

Overall Survival adjustment to mitigate the impact of crossover from the control arm to the experimental arm. The two-stage method.



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ABSTRACT

Most Phase III oncology clinical trials include Overall Survival (OS) as a key endpoint. The analysis of OS following intention-to-treat (ITT) principle is considered the ‘gold standard’, but many times this approach is not the most appropriate. A typical example occurs when control arm patients can be switched to the experimental arm once they have documented disease progression. In that case, ITT comparison underestimates the actual OS difference between treatment groups. Several alternatives, from naïve to more complex methods, have been proposed to measure the crossover impact.

This poster presents a SAS program to perform one of the best possible approaches to mitigate the crossover impact, “the two-stage method” proposed by Latimer et al.

BACKGROUND MATERIAL

The two-stage method provides a good fit to treatment change mechanics often observed in oncology. Usually, switching is only permitted after progressive disease (PD). If it occurs shortly afterwards, PD can be used as a secondary baseline for patients in the control group. Fitting a parametric model would be expected to produce a reasonable estimate of the effect resulting from crossover, provided that the model fits the data and some pivotal assumptions are met. The resulting acceleration (deceleration) factor associated with treatment change represents the additional post-progression survival achieved because of treatment change and could then be used to “shrink” survival times in switching patients to derive a counterfactual survival dataset upon which standard survival analysis could be undertaken.

The main assumptions for the two-stage method are:

- Crossover occurs soon after PD.
- The characteristics of patients that switch and do not switch are comparable at time of PD.
- No unmeasured confounders at the time of crossover are present.

The dataset ‘myeloma’ from SAS help library is used with some artificial changes, see the associated paper. (https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_phreg_sect046.htm)

CHECK OF MAIN ASSUMPTIONS

- Crossover occurs soon after PD.
The time between PD and crossover can be calculated and summarized descriptively.

```
Proc means data=myeloma_edited_1 n median min max;  
var ttcd;run;
```

Time to crossover from PD (months)			
N	Median	Minimum	Maximum
14	0.55	0.25	2.90

- The characteristics of patients that switch and do not switch are comparable at the time of PD.

To test that patient characteristics are not different between patients with and without crossover Fisher Exact Tests, Mann-Whitney-Wilcoxon Tests and Logistic Regressions using all the available data at randomization time (primary baseline variables) and at PD time (secondary baseline variables) should be used.

```
/*Continuous example (e.g. Age, hemoglobin at baseline)*/  
Proc npar1way data=myeloma_edited_1 wilcoxon;  
var logbun; class crossover; where arm=0; run;
```

Wilcoxon Two-Sample Test	
Two-Sided Pr > Z	0.4526

```
/*Categorical example (e.g. Gender, Myeloma type) */  
Proc freq data=myeloma_edited_1;  
table crossover*platelet/fisher;where arm=0;run;
```

Fisher's Exact Test	
Two-sided Pr <= P	1.0000

- No unmeasured confounders at the time of crossover are present.

The clinical input is important to check that there are no unmeasured confounders. The model should include all the prognostic factors known to have an impact in the time to PD and OS in the disease studied.

If the assumptions are considered plausibly met then the two-stage method can be applied.

PROCEDURE

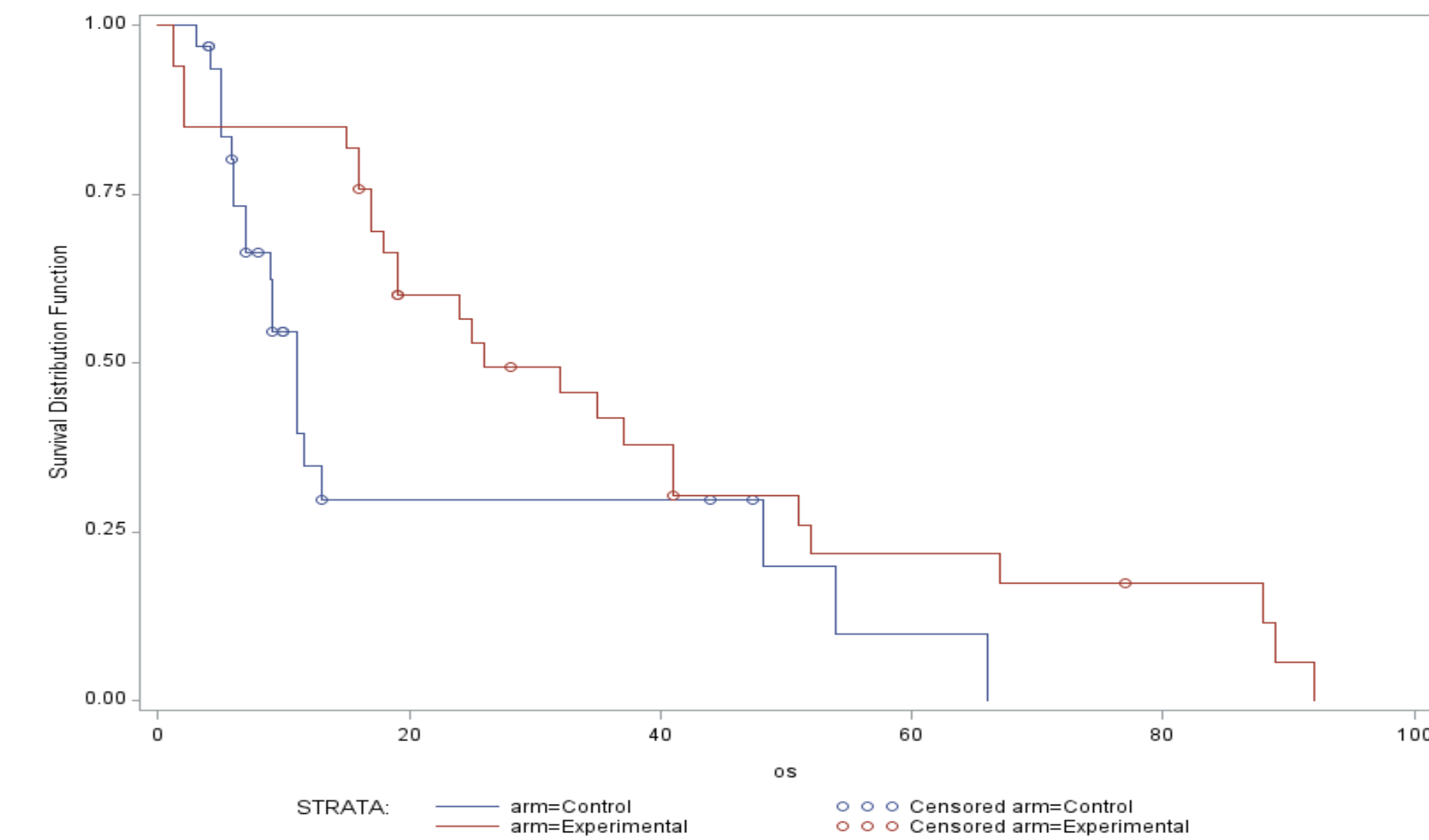
POST PROGRESSION SURVIVAL.

The SAS LIFEREG procedure will be used to adjust a parametric distribution for the post progression survival data of the control arm patients. The most widely used distribution is the Weibull distribution but other different distributions can be tested and then compared them by means of -2Log Likelihood or AIC/BIC selecting the distribution with better adjustment.

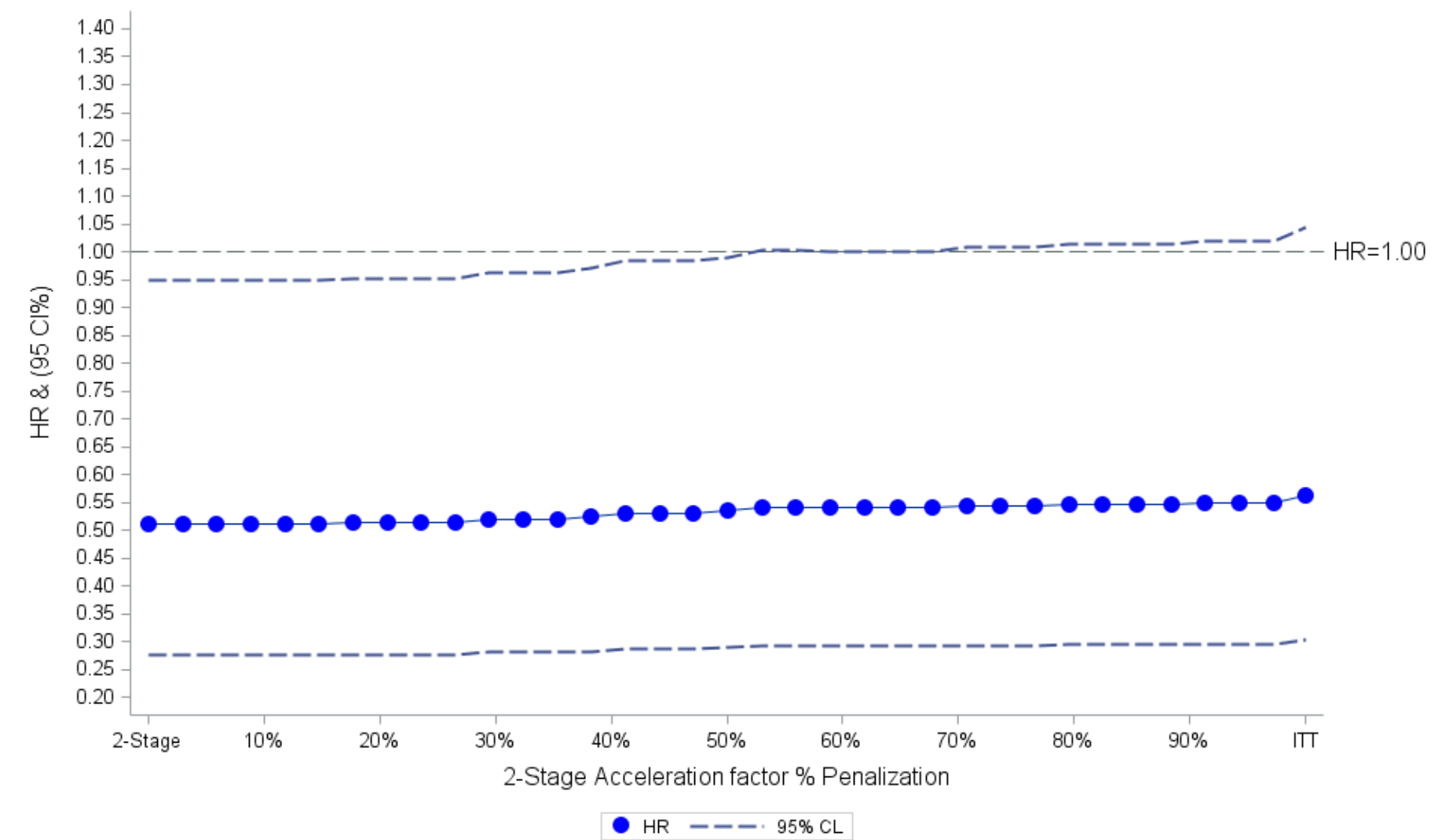
```
/*Artificial dataset,, see the paper to see derivation process*/  
proc lifereg data=myeloma_edited_2;  
  class crossover platelet; /*Potential variables with influence*/  
  model post_prog_survival*VStatus(0) = crossover logbun  
platelet/ noint /*check intercept validity or not*/;  
run;
```

A multiplicative acceleration factor (AF) is calculated and used to “shrink” post progression survival times in patients with crossover. Finally, standard survival analysis is performed with the adjusted survival times.

```
Data myeloma_edited_3;  
set myeloma_edited_1;  
post_prog_survival=(Time-pfs);  
If crossover=1 then post_prog_survival=post_prog_survival  
*exp(-0.3525/0.85);  
os=pfs+post_prog_survival;  
run;
```



As any method it may have implicit limitations caused by the assumptions that have to be met and the creation of a counterfactual distribution. Several penalizations to the acceleration factor should be applied to check the robustness of the results.



CONCLUSIONS

The two-stage method is a valid approach to obtain adjusted estimates of the OS effect in oncology clinical trials with treatment switch, provided that there is a good fit of the parametric models and the method assumptions are plausibly met.

For an actual application example in a Phase III trial. See the ADMYRE trial adjustment results presented as an Oral Poster Session at the congress of the American Society of Clinical Oncology -ASCO 2018 (Abstract #8018).

Your comments and questions are valued and encouraged
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