MSR12

# Accounting for the Additional Uncertainty Following Rank Preserving Structural Failure Time Model (RPSFTM) Crossover Adjustment in Survival Analysis: A 'SAGE' Approach

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## Objective

To evaluate whether a new approach, 'Sampling After G-Estimation' (SAGE), can more efficiently capture the uncertainty in Rank Preserving Structural Failure Time Model (RPSFTM)-adjusted hazard ratio (HR) estimation.

## Background

- Crossover in randomised control trials (RCTs) occurs when patients switch from their allocated treatment.
- This may bias treatment effects derived from an intention-to-treat (ITT) analysis, and methods to account for crossover should be applied.
- RPSFTM (Rank Preserving Structural Failure Time Model) is one method to adjust for crossover in RCTs. It uses g-estimation to find the acceleration factor $\exp(-\psi_0)$, which describes how treatment alters the timing of events; this factor is derived by balancing the event times that would be observed if no treatment had been received across randomised arms (i.e. the ITT test-statistic $Z(\psi)=0$). Survival times are then recalculated, accounting for crossover, as:[1]

$$U_i = T_i^{off} + T_i^{on}\exp(\psi_0)$$

- When RPSFTM is used to estimate crossover adjusted HRs, the additional uncertainty introduced by RPSFTM must also be captured.
- Conventional approaches to capturing uncertainty include retaining the ITT p-value (adjusting the HR standard error to preserve the ITT p-value) and bootstrapping (repeating RPSFTM for resampled datasets).[2,3]
- We propose a new, sampling-based approach, SAGE: 'Sampling After G-Estimation'.

## Methods

### Data Source

- We applied RPSFTM to account for crossover using a simulated dataset based on the Concorde study, a historic RCT in human immunodeficiency virus (HIV).[4,5]
- Concorde was a double-blind RCT in symptom-free individuals infected with HIV comparing:[4]
  - Zidovudine from randomisation.
  - Zidovudine deferred until more advanced stages of HIV (crossover arm).
- The simulated dataset used in our analysis used the same study design as Concorde. This simulated dataset is publicly available and has been used in other randomisation-based research.[5]

### Evaluating SAGE

- The SAGE approach was implemented according to the steps outlined in **Figure 1**.
- This SAGE confidence interval (CI) was compared with:
  - Naïve CI without uncertainty inflation.
  - CI retaining the ITT p-value.
  - CI using bootstrapping.

## Results

- CIs for the compared approaches are summarised in **Figure 2**.
- CIs computed using the SAGE approach were narrower than those generated via bootstrapping. Wider confidence intervals were generated in comparison with the naïve CI and retaining the ITT p-value approach.
- The SAGE approach may offer a balance between computational intensity (bootstrapping is more computationally intensive) and suitable confidence interval coverage.
- Strengths and limitations of each approach are summarised in **Table 1**.
- As the current research is based on a single simulated dataset, further research should be conducted to comprehensively evaluate the comparative ability of SAGE to capture uncertainty introduced by RPSFTM.

## Conclusion

The SAGE approach may offer a balance between reduced computational burden and suitable coverage of uncertainty when conducting RPSFTM; further work should assess performance across multiple datasets.

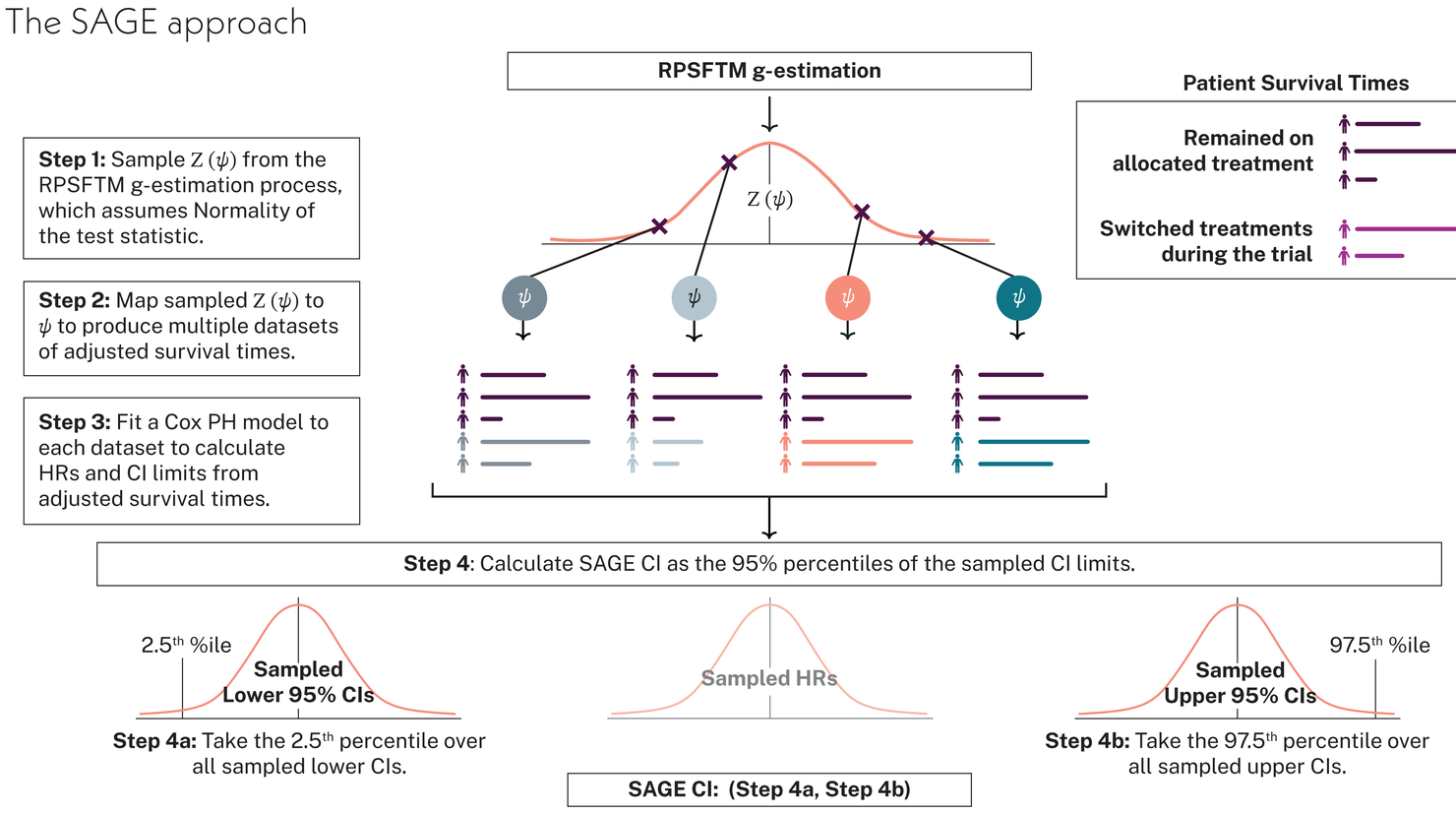
**TABLE 1**

Strengths and limitations of compared approaches

| | SAGE | Bootstrapping | Retaining the ITT p-value |
|---|---|---|---|
| **Overview of Approach** | Test statistics from the RPSFTM g-estimation process are sampled (assuming a Normal distribution) then mapped to produce multiple adjusted survival times, from which the CI limits are taken as the 2.5th and 97.5th percentiles over all calculated lower and upper HR CIs (**Figure 1**). | RPSFTM is repeated for resampled datasets and the 2.5th and 97.5th percentiles across HRs from all resampled datasets are taken as the CI limits. | The standard error of the HR is adjusted to preserve the ITT p-value. |
| **Strengths** | Less computationally intensive than bootstrapping, and does not require review of multiple diagnostics.<br><br>More transparently captures the additional uncertainty from RPSFTM than retaining the ITT p-value. | Most fully captures uncertainty from RPSFTM-adjusted HR estimation. | Least computationally intensive, and does not require review of multiple diagnostics. |
| **Limitations** | May not capture uncertainty from RPSFTM-adjusted HR estimation as completely as bootstrapping. | Computationally intensive.<br><br>Reviewing diagnostics for each iteration can be time consuming. | May not fully reflect the additional uncertainty introduced by RPSFTM. |

**FIGURE 1**

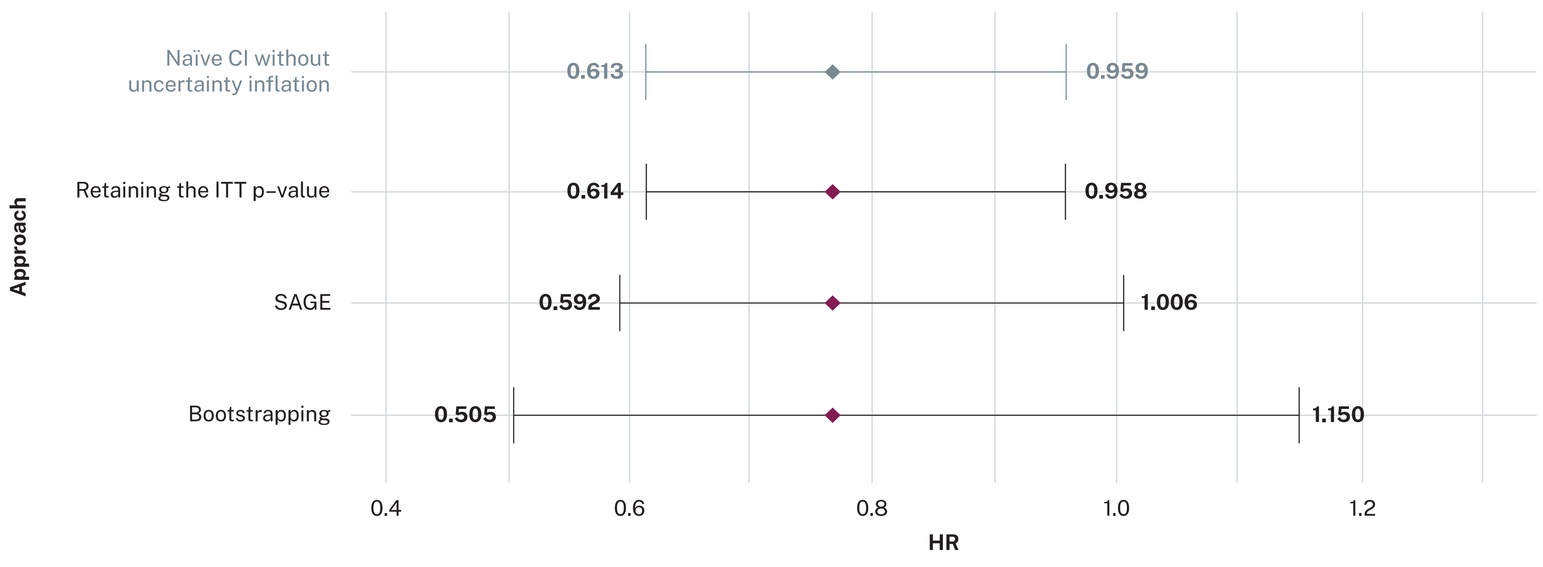
The SAGE approach




The lower SAGE CI limit is calculated as the 2.5th percentile over all sampled lower CIs and the upper SAGE CI limit is calculated as the 97.5th percentile over all sampled upper CIs. Calculated CIs reflect uncertainty in RPSFTM-adjusted HRs.

**FIGURE 2**

RPSFTM-adjusted HR and associated 95% CIs across the different approaches




**Abbreviations: CI:** confidence interval; **HIV:** human immunodeficiency virus; **HR:** hazard ratio; **ITT:** intention-to-treat; **PH:** proportional hazards; **RCT:** randomised controlled trial; **RPSFTM:** Rank Preserving Structural Failure Time Model; **SAGE:** Sampling After G-Estimation.

**References:** [1]Allison A. et al. The R J. 2017;9:342; [2]Robins J.M. and Tsiatis A.A. Commun. Stat.-Theory Methods 1991;20:2609–31; [3]White I.R. Stat. Methods Med. Res. 2005;14:327–47; [4]Concorde Coordinating Committee. The Lancet 1994;343:871–81; [5]White I.R. et al. Stata J. 2002;2:140–50. **Acknowledgements:** The authors thank Ben James and Jenny Chen, Costello Medical, for graphic design assistance. We also thank Alex Porteous for his review and editorial assistance in the preparation of this poster.

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