Chapter 695

Two-Group Survival Comparison Tests (Simulation)

Introduction

This procedure uses simulation to determine power or sample size for the following survival comparison tests:

- Logrank

- Gehan-Wilcoxon

- Tarone-Ware

- Peto-Peto

- Modified Peto-Peto

- Fleming-Harrington with flexible *p* and *q*

Survival rates (hazard rates, median survival times, proportion surviving, or mortality) can be piece-wise customized to specify proportional hazard scenarios or non-proportional hazard scenarios. The treatment group survival rates can be specified directly or based on hazard ratios (or mortality ratios).

Loss-to-follow-up and noncompliance proportions can be entered with piece-wise flexibility. Noncompliance survival rates can be specified directly or can be set to the opposite treatment group survival rate.

Accrual times and accrual patterns are completely flexible.

Four Different Effect Size Parameterizations

There are four closely-related effect size parameterizations that are available in this procedure and documented in this chapter. The parameterization can be in terms of hazard rates, median survival times, proportions surviving a given time period, or mortality during a given time period. When median survival times, proportions surviving, or mortality are used, the values are converted to the corresponding hazard rates before the simulation process begins.

Hazard Rate Parameterization

In this case, the hazard rates for the control and treatment groups are specified directly.

Median Survival Time Parameterization

Here, the median survival time is specified. These are transformed to hazard rates using the relationship $h = \ln(2) / MST$.

Proportion Surviving Parameterization

In this case, the proportion surviving until a given time $T0$ is specified. These are transformed to hazard rates using the relationship $h = -\ln(S(T0)) / T0$. When separate proportions surviving are given for each time period, $T0$ is taken to be the time period unit.

Mortality Parameterization

Here, the mortality until a given time $T0$ is specified. These are transformed to hazard rates using the relationship $h = -\ln(1 - M(T0)) / T0$. When separate mortalities are given for each time period, $T0$ is taken to be the time period unit.

Technical Details

This section outlines the simulation procedure and the test statistic details.

Simulation Procedure

In this procedure, a large number of simulations are used to calculate power using the following steps:

1. The total sample size is divided into the control and treatment group sample sizes (N1 and N2) according to the Group Allocation specified.

2. Based on the specified survival rates, and noncompliance proportions and survival rates, a hazard rate function is generated for each subject of each group. The hazard rate function is used to generate a random survival time and the loss proportion is used to determine whether the simulated subject is right censored due to loss before the event.

3. A starting time for each subject is generated based on the accrual time and the accrual pattern.

4. For each sample (of N1 + N2 subjects), a test statistic is produced. Based on the test statistic, it is determined whether the null hypothesis is rejected for each sample.

5. The proportion of rejected null hypotheses is the estimated power.

Test Statistics

This section presents methods for testing that the survival curves, and thus the hazard rates, of two or more populations are equal. The specific hypothesis set that is being tested is

$$H_0 : h_1(T) = h_2(T) \text{ for all t} \leq \tau$$

$$H_1 : h_1(T) \neq h_2(T) \text{ for some t} \leq \tau$$

In words, the null hypothesis is that the hazard rates of the two populations are equal at all times less than the maximum observed time and the alternative hypothesis is that the two hazard rates differ at some time less than the observed maximum time.

Two-Group Survival Comparison Tests (Simulation)

The general form of the test statistic is

$$Z = \frac{\sum_{i=1}^{D} W(t_i)\left[d_{i1} - Y_{i1}\left(\frac{d_i}{Y_i}\right)\right]}{\sqrt{\sum_{i=1}^{D} W(t_i)^2 \frac{Y_{i1}}{Y_i}\left(1 - \frac{Y_{i1}}{Y_i}\right)\left(\frac{Y_i - d_i}{Y_i - 1}\right)d_i}}$$

where

> D is the number of distinct event times
>
> $W(t_i)$ is the weight function at time t_i
>
> Y_{i1} is the number at risk in the Group 1 sample at time t_i
>
> Y_i is the combined number at risk at time t_i
>
> d_{i1} is the number of events in the Group 1 sample at time t_i
>
> d_i is the combined number of events at time t_i

Details of the above formulas can be found in Klein and Moeschberger (1997), pages 191-202, and Andersen, Borgan, Gill, and Keiding (1992), pages 345-356.

Six different choices for the weight function, $W(T)$, with the flexible p and q for the Fleming-Harrington weight function, result in a variety of tests that are available in this procedure. The most commonly used test is the Logrank test, which has equal weighting. The other tests shift the heaviest weighting to the beginning or end of the trial. This may be appropriate in some studies, but the use of one of these other weighting schemes should be designated before the data have been seen. Because of the different weighting patterns, they will often give quite different results.

The following table describes each of these tests.

Test	**Weight**	**Comments**
Logrank	1	This is the most commonly used test. Equal weights across all times. This test has optimum power when the hazard rates of the K populations are proportional to each other.
Gehan-Wilcoxon	Y_i	Places very heavy weight on hazards at the beginning of the study.
Tarone-Ware	$\sqrt{Y_i}$	Places heavy weight on hazards at the beginning of the study.
Peto-Peto	$\tilde{S}(t_i)$	Places a little more weight on hazards at the beginning of the study.
Modified Peto-Peto	$\tilde{S}(t_i)Y_i/(Y_i + 1)$	Places a little more weight on hazards at the beginning of the study.
Fleming-Harrington (0,0)	$1 - \hat{S}(t_{i-1})$	Places heavy weight on hazards at the end of the study.

Fleming-Harrington (1,0) $\hat{S}(t_{i-1})$ Places almost equal weight at all times.

Fleming-Harrington (1,1) $\hat{S}(t_{i-1})(1 - \hat{S}(t_{i-1}))$ Places heavy weight on hazards at the end of the study.

Fleming-Harrington (0.5,0.5) $\sqrt{\hat{S}(t_{i-1})(1 - \hat{S}(t_{i-1}))}$ Places a little more weight on hazards at the end of the study.

Fleming-Harrington (0.5,2) $(1 - \hat{S}(t_{i-1}))^2 \sqrt{\hat{S}(t_{i-1})}$ Places very heavy weight on hazards at the end of the study.

This table uses the following definitions.

$$\hat{S}(t) = \prod_{t_i \leq t} \left(1 - \frac{d_i}{Y_i}\right)$$

$$\tilde{S}(t) = \prod_{t_i \leq t} \left(1 - \frac{d_i}{Y_i + 1}\right)$$

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design and Options tabs. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tabs

The Design tabs contain most of the parameters and options for the general setup of the procedure.

Solve For

Solve For

Solve for either power or sample size.

The parameter selected here is the parameter displayed on the vertical axis of the plot.

Because this is a simulation based procedure, the search for the sample size may take several minutes or hours to complete. You may find it quicker and more informative to solve for Power for a range of sample sizes.

Test and Simulations

Test Type

Specify the hypothesis test that will be calculated in the simulations. Details for the tests are given in the Test Statistics section above.

The most common test for comparing two hazard rates is the logrank test.

Alternative Hypothesis

Specify the direction of the alternative hypothesis for the comparison of hazard rates. For one-sided tests, the direction should be consistent with the direction specified under the Effect Size.

Simulations

Specify the number of Monte Carlo iterations, M.

The following table gives an estimate of the precision that is achieved for various simulation sizes when the power is near 0.50 and 0.95. The values in the table are the "Precision" amounts that are added and subtracted to form a 95% confidence interval.

Simulation Size M	Precision when Power = 0.50	Precision when Power = 0.95
100	0.100	0.044
500	0.045	0.019
1000	0.032	0.014
2000	0.022	0.010
5000	0.014	0.006
10000	0.010	0.004
50000	0.004	0.002
100000	0.003	0.001

When solving for power, a large number of simulations (100,000 or 1,000,000) will finish in several minutes. When solving for N1, perhaps 10,000 simulations can be run for each iteration. Then, a final run with the resulting N1 solving for power can be run with more simulations.

Power and Alpha

Power

Power is the probability of rejecting the null hypothesis when it is false. Power is equal to 1-Beta, so specifying power implicitly specifies beta.

Beta is the probability obtaining a false negative on the statistical test. That is, it is the probability of accepting a false null hypothesis.

In the context of simulated survival comparison tests, the power is the proportion of the alternative hypothesis simulations for which the null hypothesis is rejected.

The valid range is between 0 and 1.

Different disciplines and protocols have different standards for setting power. A common choice is 0.90, but 0.80 is also popular.

You can enter a range of values such as *0.70 0.80 0.90* or *0.70 to 0.90 by 0.1*.

Alpha

Alpha is the probability of obtaining a false positive on the statistical test. That is, it is the probability of rejecting a true null hypothesis.

The null hypothesis is usually that the parameters (the means, proportions, etc.) are all equal.

In the context of simulated survival comparison tests, alpha is the proportion of the null hypothesis simulations for which the null hypothesis is rejected.

Since Alpha is a probability, it is bounded by 0 and 1. Commonly, it is between 0.001 and 0.250.

Alpha is often set to 0.05 for two-sided tests and to 0.025 for one-sided tests.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size (When Solving for Sample Size)

Group Allocation

Select the option that describes the constraints on *N1* or *N2* or both.

The options are

- **Equal (N1 = N2)**

  This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.

- **Enter R = N2/N1, solve for N1 and N2**

  For this choice, you set a value for the ratio of *N2* to *N1*, and then PASS determines the needed *N1* and *N2*, with this ratio, to obtain the desired power. An equivalent representation of the ratio, *R*, is

$$N2 = R * N1.$$

- **Enter percentage in Group 1, solve for N1 and N2**

  For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed *N1* and *N2* with this percentage to obtain the desired power.

R (Group Sample Size Ratio)

This option is displayed only if Group Allocation = "Enter R = N2/N1, solve for N1 and N2."

R is the ratio of *N2* to *N1*. That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of *N2* to *N1* while solving for *N1* and *N2*. Only sample size combinations with this ratio are considered.

N2 is related to *N1* by the formula:

$$N2 = [R \times N1],$$

where the value *[Y]* is the next integer $\geq Y$.

For example, setting *R* = 2.0 results in a Group 2 sample size that is double the sample size in Group 1 (e.g., *N1* = 10 and *N2* = 20, or *N1* = 50 and *N2* = 100).

R must be greater than 0. If *R* < 1, then *N2* will be less than *N1*; if *R* > 1, then *N2* will be greater than *N1*. You can enter a single or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for N1 and N2."

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for *N1* and *N2*. Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

Sample Size (When <u>Not</u> Solving for Sample Size)

Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal (N1 = N2)**

  This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.

- **Enter N1 and N2 individually**

  This choice permits you to enter different values for *N1* and *N2*.

- **Enter N1 and R, where N2 = R * N1**

  Choose this option to specify a value (or values) for *N1*, and obtain *N2* as a ratio (multiple) of *N1*.

- **Enter total sample size and percentage in Group 1**

  Choose this option to specify a value (or values) for the total sample size (*N*), obtain *N1* as a percentage of *N*, and then *N2* as *N - N1*.

Sample Size Per Group

This option is displayed only if Group Allocation = "Equal (N1 = N2)."

The Sample Size Per Group is the number of items or individuals sampled from each of the Group 1 and Group 2 populations. Since the sample sizes are the same in each group, this value is the value for *N1*, and also the value for *N2*.

The Sample Size Per Group must be ≥ 2. You can enter a single value or a series of values.

N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = "Enter N1 and N2 individually" or "Enter N1 and R, where N2 = R * N1."*

N1 is the number of items or individuals sampled from the Group 1 population.

N1 must be ≥ 2. You can enter a single value or a series of values.

N2 (Sample Size, Group 2)

This option is displayed only if Group Allocation = "Enter N1 and N2 individually."

N2 is the number of items or individuals sampled from the Group 2 population.

N2 must be ≥ 2. You can enter a single value or a series of values.

R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter N1 and R, where N2 = R * N1."*

R is the ratio of *N2* to *N1*. That is,

$$R = N2/N1$$

Use this value to obtain *N2* as a multiple (or proportion) of *N1*.

N2 is calculated from *N1* using the formula:

$$N2=[R \ x \ N1],$$

where the value *[Y]* is the next integer ≥ *Y*.

For example, setting $R = 2.0$ results in a Group 2 sample size that is double the sample size in Group 1.

R must be greater than 0. If $R < 1$, then *N2* will be less than N1; if $R > 1$, then *N2* will be greater than *N1*. You can enter a single value or a series of values.

Total Sample Size (N)

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines *N1* and *N2*.

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 2.

You can enter a single value or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

Effect Size

Input Type

Indicate what type of values to enter to specify the effect size. Regardless of the entry type chosen, the test statistics used in the power and sample size calculations are the same. This option is simply given for convenience in specifying the effect size.

The choices are

- **Hazard Rate**

  Enter h1, the hazard rate of the control group, and either h2, the hazard rate of the treatment group, or HR = h2/h1, the hazard ratio.

- **Median Survival Time**

  Enter T1, the median survival time of the control group, and either T2, the median survival time of the treatment group, or HR = T1/T2, the hazard ratio.

- **Proportion Surviving**

  Enter S1, the proportion surviving past time T0 in the control group, and either S2, the proportion surviving past time T0 in the treatment group, or HR, the hazard ratio.

- **Mortality**

  Enter M1, the mortality rate through time T0 in the control group, and either M2, the mortality rate through time T0 in the treatment group, or MR = M2/M1, the mortality ratio.

Effect Size = Hazard Rate

h1 (Hazard rate of Control Group)

Specify one or more values for the hazard rate of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard rate values is entered directly, each represents the hazard rate assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the hazard rate for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

1.3

1.7

1.9

1.5

If the time is years, the hazard rate for the first year would be 1.3, the hazard rate for the second year would be 1.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

Treatment Group Parameter

Specify whether the hazard rate of the treatment group will be entered directly or based on the Hazard Ratio (h2/h1).

h2 (Hazard Rate of Treatment Group)

Specify one or more values for the hazard rate of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard rate values is entered directly, each represents the hazard rate assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the hazard rate for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

1.3

1.7

1.9

1.5

If the time is years, the hazard rate for the first year would be 1.3, the hazard rate for the second year would be 1.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

HR (Hazard Ratio = h2/h1)

Specify one or more values for the hazard ratio of the Treatment group to the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard ratio values is entered directly, each represents the hazard ratio for a treatment subject at risk to a control subject.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the hazard ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the hazard ratio for the first year would be 0.9, the hazard ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

Effect Size = Median Survival Time

T1 (Median Survival Time, Control)

Specify one or more values for the median survival time of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric median survival time values is entered directly, each represents the median time to an event assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the median survival time for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

2.3

2.7

2.9

3.5

If the time is years, the median survival time for the first year would be 2.3, the median survival time for the second year would be 2.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

Treatment Group Parameter

Specify whether the median survival time of the treatment group will be entered directly or based on the Hazard Ratio (T1/T2 = h2/h1).

T2 (Median Survival Time, Treatment)

Specify one or more values for the median survival time of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric median survival time values is entered directly, each represents the median time to an event assuming an exponential survival distribution.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the median survival time for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

2.3

2.7

2.9

3.5

If the time is years, the median survival time for the first year would be 2.3, the median survival time for the second year would be 2.7, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

HR (Hazard Ratio = T1/T2 = h2/h1)

Specify one or more values for the hazard ratio of the Treatment group to the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard ratio values is entered directly, each represents the hazard ratio for a treatment subject at risk to a control subject.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the hazard ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the hazard ratio for the first year would be 0.9, the hazard ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

Effect Size = Proportion Surviving

S1 (Proportion Surviving, Control)

Specify one or more values for the proportion surviving (proportion without events during the corresponding time) of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric proportion surviving values is entered directly, each represents the probability that no event occurs for a subject at risk during the time T0.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the proportion surviving for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.89

0.91

0.77

0.85

If the time is years, the proportion surviving for the first year would be 0.89, the proportion surviving for the second year would be 0.91, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

Treatment Group Parameter

Specify whether the hazard rate of the treatment group will be entered directly or based on the Hazard Ratio (h2/h1).

S2 (Proportion Surviving, Treatment)

Specify one or more values for the proportion surviving (proportion without events during the corresponding time) of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric proportion surviving values is entered directly, each represents the probability that no event occurs for a subject at risk during the time T0.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the proportion surviving for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.89

0.91

0.77

0.85

If the time is years, the proportion surviving for the first year would be 0.89, the proportion surviving for the second year would be 0.91, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

HR (Hazard Ratio = h2/h1)

Specify one or more values for the hazard ratio of the Treatment group to the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric hazard ratio values is entered directly, each represents the hazard ratio for a treatment subject at risk during the time T0 to a control subject during the same period.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the hazard ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the hazard ratio for the first year would be 0.9, the hazard ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

T0 (Proportion Surviving Time)

Specify the time that corresponds to the proportion surviving values S1, S2, NCS1, and NCS2 if they are entered directly. When columns are used, T0 is ignored.

Effect Size = Mortality

M1 (Mortality of Control Group)

Specify one or more values for the mortality (proportion with events during the corresponding time) of the Control group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time T0.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the mortality for the first year would be 0.11, the mortality for the second year would be 0.09, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

Treatment Group Parameter

Specify whether the mortality of the treatment group will be entered directly or based on the Mortality Ratio (M2/M1).

M2 (Mortality of Treatment Group)

Specify one or more values for the mortality (proportion with events during the corresponding time) of the Treatment group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time T0.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the mortality for the first year would be 0.11, the mortality for the second year would be 0.09, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

MR (Mortality Ratio = M2/M1)

Specify one or more values for the mortality ratio of the TREATMENT group to the CONTROL group.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric mortality ratio values is entered directly, each represents the ratio of the mortality for a treatment subject at risk during the time T0 to a control subject during the same period.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the mortality ratio for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.9

0.8

0.7

0.8

If the time is years, the mortality ratio for the first year would be 0.9, the mortality ratio for the second year would be 0.8, and so on.

Range: Numeric values must be greater than zero. Columns may be specified by name or number, and the values in the columns must be greater than zero.

T0 (Mortality Time)

Specify the time that corresponds to the mortality values M1, M2, NCM1, and NCM2 if they are entered directly. When columns are used, T0 is ignored.

Proportion Lost (Per Time Period)

Controls Lost

Specify one or more values for the proportion of Controls that are lost-to-follow-up (right-censored) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric loss values is entered directly, each represents the probability that an at-risk subject will be lost-to-follow-up during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the loss proportion for the first year would be 0.05, the loss proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

Treatments Lost

Specify one or more values for the proportion of Treatments that are lost-to-follow-up (right-censored) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric loss values is entered directly, each represents the probability that an at-risk subject will be lost-to-follow-up during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the loss proportion for the first year would be 0.05, the loss proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

For Treatments Lost under H0, Use

Specify whether the simulations of the treatment subjects under the Null hypothesis should use the loss values specified under "Controls Lost:" or the values specified under "Treatments Lost:".

Noncompliance (Per Time Period)

Noncompliance Proportion (Control)

Specify one or more values for the proportion of Controls that are noncompliant (change treatment structure from that of other controls) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric noncompliance values is entered directly, each represents the probability that an at-risk subject will become noncompliant during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the noncompliance proportion for the first year would be 0.05, the noncompliance proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

NCM1 (Noncompliance Mortality, Control)

Specify one or more values for the noncompliance mortality (proportion with events during the corresponding time) of the Control group.

Values can be entered by number directly, by spreadsheet column, or by specifying a switch to M2 mortality.

Numeric Entry: If one or more numeric noncompliance mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time T0.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the noncompliance mortality for the first year would be 0.11, the noncompliance mortality for the second year would be 0.09, and so on.

M2: If M2 is entered, the value(s) entered for M2 will be used for the mortality of M1 when noncompliant.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

At time of noncompliance, start NCM1 at

At the time of noncompliance, the simulated subjects" mortalities can switch to the beginning of the specified noncompliance mortality or the specified noncompliance mortality at the time of noncompliance.

Noncompliance Proportion (Treatment)

Specify one or more values for the proportion of Treatments that are noncompliant (change treatment structure from that of other treatment subjects) during each time period of the total time.

Values can be entered by number directly or by spreadsheet column.

Numeric Entry: If one or more numeric noncompliance values is entered directly, each represents the probability that an at-risk subject will become noncompliant during each time period of the total time.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the loss proportion for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.05

0.05

0.10

0.15

If the time is years, the noncompliance proportion for the first year would be 0.05, the noncompliance proportion for the second year would be 0.05, and so on.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

NCM2 (Noncompliance Mortality, Treatment)

Specify one or more values for the noncompliance mortality (proportion with events during the corresponding time) of the Treatment group.

Values can be entered by number directly, by spreadsheet column, or by specifying a switch to M1 mortality.

Numeric Entry: If one or more numeric noncompliance mortality values is entered directly, each represents the probability that an event occurs for a subject at risk during the time T0.

Column Entry: Enter columns by beginning the entry with an equals sign (as in "=C1" or "=1 2 3"). Each row of the spreadsheet contains the mortality for a unit of the total time. The number of rows with values in the column should match the number of time periods entered under "Total Time".

For example, if the Total Time is set to "4" and you enter "=1" here, the indicated column could contain:

0.11

0.09

0.23

0.15

If the time is years, the noncompliance mortality for the first year would be 0.11, the noncompliance mortality for the second year would be 0.09, and so on.

M1: If M1 is entered, the value(s) entered for M1 will be used for the mortality of M2 when noncompliant.

Range: Numeric values must be between zero and one. Columns may be specified by name or number, and the values in the columns must be between zero and one.

At time of noncompliance, start NCM2 at

At the time of noncompliance, the simulated subjects" mortalities can switch to the beginning of the specified noncompliance mortality or the specified noncompliance mortality at the time of noncompliance.

For Treatment Noncompliance under H0, use

Specify whether the simulations of the treatment subjects under the Null hypothesis should use the noncompliance values specified under Control Noncompliance or the values specified under Treatment Noncompliance.

Duration (Number of Time Periods)

Accrual Time (Integers Only)

Enter one or more values for the number of time periods (months, years, etc.) during which subjects are entered into the study.

The total duration of the study is equal to the Accrual Time plus the Follow-Up Time.

These values must be integers.

Range: Accrual times can range from 0 to the Total Time. That is, the accrual time must be less than or equal to the Total Time.

Enter "0" when all subjects begin the study together.

Accrual Pattern

Specify the type of accrual (patient entry) pattern. Two types of entries are possible:

- **Equal (Uniform)**

  If you want to specify a uniform accrual rate for all time periods, enter *Equal* here.

- **Linear Increasing Probability w/Time**

  The probability of accrual increases linearly during the accrual time. This is used to specify slow early enrollment and heavy late enrollment.

- **Linear Decreasing Probability w/Time**

  The probability of accrual decreases linearly during the accrual time. This is used to specify heavy early enrollment and slow late enrollment.

- **Non-Uniform (Spreadsheet Entry)**

  Use this option when you want to specify one or more accrual patterns with different accrual rates per time period. You will specify the different accrual rates for each time period in the spreadsheet.

Accrual Values in Columns

Specify the columns of the spreadsheet containing the different accrual (patient entry) rates. One value per row is entered in spreadsheet cells for each time period. Each value is the proportion of the total number of subjects that enroll during the corresponding time period.

Syntax

Enter an equals sign followed by a list of columns containing the accrual patterns. For example, if you have entered two sets of accrual patterns in columns 1 and 2, you would enter "=C1 C2."

Standardized

Note that cell values in a column are standardized so they sum to one. Thus, the accrual patterns 2 1 1 and 50 25 25 both result in the same accrual pattern as 0.50 0.25 0.25 .

Number of Rows and Columns

The number of rows in each column should equal the Accrual Time. The number of columns is up to you. A separate analysis is conducted for each column.

Spreadsheet Cells

In a specified column, the proportion of all subjects that are expected to enroll during the first time period is specified in row one. The proportion of all subjects that are expected during the second time period is specified in row two. And so on.

For example, if you had specified three accrual-time periods and you wanted to specify double the accrual rate in the first period than in the other two, the spreadsheet would appear as

C1
2
1
1

Total Time (Integers Only)

Enter one or more values for the number of time periods (months, years, etc.) in the study.

The follow-up time is equal to the Total Time minus the Accrual Time.

These values must be integers.

Range: Total times must be integers, 1 or greater.

Options Tab

The Options tab contains limits on the number of iterations and various options about individual tests.

Maximum Sample Size Searched

Maximum N1 Before Search Termination

Specify the maximum N1 before the search for N1 is aborted.

Since simulations for large sample sizes are very computationally intensive and hence time-consuming, this value can be used to stop searches when N1 is larger than reasonable sample sizes for the study.

This applies only when "Find (Solve For)" is set to N1.

The procedure uses a binary search when searching for N1. If a value for N1 is tried that exceeds this value, and the power is not reached, a warning message will be shown on the output indicating the desired power was not reached.

We recommend a value of at least 20000.

Random Numbers

Random Number Pool Size

You can speed up the simulation by creating a large pool of random numbers from which random samples are drawn. This is the size of the pool.

If you do not want to draw numbers from a pool, enter "0" here.

If you want to use a pool, the minimum pool size is 10000. Also, the pool size should be at least twice the number of simulations.

Example 1 – Calculating Sample Size

A clinical trial is to be conducted over a three year period to compare the survival distribution of a new treatment to that of the current treatment. The hazard rate of the current treatment is 1.4. Although the researchers do not know the true hazard rate of the new treatment, they would like to determine the sample size needed to detect a difference in hazard rates if the hazard rate under the new treatment is 0.8. The desired power is 0.90. Testing will be done at the 0.05 significance level with a two-sided Gehan-Wilcoxon test. All enrollees are enlisted at the beginning of the study.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Two-Group Survival Comparison Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design 1 Tab	
Solve For	**Sample Size**
Test Type...	**Gehan-Wilcoxon**
Alternative Hypothesis	**H1: Hazard1 ≠ Hazard2**
Simulations	**10000**
Power...	**0.9**
Alpha..	**0.05**
Group Allocation	**Equal (N1 = N2)**
Input Type..	**Hazard Rate**
h1	**1.4**
Treatment Group Parameter	**h2 (Hazard Rate)**
h2	**1.0**
Design 2 Tab	
Controls Lost..	**0**
Treatments Lost......................................	**0**
Noncompliance Proportion (Control)	**0**
Noncompliance Proportion (Treatment) .	**0**
Accrual Time...	**0**
Total Time...	**3**

Output

Click the Calculate button to perform the calculations and generate the following output. The calculations will take a few moments to complete. The results will vary slightly due to simulation differences.

Numeric Results and Plots

Scenario 1 Numeric Results for Testing Hazard 1 = Hazard 2.
Hypotheses: H0: Hazard1 = Hazard2; H1: Hazard1 ≠ Hazard2
Test Statistic: Gehan-Wilcoxon Test
Simulations: 10000

Numeric Summary for Scenario 1

------------------ Power -------------------			------------------------- Alpha -------------------------				
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
0.903	0.897	0.909	0.050	0.053	0.049	0.058	0.097

					Accrual	Accrual	Total
N1	N2	HR	h1	h2	Time	Pattern	Time
92	93	0.571	1.400	0.800	0.0	Equal	3.0

		----------------- Noncompliance -----------------			
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0.000	0.000	0.000	1.000	0.000	1.000

Whole Study Averages

--------------- Cum. Subject Time --------------				--------------------- Events ---------------------			
----------- H0 -----------		--------- H1 ---------		--------- H0 ---------		--------- H1 ---------	
G1	G2	G1	G2	G1	G2	G1	G2
64.6	65.4	64.8	105.7	90.6	91.6	90.6	84.6

References
Klein, J.P.; Moeschberger, M.L.. 1997. Survival Analysis. Springer-Verlag. New York.
Piantadosi, S.. 2005. Clinical Trials, A Methodologic Perspective, 2nd Ed. John Wiley & Sons, Inc. New Jersey.

Report Definitions
Power is the probability of rejecting a false null hypothesis at one of the looks. It is the total proportion
  of alternative hypothesis simulations for which H0 is rejected.
Power 95% LCL and UCL are the lower and upper confidence limits for the power estimate. The width of the
  interval is based on the number of simulations.
Target Alpha is the user-specified probability of rejecting a true null hypothesis. It is the total alpha
  spent.
Actual Alpha is the alpha level that was actually achieved by the experiment. It is the total proportion of
  the null hypothesis simulations that are outside the significance boundaries.
Alpha 95% LCL and UCL are the lower and upper confidence limits for the actual alpha estimate. The width of
  the interval is based on the number of simulations.
Beta is the probability of accepting a false null hypothesis. It is the total proportion of alternative
  hypothesis simulations for which H0 is not rejected.
N1 and N2 are the sample sizes of each group.
HR is the hazard ratio h2/h1 at which power is computed.
h1 is the hazard rate of the control group. It is the hazard rate that is simulated for both groups under H0,
  and for group 1 under H1.
h2 is the hazard rate of the treatment group. It is the hazard rate that is simulated for group 2 under H1.
Accrual Time is the time during which subjects are enlisted into the study. It is sometimes known as the
  enlistment period or recruitment period.
Accrual Pattern describes the distribution of accrual accross the Accrual Time.
Total Time is the total length of the study. It is the sum of the accrual time and the follow-up time.
Loss1 and Loss2 are the loss rates (lost to follow-up and right censored) for the control and treatment
  groups, respectively.
Noncompliance Proportion 1 and Noncompliance Proportion 2 are the proportion noncompliant in each time period
  for the control and treatment groups, respectively.
Noncompliance h1 and Noncompliance h2 are the noncompliance hazard rates for the control and treatment groups,
  respectively.
For Whole Study Averages, H0 and H1 refer to the simulations under the null and altervative hypotheses,
  respectively.
G1 and G2 refer to the simulations for Groups 1 and 2, respectively.

Two-Group Survival Comparison Tests (Simulation)

Cumulative Subject Time is the average total time of subject involvement. It is the average sum of survival
   times, including event survival times and censored survival times.
Events is the average number of events in the study before study termination.

Summary Statements
Studies with group sample sizes of 92 and 93 achieve 90% power to detect a hazard ratio of
0.571 at the 0.053 significance level (alpha) using a two-sided Gehan-Wilcoxon Test.

Detailed Input

Time Period	Accrual Pattern	Control Hazard Rate h1	Trt Hazard Rate h2	Control Loss Ls1	Trt Loss Ls2	NComp Prop Control NCP1	NComp Hazard Control NCh1	NComp Prop Trt NCP2	NComp Hazard Trt NCh2
1	100% Accrual	1.400	0.800	0.000	0.000	0.000	1.000	0.000	1.000
2	100% Accrual	1.400	0.800	0.000	0.000	0.000	1.000	0.000	1.000
3	100% Accrual	1.400	0.800	0.000	0.000	0.000	1.000	0.000	1.000

Sample sizes of 92 and 93 are needed to achieve 90% power for the Gehan-Wilcoxon test. The additional portion of the output is not shown here, since it used to compare multiple scenarios. Multiple scenarios occur when more than one value is entered for one or more of the parameters on the design tabs. In this example there is only one scenario.

Example 2 – Validation using Lakatos (1988)

Lakatos (1988), pages 231-234, presents an example that will be used to validate this procedure. In this example, a two-year trial is investigated. All subjects begin the trial together, so there is no accrual period. The hazard rates are 1.0 and 0.5 for the control and treatment groups, respectively. The yearly loss to follow-up is 3% per year in both groups. Noncompliance and drop-in rates are assumed to be 4% and 5% per year, respectively. The power is set to 90%. A two-sided Logrank test with alpha set to 0.05 is assumed. Equal allocation of the sample to both control and experiment groups is used. Lakatos obtains a total sample size of 139.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Two-Group Survival Comparison Tests (Simulation)** procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	**Value**
Design 1 Tab	
Solve For	**Sample Size**
Test Type..	**Logrank**
Alternative Hypothesis	**H1: Hazard1 ≠ Hazard2**
Simulations	**10000**
Power..	**0.9**
Alpha...	**0.05**
Group Allocation	**Equal (N1 = N2)**
Input Type...	**Hazard Rate**
h1	**1.0**
Treatment Group Parameter	**h2 (Hazard Rate)**
h2	**0.5**
Design 2 Tab	
Controls Lost..	**0.03**
Treatments Lost......................................	**0.03**
Noncompliance Proportion (Control)	**0.04**
NCh1...	**0.5**
Noncompliance Proportion (Treatment) .	**0.05**
NCh2...	**1.0**
Accrual Time...	**0**
Total Time...	**2**

Output

Click the Calculate button to perform the calculations and generate the following output. The calculations will take a few moments to complete. The results will vary slightly due to simulation differences.

Numeric Results and Plots

Scenario 1 Numeric Results for Testing Hazard 1 = Hazard 2.
Hypotheses: H0: Hazard1 = Hazard2; H1: Hazard1 ≠ Hazard2
Test Statistic: Logrank Test
Simulations: 10000

Numeric Summary for Scenario 1

----------------- Power -------------------			------------------------- Alpha -------------------------				
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
0.902	0.896	0.908	0.050	0.049	0.045	0.053	0.098

				Accrual	Accrual	Total	
N1	N2	HR	h1	h2	Time	Pattern	Time
69	70	0.500	1.000	0.500	0.0	Equal	2.0

		----------------- Noncompliance -----------------			
Loss1	Loss2	Prop 1	h1	Prop 2	h2
0.030	0.030	0.040	0.500	0.050	1.000

Whole Study Averages

--------------- Cum. Subject Time --------------				--------------------- Events ---------------------			
----------- H0 -----------		--------- H1 ---------		--------- H0 ---------		--------- H1 ---------	
G1	G2	G1	G2	G1	G2	G1	G2
58.9	59.8	59.0	85.4	57.9	58.7	57.9	44.1

Detailed Input

Time Period	Accrual Pattern	Control Hazard Rate h1	Trt Hazard Rate h2	Control Loss Ls1	Trt Loss Ls2	NComp Prop Control NCP1	NComp Hazard Control NCh1	NComp Prop Trt NCP2	NComp Hazard Trt NCh2
1	100% Accrual	1.000	0.500	0.030	0.030	0.040	0.500	0.050	1.000
2	100% Accrual	1.000	0.500	0.030	0.030	0.040	0.500	0.050	1.000

The total sample size is 69 + 70 = 139, which matches the published result of Lakatos (1988). The total sample size of each run may vary slightly due to simulation differences.