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Inverse Probability of Censoring Weighting for Selective Crossover in Oncology Clinical Trials.

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ABSTRACT
In Randomized Clinical Trials, selective crossover occurs when a patient randomized to one treatment arm changes to the alternative treatment during the study. This situation disturbs the integrity of the randomized comparison and creates a scenario of informative missing data where the estimated treatment difference for long-term endpoints, like overall survival or progression free survival, will be biased. The inverse probability of censoring weighting technique (IPCW) was designed to recreate an unbiased scenario where nobody switched to other treatment, and allows us to assess the real clinical benefit of the experimental arm compared with the control arm. In this paper we show how to perform this technique using SAS® software and how it behaves compared with the traditional censored analysis.

KEYWORDS
Inverse Probability of Censoring Weighting; Logistic Regression; Overall Survival; Selective Crossover; Censoring analysis.

INTRODUCTION

In oncology, when the clinical benefit of an experimental arm compared with a control arm is assessed, time-to-event techniques like Cox Regression or the log-rank test are commonly used. When crossover is allowed, long-term efficacy endpoints like Overall Survival or even Progression Free Survival may be affected if a patient switches to the other arm before the event of interest happened and the comparison results obtained may be biased. The most common and simplest approaches to measure its impact would be censoring or excluding the patients who did crossover. Several bias could be introduced since the decision of switching might not be at random and is usually related to clinical worsening. Other traditional methods consist of censoring the patient by the time of switching or just ignore it and continue the analysis as if nobody switched (ITT analysis).

The Inverse Probability of Censoring Weighting (IPCW) is an alternative method, which was first developed in the 1990s by Robins et al. [1], attempts to reduce the bias caused by treatment change recreating a scenario where any patient switched to the alternative treatment arm. The weights estimated to reduce the bias are usually based on a logistic regression model, where the response variable tells whether the patient switched to the other treatment or not.

ANALYSIS AND RESULTS

To have a better understanding of the IPCW method, let's imagine a clinical trial that compares two treatment arms, A and B, and let's say that treatment B is performing worse than treatment A and hence patients from treatment B are switching to treatment A. The bias described in the introduction has been introduced by the crossover from treatment B to A.

The key components in the IPCW technique are the estimated weights that later are introduced in the Cox regression model to diminish the bias introduced by treatment change. But, what are these weights and how are they estimated?

In our hypothetical clinical trial where patients from treatment B are switching to treatment A, we need to compensate the impact of switching. Therefore the basic idea is that, in treatment B, we try to find patients with similar characteristics to those patients that switched treatment and give the patient that stayed a higher weight and attribute a zero weight to the patients moving to treatment A from the time of crossover onwards. That way, the patients that stayed are weighted in a way that compensates the switch of patient to the other arm. However, as pointed out by an evaluation of pazopanib for renal cancer [5], IPCW is subject to the assumption of no unmeasured confounders and randomization is not preserved.

To obtain these weights, the likelihood of remaining uncensored is going to be estimated. This procedure can be easily done by means of a logistic regression. Specifically, we need to perform two logistic regression models, one using only baseline covariates and other using both baseline and time dependent covariates. The coefficient between these two estimated probabilities of switching is going to give us the assigned weights. Subsequently, patients who switched will have a lower weight that patients that did not, and patients in treatment arm A will have a weight equal to 1 since there is no need to compensate for switching. More formally, this procedure follows the next formula.

$$w_{ij} = \frac{\prod_{k=0}^{j} P(C(k)_i = 0 | C(k-1)_i = 0, X_i)}{\prod_{k=0}^{j} P(C(k)_i = 0 | C(k-1)_i = 0, X_i, Z(k)_i)}$$

The numerator calculates, for each patient i, the probability of remaining uncensored at the end of time k given that the patient was also uncensored at the end of time $k-1$, and given some baseline covariates X.

The denominator calculates, for each patient i, the probability of remaining uncensored at time k given that the patient was also uncensored at the end of time $k-1$, and given some baseline covariates X and time dependent covariates Z.

Dummy data was simulated to show how the IPCW technique works, SAS code was used for it. 800 patients were created following an exponential distribution, 400 patients in each arm. A variable called “time” which represents the overall survival of the trial is generated and the survival mean for treatment arm A is fixed as 25 weeks and 5 weeks for the survival mean in treatment B. Three baseline covariates and two time dependent covariates were also randomly simulated. The baseline covariates were prior time to progression in the previous therapy, age and number of regions affected before entering the study, and the time dependent covariates were performance status and the number of grade 3 adverse events at the beginning and at the end of cycle 2. As this is an example and to maintain the simplicity, only baseline and cycle 2 data was simulated. In general, time dependent covariates were simulated so patients in treatment B have worse safety data than patients in treatment A. Afterwards the censoring status using a Bernoulli distribution in variables called “event” and “event_c” is generated. The difference between “event” and “event_c” is that “event” is the actual status of the time to event variable, meanwhile “event_c” censors the status of the time to event variable when a patient does crossover even if the event did not occur. For patient without crossover, “event” and “event_c” are equivalent. Again, trying to be more realistic, we need to take into account that the new treatment is going to modify the time to event. Consequently we are going to create a new variable called “time2” which contains the overall survival taking into consideration the possible effect of the new treatment in patients that switched. The reason of these two variables is that we want to compare the performance of the censoring analysis versus the IPCW, so “time” doesn't know what happens after the switch because it censors the patient at that time, while “time2” adds the effect of the next subsequent therapy.

Summing up, we have a complete dataset with baseline and time dependent covariates, censor variables and two time to event variables measured at baseline and at the end of cycle 2. A snapshot of the dataset with the simulated data is shown below.

id	arm	time	prior_ttp	regions	age	crossover	event	time2	event_c	ps	aes
378	1	44.677051813	34.496437079	1	44	0	0	44.677051813	0	0	2
378	1	44.677051813	34.496437079	1	44	0	0	44.677051813	0	0	3
391	1	56.203889186	7.1908365858	0	37	0	0	56.203889186	0	0	1
391	1	56.203889186	7.1908365858	0	37	0	0	56.203889186	0	0	3
392	1	0.5953042369	17.425290751	0	51	0	0	0.5953042369	0	0	3
392	1	0.5953042369	17.425290751	0	51	0	0	0.5953042369	0	0	1
393	1	4.7350164374	23.676061111	0	56	0	0	4.7350164374	0	0	1
393	1	4.7350164374	23.676061111	0	56	0	0	4.7350164374	0	0	3
401	0	13.749661499	0.4785300583	1	42	1	1	21.749661499	0	1	3
401	0	13.749661499	0.4785300583	1	42	1	1	21.749661499	0	1	3
402	0	6.5643588337	1.7406880022	3	30	1	1	14.564358834	0	0	1
402	0	6.5643588337	1.7406880022	3	30	1	1	14.564358834	0	0	3
403	0	0.3100976149	6.3269966397	4	61	1	0	8.3100976149	0	1	4
403	0	0.3100976149	6.3269966397	4	61	1	0	8.3100976149	0	1	7
404	0	1.4149989374	1.5652549782	6	56	1	0	9.4149989374	0	0	4
404	0	1.4149989374	1.5652549782	6	56	1	0	9.4149989374	0	0	6
405	0	2.428016943	1.909261601	5	50	1	1	2.428016943	0	1	3
405	0	2.428016943	1.909261601	5	50	1	1	2.428016943	0	1	6
407	0	1.8284177562	5.1139269546	1	58	1	1	9.8284177562	0	1	2
407	0	1.8284177562	5.1139269546	1	58	1	1	9.8284177562	0	1	1

We need to keep in mind that we are estimating the probability of remaining uncensored and for that we first can use the PROC LOGISTIC with only baseline variables and specifying which is the event we are modeling. In this case 0 means uncensored as specified in the formula, so we need to specify it. Note that the dataset “a10” has two observations per patient as shown in the snapshot. Since we are no using the time dependent covariates, we should remove the duplicated observations to avoid possible problems.

```
/*Logistic model with baseline variables*/

proc logistic descending data=a10;
model crossover(event='0')=prior_ttp age prior_areas;
output out=out1 prob=tn;
run;
```

Next, we need to estimate again the probability of remaining uncensored but using both baseline and time dependent covariates. In this case we use PROC GENMOD because it allows us to model longitudinal data in a logistic regression model. In this case the event of interest is not specified so we need to sort the data in a way that the procedure models the probability of crossover = 0. This is achieved by the next SAS commands.

```
proc sort data=a10;by descending crossover;run;

/*Logistic model with baseline and time dependent variables*/

proc genmod data=a10 descending order=data;
class crossover id;
model crossover=prior_ttp age prior_areas ps aes / d=bin link=logit;
repeated subject=id;
estimate "ps" ps 1 -1 / exp;
estimate "aes" aes 1 -1 / exp;
output out=out2 prob=td;
run;
```

After this execution, it may be a good idea to check the log to see if we are correctly modeling the probability of crossover = 0. In our case, we see that the modeling is performed correctly and hence we can continue with the analysis.

```
NOTE: PROC GENMOD is modeling the probability that crossover='0'.
NOTE: Algorithm converged.
```

Now we only need to merge the obtained probabilities and obtain the weights which are in the dataset “a12” in the variable “w”.

```
proc sort data=out1;by id;run;
proc sort data=out2;by id;run;

data a11;
merge out1 out2;
by id;
run;

data a12(drop= tn td);
set a11;
by id;
w=tn/td;
run;
```

Once we have the weights to perform the IPCW method, we are going to compare the performance of this method with the performance of the censoring analysis. Because we have simulated the data, we know that the mean overall survival of treatment A is 25 and the mean overall survival of treatment B is 5 and hence we should expect Hazard Ratios that show these differences.

Let's estimate the Hazard Ratio of the censoring analysis. Recall that “time” is the time to event variable that censors patient by the time of switching and hence is the variable we need to use for censoring analysis.

```
/*Hazard Ratios with crossover using Censoring Analysis*/

proc phreg data=a12;
model time*event_c(0)=arm;
run;
```

To estimate the Hazard Ratio of the IPCW method, we need to implement a weighted Cox regression model. Luckily, SAS allows us via the option “freq” to weight the data and there is where we have introduce the estimated weights. It's also important to use the option “notruncate” to avoid truncation problems with the weights.

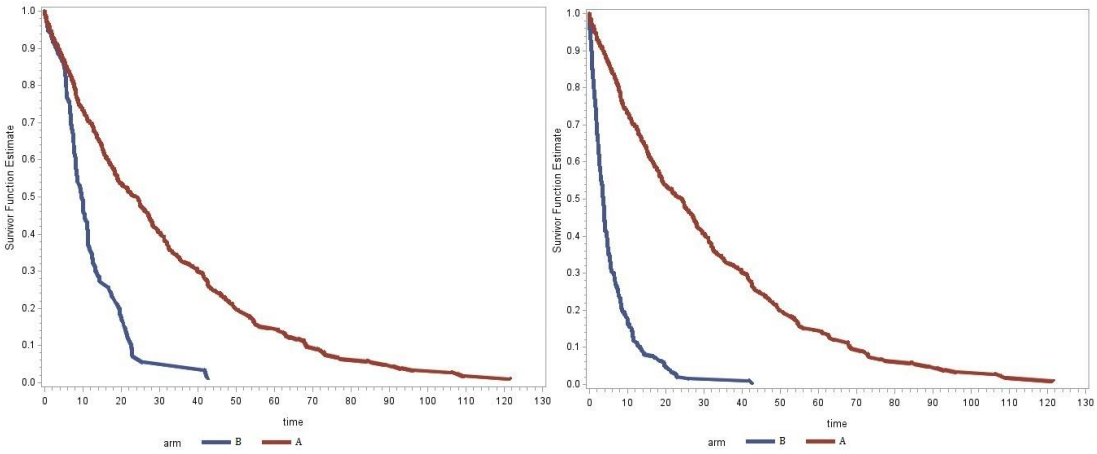
```
/*Hazard Ratios with crossover using IPCW technique*/

proc phreg data=a12;
model time2*evento(0)=arm;
freq w/notruncate;
run;
```

Once we have performed both Cox regression models we can assess how well the models detect the difference between the treatment arms. Recall that we simulated a Hazard Ratio equal to 5 or 0.2, depending on the arm that is considered as reference.

As we expected IPCW outperforms the Censoring Analysis given a more accurate, although still biased, Hazard Ratio estimate.

Crossover	Technique	Hazard Ratio	95%CI
Allowed	Censoring Analysis	0.401	0.338 – 0.476
	IPCW	0.256	0.224 – 0.292

These results also can be viewed graphically. The plot on the left corresponds to censoring analysis and the plot on the right to the IPCW method.



An important issue to have in mind is that the weights used in the Cox regression model introduce variability in the model and hence the 95% CI of the IPCW method are unadjusted. This problem can be fixed using bootstrapping [4].

CONCLUSION

This paper shows an example of how to perform the Inverse Probability of Censoring Weighting technique using SAS® software. It recreates the scenario where crossover is allowed and hence obtains a less biased estimation of the clinical benefit of the experimental arm compared with the control arm than the one obtained using censoring analysis.

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