this estimate for φ_0 the counter factual latent survival U_i for the control arm can then be compared with the observed survival time T_i of the experimental arm using standard statistical methods. Robins and Tsiatis noted that when considering confidence intervals (CIs) for HRs estimated from RPSFT corrected data, the P value from the test used in the g-estimation procedure should be used to create symmetric CIs [6]. This is typically done by estimating an adjusted standard error (SE_{ADJ}) for the treatment effect (β) using equation 1, where X^2_{ITT} is the chi-square statistic from the log rank test used for g-estimation applied to the ITT comparison.

$$SE_{ADJ}\left(\hat{\beta}\right) = \frac{\hat{\beta}}{\sqrt{X^2_{ITT}}} \quad (1)$$

The present analysis describes an extension to this approach for use in parametric extrapolation and comparison with the alternative approach of bootstrapping with a small simulation study. The simulation study and a reanalysis of published data are used to illustrate the impact of not performing such a correction on PSA in a decision analytic model.

Estimating the Covariance Matrix Using an Adjustment Factor

The method assumes that an RPSFT model has been used to estimate counterfactual survival times for patients on standard care and assuming that treatment switching had not occurred following the approaches described in detail in the literature [6,8,12]. Following this step, the algorithm to apply the adjustment to a parametric covariance matrix is as follows:

1. Fit a parametric survival model to the observed data for the experimental arm and the counterfactual control arm survival, including a treatment effect parameter (coded to indicate being on control arm therapy relative to experimental arm, so the intercept represents the effect of experimental treatment). This is done so all the additional variance from the RPSFT method is contained in the treatment effect and is not split between the treatment effect and the intercept.
2. Derive an adjustment factor using equation 2, where $SE_{ADJ}(\beta)$ is defined as with equation 1, where β is the estimate of the treatment effect from the parametric model, and $SE_{OBS}(\beta)$ is the estimated standard error.

$$F = \frac{SE_{ADJ}(\beta)}{SE_{OBS}(\beta)} \quad (2)$$

3. Multiply all components of the covariance matrix that involve covariance with treatment effect by this adjustment factor. This assumes that the correlation between the parametric model parameters and treatment effect is not modified through the use of the RPSFT adjustment. This is illustrated for a Weibull model with parameters μ (intercept), β (treatment effect for control relative to experimental) and γ (shape) in equations 3 and 4; however, very similar derivations apply for other parametric survival models. Equation 3 shows the