

Practical Survival Analysis Techniques for Clinical Trials Using SAS

-- A comprehensive guide for biostatisticians and statistical programmers

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What We'll Cover



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RMST, Max-Combo Test



Treatment Crossover Adjustments

RPSFT, 2SAFT, IPCW

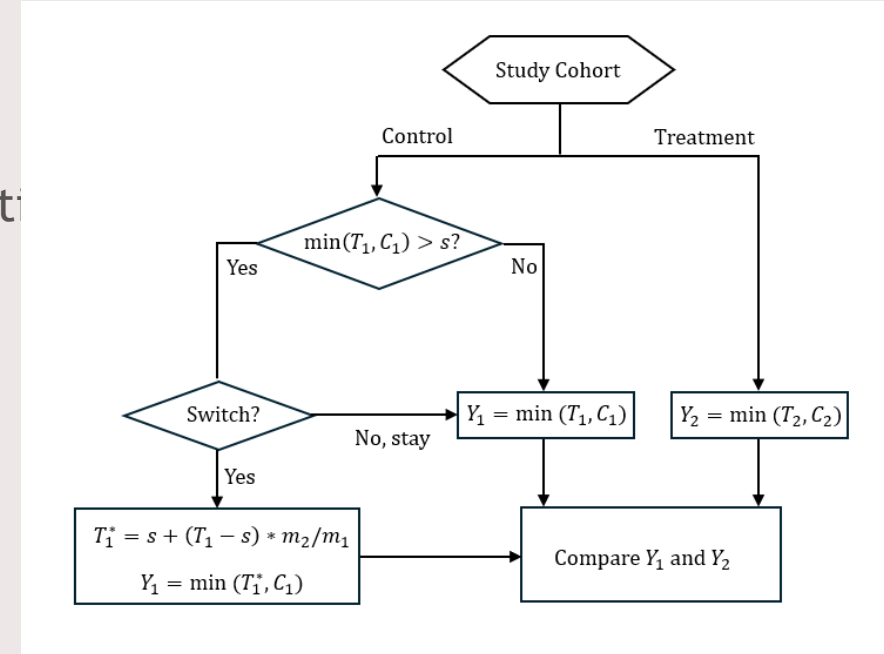
Data Generation Framework

Parameters for data generation:

- Survival time in control and treatment groups: T_1 and T_2
- T_1 and T_2 are assumed to follow an **exponential** distribution
- Median survival time represented by m_1 and m_2
- Censoring times for two groups: C_1 and C_2
- Switching time represented by s
- Switching probability denoted as p
- Observed survival time represented by Y_1 and Y_2

Two datasets were generated for this guidance:

- **Surv_1** dataset: subject-level data of **500 subjects** with age, gender, treatment arm, overall survival time, censoring indication and switching time.
- **Surv_2** dataset: structured in the **counting process** style of input based on **Surv_1** dataset, where an observation corresponds to a time interval until survival time is reached.



Sample Data

Description of sample data:

- **Subject**: unique subject ID.
- **Age**: age of subject.
- **Gender**: gender of subject.
- **Arm**: specifying which treatment the subject received.
- **Time**: overall survival time in months.
- **Status**: censoring indicator for overall survival time.

Equal to 1 if subject died and 0 otherwise.

- **Switch**: cross over time in number of months.
- **T_start** (only in *Surv_2*): beginning of the time interval in number of months.
- **T_end** (only in *Surv_2*): end of the time interval in number of months.
- **Hgb** (only in *Surv_2*): blood hemoglobin in g/dL (time varying covariates).

Variables in Creation Order						
#	Variable	Type	Len	Format	Informat	Label
1	Subject	Num	8	BEST.		Subject ID
2	Age	Num	8	BEST.		Age
3	Gender	Char	6	\$8.	\$8.	Gender
4	Arm	Char	9	\$9.	\$9.	Treatment Arm
5	Time	Num	8	BEST.		Overall Survival
6	Status	Num	8	BEST.		Censoring Indicator
7	Switch	Num	8	BEST.		Crossover Time
8	T_start	Num	8	BEST.		Beginning of Time Interval
9	T_end	Num	8	BEST.		End of Time Interval
10	Hgb	Num	8	BEST.		Hemoglobin

Primary Analysis

Log-Rank Test

- **Purpose:** compares survival distributions between two or more groups.
- **Key Feature:** adjusts for confounding variables using stratification (e.g., gender).
- **Assumption:** hazard ratio between groups is constant across strata.
- **Interpretation:** Chi-square and p-value indicate if survival differences are statistically significant.

```
proc lifetest data=surv_1;  
time Time*Status(0);  
strata gender / group = arm;  
run;
```

Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	12.6519	1	0.0004
Wilcoxon	11.0244	1	0.0009

Cox Proportional Hazards Model

- **Purpose:** estimates the effect of covariates (e.g., treatment) on survival time.
- **Key Feature:** allows different baseline hazards across strata, assumes common effect of covariates.
- **Assumption:** proportional hazards (effect of covariates is constant over time).
- **Interpretation:** hazard ratio with 95% confidence interval quantifies treatment effect.

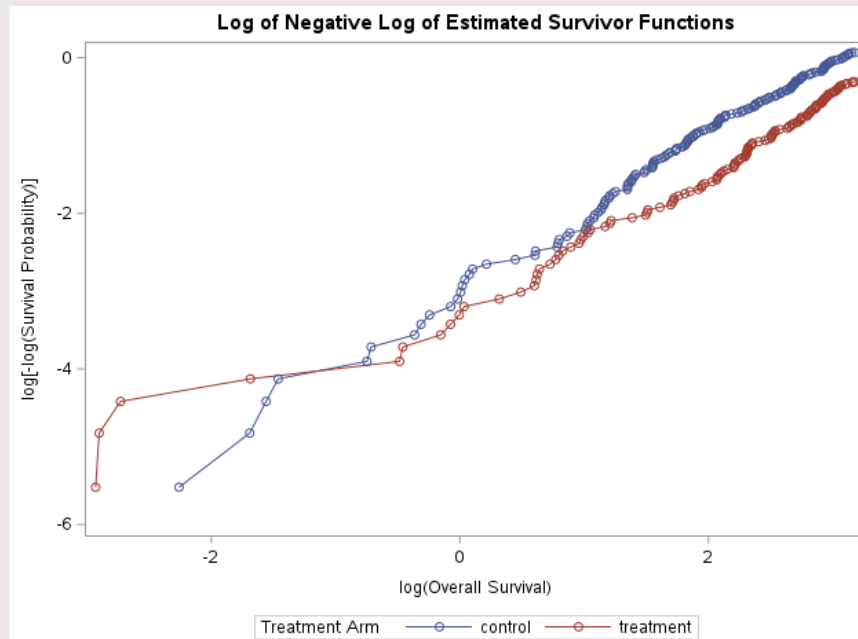
```
proc phreg data=surv_1;  
class gender arm(ref='control');  
strata gender;  
model Time*Status(0)=arm/risklimits;  
hazardratio arm / cl = wald;  
run;
```

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	12.5840	1	0.0004
Score	12.6519	1	0.0004
Wald	12.4732	1	0.0004

PH Assumption

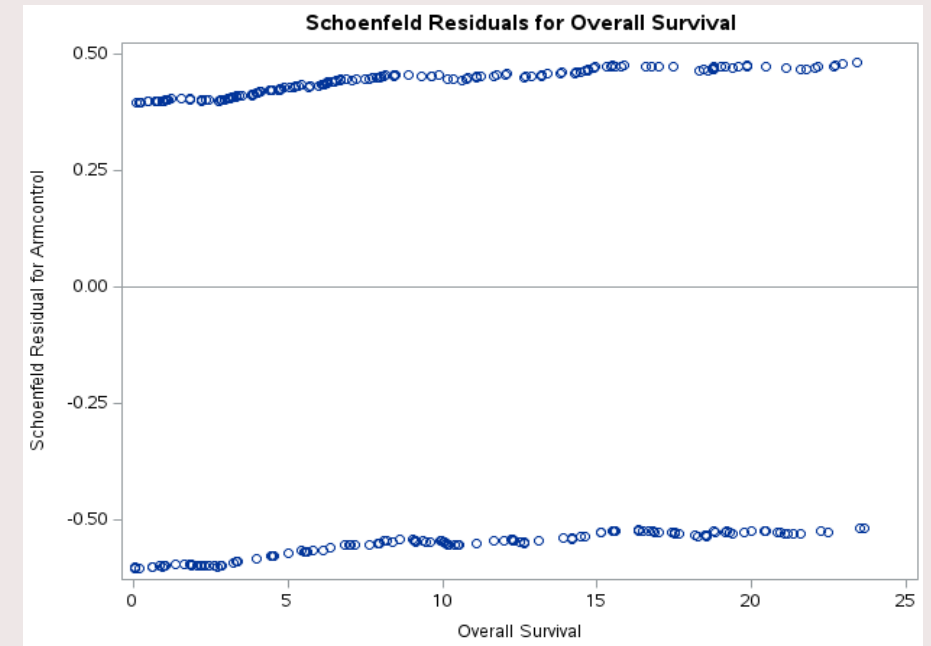
Log-minus-log: parallel curves of two arms indicate that the PH assumption holds

```
proc lifetest data=surv_1 plots=(lls);  
time Time*Status(0);  
strata arm;  
run;
```



Schoenfeld residuals: patterns or trends can reveal violations of the assumption

```
proc phreg data=surv_1;  
class arm;  
model Time*Status(0) = arm;  
output out=out ressch=schres;  
run;  
  
proc sgplot data=out;  
scatter y=schres x=Time / name='scatter';  
title "Schoenfeld Residuals for Overall Survival";  
refine 0;  
run;
```



Non-proportional Hazards

Restricted Mean Survival Time (RMST)

- RMST is defined as the expected survival time up to a pre-specified time point τ .

$$RMST(\tau) = \int_0^{\tau} S(t) dt$$

- The difference in RMST is a common measure of absolute treatment effect.

$$\theta = RMST_1(\tau) - RMST_2(\tau)$$

- The default RMST method uses min-max value for τ unless it is pre-specified.

```
proc lifetest data=surv_1 rmst;  
time Time*Status(0);  
strata arm / diff = all;  
run;
```

Restricted Mean Survival Time Comparisons					
Stratum Comparison		Difference	Standard Error	Chi-Square	Pr > ChiSq
control	treatment	-2.93567	0.7634	14.7891	0.0001

Max-Combo Test

- Max-combo test combines multiple weighted log-rank tests using Fleming-Harrington weights.

$$w(t) = \hat{S}(t)^{\rho}(1 - \hat{S}(t))^{\gamma}$$

- The maximum Z statistics is maximum among weights function (0,0), (0,1), (1,0) and (1,1).

$$Z_{max} = \max(Z_{0,0}, Z_{0,1}, Z_{1,0}, Z_{1,1})$$

- It provides robustness across various non-proportional hazard patterns.

```
%combo_wlr(data=surv_1, group=arm, time=Time, event=Status, weights=%str(0,0 1,0 0,1 1,1));
```

Weighted log-rank tests

Test	Z statistic	P
Fleming(0,0)	3.54507	0.0004
Fleming(1,0)	3.71921	0.0002
Fleming(0,1)	2.47705	0.0132
Fleming(1,1)	2.97755	0.0029

Combination test

Z max	P
3.71921	0.0004

Treatment Crossover

Rank Preserving Structure Failure Time (RPSFT)

- RPSFT model assumes a common factor for patients who switch from control to treatment group which preserves the ranking of failure time.

$$T = T_{off} + e^{\psi} T_{on}$$

- T_{off} and T_{on} indicate the time 'off' and 'on' treatment group. e^{ψ} is the acceleration factor.
- The estimation of ψ can be implemented with various methods (log-rank test, Weibull test and Cox model).
- The optimal value is the value that set test statistics equal to 0, which implies treatment group not related to survival time.

```
%rpsft(data=surv_1, aval=time, cnsr=status, trt=arm, xo_time=switch, psi_start=-1, psi_end=1, psi_step=0.1, recnsr='N');
```

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
Arm	treatment	1	-0.45517	0.11776	14.9401	0.0001	0.634	0.504 0.799	Treatment Arm treatment

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	15.0743	1	0.0001
Score	15.1955	1	<.0001
Wald	14.9401	1	0.0001

Two-stage Accelerated Failure Time (2SAFT)

- Similarly, the two-stage AFT model assumes the counterfactual survival time by:

$$T = T_A + e^{\psi} T_B$$

- T_A and T_B indicate the time 'off' and 'on' treatment group. e^{ψ} is the acceleration factor.
- In the first stage, an accelerated failure model (e.g. Lognormal, Weibull or Gamma distribution) is fitted to estimate ψ .
- The second stage is to recalculate the counterfactual survival time for patients who switch from control to treatment group using the estimated ψ .

```
%twosaft(data=surv_1, aval=time, cnsr=status, trt=arm, xo_time=switch, af_dist=weibull, recnsr='N');
```

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
Arm	treatment	1	-0.47310	0.11781	16.1258	<.0001	0.623	0.495 0.785	Treatment Arm treatment

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	16.2705	1	<.0001
Score	16.4230	1	<.0001
Wald	16.1258	1	<.0001

Treatment Crossover

Inverse Probability of Censoring Weighting (IPCW)

- **Goal:** Adjust for treatment crossover by creating a pseudo-population in which censoring due to switching is balanced.
- **Key Assumption:** All confounders (baseline + time-varying) associated with switching and outcome are measured.
- **Weight Construction:**
 - **Numerator:** Probability of remaining uncensored using baseline covariates only.
 - **Denominator:** Probability using baseline + time-varying covariates.
- **Application:** Apply weights to Cox model to estimate treatment effect under a no-crossover scenario.
- **Interpretation:** Produces hazard ratio estimates reflecting survival outcomes as if no patients had crossed over.

$$w_{ij} = \prod_{k=1}^j \frac{P(C_i > t_k | C_i > t_{k-1}, X_i)}{P(C_i > t_k | C_i > t_{k-1}, X_i, Z_i)}$$

```
%ipcw(data=surv_2, subject=subject, trt=arm, censor=status, xo_time=switch, bl_covar=gender, t_start=t_start, t_end=t_end, tv_covar=hgb);
```

Analysis of Maximum Likelihood Estimates									
with Model-Based Variance Estimate									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
Arm	control	1	0.20448	0.07940	13.7561	0.0002	1.342	1.149 1.568	Treatment Arm control

Analysis of Maximum Likelihood Estimates										
with Sandwich Variance Estimate										
Parameter		DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
Arm	control	1	0.29448	0.11461	1.443	6.6022	0.0102	1.342	1.072 1.681	Treatment Arm control

SAS Macro

Appendix I

```
%macro combo_wlr(  
  data=,          /* input dataset */  
  group=,         /* Randomized treatment (1=treatment, 0=control) */  
  time=,          /* Survival time */  
  event=,         /* Death/event indicator */  
  weights=        /* Combination of weight functions */  
);
```

Appendix III

```
%macro twosaft(  
  data=,          /* Input dataset */  
  aval=,          /* Survival time */  
  cnsr=,          /* Death/event indicator */  
  trt=,           /* Randomized treatment (1=treatment, 0=control) */  
  xo_time=,       /* Time of crossover (0 if never crossed) */  
  af_dist=,  
  recnsr=         /* Recensoring */  
);
```

Appendix II

```
%macro rpsft(  
  data=,          /* Input dataset */  
  aval=,          /* Survival time */  
  cnsr=,          /* Death/event indicator */  
  trt=,           /* Randomized treatment (1=treatment, 0=control) */  
  xo_time=,       /* Time of crossover (0 if never crossed) */  
  psi_start=,     /* Lower bound for psi parameter */  
  psi_end=,       /* Upper bound for psi parameter */  
  psi_step=,      /* Interval for psi parameter */  
  recnsr=         /* Recensoring */  
);
```

Appendix IV

```
%macro ipcw(data, subject, trt, censor, xo_time, bl_covar, t_start, t_end, tv_covar);
```

Reference

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- Royston, P., Parmar, M.K. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol* 13, 152 (2013).



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Thank you

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