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. We present a SAS® program to execute one of the best possible approaches to mitigate the crossover impact, "the two-stage method" proposed by Latimer et al.

INTRODUCTION
This paper presents a SAS program to perform survival analysis by using the “two-stage” method, to adjust the survival estimates when crossover occurs and the ITT OS outcome is likely to be biased against the experimental arm.

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.

In order to facilitate the reading comprehension a fabricated example from a SAS Help dataset will be used throughout the paper.

DATASET DERIVATION
Datasets and derived numbers have to be taken with caution because the intention of them is to show how the process is developed and some licenses are performed that may not be applicable in a “real world” trial.

*https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_phreg_sect046.htm;

data Myeloma;
  input Time VStatus LogBUN HGB Platelet Age LogWBC Frac LogPBM Protein SCalc;
  label Time='Survival Time'
    VStatus='0=Alive 1=Dead';
datalines;
1.25 1 2.2175 9.4 1 67 3.6628 1 1.9542 12 10
1.25 1 1.9395 12.0 1 38 3.9868 1 1.9542 20 18
2.00 1 1.5185 9.8 1 81 3.8751 1 2.0000 2 15
2.00 1 1.7482 11.3 0 75 3.8062 1 1.2553 0 12
2.00 1 1.3010 5.1 0 57 3.7324 0 1.7324 5 9
3.00 1 1.5441 6.7 1 46 4.4757 0 1.9345 12 10
5.00 1 2.2355 10.1 1 50 4.9542 1 1.6628 4 9
5.00 1 1.6812 6.5 1 74 3.7324 0 1.7324 5 9
6.00 1 1.3617 9.0 1 77 3.5441 0 1.4624 1 8
6.00 1 2.1139 10.2 0 70 3.5441 1 1.3617 1 8
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<th>Value</th>
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<th>Time</th>
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<td>57.3832</td>
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<td>19.0</td>
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<td>10.8</td>
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<tr>
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<td>82.3748</td>
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<td>1.7559</td>
<td>12.8</td>
<td>1</td>
<td>72.3724</td>
<td>1.4472</td>
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<tr>
<td>53.0</td>
<td>0</td>
<td>1.1139</td>
<td>12.0</td>
<td>1</td>
<td>66.3612</td>
<td>2.0000</td>
<td>1</td>
<td>2.0000</td>
</tr>
<tr>
<td>57.0</td>
<td>0</td>
<td>1.2553</td>
<td>12.5</td>
<td>1</td>
<td>66.3685</td>
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<td>77.0</td>
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<td>1</td>
<td>60.3681</td>
<td>0.9542</td>
<td>0</td>
<td>0.9542</td>
</tr>
</tbody>
</table>

*Let's assume 32 patients in the control arm and 33 in the experimental arm;*

```plaintext
Proc sort data=myeloma out=auxiliar1;by Time;run;

Proc format;
value arm
0='Control'
1='Experimental';
run;
```
Data auxiliar2;
set auxiliar1;
If 5<_n_<=32 or 55<_n_<=60 then arm=0;
else arm=1;
format arm arm.;
format arm arm.;
run;

*Let's assume that 50% of control arm patients performed crossover, in order to get an improvement we are going to select them as a biased selection too. Crossover time is estimated to occur a bit later than PFS;

Proc format;
value cross
0='No crossover'
1='Crossover';
run;

Data auxiliar3;
set auxiliar2;
x2=ranuni(345);
If arm=0 then do;
If x2<0.5 then crossover=0;
else crossover=1;
end;
format crossover cross.;
pfs=Time/2;
If crossover=1 then cross_time=pfs+Time/20;
run;

*This dataset is generated in order to be used as a guide to implement the two-stage adjustment method. Data is not real and it is assumed that correct information will be available;
Data myeloma_edited;
set auxiliar3;
run;

ORIGINAL RESULTS
ITT comparison, without discounting the potential crossover effect the results shows an improvement trend in favor of the experimental arm.

Proc lifetest data=myeloma_edited plots=s;
time Time*VStatus(0);
strata arm;
run;
Proc phreg data=myeloma_edited;
model Time*VStatus(0)=arm/RISKLIMITS;
run;
Test of Equality over Strata

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr &gt; Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>3.5101</td>
<td>1</td>
<td>0.0610</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>4.3545</td>
<td>1</td>
<td>0.0369</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>2.3984</td>
<td>1</td>
<td>0.1215</td>
</tr>
</tbody>
</table>

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>1</td>
<td>-0.57483</td>
<td>0.31525</td>
<td>3.3249</td>
<td>0.0682</td>
<td>0.563</td>
<td>0.303</td>
</tr>
</tbody>
</table>

It might be expected that patients who switched from the control arm to the experimental arm obtained some benefit and ITT comparison may be biased. There are several approaches from naïve to more complex methods to measure the crossover impact, here we present “the two-stage method” proposed by Latimer et al.

PIVOTAL ASSUMPTIONS

The two-stage method provides a reasonable estimate of the effect resulting from switching to the experimental treatment in oncology trials.

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 time between PD and crossover can be calculated and summarized descriptively.

```plaintext
Data myeloma_edited_1;
set myeloma_edited;
If crossover=1 then ttcd=cross_time-pfs;
run;

Proc means data=myeloma_edited_1 n median min max;
var ttcd; /*Time to crossover measured in months*/
run;
```
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 (see an example below). 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 PD and OS in the disease studied.

```sas
Proc npar1way data=myeloma_edited_1 wilcoxon;
var logbun;
class crossover;
where arm=0;
run;
```

**Wilcoxon Two-Sample Test**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-0.7606</td>
</tr>
<tr>
<td>One-Sided Pr &lt; Z</td>
<td>0.2234</td>
</tr>
<tr>
<td>Two-Sided Pr &gt;</td>
<td>0.4469</td>
</tr>
<tr>
<td>t Approximation</td>
<td></td>
</tr>
<tr>
<td>One-Sided Pr &lt; Z</td>
<td>0.2263</td>
</tr>
<tr>
<td>Two-Sided Pr &gt;</td>
<td>0.4526</td>
</tr>
</tbody>
</table>

*Z includes a continuity correction of 0.5.*

```sas
Proc freq data=myeloma_edited_1;
table crossover*platelet/fisher;
where arm=0;
run;
```

**Fisher's Exact Test**

<table>
<thead>
<tr>
<th>Cell (1,1) Frequency (F)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-sided Pr &lt;= F</td>
<td>0.5972</td>
</tr>
<tr>
<td>Right-sided Pr &gt;= F</td>
<td>0.7900</td>
</tr>
<tr>
<td>Table Probability (P)</td>
<td>0.3872</td>
</tr>
<tr>
<td>Two-sided Pr &lt;= P</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

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

**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. Following Latimer et al methodology a parametric survival distribution will be used and afterwards the ‘accelerated/decelerated’ factor will be applied to the crossover 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.

```sas
Data myeloma_edited_2;
set myeloma_edited_1;
post_prog_survival=(Time-pfs);
If arm=0;
run;

proc lifereg data=myeloma_edited_2;
   class crossover platelet;
   model post_prog_survival*VStatus(0) = crossover logbun platelet; /*check intercept validity or not*/
run;
```
### Analysis of Maximum Likelihood Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>95% Confidence Limits</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>3.8611</td>
<td>0.9735</td>
<td>1.9530</td>
<td>5.7692</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>crossover</td>
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<td>0.3525</td>
<td>0.3975</td>
<td>-0.4266</td>
<td>1.1317</td>
<td>0.79</td>
</tr>
<tr>
<td>crossover</td>
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<td>0.0000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3752</td>
</tr>
<tr>
<td>LogBUN</td>
<td>1</td>
<td>-1.0611</td>
<td>0.6489</td>
<td>-2.3330</td>
<td>0.2108</td>
<td>0.1020</td>
</tr>
<tr>
<td>Platelet</td>
<td>0</td>
<td>-0.5931</td>
<td>0.5428</td>
<td>-1.6570</td>
<td>0.4708</td>
<td>1.19</td>
</tr>
<tr>
<td>Platelet</td>
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<td>0.0000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.2746</td>
</tr>
<tr>
<td>Scale</td>
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<td>0.8500</td>
<td>0.1331</td>
<td>0.6253</td>
<td>1.1554</td>
<td>0.2746</td>
</tr>
<tr>
<td>Weibull Shape</td>
<td>1</td>
<td>1.1765</td>
<td>0.1843</td>
<td>0.8655</td>
<td>1.5992</td>
<td>-</td>
</tr>
</tbody>
</table>

The statistical model measures the hypothetical effect of experimental treatment in patients of the control arm compared to patients with similar characteristics who do not switch treatment to "accelerate/decelerate" data. A multiplicative acceleration factor (AF) is calculated and used to "shrink" post progression survival times in patients with crossover.

### OS COMPARISON

Finally, once post progression survival times in patients with crossover is shrink, standard survival analysis is performed with the adjusted survival times.

```sas
Data myeloma_edited_3;
set myeloma_edited_1;
*Post progression survival;
pdag = time-pfs;
If crossover=1 then post_prog_survival=post_prog_survival*exp(-0.3525/0.8500);
os=pfs+post_prog_survival;
run;
Proc lifetest data=myeloma_edited_3 plots=s;
time os*VStatus(0);
strata arm;
run;
Proc phreg data=myeloma_edited_3;
model os*VStatus(0)=arm/RISKLIMITS;
run;
```

![Survival Plot](image_url)
SENSITIVITY ANALYSES
As any method used to adjust the crossover effect it may have implicit limitations caused by the assumptions that have to be met and the creation of a counterfactual distribution. In order to address potential deviations from the model assumptions, several penalizations to the acceleration factor have to be applied to check the robustness of the results.

**data** AF_values;  
do i=0 To 100;  
val=Exp((-0.3525/0.8500) + i*(0.01)); /*0.01 AF increments up to 1 (ITT)*/  
if val>1 then val=1;  
output;  
end;  
run;  
proc sort nodupkey;by val;run;

**proc sql;**  
create table Twostage_simulation as  
Select *  
from myeloma_edited_1 a, AF_values b;  
run;

**Data** Twostage_all_sims;  
set Twostage_simulation;  
*Post progression survival;*  
post_prog_survival=(Time-pfs);  
If crossover=1 then post_prog_survival=post_prog_survival*val;  
os=pfs+post_prog_survival;  
run;

**proc phreg data=Twostage_all_sims;**  
by i;  
ods output ParameterEstimates=estimacion;  
model os*VStatus(0)=arm /risklimit;  
run;  

*Graph;  

data tst_a;  
set Twostage_all_sims;  
pctnpen=((val-(exp(-0.3525/0.8500)))/(1-exp(-0.3525/0.8500))))*100;  
keep i pctnpen;  
run;  
proc sort nodupkey;by i;run;

**Data** tst;  
merge estimacion tst_a;  
by i;  
run;  

Test of Equality over Strata

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr &gt; Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>4.7555</td>
<td>1</td>
<td>0.0292</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>4.7323</td>
<td>1</td>
<td>0.0296</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>3.4512</td>
<td>1</td>
<td>0.0632</td>
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</table>

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Limits</th>
<th>Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>1</td>
<td>-0.66985</td>
<td>0.31463</td>
<td>4.5327</td>
<td>0.0333</td>
<td>0.512</td>
<td>0.276</td>
<td>0.948</td>
</tr>
</tbody>
</table>
CONCLUSION

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 congress of the American Society of Clinical Oncology- ASCO 2018 (Abstract #8018).
Contact Information
Your comments and questions are valued and encouraged.

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