Chapter 705

Logrank Tests (Lachin and Foulkes)

Introduction

This module computes the sample size and power of the logrank test for equality (or non-inferiority) of survival distributions under the assumption of proportional hazards. Accrual time and follow-up time are included among the parameters to be set.

A clinical trial is often employed to test the equality of survival distributions for two treatment groups. For example, a researcher might wish to determine if Beta-Blocker A enhances the survival of newly diagnosed myocardial infarction patients over that of the standard Beta-Blocker B. The question being considered is whether the pattern of survival is different.

The two-sample t-test is not appropriate for two reasons. First, the data consist of the length of survival (time to failure), which is often highly skewed, so the usual normality assumption cannot be validated. Second, since the purpose of the treatment is to increase survival time, it is likely (and desirable) that some of the individuals in the study will survive longer than the planned duration of the study. The survival times of these individuals are then said to be *censored*. These times provide valuable information, but they are not the actual survival times. Hence, special methods have to be employed which use both regular and censored survival times.

The logrank test is one of the most popular tests for comparing two survival distributions. It is easy to apply and is usually more powerful than an analysis based simply on proportions. It compares survival across the whole spectrum of time, not just at one or two points. This module allows the sample size and power of the logrank test to be analyzed under very general conditions.

Power and sample size calculations for the logrank test have been studied by several authors. **PASS** uses the methods of Lachin and Foulkes (1986) because of their generality. Although small differences among methods can be found depending upon which assumptions are adopted, there is little practical difference between the techniques.

The power calculations used here assume an underlying exponential distribution. However, this assumption is rarely accurate in an actual clinical trial. How is this assumption justified? First, the logrank test and the test derived using the exponential distribution have nearly the same power when the data are in fact exponentially distributed. Second, under the proportional hazards model (which is assumed by the logrank test), the survival distribution can be transformed to exponential and the logrank test remains the same under monotonic transformations.

Technical Details

Some rather complicated formulas are used to define the input parameters. You need not understand the formulas. However, you should understand the individual parameters used in these formulas.

Basic Model

Suppose a clinical trial consists of two independent treatment groups labeled "1" and "2" (you could designate group one as the control group and group two as the treatment group). If the total sample size is N, the sizes of the two groups are n_1 and n_2. Usually, you would plan to have $n_1 = n_2$. Define the proportion of the total sample in each group as

$$Q_i = \frac{n_i}{N}, i = 1,2$$

Individuals are recruited during an accrual period of R years (or months or days). They are followed for an additional period of time until a total of T years is reached. Hence, the follow-up period is T-R years. At the end of the study, the logrank test is conducted at significance level α with power $1 - \beta$.

If we assume an exponential model with hazard rates λ_1 and λ_2 for the two groups, Lachin and Foulkes (1986, Eq. 2.1) establish the following equation relating N and power:

$$\sqrt{N}|\lambda_1 - \lambda_2| = Z_\alpha \sqrt{\phi(\bar{\lambda})\left(\frac{1}{Q_1} + \frac{1}{Q_2}\right)} + Z_\beta \sqrt{\frac{\phi(\lambda_1)}{Q_1} + \frac{\phi(\lambda_2)}{Q_2}}$$

where

$$\bar{\lambda} = Q_1\lambda_1 + Q_2\lambda_2$$

$$\phi(\lambda) = N\sigma^2(\hat{\lambda})$$

$$Z_\theta = \Phi(1 - \theta)$$

$\Phi(z)$ is the area to the left of z under the standard normal density, $\hat{\lambda}$ is the maximum likelihood estimate of λ, and that $\sigma^2(\hat{\lambda})$ represents the variance of $\hat{\lambda}$.

Exponential Distribution

The hazard rate from the exponential distribution, λ, is usually estimated using maximum likelihood techniques. In the planning stages, you have to obtain an estimate of this parameter. To see how to accomplish this, let's briefly review the exponential distribution. The density function of the exponential is defined as

$$f(t) = \lambda e^{-\lambda t}, t \geq 0, \lambda > 0.$$

The cumulative survival distribution function is

$$S(t) = e^{-\lambda t}, t \geq 0.$$

Solving this for λ yields

$$\lambda = -\frac{\log(S(t))}{t}$$

Note that $S(t)$ gives the probability of surviving t years. To obtain a planning estimate of λ, you need only know the proportion surviving during a particular time period. You can then use the above equation to calculate λ.

Patient Entry

Patients are enrolled during the accrual period. **PASS** lets you specify the pattern in which subjects are enrolled. Suppose patient entry times are distributed as $g(t)$ where t_i is the entry time of the ith individual and $0 \leq t_i \leq R$. Let $g(t)1$ follow the truncated exponential distribution with parameter A, which has the density

$$g(t) = \begin{cases} \dfrac{Ae^{-At}}{1 - e^{-AR}} & 0 \leq t \leq R, A \neq 0 \\[2ex] 1/R & 0 \leq t \leq R, A = 0 \end{cases}$$

Note that R is accrual time. The corresponding cumulative distribution function is

$$G(t) = \begin{cases} \dfrac{1 - e^{-At}}{1 - e^{-AR}} & 0 \leq t \leq R, A \neq 0 \\[2ex] t / R & 0 \leq t \leq R, A = 0 \end{cases}$$

A is interpreted as follows:

$A > 0$ results in a convex (faster than expected) entry distribution.

$A < 0$ results in a concave (slower than expected) entry distribution.

$A = 0$ results in the uniform entry distribution in which $g(t) = 1/R$.

Rather than specify A directly, **PASS** has you enter the percentage of the accrual time that will be needed to enroll 50% of the subjects. Using an iterative search, the value of A corresponding to this percentage is calculated and used in the calculations.

Losses to Follow-Up

The staggered patient entry over the accrual period results in censoring times ranging from *T - R* to *T* years during the follow-up period. This is often referred to as administrative censoring, since it is caused by the conclusion of the study rather than by some random factor working on an individual. To model the losses to follow-up which come from other causes, we use the exponential distribution with hazard rates η_1 and η_2. Since these rates are difficult and confusing to define directly, **PASS** lets you input the proportion lost due to other causes over a specified period of time and uses the following equation to determine the hazard rates:

$$\eta = -\frac{\log(1 - P(t))}{t}$$

General Model

Combining all these parameters into the model results in

$$\phi(\lambda, \eta, \gamma) = \lambda^2 \left(\frac{\lambda}{\lambda + \eta} + \frac{\lambda \gamma e^{-(\lambda + \eta)T} \left[1 - e^{(\lambda + \eta - \gamma)R} \right]}{(1 - e^{-\gamma R})(\lambda + \eta)(\lambda + \eta - \gamma)} \right)^{-1}.$$

This expression may then be used in an equation that relates these parameters to sample size and power

$$\sqrt{N}|\lambda_1 - \lambda_2| = Z_\alpha \sqrt{\phi(\bar{\lambda}) \left(\frac{1}{Q_1} + \frac{1}{Q_2} \right)} + Z_\beta \sqrt{\frac{\phi(\lambda_1)}{Q_1} + \frac{\phi(\lambda_2)}{Q_2}}$$

Example 1 – Finding the Power

A researcher is planning a clinical trial using a parallel, two-group, equal sample allocation design to compare the survivability of a new treatment with that of the current treatment. The proportion surviving one-year after the current treatment is 0.50. The new treatment will be adopted if the proportion surviving after one year increases to 0.75.

The trial will include a recruitment period of one-year after which participants will be followed for an additional two-years. It is assumed that patients will enter the study uniformly over the accrual period. The researcher estimates a loss-to-follow rate of 15% during the first year in both the control and the experimental groups.

The researcher decides to investigate various sample sizes between 10 and 250 at both the 0.01 and 0.05 significance levels.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For ....**Power**
Alternative Hypothesis ....**Ha: S1 ≠ S2**
Alpha..**0.01 0.05**
N (Total Sample Size)....................................**10 25 50 100 150 200 250**
Proportion in Group 1.....................................**0.5**
Proportion Lost to Follow-Up 1 ....**0.15**
Proportion Lost to Follow-Up 2 ....**0.15**
S1 (Proportion Surviving in Group 1) **0.50**
S2 (Proportion Surviving in Group 2) **0.75**
T0 (Fixed Time Point) **1**
R (Accrual Time)..**1**
% Time Until 50% Accrual **50**
Follow-Up Time, T-R......................................**2**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For:	Power
Groups:	1 = Control, 2 = Treatment
Alternative Hypothesis:	Ha: S1 ≠ S2
Accrual Rate:	50% of Accrual Time Results in 50% of Total Enrollment
Proportion Lost to Follow-Up through T0:	0.15 in Group 1 and 0.15 in Group 2
T0 (Fixed Time Point):	1

	Sample Size			Proportion in Group 1	Proportion Surviving Past Time T0		Time		
							Accrual	Follow-Up	
Power	N	N1	N2	P1	S1	S2	R	T - R	Alpha
0.06718	10	5	5	0.5	0.5	0.75	1	2	0.01
0.18406	10	5	5	0.5	0.5	0.75	1	2	0.05
0.17527	25	12	13	0.5	0.5	0.75	1	2	0.01
0.36633	25	12	13	0.5	0.5	0.75	1	2	0.05
0.38357	50	25	25	0.5	0.5	0.75	1	2	0.01
0.61606	50	25	25	0.5	0.5	0.75	1	2	0.05
0.72756	100	50	50	0.5	0.5	0.75	1	2	0.01
0.88428	100	50	50	0.5	0.5	0.75	1	2	0.05
0.90273	150	75	75	0.5	0.5	0.75	1	2	0.01
0.97052	150	75	75	0.5	0.5	0.75	1	2	0.05
0.96998	200	100	100	0.5	0.5	0.75	1	2	0.01
0.99328	200	100	100	0.5	0.5	0.75	1	2	0.05
0.99167	250	125	125	0.5	0.5	0.75	1	2	0.01
0.99858	250	125	125	0.5	0.5	0.75	1	2	0.05

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N, N1, and N2	The sample sizes of both, the control, and the treatment groups, respectively.
P1	The proportion of the total sample that is in group 1, the control group. P1 = N1 / N.
S1	The proportion of group 1 (control) expected to survive past T0.
S2	The proportion of group 2 (treatment) expected to survive past T0.
R	The accrual (recruitment) time.
T - R	The follow-up time. Hence, T is the total time of the study.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group design will be used to test whether the Group 2 (treatment) survival proportion is different from the Group 1 (control) survival proportion (H0: S1 = S2 versus Ha: S1 ≠ S2). The comparison will be made using a two-sided, two-sample logrank test, with a Type I error rate (α) of 0.01. Patients will enter the study during an accrual period of 1 time period. 50% of the enrollment will be complete when 50% of the accrual time has passed (uniform accrual). A follow-up period of 2 time periods will have 15% lost to follow-up in the control group and 15% lost to follow-up in the treatment group (per 1 time period). To detect a Group 1 (control) survival proportion of 0.5 and a Group 2 (treatment) survival proportion of 0.75 (in 1 time period), or a difference of 0.25, with a sample size of 5 subjects in Group 1 and 5 subjects in Group 2 (totaling 10 subjects), the power is 0.06718.

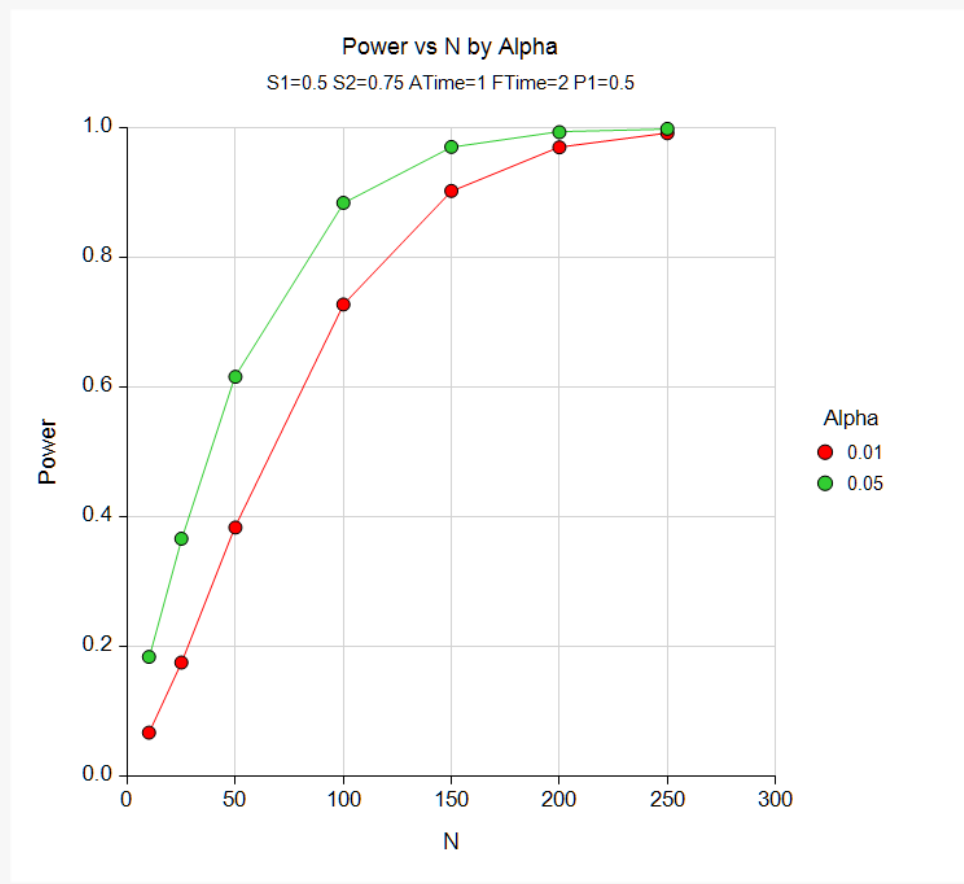**References**
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Lachin, John M. and Foulkes, Mary A. 1986. 'Evaluation of Sample Size and Power for Analyses of Survival with
    Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics,
    Volume 42, September, pages 507-516.
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This report shows the values of each of the parameters, one scenario per row. Note that approximately 100 patients, 50 per group, will be needed to achieve about 90% power at the 0.05 significance level.

Plots Section

Plots
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This plot shows the relationship between sample size and power for the two significance levels.

Example 2 – Finding the Sample Size

Continuing with the previous example, the researcher wants to investigate the sample size necessary to achieve 80% or 90% power for various values of the proportion surviving in the treatment group from 0.55 to 0.80 at the 0.05 significance level. All other parameters will remain the same.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For ....**Power**
Alternative Hypothesis ....**Ha: S1 ≠ S2**
Power...**0.80 0.90**
Alpha..**0.05**
Proportion in Group 1.....................................**0.5**
Proportion Lost to Follow-Up 1 ....**0.15**
Proportion Lost to Follow-Up 2 ....**0.15**
S1 (Proportion Surviving in Group 1) **0.5**
S2 (Proportion Surviving in Group 2) ....**0.55 to 0.80 by 0.05**
T0 (Fixed Time Point) **1**
R (Accrual Time)..**1**
% Time Until 50% Accrual **50**
Follow-Up Time, T-R.......................................**2**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Ha: S1 ≠ S2
Accrual Rate: 50% of Accrual Time Results in 50% of Total Enrollment
Proportion Lost to Follow-Up through T0: 0.15 in Group 1 and 0.15 in Group 2
T0 (Fixed Time Point):   1

| | Sample Size | | | Proportion in Group 1 | Proportion Surviving Past Time T0 | | Time | | |
| | | | | | | | Accrual | Follow-Up | |
Power	N	N1	N2	P1	S1	S2	R	T - R	Alpha
0.80017	2090	1045	1045	0.5	0.5	0.55	1	2	0.05
0.90004	2798	1399	1399	0.5	0.5	0.55	1	2	0.05
0.80050	515	257	258	0.5	0.5	0.60	1	2	0.05
0.90024	690	345	345	0.5	0.5	0.60	1	2	0.05
0.80010	225	112	113	0.5	0.5	0.65	1	2	0.05
0.90001	302	151	151	0.5	0.5	0.65	1	2	0.05
0.80177	125	62	63	0.5	0.5	0.70	1	2	0.05
0.90098	168	84	84	0.5	0.5	0.70	1	2	0.05
0.80357	79	39	40	0.5	0.5	0.75	1	2	0.05
0.90107	106	53	53	0.5	0.5	0.75	1	2	0.05
0.80432	54	27	27	0.5	0.5	0.80	1	2	0.05
0.90274	73	36	37	0.5	0.5	0.80	1	2	0.05

Power   The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N, N1, and N2   The sample sizes of both, the control, and the treatment groups, respectively.
P1   The proportion of the total sample that is in group 1, the control group. P1 = N1 / N.
S1   The proportion of group 1 (control) expected to survive past T0.
S2   The proportion of group 2 (treatment) expected to survive past T0.
R   The accrual (recruitment) time.
T - R   The follow-up time. Hence, T is the total time of the study.
Alpha   The probability of rejecting a true null hypothesis.
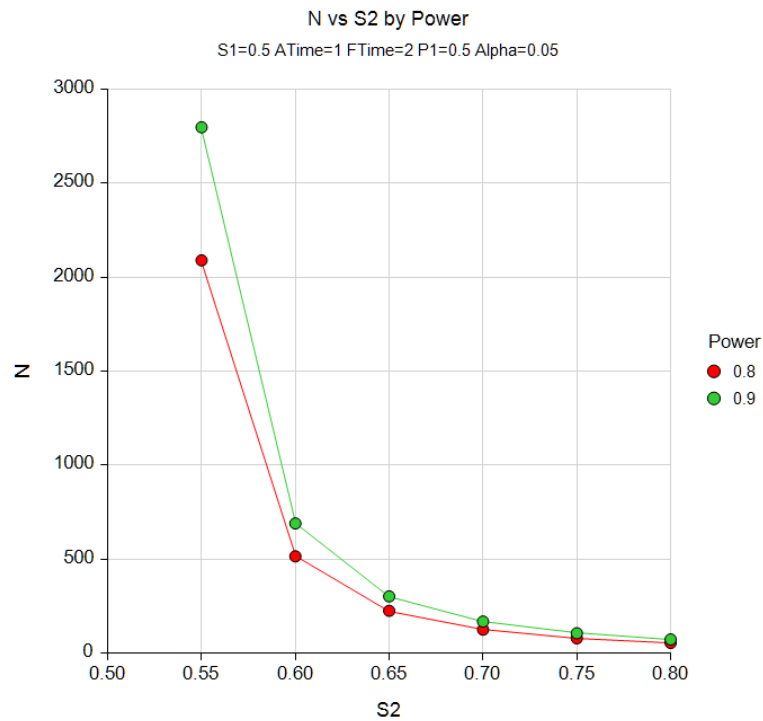
Summary Statements

A parallel, two-group design will be used to test whether the Group 2 (treatment) survival proportion is different from the Group 1 (control) survival proportion (H0: S1 = S2 versus Ha: S1 ≠ S2). The comparison will be made using a two-sided, two-sample logrank test, with a Type I error rate (α) of 0.05. Patients will enter the study during an accrual period of 1 time period. 50% of the enrollment will be complete when 50% of the accrual time has passed (uniform accrual). A follow-up period of 2 time periods will have 15% lost to follow-up in the control group and 15% lost to follow-up in the treatment group (per 1 time period). To detect a Group 1 (control) survival proportion of 0.5 and a Group 2 (treatment) survival proportion of 0.55 (in 1 time period), or a difference of 0.05, with 80% power, the number of needed subjects will be 1045 in Group 1 and 1045 in Group 2 (totaling 2090 subjects).

References

Lachin, John M. and Foulkes, Mary A. 1986. 'Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics, Volume 42, September, pages 507-516.

Plots

This study shows the huge increase in sample size necessary to detect values of *S2* below 0.65. It also shows that roughly 35% more participants are required for 90% power than for 80% power in this situation.

Example 3 – Validation using Lachin and Foulkes (1986)

Lachin and Foulkes (1986), the developers of formulas used in this routine, give an example on page 509 in which $\lambda_1 = 0.3$, $\lambda_2 = 0.2$, $N = 378$, $\alpha = 0.05$ (one-sided), $R = 3$, $T = 3$, and $\beta = 0.1$. There is no loss to follow up and uniform patient entry is assumed.

The first step is to determine the proportion surviving at the end of one year for each group using the formula:

$$S(t) = e^{-\lambda t}$$

For group 1 we have

$$S_1(1) = e^{-0.3(1)}$$

$$= 0.74081822$$

For group 2 we have

$$S_2(1) = e^{-0.2(1)}$$

$$= 0.81873075$$

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Power**
Alternative Hypothesis	**Ha: S1 < S2**
Alpha	**0.05**
N (Total Sample Size)	**378**
Proportion in Group 1	**0.5**
Proportion Lost to Follow-Up 1	**0.0**
Proportion Lost to Follow-Up 2	**0.0**
S1 (Proportion Surviving in Group 1)	**0.74081822**
S2 (Proportion Surviving in Group 2)	**0.81873075**
T0 (Fixed Time Point)	**1**
R (Accrual Time)	**3**
% Time Until 50% Accrual	**50**
Follow-Up Time, T-R	**2**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Power
Groups: 1 = Control, 2 = Treatment
Alternative Hypothesis: Ha: S1 < S2
Accrual Rate: 50% of Accrual Time Results in 50% of Total Enrollment
Proportion Lost to Follow-Up through T0:   0 in Group 1 and 0 in Group 2
T0 (Fixed Time Point):   1

| | Sample Size | | | Proportion in Group 1 | Proportion Surviving Past Time T0 | | Time | | |
Power	N	N1	N2	P1	S1	S2	Accrual R	Follow-Up T - R	Alpha
0.90123	378	189	189	0.5	0.74082	0.81873	3	2	0.05

The power of 0.90 matches the value published in Lachin's article.

Example 4 – Non-Inferiority Test

This example will show how to use this module to calculate power and sample size for non-inferiority trials. Remember that non-inferiority is established by showing that the new treatment is no worse than the standard treatment, except for a small amount called the margin of equivalence.

Consider the following example. Suppose the median survival time of the standard drug is 15 months. Unfortunately, this drug has serious side effects. A promising new drug has been developed that has much milder side effects. A non-inferiority trial is to be designed to show that the new drug is not inferior to the standard drug. The margin of equivalence is set at 3 months, so, to establish non-inferiority, the study has to conclude that the median survival time of the new drug is at least 12 months.

The trial will accept subjects for 18 months. It will continue for an additional 6 months after the accrual period. Although the study planners anticipate some dropout, they want to begin their analysis without considering dropout. They set the significance level at 0.05. They want to determine the necessary sample size to achieve 80% and 90% power. The calculations proceed as follows.

Use the *Survival Parameter Conversion Tool* to convert the "median survival rates" to "proportions surviving" so that they can be entered into the panel. Press the **Survival Parameter Conversion Tool** button that is next to the S1 box to display this window. Enter **24** for **T0**, **12** for **Median Survival Time 1 (T1)**, and **15** for **Median Survival Time 2 (T2)**. This results in values for S1 and S2 of 0.25 and 0.329876977693224, respectively.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For ....**Sample Size**
Alternative Hypothesis ....**Ha: S1 < S2**
Power...**0.80 0.90**
Alpha..**0.05**
Proportion in Group 1......................................**0.5**
Proportion Lost to Follow-Up 1 ....**0.0**
Proportion Lost to Follow-Up 2 ....**0.0**
S1 (Proportion Surviving in Group 1).............**0.25**
S2 (Proportion Surviving in Group 2) **0.329876977693224**
T0 (Fixed Time Point) **24**
R (Accrual Time)..**18**
% Time Until 50% Accrual **50**
Follow-Up Time, T-R......................................**6**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For:	Sample Size
Groups:	1 = Control, 2 = Treatment
Alternative Hypothesis:	Ha: S1 < S2
Accrual Rate:	50% of Accrual Time Results in 50% of Total Enrollment
Proportion Lost to Follow-Up through T0:	0 in Group 1 and 0 in Group 2
T0 (Fixed Time Point):	24

	Sample Size			Proportion in Group 1	Proportion Surviving Past Time T0		Time		
Power	N	N1	N2	P1	S1	S2	Accrual R	Follow-Up T - R	Alpha
0.80030	957	478	479	0.5	0.25	0.32988	18	6	0.05
0.90018	1326	663	663	0.5	0.25	0.32988	18	6	0.05

Thus, a sample size of about 663 per group would be needed for 90% power, and a sample of 479 per group would be needed for 80% power.