

# SAS Macro to Implement Survival Analyses for Oncology Trials

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## ABSTRACT

The primary objective in Oncology clinical trials is to determine the effect of drug treatment on the survival experience of patients. Survival analyses are often implemented in SAS® for this purpose. However, analyses can be similar across studies, resulting in SAS programs being repetitive. The motivation is to implement common survival analyses as a SAS macro, and to have the macro validated for multiple uses.

In this SAS macro, we have incorporated two procedures for survival analyses; PROC LIFETEST and PROC PHREG. The LIFETEST procedure output descriptive statistics, survival rates, the number of patient at risk, and p-values of log-rank, Wilcoxon and trend tests. The PHREG procedure provides hazard ratios and the confidence intervals of the ratios. This SAS macro is suitable for regulatory reporting and can be used in the clinical phases of drug development. The final output consists of statistics that are arranged in the Distribution, Probabilities, Hazard Ratios and P-values sections.

This paper discusses the syntax and macro variables used in creating this SAS macro. A sample output table from this SAS macro is included to illustrate the table sections and format.

**Keywords:** PROC LIFETEST, PROC PHREG, log-rank test, Wilcoxon test, trend test, hazard ratios.

## SYNTAX

The survival analyses are performed based on SAS's PROC LIFETEST and PROC PHREG. Table 1 shows the main syntax of this SAS macro. There are two sets of syntax for PROC LIFETEST, both containing a TIME statement, and a STRATA or TEST statement. The TIME statement allows you to specify the survival time variable and censoring variable. Note that the default value for censored observations is 1, as indicated in the parenthesis. When a variable is specified in the STRATA statement of LIFETEST, SAS computes Kaplan Meier estimates for each level of the variable. In addition, it performs tests of homogeneity, i.e. log-rank and Wilcoxon tests. When a TEST statement is included in PROC LIFETEST, SAS performs a trend test to test for a survival trend in an ordinal variable. PROC PHREG models the hazard function. It is also incorporated into this macro to compute all possible pairwise hazard ratios and the confidence intervals for the ratios.

**Table 1 Syntax of PROC LIFETEST and PROC PHREG**

```
/* PROC LIFETEST computes the Kaplan Meier estimates for each level */
/* and performs tests of homogeneity */

proc lifetest data=dataset-name;
    time time-variable*censor(1);
    strata strata-variable;

/* TEST statement in PROC LIFETEST performs trend test */

proc lifetest data=dataset-name;
    time time-variable*censor(1);
    test strata-variable;

/* PROC PHREG computes the pairwise hazard ratios among the strata */

proc phreg data=dataset-name;
    model time-variable*censor(1)=strata-variable/ rl alpha=0.1;
```

## MACRO VARIABLES

We have created 14 required macro variables for the function of the SAS macro. In Table 2, we have given a description of the macro variables. The first few macro variables, DATA, TIMEVAR, TRT, STATUS, and UNIT require the input of model parameters, with the exception of DATA, which requires the input of the dataset name. REFCAT, SCORE\_EQ and CI requests for type of method in constructing test statistics and confidence intervals. Most of these macro variables are used in PROC LIFETEST and PROC PHREG. For example, the survival time and censoring are represented by TIMEVAR and STATUS respectively. The results are stratified based on the levels of the variable specified in TRT. The macro variable UNIT provides

a time unit reference to the survival time variable. The list of time points specified in the macro variable D reference the survival rates beyond some point in time. CI provides the alpha value for computing the  $100(1-\alpha)\%$  confidence intervals. SCORE\_EQ is used in the LIFETEST procedure but only in performing trend test where you could specify the use of equally spaced groups. Unlike other macro variables, REFCAT is used solely in the PHREG procedure as reference groups for computing hazard ratios. Finally, PROB, HAZARD, LOG, WIL, and TREND request for the survival rates, hazard ratios, log-rank, Wilcoxon and trend p-values to be printed accordingly in the output table.

**Table 2 Macro variables for the operation of SAS macro**

| Variables | Description                                                                                                                                         | Valid Values                                                                                             |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| DATA      | Survival dataset.                                                                                                                                   |                                                                                                          |
| TIMEVAR   | Survival time variable in the DATA parameter.                                                                                                       |                                                                                                          |
| TRT       | Variable from &DATA used for stratification in analysis and summary.                                                                                | Any ordinal or categorical variable. For example, gender, dose, or treatment.                            |
| STATUS    | Censoring indicator corresponding to TIMEVAR whose values must be 0 or 1, and 1 indicates censored observation.                                     |                                                                                                          |
| UNIT      | Time unit variable corresponding to TIMEVAR.                                                                                                        |                                                                                                          |
| REFCAT    | Reference group for obtaining hazard ratio(s).<br>(Use <code>_ALL_</code> to generate all pairwise hazard ratios based on levels of TRT parameter.) | <code>_ALL_</code> , or any value of the variable set to the TRT parameter.<br>Default: <code>ALL</code> |
| SCORE_EQ* | Requests the use of equally-spaced scores for trend test.<br>(This only applies when TRT parameter contains an ordinal variable.)                   | Y, N<br>Default: N                                                                                       |
| D         | List of $\leq 10$ time points to be included in the Probabilities Section.<br>(See parameter PROB below.)                                           | Any non-negative number(s).<br>Multiple values must be separated by space.<br>Default: 6 12              |
| CI        | Confidence level for all confidence intervals of survival time quartiles and survival estimates.                                                    | Any number between 0 and 1, not inclusive of 0 and 1.<br>Default: 0.05                                   |
| PROB*     | Includes Probabilities section in the output.                                                                                                       | Y, N<br>Default: Y                                                                                       |
| HAZARD*   | Includes Hazard Ratios section in the output.                                                                                                       | Y, N<br>Default: Y                                                                                       |
| LOG*      | Includes pairwise log-rank p-value(s) in p-value section.                                                                                           | Y, N<br>Default: Y                                                                                       |
| WIL*      | Includes pairwise Wilcoxon p-values in p-value section.                                                                                             | Y, N<br>Default: N                                                                                       |
| TREND*    | Includes trend p-value in p-value section.<br>(This only applies when TRT parameter contains an ordinal variable.)                                  | Y, N<br>Default: N                                                                                       |

Abbreviations: Y= Yes; N= No.

\*: When parameter is set to Y, user requests the use of the functions as described.

## SURVIVAL DATASET

The survival data should at least consist of variables that satisfy the macro variables TIMEVAR, TRT, STATUS, and UNIT. Here, we have created a sample dataset in Table 3 with the following variables: PATNO, DOSE, SURV, SURVUN, and CENSOR. PATNO refers to the patient number, DOSE (50, 100, 200 mg) indicates the treatment dose received by the patients, SURV is the survival time, SURVUN (i.e. days, months, or years) is the survival time unit, and CENSOR (1=Alive, 0=Deceased) indicates censored observations.

**Table 3 Sample survival dataset**

| PATNO    | DOSE | SURV | SURVUN | CENSOR |
|----------|------|------|--------|--------|
| 1250     | 50   | 6.2  | MONTHS | 0      |
| 1254     | 50   | 5.6  | MOTNHS | 0      |
| 1255     | 50   | 6.7  | MONTHS | 1      |
| 1267     | 50   | 4.3  | MONTHS | 0      |
| <b>N</b> |      |      |        |        |
| 1310     | 100  | 3.6  | MOTNHS | 0      |
| 1321     | 100  | 1.4  | MONTHS | 1      |
| 1324     | 100  | 2.1  | MONTHS | 0      |
| 1329     | 100  | 7.4  | MONTHS | 1      |

| N    |     |     |        |   |
|------|-----|-----|--------|---|
| 1401 | 200 | 1.7 | MOTNHS | 0 |
| 1411 | 200 | 3.9 | MONTHS | 0 |
| 1428 | 200 | 2.8 | MONTHS | 0 |
| 1459 | 200 | 3.5 | MONTHS | 1 |
| N    |     |     |        |   |

### SAMPLE OUTPUT TABLE

The output table from this SAS macro consists of four main sections, specifically, Distribution, Probabilities, Hazard Ratios and P-values. A summary of the output table is given in Table 4. Whilst the statistics in the Distribution, Probabilities and P-values sections are obtained from PROC LIFETEST, the hazard ratios are obtained from PROC PHREG.

Table 5 presents format of the output table with the results stratified on the treatment dose received by patients. Descriptive statistics of the survival time variable specified in the macro variable TRT are first reported for each dose. This includes the number of events, the censoring rate, and the percentiles of the survival distribution function. Since the descriptive statistics provide useful priori information to the survival experience of patients, it is made a default section of the table.

The 3, 6, 9 and 12 months time points listed in the Probabilities section are according to the values specified in the macro variable D. The SAS macro prints the survival rates and number of subjects at risk that correspond to these time points. If any time point specified in macro variable D is not an observed survival time, then the survival rate of the first smaller observed time point will be selected. However, if the specified time point is negative, then the macro will suppress printing of the survival rates for that time point. The *time-to-event* and *time\_unit* in the Probabilities section are replaced by the label of the survival time variable and value of the macro variable UNIT respectively. Note that the time unit (i.e. days, months, or years) should be consistent as the first value is used as *time\_unit*.

The hazard ratios also provide a meaningful measure of drug effect between groups. For studies with more than 2 treatment groups, all possible pairwise hazard ratios and confidence intervals for the hazard ratios will be reported when REFCAT= ALL\_ is specified. Otherwise, pairwise hazard ratios will be reported for the groups specified in the macro variable REFCAT. The groups specified in REFCAT are used as reference groups in the computation of the hazard ratios, and are displayed as the column variables.

Both the log-rank and Wilcoxon tests are used to determine whether there are any significance differences between any two survival functions. We have included both the log-rank and Wilcoxon tests to provide a better assessment of the differences in survival functions during the early and late study period. However, the display of log-rank and Wilcoxon p-values are optional, and will be printed upon request. Note that the pairwise log-rank and Wilcoxon p-values are arranged in an upper triangular matrix.

The trend test also tests for no difference in the survival experience among groups. In addition, it provides evidence to support the presence of a survival trend in a relevant variable. In our case, we have used the macro variable TRT to represent an ordinal variable. If an ordinal variable is specified in TRT, a trend test statistic could be computed with specification of the use of equally spaced groups in macro variable SCORE\_EQUAL. The trend test p-value will be printed upon request.

**Table 4 Summary of Sample Output Table**

1. Distribution Section  
Number of events and censoring rate (in percentage) reported.  
Quartiles, minimum, and maximum of the survival time distribution reported. This section provides the 25<sup>th</sup> percentile, median, 75<sup>th</sup> percentile and the minimum and maximum survival time for each stratification variable. Confidence intervals for quartiles will also be reported.
2. Probabilities Section  
Probability that *time-to-event* is at least *xx time\_unit* reported. It provides the survival rates (in percentage) of subjects at each indicated time point for each stratification variable. The confidence intervals for the survival rates will also be reported.
3. Hazard Ratios Section  
Pairwise hazard ratios are reported. The confidence intervals for the hazard ratio will also be reported if hazard ratios are requested.
4. P-values Section  
Log-rank p-values, Wilcoxon p-values, and trend p-value are each optionally reported.

The log-rank and Wilcoxon p-values are results of testing for no difference between the survival curves of the stratification variable. The trend p-value is the result of testing for no difference in the event among the levels of the ordinal variable.

## CONCLUSION

The SAS macro was developed to implement survival analyses for Oncology trials. The example output table provides descriptive statistics and tests of homogeneity to determine survival experience of patients among treatments.

With the use of this tool, we can standardize reports structure, and provide better consistency across studies to support regulatory submissions. In addition, it expedites reporting with less time spent on analyses. Hence, time savings result.

## REFERENCES

SAS Institute Inc., *SAS/STAT® User's Guide, Version 8*, Cary, NC: SAS Institute Inc., 1999. 3884 pp.

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Table 5 Sample Output Table Stratified on Treatment Dose

SURVIVAL TIME (MONTHS)

| Statistics                                    | DOSE (mg) |            |          |            |          |            |              |           |
|-----------------------------------------------|-----------|------------|----------|------------|----------|------------|--------------|-----------|
|                                               | 50        |            | 100      |            | 200      |            | All Patients |           |
|                                               | N=94      | 95% CI     | N=100    | 95% CI     | N=115    | 95% CI     | N=309        | 95% CI    |
| Number of Events                              | 55        |            | 53       |            | 40       |            | 148          |           |
| Censoring Rate (%)                            | 41.5      |            | 47.0     |            | 65.2     |            | 52.1         |           |
| Minimum (Observed)                            | 0.1       |            | 0.1      |            | 0.2      |            | 0.1          |           |
| 25th Percentile                               | 6.2       | 4.4, 7.3   | 4.6      | 3.9, 5.7   | 4.2      | 2.9, 5.6   | 4.9          | 4.2, 5.6  |
| Median                                        | 9.7       | 7.9, 12.0  | 7.5      | 6.3, 9.3   | 6.5      | 6.1, NA    | 7.9          | 7.1, 9.3  |
| 75th Percentile                               | 14.6      | 12.1, NA   | 10.6     | 9.7, NA    |          | 7.1, NA    | 13.7         | 11.4, NA  |
| Maximum (Observed)                            | 16.6*     |            | 11.0*    |            | 8.1*     |            | 16.6*        |           |
| Probability that survival time is at least:** |           |            |          |            |          |            |              |           |
| 3 MONTHS                                      | 92% (85)  | 87% , 98%  | 91% (85) | 85% , 97%  | 82% (84) | 75% , 89%  | 88% (255)    | 84% , 92% |
| 6 MONTHS                                      | 75% (68)  | 66% , 84%  | 62% (50) | 52% , 72%  | 62% (27) | 51% , 72%  | 66% (145)    | 61% , 72% |
| 9 MONTHS                                      | 53% (43)  | 42% , 63%  | 40% (20) | 29% , 52%  | 39% (4)  | 18% , 61%  | 44% (62)     | 37% , 51% |
| 12 MONTHS                                     | 38% (18)  | 27% , 50%  | 19% (2)  | 1% , 37%   | 39% (4)  | 18% , 61%  | 30% (18)     | 22% , 38% |
| Hazard Ratio #                                |           |            |          |            |          |            |              |           |
| 50                                            |           |            | 0.62     | 0.41, 0.93 | 0.53     | 0.33, 0.84 |              |           |
| 100                                           | 1.61      | 1.08, 2.42 |          |            | 0.85     | 0.56, 1.31 |              |           |
| 200                                           | 1.89      | 1.19, 3.01 | 1.17     | 0.77, 1.80 |          |            |              |           |
| Log-rank p-value                              |           |            |          |            |          |            |              |           |
| 50 vs                                         |           |            | 0.020    |            | 0.014    |            |              |           |
| 100 vs                                        |           |            |          |            | 0.418    |            |              |           |
| 200 vs                                        |           |            |          |            |          |            |              |           |
| Wilcoxon p-value                              |           |            |          |            |          |            |              |           |
| 50 vs                                         |           |            | 0.050    |            | 0.021    |            |              |           |
| 100 vs                                        |           |            |          |            | 0.342    |            |              |           |
| 200 vs                                        |           |            |          |            |          |            |              |           |
| Trend p-value                                 |           |            |          |            |          |            |              |           |
| Overall=                                      | 0.005     |            |          |            |          |            |              |           |

CI = Confidence Interval

NA = Not available due to insufficient event time data

\* The marked survival times are censored observations

\*\* Values in parenthesis indicate number of subjects at risk

# Reference groups are in columns