

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

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PhUSE Annual Conference, 12th-15th Oct 2014, London, UK

Introduction



- In oncology, the comparison of two treatment arms is usually performed using Cox regression or the log-rank test.
- When crossover is allowed, bias is introduced and results are no longer reliable.
- New methods such as Inverse Probability of Censoring Weighting (IPCW), introduced by Robins et al. in 1990, can be used to reduce bias and obtain more accurate results.

Introduction



- IPCW attempts to reduce the bias caused by treatment change recreating a scenario where any patient switched to the alternative treatment arm.
- This recreation is done using a weighted Cox regression, where the weights are usually based on a logistic regression that models whether the patient switched to the other treatment or not.
- We want to compare how IPCW behaves compared with more traditional methods such as censoring analysis.

Analysis



- Let's suppose that we have the next clinical trial:
 - Treatment A vs Treatment B

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 - Assume that treatment B performs worse and hence patients switch to treatment A.

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- Let's suppose that we have the next clinical trial:
 - Treatment A vs Treatment B.
 - Assume that treatment B performs worse and hence patients switch to treatment A.
 - Crossover introduces bias in the overall comparison.

Analysis



- How can we deal with crossover?
 - Censoring Analysis.

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 - ITT.

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 - Censoring Analysis.
 - ITT.
 - Inverse Probability of Censoring Weighting.

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 - We want to compensate the effect of switching.
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 - Cluster patients with similar characteristics based on baseline and postrandomization covariates.



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- Inverse Probability of Censoring Weighting (IPCW).
 - In each cluster, patients who stayed will have higher weight values and patients who switched will have lower values.
 - Weights are estimated based on the probability of remaining uncensored by crossover. This can be done by means of a logistic regression model.
 - Specifically, we need to build two logistic regression models. One using only baseline characteristics and other using both baseline covariates and postrandomization covariates, which are usually time dependent.

Analysis



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

Analysis



- An example with dummy data:
 - 800 patients (400 patients in each treatment arm).

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 - Two time dependent covariates: Performance Status (PS) and the number of Adverse Events Grade 3.

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 - Event and Event_c, which are the censoring status.

Analysis



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 - 800 patients (400 patients in each treatment arm).
 - Time, which is the OS for each patient.
 - Three Baseline covariates: prior time to progression, age and number of affected regions.
 - Two time dependent covariates: Performance Status (PS) and the number of Adverse Events Grade 3.
 - Event and Event_c, which are the censoring status.
 - Time2, which includes the effect of the new treatment.

Analysis

- An example with dummy data:

id	am	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

Analysis



- An example with dummy data:
 - Logistic regression with baseline covariates.

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

- An example with dummy data:
 - Logistic regression with baseline covariates.
- Logistic regression with both baseline and time dependent covariates.

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

```
proc genmod data=a10 descending order=data;  
class evento_c id;  
model evento_c=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;
```

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

- An example with dummy data:
 - Merge the output datasets and calculated the weights.

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

Analysis



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 - Merge the output datasets and calculated the weights.

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

- Hazard Ratio estimation.

Censoring Analysis

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

Analysis



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 - Merge the output datasets and calculated the weights.

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

- Hazard Ratio estimation.

Censoring Analysis

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

IPCW

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

Analysis

- An example with dummy data:

- Results:

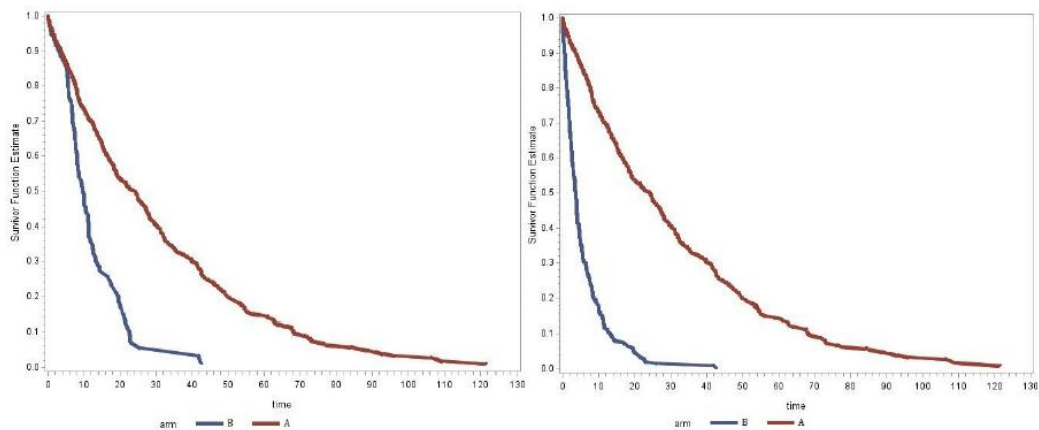
Crossover	Technique	Hazard Ratio	95%CI
Allowed	Censoring Analysis	0.401	0.338 – 0.476
	IPCW	0.256	0.224 – 0.292

Analysis

- An example with dummy data:

Results:

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



Conclusion



We can obtain a less biased estimation of Hazard Ratios when dealing with crossover and diminish the problems caused by classical method such as censoring analysis.

Questions

