Chapter 721

Assurance for Logrank Tests (Freedman)

Introduction

This procedure calculates the assurance of one- or two-sided logrank tests which are analyzed under the assumption of proportional hazards. The calculation is based on a user-specified prior distribution of the applicable parameters. This procedure may also be used to determine the needed sample size to obtain a specified assurance.

Time periods are not stated. Rather, it is assumed that enough time elapses to allow for a reasonable proportion of responses to occur. Refer to the *Logrank Tests (Freedman)* procedure for more details on this version of the logrank test. The formulas used in this module come from Machin *et al.* (2018). They are also given in Fayers and Machin (2016) where they are applied to sizing quality of life studies. They were originally published in Freedman (1982) and are often referred to by that name. The assurance calculation used in this procedure is based on O'Hagan, Stevens, and Campbell (2005).

Assurance

The assurance of a design is the expected value of the power with respect to one or more prior distributions of the design parameters. Assurance is also referred to as *Bayesian assurance*, *expected power*, *average power*, *statistical assurance*, *hybrid classical-Bayesian procedure,* or *probability of success*.

The power of a design is the probability of rejecting the null hypothesis, conditional on a given set of design attributes, such as the test statistic, the significance level, the sample size, and the effect size to be detected. As many of the parameters are typically unknown quantities, the stated power may be very different from the true power if the specified parameter values are inaccurate.

While power is conditional on individual design parameter values, and is highly sensitive to those values, assurance is the average power across a presumed prior distribution of the parameters. Thus, assurance adds a Bayesian element to the frequentist framework, resulting in a hybrid approach to the probability of trial or study success. It should be noted that when it comes time to perform the statistical test on the resulting data, these methods for calculating assurance assume that the traditional (frequentist) tests will be used.

The next section describes some of the ways in which the prior distributions for effect size parameters may be determined.

Elicitation

In order to calculate assurance, a suitable prior distribution for the applicable parameters must be determined. This process is called the *elicitation* of the prior distribution.

The elicitation may be as simple as choosing a distribution that seems plausible for the parameter(s) of interest, or as complex as combining the informed advice of several experts based on experience in the field, available pilot data, or previous studies. The accuracy of the assurance value depends on the accuracy of the elicited prior distribution. The assumption (or hope) is that an informed prior distribution will produce a more accurate estimate of the probability of trial success than a single value estimate. Because clinical trials and other studies are often costly, many institutions now routinely require an elicitation step.

Two reference texts that focus on elicitation are O'Hagan, Buck, Daneshkhah, Eiser, Garthwaite, Jenkinson, Oakley, and Rakow (2006) and Dias, Morton, and Quigley (2018).

Logrank Test

We assume that a study is to be made comparing the survival (or healing) of a control group with an experimental group. The control group (group 1) consists of patients that will receive the existing treatment. In cases where no existing treatment exists, group 1 consists of patients that will receive a placebo. Group 2 will receive the new treatment.

We assume that the critical event of interest is death and that two treatments have survival distributions with instantaneous death (hazard) rates, λ_1 and λ_2. These hazard rates are a subject's probability of death in a short period of time.

Hazard Ratio

The hazard ratio, λ_2/λ_1, is used to compare two hazard rates.

$$HR = \frac{\lambda_2}{\lambda_1}$$

Note that since HR is formed by dividing the hazard rate of the experimental group by that of the control group, a treatment that has a smaller hazard rate than the control will have a hazard ratio that is less than one.

The hazard ratio may be formulated in several ways. If the proportions surviving during the study are called *S1* and *S2* for the control and experimental groups, the hazard ratio is given by

$$HR = \frac{\mathrm{Log}(S_2)}{\mathrm{Log}(S_1)}$$

Power of the Logrank test

We assume that the logrank test will be used to analyze the data once they are collected. However, often Cox's proportional hazards regression is used to do the actual analysis. These two methods give similar results and have similar power.

Freedman (1982) gives the power of the logrank test assuming proportional hazards as

$$z_{1-\beta} = \frac{|HR - 1|\sqrt{N(1 - w)\varphi[(1 - S_1) + \varphi(1 - S_2)]/(1 + \varphi)}}{(1 + \varphi HR)} - z_{1-\alpha/k}$$

where k is 1 for a one-sided hypothesis test or 2 for a two-sided test, α and β are the error rates defined as usual, the z's are points from the standard normal distribution, w is the proportion that are lost to follow up, and φ represents the sample size ratio between the two groups.

$$\varphi = \frac{N_2}{N_1}$$

Note that the null hypothesis is that the hazard ratio is one, i.e., that

$$H_0: \frac{\lambda_2}{\lambda_1} = 1$$

is equivalent to null hypothesis that the survival proportions are equal, that

$$H_0: S_1 = S_2$$

The alternative hypothesis can be any one of

Two-Sided:	$H_1: S_2 \neq S_1$	(or $H_1: HR \neq 1$)
Upper One-Sided:	$H_1: S_2 > S_1$	(or $H_1: HR > 1$)
Lower One-Sided:	$H_1: S_2 < S_1$	(or $H_1: HR < 1$)

depending upon the desire of the researcher or the protocol instructions.

Assurance Calculation

This assurance computation described here is based on O'Hagan, Stevens, and Campbell (2005).

Let $P_1(H|S_1, S_2, w)$ be the power function described above where H is the event that the null hypothesis is rejected conditional on the parameter values. The specification of $S_1, S_2,$ and w is critical to the power calculation, but the actual values are seldom known. Assurance is defined as the expected power where the expectation is with respect to a joint prior distribution for $S_1, S_2,$ and w. Hence, assurance is

$$Assurance = E_{S_1, S_2, w}\left(P_1(H|S_1, S_2, w)\right) = \iiint P_1(H|S_1, S_2, w)f(S_1, S_2, w)dS_1 dS_2 dw$$

where $f(S_1, S_2, w)$ is the joint prior distribution of $S_1, S_2,$ and w.

In **PASS**, the joint prior distribution can be specified as either a discrete approximation to the joint prior distribution, or as individual prior distributions, one for each parameter.

Specifying a Joint Prior Distribution

If the joint prior distribution is to be specified directly, the distribution is specified in **PASS** using a discrete approximation to the function $f(S_1, S_2, w)$. This provides flexibility in specifying the joint prior distribution. In the three-parameter case, four columns are entered on the spreadsheet: three for the parameters and a fourth for the probability. Each row gives a value for each parameter and the corresponding parameter-combination probability. The accuracy of the distribution approximation is controlled by the number of points (spreadsheet rows) that are used.

An example of entering a joint prior distribution is included at the end of the chapter.

Specifying Individual Prior Distributions

Ciarleglio, Arendt, and Peduzzi (2016) suggest that more flexibility is available if the joint prior distribution is separated into three independent univariate distributions as follows:

$$f(S_1, S_2, w) = f_1(S_1)f_2(S_2)f_3(w)$$

where $f_1(S_1)$ is the prior distribution of S_1, $f_2(S_2)$ is the prior distribution of S_2, and $f_3(w)$ is the prior distribution of w. This method is also available in **PASS**. In this case, the definition of assurance becomes

$$Assurance = E_{S_1, S_2, w}\left(P_1(H|S_1, S_2, w)\right) = \iiint P_1(H|S_1, S_2, w)f_1(S_1)f_2(S_2)f_3(w)dS_1 dS_2 dw$$

Using this definition, the assurance can be calculated using numerical integration. There are a variety of pre-programmed, univariate prior distributions available in **PASS**.

Fixed Values (No Prior) and Custom Values

For any given parameter, **PASS** also provides the option of entering a single fixed value for the prior distribution, or a series of values and corresponding probabilities (using the spreadsheet), rather than one of the pre-programmed distributions.

Numerical Integration in PASS (and Notes on Computation Speed)

When the prior distribution is specified as independent univariate distributions, **PASS** uses a numerical integration algorithm to compute the assurance value as follows:

The domain of each prior distribution is divided into M intervals. Since many of the available prior distributions are unbounded on one (e.g., Gamma) or both (e.g., Normal) ends, an approximation is made to make the domain finite. This is accomplished by truncating the distribution to a domain between the two quantiles: $q_{0.001}$ and $q_{0.999}$.

The value of M controls the accuracy and speed of the algorithm. If only one parameter is to be given a prior distribution, then a value of M between 50 and 100 usually gives an accurate result in a timely manner. However, if two parameters are given priors, the number of iterations needed increases from M to M^2. For example, if M is 100, 10000 iterations are needed. Reducing M from 100 to 50 reduces the number of iterations from 10000 to 2500.

The algorithm runtime increases when searching for sample size rather than solving for assurance, as a search algorithm is employed in this case. When solving for sample size, we recommend reducing M to 20 or less while exploring various scenarios, and then increasing M to 50 or more for a final, more accurate, result.

List of Available Univariate Prior Distributions

This section lists the univariate prior distributions that may be used for any of the applicable parameters when the Prior Entry Method is set to Individual.

No Prior

If 'No Prior' is chosen for a parameter, the parameter is assumed to take on a single, fixed value with probability one.

Beta (Shape 1, Shape 2, a, c)

A random variable X that follows the beta distribution is defined on a finite interval [a, c]. Two shape parameters (α and β) control the shape of this distribution. Two location parameters a and c give the minimum and maximum of X.

The probability density function of the beta distribution is

$$f(x|\alpha,\beta,a,c) = \frac{\left(\frac{x-a}{c-a}\right)^{\alpha-1}\left(\frac{c-x}{c-a}\right)^{\beta-1}}{(c-a)B(\alpha,\beta)}$$

where $B(\alpha,\beta) = \Gamma(\alpha)\,\Gamma(\beta)/\,\Gamma(\alpha+\beta)$ and $\Gamma(z)$ is the gamma function.

The mean of X is

$$\mu_X = \frac{\alpha c + \beta a}{\alpha + \beta}$$

Various distribution shapes are controlled by the values of α and β. These include

Symmetric and Unimodal

$\alpha = \beta > 1$

U Shaped

$\alpha = \beta < 1$

Bimodal

$\alpha, \beta < 1$

Uniform

$\alpha = \beta = 1$

Parabolic

$\alpha = \beta = 2$

Bell-Shaped

$\alpha = \beta > 2$

Gamma (Shape, Scale)

A random variable X that follows the gamma distribution is defined on the interval $(0, \infty)$. A shape parameter, κ, and a scale parameter, θ, control the distribution.

The probability density function of the gamma distribution is

$$f(x|\kappa, \theta) = \frac{x^{\kappa-1}e^{-\frac{x}{\theta}}}{\theta^{\kappa}\Gamma(\kappa)}$$

where $\Gamma(z)$ is the gamma function.

The mean of X is

$$\mu_X = \frac{\kappa}{\theta}$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where *Min* and *Max* are two truncation bounds.

Inverse-Gamma (Shape, Scale)

A random variable X that follows the inverse-gamma distribution is defined on the interval $(0, \infty)$. If $Y \sim$ gamma, then $X = 1 / Y \sim$ inverse-gamma. A shape parameter, α, and a scale parameter, β, control the distribution.

The probability density function of the inverse-gamma distribution is

$$f(x|\alpha,\beta) = \frac{\beta^\alpha x^{\alpha-1} e^{-\frac{\beta}{x}}}{\Gamma(\alpha)}$$

where $\Gamma(z)$ is the gamma function.

The mean of X is

$$\mu_X = \frac{\beta}{\alpha - 1} \text{ for } \alpha > 1$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

Logistic (Location, Scale)

A random variable X that follows the logistic distribution is defined on the interval $(-\infty, \infty)$. A location parameter, μ, and a scale parameter, s, control the distribution.

The probability density function of the logistic distribution is

$$f(x|\mu,s) = \frac{e^{-\frac{x-\mu}{s}}}{s\left(1 + e^{-\frac{x-\mu}{s}}\right)^2}$$

The mean of X is

$$\mu_X = \mu$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

Lognormal (Mean, SD)

A random variable X that follows the lognormal distribution is defined on the interval $(0, \infty)$. A location parameter, $\mu_{\log(X)}$, and a scale parameter, $\sigma_{\log(X)}$, control the distribution. If Z ~ standard normal, then $X = e^{\mu+\sigma Z} \sim$ lognormal. Note that $\mu_{\log(X)} = E(\log(X))$ and $\sigma_{\log(X)} = Standard\ Deviation(\log(X))$.

The probability density function of the lognormal distribution is

$$f(x|\mu,\sigma) = \frac{e^{-\frac{1}{2}\left(\frac{\log x-\mu}{\sigma}\right)^2}}{x\sigma\sqrt{2\pi}}$$

The mean of X is

$$\mu_X = e^{\mu+\frac{\sigma^2}{2}}$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

LogT (Mean, SD)

A random variable X that follows the logT distribution is defined on the interval $(0, \infty)$. A location parameter, $\mu_{\log(X)}$, a scale parameter, $\sigma_{\log(X)}$, and a shape parameter, ν, control the distribution. Note that ν is referred to as the *degrees of freedom*.

If t ~ Student's t, then $X = e^{\mu+\sigma t} \sim$ logT.

The probability density function of the logT distribution is

$$f(x|\mu,\sigma,\nu) = \frac{\Gamma\left(\frac{\nu+1}{2}\right)}{x\Gamma\left(\frac{\nu}{2}\right)\sigma\sqrt{\nu\pi}}\left(1 + \frac{1}{\nu}\left(\frac{\log x-\mu}{\sigma}\right)^2\right)^{\left(\frac{-\nu-1}{2}\right)}$$

The mean of X is not defined.

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

Normal (Mean, SD)

A random variable X that follows the normal distribution is defined on the interval $(-\infty, \infty)$. A location parameter, μ, and a scale parameter, σ, control the distribution.

The probability density function of the normal distribution is

$$f(x|\mu, \sigma) = \frac{e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}}{\sigma\sqrt{2\pi}}$$

The mean of X is

$$\mu_X = \mu$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \le X \le Max)$ where *Min* and *Max* are two truncation bounds.

T (Mean, SD, DF)

A random variable X that follows Student's t distribution is defined on the interval $(-\infty, \infty)$. A location parameter, μ, a scale parameter, σ, and a shape parameter, ν, control the distribution. Note that ν is referred to as the *degrees of freedom* or *DF*.

The probability density function of the Student's t distribution is

$$f(x|\mu, \sigma, \nu) = \frac{\Gamma\left(\frac{\nu+1}{2}\right)}{\Gamma\left(\frac{\nu}{2}\right)\sigma\sqrt{\nu\pi}}\left(1 + \frac{1}{\nu}\left(\frac{x-\mu}{\sigma}\right)^2\right)^{\left(\frac{-\nu-1}{2}\right)}$$

The mean of X is μ if $\nu > 1$.

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \le X \le Max)$ where *Min* and *Max* are two truncation bounds.

Triangle (Mode, Min, Max)

Let a = minimum, b = maximum, and c = mode. A random variable X that follows a triangle distribution is defined on the interval (a, b).

The probability density function of the triangle distribution is

$$f(x|a, b, c) = \begin{cases} \dfrac{2(x-a)}{(b-a)(c-a)} & \text{for } a \le x < c \\[2mm] \dfrac{2}{b-a} & \text{for } x = c \\[2mm] \dfrac{2(b-x)}{(b-a)(b-c)} & \text{for } c < x \le b \end{cases}$$

The mean of X is

$$\frac{a+b+c}{3}$$

Uniform (Min, Max)

Let a = minimum and b = maximum. A random variable X that follows a uniform distribution is defined on the interval $[a, b]$.

The probability density function of the uniform distribution is

$$f(x|a, b) = \begin{cases} \dfrac{1}{b-a} & \text{for } a \le x \le b \end{cases}$$

The mean of X is

$$\frac{a+b}{2}$$

Weibull (Shape, Scale)

A random variable X that follows the Weibull distribution is defined on the interval $(0, \infty)$. A shape parameter, κ, and a scale parameter, λ, control the distribution.

The probability density function of the Weibull distribution is

$$f(x|\kappa, \lambda) = \frac{\kappa}{\lambda}\left(\frac{x}{\lambda}\right)^{\kappa-1} e^{-\left(\frac{x}{\lambda}\right)^{\kappa}}$$

The mean of X is

$$\mu_X = \kappa\Gamma\left(1 + \frac{1}{\kappa}\right)$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \le X \le Max)$ where Min and Max are two truncation bounds.

Custom (Values and Probabilities in Spreadsheet)

This custom prior distribution is represented by a set of user-specified points and associated probabilities, entered in two columns of the spreadsheet. The points make up the entire set of values that are used for this parameter in the calculation of assurance. The associated probabilities should sum to one. Note that custom values and probabilities can be used to approximate any continuous distribution.

For example, a prior distribution of X might be

X_i	P_i
10	0.2
20	0.2
30	0.3
40	0.2
50	0.1

In this example, the mean of X is

$$\mu_X = \sum_{i=1}^{5} X_i P_i$$

Example 1 – Assurance Over a Range of Sample Sizes

A clinical trial is being planned to test the effectiveness of a new treatment compared to the existing treatment. The current treatment for this disease achieves 50% survival after two years. The researchers want to compare the assurance across sample sizes when the proportion surviving in the experimental group survival is 70%.

To complete their sample size study, the researchers want to run an assurance analysis for a range of group sample sizes from 50 to 300. An elicitation exercise determined that the prior distribution of S1 should be normal with mean 0.5 and standard deviation 0.04 truncated between 0.45 to 0.55. The elicitation also concluded that prior distribution of S2 should be Normal (0.7, 0.08) truncated between 0.4 and 0.8. Finally the prior distribution of *w* should be Normal (0.05, 0.02) truncated at zero.

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	**Assurance**
Prior Entry Method..	**Individual (Enter a prior distribution for each applicable parameter)**
Alternative Hypothesis	**Two-Sided (H1: S1 ≠ S2)**
Alpha..	**0.05**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**50 100 150 200 250 300**
Prior Distribution of w...................................	**Normal (Mean, SD)**
Mean..	**0.05**
SD..	**0.02**
Truncation Boundaries..................................	**Left**
Left Boundary	**0**
Prior Distribution of S1	**Normal (Mean, SD)**
Mean..	**0.5**
SD..	**0.04**
Truncation Boundaries..................................	**Left and Right**
Left Boundary	**0.45**
Right Boundary	**0.55**
Prior Distribution of S2	**Normal (Mean, SD)**
Mean..	**0.7**
SD..	**0.08**
Truncation Boundaries..................................	**Left and Right**
Left Boundary	**0.4**
Right Boundary	**0.8**

Options Tab

Number of Computation Points for each **50**
 Prior Distribution
Maximum N1 in Sample Size Search **5000**

Output

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

Numeric Reports

Numeric Results
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Solve For: Assurance
Groups: 1 = Control, 2 = Treatment
Hazard Ratio (HR):   Hazard Rate 2 / Hazard Rate 1
Hypotheses: H0: S1 = S2 vs. H1: S1 ≠ S2
Test Statistic: Logrank or Cox Regression
Prior Type: Independent Univariate Distributions

Prior Distributions
S1: Normal (Mean = 0.5, SD = 0.04), Left Boundary = 0.45, Right Boundary = 0.55.
S2: Normal (Mean = 0.7, SD = 0.08), Left Boundary = 0.4, Right Boundary = 0.8.
w: Normal (Mean = 0.05, SD = 0.02), Left Boundary = 0.
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		Required Number of Events			Sample Size			Expected Proportion Lost During Follow Up	Expected Proportion Surviving in Group 1	Expected Proportion Surviving in Group 2	Hazard Ratio	
Assurance*	Power‡	E1	E2	E	N1	N2	N	E(w)	E(S1)	E(S2)	HR	Alpha
0.46442	0.44738	20	19	39	50	50	100	0.05025	0.5	0.68494	0.54595	0.05
0.67732	0.73385	39	39	78	100	100	200	0.05025	0.5	0.68494	0.54595	0.05
0.77891	0.88596	59	58	117	150	150	300	0.05025	0.5	0.68494	0.54595	0.05
0.83395	0.95496	78	77	155	200	200	400	0.05025	0.5	0.68494	0.54595	0.05
0.86735	0.98327	97	97	194	250	250	500	0.05025	0.5	0.68494	0.54595	0.05
0.88941	0.99407	117	116	233	300	300	600	0.05025	0.5	0.68494	0.54595	0.05

* The number of points used for computation of the prior(s) was 50.
‡ Power was calculated using S1 = E(S1) = 0.5, S2 = E(S2) = 0.68494, and w = E(w) = 0.05025.

Assurance   The expected power where the expectation is with respect to the prior distribution(s).
Power   The power calculated using the means of the prior distributions as the values of the corresponding parameters.
E1   The required number of events in group 1, the control group.
E2   The required number of events in group 2, the treatment group.
E   The total number of events required. E = E1 + E2.
N1   The number of subjects in group 1, the control group.
N2   The number of subjects in group 2, the treatment group.
N   The total sample size. N = N1 + N2.
E(w)   The expected value over its prior distribution of the proportion of subjects that will be lost during follow-up.
E(S1)   The expected value over its prior distribution of the proportion of group 1 (control) subjects surviving to the end
              of the study without an event.
E(S2)   The expected value over its prior distribution of the proportion of group 2 (treatment) subjects surviving to the
              end of the study without an event.
HR   The Hazard Ratio. HR = λ2 / λ1, where λ1 and λ2 are the hazard rates of groups 1 and 2, respectively. Note that
              1 / λi is the average time until an event for a subject in group i.
Alpha   The probability of rejecting a true null hypothesis.

Summary Statements
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A parallel two-group design will be used to test whether the Group 1 (control) proportion surviving (S1) is different from the Group 2 (treatment) proportion surviving (S2) (H0: S1 = S2 versus H1: S1 ≠ S2). The comparison will be made using a two-sided, two-sample logrank test (or an appropriate Cox regression coefficient test), assuming proportional hazards, with a Type I error rate (α) of 0.05. The prior distribution used for the proportion surviving of Group 1 is Normal (Mean = 0.5, SD = 0.04), Left Boundary = 0.45, Right Boundary = 0.55. The prior distribution used for the proportion surviving of Group 2 is Normal (Mean = 0.7, SD = 0.08), Left Boundary = 0.4, Right Boundary = 0.8. The prior distribution used for the proportion of subjects that are lost during follow-up is Normal (Mean = 0.05, SD = 0.02), Left Boundary = 0. With sample sizes of 50 for Group 1 (control) and 50 for Group 2 (treatment), the assurance (average power) is 0.46442.

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References
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These reports show the assurance values obtained by each sample size.

Plots Section
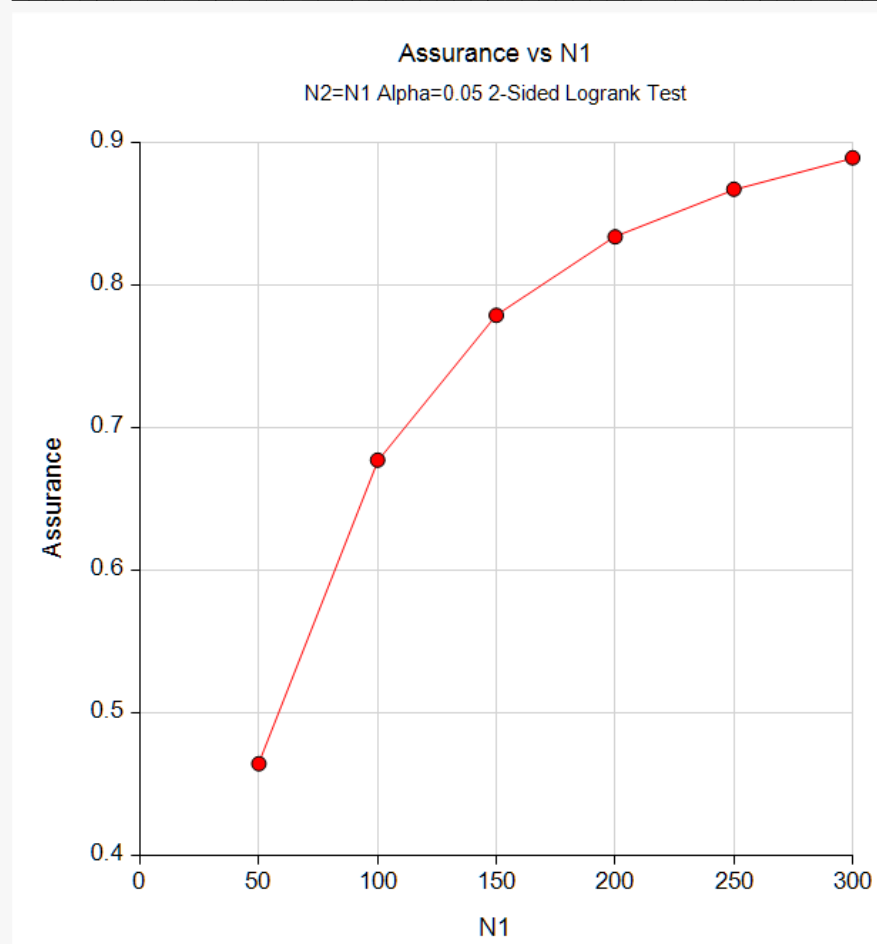
Plots
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This plot shows the relationship between the assurance and sample size. Note the diminishing impact on assurance of each increase in the number of subjects.

Comparison Plots Section

Comparison Plots
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This plot compares the assurance and power across values of sample size. Note that assurance does not increase as fast as power.

Example 2 – Validation using Hand Computation

We could not find a validation example in the literature for this procedure, so we have developed a validation example of our own.

Suppose a one-sided, logrank test will be used in which N1 = N2 = 70 and the significance level is 0.025.
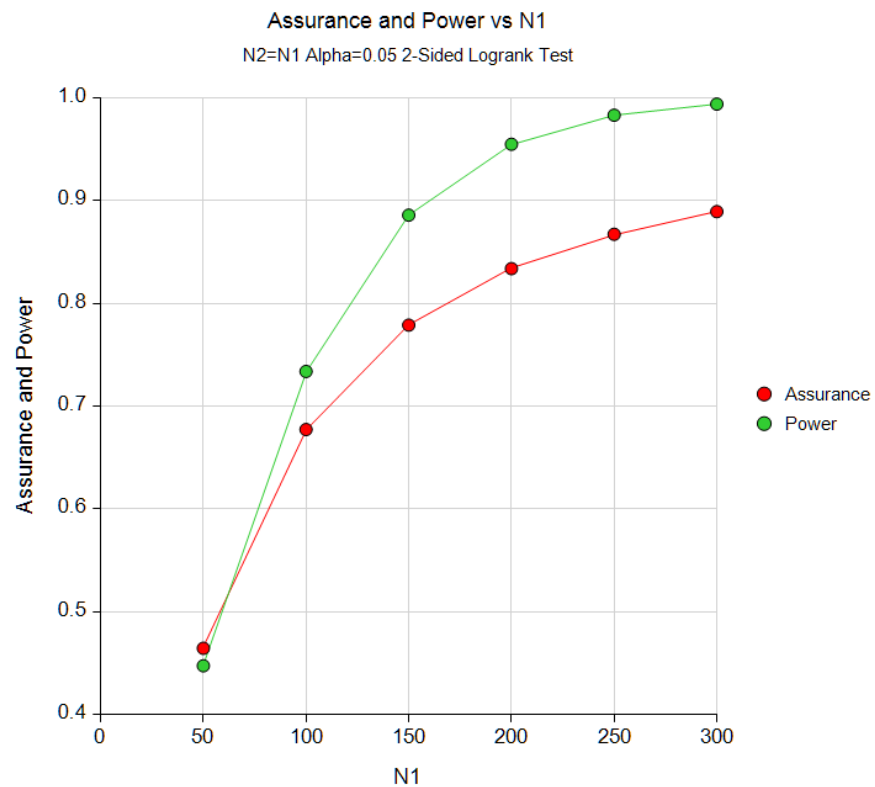
The prior distribution of S1 will be approximated by the following table.

S1	Prob
0.46	0.2
0.5	0.6
0.54	0.2

The prior distribution of the S2 will be approximated by the following table.

S2	Prob
0.55	0.2
0.7	0.6
0.85	0.2

The prior distribution of w will be approximated by the following table.

w	Prob
0.0	0.3
0.05	0.4
0.1	0.3

The *Logrank Tests (Freedman)* procedure is used to compute the power for each of the 27 combinations of *S1*, *S2*, and *w* (*PL*). The results of these calculations are shown next.

Numeric Results

Solve For: Power
Groups: 1 = Control Group, 2 = Experimental
Hypotheses: One-Sided
Distribution Assumption: Proportional Hazards

Power	Required Number of Events			Sample Size			Proportion Lost During Follow-Up	Proportion Surviving		Hazard Ratio	
Power	E1	E2	E	N1	N2	N	PL	S1	S2	HR	Alpha
0.19008	35	35	70	70	70	140	0.00	0.46	0.55	0.76988	0.025
0.81086	30	29	59	70	70	140	0.00	0.46	0.70	0.45932	0.025
0.99512	25	24	49	70	70	140	0.00	0.46	0.85	0.20929	0.025
0.08724	34	33	67	70	70	140	0.00	0.50	0.55	0.86250	0.025
0.66948	28	28	56	70	70	140	0.00	0.50	0.70	0.51457	0.025
0.98689	23	23	46	70	70	140	0.00	0.50	0.85	0.23447	0.025
0.03293	32	32	64	70	70	140	0.00	0.54	0.55	0.97022	0.025
0.49428	27	27	54	70	70	140	0.00	0.54	0.70	0.57884	0.025
0.96763	22	21	43	70	70	140	0.00	0.54	0.85	0.26375	0.025
0.18273	33	33	66	70	70	140	0.05	0.46	0.55	0.76988	0.025
0.79079	28	28	56	70	70	140	0.05	0.46	0.70	0.45932	0.025
0.99323	23	23	46	70	70	140	0.05	0.46	0.85	0.20929	0.025
0.08485	32	32	64	70	70	140	0.05	0.50	0.55	0.86250	0.025
0.64719	27	27	54	70	70	140	0.05	0.50	0.70	0.51457	0.025
0.98288	22	22	44	70	70	140	0.05	0.50	0.85	0.23447	0.025

0.03271	31	30	61	70	70	140	0.05	0.54	0.55	0.97022	0.025
0.47465	26	25	51	70	70	140	0.05	0.54	0.70	0.57884	0.025
0.95999	21	20	41	70	70	140	0.05	0.54	0.85	0.26375	0.025
0.17537	32	31	63	70	70	140	0.10	0.46	0.55	0.76988	0.025
0.76892	27	26	53	70	70	140	0.10	0.46	0.70	0.45932	0.025
0.99064	22	22	44	70	70	140	0.10	0.46	0.85	0.20929	0.025
0.08244	30	30	60	70	70	140	0.10	0.50	0.55	0.86250	0.025
0.62377	26	25	51	70	70	140	0.10	0.50	0.70	0.51457	0.025
0.97770	21	20	41	70	70	140	0.10	0.50	0.85	0.23447	0.025
0.03248	29	29	58	70	70	140	0.10	0.54	0.55	0.97022	0.025
0.45455	24	24	48	70	70	140	0.10	0.54	0.70	0.57884	0.025
0.95070	20	19	39	70	70	140	0.10	0.54	0.85	0.26375	0.025

The assurance calculation is made by summing the quantities $\left[(power_{i,j,k})(p(S1_i))\left(p(S2_j)\right)(p(w_k))\right]$ as follows

$$Assurance = (0.19008 \times 0.2 \times 0.2 \times 0.3) + (0.81086 \times 0.3 \times 0.6 \times 0.3) + \cdots + (0.95070 \times 0.2 \times 0.2 \times 0.3)$$
$$= 0.59944.$$

To run this example, the spreadsheet will need to be loaded with the following six columns in which the first two are for S1, the second two are for S2, and the third two are for w.

C1	C2	C3	C4	C5	C6
0.46	0.2	0.55	0.2	0	0.3
0.5	0.6	0.7	0.6	0.05	0.4
0.54	0.2	0.85	0.2	0.1	0.3

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 ....**Assurance**
Prior Entry Method...**Individual (Enter a prior distribution for each applicable parameter)**
Alternative Hypothesis ....**One-Sided (H1: S1 < S2)**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **70**
Prior Distribution of w...................................**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C5**
Column of Pr(Values)....................................**C6**
Prior Distribution of S1 ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C1**
Column of Pr(Values)....................................**C2**

Prior Distribution of S2 ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C3**
Column of Pr(Values)....................................**C4**

Options Tab

Number of Computation Points for each........**50**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data
───

Row	C1	C2	C3	C4	C5	C6
1	0.46	0.2	0.55	0.2	0.00	0.3
2	0.50	0.6	0.70	0.6	0.05	0.4
3	0.54	0.2	0.85	0.2	0.10	0.3

───

Output

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

Numeric Results
───

Solve For:	Assurance
Groups:	1 = Control, 2 = Treatment
Hazard Ratio (HR):	Hazard Rate 2 / Hazard Rate 1
Hypotheses:	H0: S1 ≥ S2 vs. H1: S1 < S2
Test Statistic:	Logrank or Cox Regression
Prior Type:	Independent Univariate Distributions

Prior Distributions
S1:   Point List (Values = C1, Probs = C2).
  C1: 0.46 0.5 0.54
  C2: 0.2 0.6 0.2
S2:   Point List (Values = C3, Probs = C4).
  C3: 0.55 0.7 0.85
  C4: 0.2 0.6 0.2
w: Point List (Values = C5, Probs = C6).
  C5: 0 0.05 0.1
  C6: 0.3 0.4 0.3

───

		Required Number of Events			Sample Size			Expected Proportion Lost During Follow Up	Expected Proportion Surviving in Group 1	Expected Proportion Surviving in Group 2	Hazard Ratio	
Assurance	Power‡	E1	E2	E	N1	N2	N	E(w)	E(S1)	E(S2)	HR	Alpha
0.59944	0.64719	27	27	54	70	70	140	0.05	0.5	0.7	0.51457	0.025

───

‡ Power was calculated using S1 = E(S1) = 0.5, S2 = E(S2) = 0.7, and w = E(w) = 0.05.

PASS has also calculated the assurance as 0.59944 which validates the procedure.

Example 3 – Finding the Sample Size Needed to Achieve a Specified Assurance

Continuing with Example 1, the researchers want to investigate the sample sizes necessary to achieve assurances of 0.4, 0.6, and 0.8.

In order to reduce the runtime during this exploratory phase of the analysis, the number of points in the prior computation is reduced to 30. This slightly reduces the accuracy, but greatly reduces the runtime.

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 ....**Sample Size**
Prior Entry Method.......................................**Individual (Enter a prior distribution for each applicable parameter)**
Alternative Hypothesis ....**Two-Sided (H1: S1 ≠ S2)**
Assurance..**0.4 0.6 0.8**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
Prior Distribution of w.................................**Normal (Mean, SD)**
Mean...**0.05**
SD..**0.02**
Truncation Boundaries.................................**Left**
Left Boundary **0**
Prior Distribution of S1 ....**Normal (Mean, SD)**
Mean...**0.5**
SD..**0.04**
Truncation Boundaries.................................**Left and Right**
Left Boundary **0.45**
Right Boundary **0.55**
Prior Distribution of S2 ....**Normal (Mean, SD)**
Mean...**0.7**
SD..**0.08**
Truncation Boundaries.................................**Left and Right**
Left Boundary **0.4**
Right Boundary **0.8**

Options Tab

Number of Computation Points for each........**30**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Output

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

Numeric Reports

Numeric Results
_____

Solve For:	Sample Size
Groups:	1 = Control, 2 = Treatment
Hazard Ratio (HR):	Hazard Rate 2 / Hazard Rate 1
Hypotheses:	H0: S1 = S2 vs. H1: S1 ≠ S2
Test Statistic:	Logrank or Cox Regression
Prior Type:	Independent Univariate Distributions

Prior Distributions
S1: Normal (Mean = 0.5, SD = 0.04), Left Boundary = 0.45, Right Boundary = 0.55.
S2: Normal (Mean = 0.7, SD = 0.08), Left Boundary = 0.4, Right Boundary = 0.8.
w: Normal (Mean = 0.05, SD = 0.02), Left Boundary = 0.
_____

Assurance*			Required Number of Events			Sample Size			Expected Proportion Lost During Follow Up	Expected Proportion Surviving in Group 1	Expected Proportion Surviving in Group 2	Hazard Ratio	
Actual	Target	Power‡	E1	E2	E	N1	N2	N	E(w)	E(S1)	E(S2)	HR	Alpha
0.40020	0.4	0.37482	16	15	31	40	40	80	0.05022	0.5	0.68561	0.54454	0.05
0.60166	0.6	0.62609	30	30	60	77	77	154	0.05022	0.5	0.68561	0.54454	0.05
0.80087	0.8	0.91698	65	64	129	166	166	332	0.05022	0.5	0.68561	0.54454	0.05
_____

* The number of points used for computation of the prior(s) was 30.
‡ Power was calculated using S1 = E(S1) = 0.5, S2 = E(S2) = 0.68561, and w = E(w) = 0.05022.

This report shows the assurance values obtained by each sample size.

Plots Section
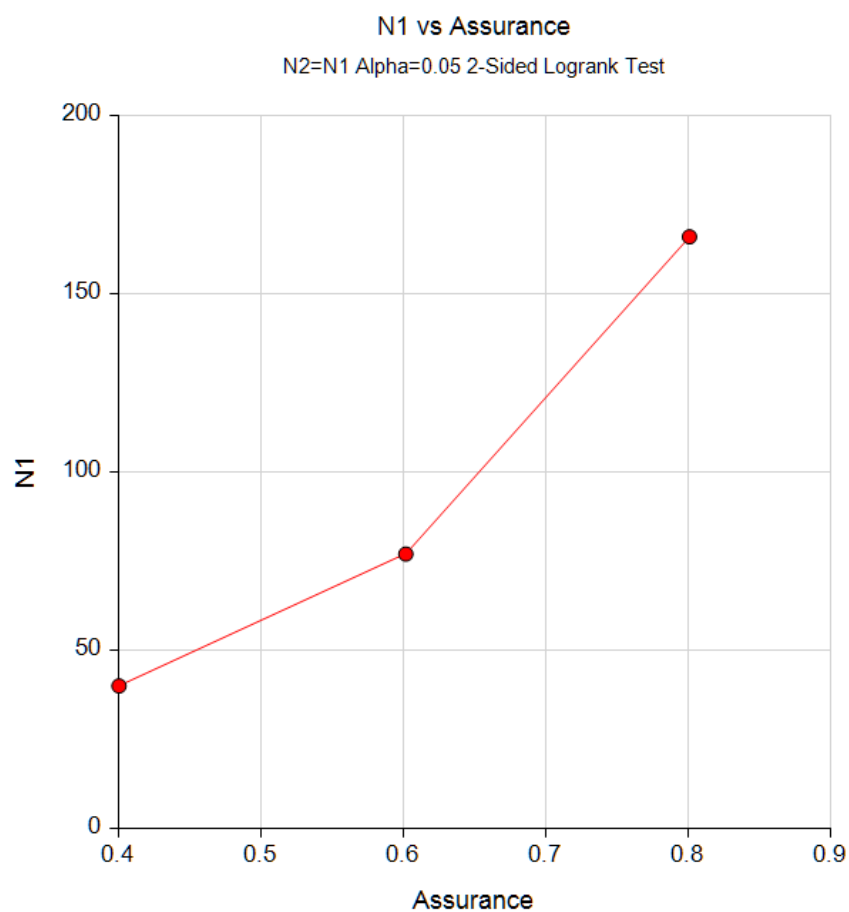
Plots
_____

This plot shows the relationship between the assurance and sample size. Note the large increase in required sample size that occurs between an assurance of 0.6 and 0.8.

Example 4 – Joint Prior Distribution

The following example shows the complexity required to specify a joint distribution for three or more parameters.

Suppose a one-sided, logrank test will be used in which N1 = N2 = (100 200 300 400 500) and the significance level is 0.025. Further suppose that the joint prior distribution of the S1, S2, and w is approximated by the following table. In a real study, the values in this table would be provided by an elicitation study.

Note that the program will rescale the probabilities so they sum to one.

S1	S2	w	Prob
0.60	0.55	0.0	0.2
0.65	0.55	0.0	0.4
0.70	0.55	0.0	0.2
0.63	0.58	0.0	0.4
0.68	0.58	0.0	0.6
0.73	0.58	0.0	0.4
0.66	0.61	0.0	0.2
0.71	0.61	0.0	0.4
0.76	0.61	0.0	0.2
0.60	0.55	0.1	0.3
0.65	0.55	0.1	0.5
0.70	0.55	0.1	0.3
0.63	0.58	0.1	0.5
0.68	0.58	0.1	0.7
0.73	0.58	0.1	0.5
0.66	0.61	0.1	0.3
0.71	0.61	0.1	0.5
0.76	0.61	0.1	0.3

To run this example, the spreadsheet will need to be loaded with the following four columns.

C1	C2	C3	C4
0.60	0.55	0.0	0.2
0.65	0.55	0.0	0.4
0.70	0.55	0.0	0.2
0.63	0.58	0.0	0.4
0.68	0.58	0.0	0.6
0.73	0.58	0.0	0.4
0.66	0.61	0.0	0.2
0.71	0.61	0.0	0.4
0.76	0.61	0.0	0.2
0.60	0.55	0.1	0.3
0.65	0.55	0.1	0.5
0.70	0.55	0.1	0.3
0.63	0.58	0.1	0.5
0.68	0.58	0.1	0.7

0.73	0.58	0.1	0.5
0.66	0.61	0.1	0.3
0.71	0.61	0.1	0.5
0.76	0.61	0.1	0.3

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 ....**Assurance**
Prior Entry Method..**Combined (Enter parameter values and probabilities on spreadsheet)**
Alternative Hypothesis ....**One-Sided (H1: S1 > S2)**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **100 200 300 400 500**
Column of w Values......................................**C3**
Column of S1 Values **C1**
Column of S2 Values **C2**
Column of Pr(Values)....................................**C4**

Options Tab

Number of Computation Points for each........**50**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data

Row	C1	C2	C3	C4
1	0.60	0.55	0.0	0.2
2	0.65	0.55	0.0	0.4
3	0.70	0.55	0.0	0.2
4	0.63	0.58	0.0	0.4
5	0.68	0.58	0.0	0.6
6	0.73	0.58	0.0	0.4
7	0.66	0.61	0.0	0.2
8	0.71	0.61	0.0	0.4
9	0.76	0.61	0.0	0.2
10	0.60	0.55	0.1	0.3
11	0.65	0.55	0.1	0.5
12	0.70	0.55	0.1	0.3
13	0.63	0.58	0.1	0.5
14	0.68	0.58	0.1	0.7
15	0.73	0.58	0.1	0.5
16	0.66	0.61	0.1	0.3
17	0.71	0.61	0.1	0.5
18	0.76	0.61	0.1	0.3

Output

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

Numeric Results
───

Solve For:	Assurance
Groups:	1 = Control, 2 = Treatment
Hazard Ratio (HR):	Hazard Rate 2 / Hazard Rate 1
Hypotheses:	H0: S1 ≤ S2 vs. H1: S1 > S2
Test Statistic:	Logrank or Cox Regression
Prior Type:	Joint Multivariate Distribution

Prior Distribution
Point Lists
S1:   C1:   0.6 0.65 0.7 0.63 0.68 0.73 0.66 0.71 0.76 0.6 0.65 0.7 0.63 0.68 0.73 0.66 0.71 0.76
S2:   C2:   0.55 0.55 0.55 0.58 0.58 0.58 0.61 0.61 0.61 0.55 0.55 0.55 0.58 0.58 0.58 0.61 0.61 0.61
w: C3:   0 0 0 0 0 0 0 0 0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1
Prob: C4:   0.2 0.4 0.2 0.4 0.6 0.4 0.2 0.4 0.2 0.3 0.5 0.3 0.5 0.7 0.5 0.3 0.5 0.3
───

		Required Number of Events			Sample Size			Expected Proportion Lost During Follow Up	Expected Proportion Surviving in Group 1	Expected Proportion Surviving in Group 2	Hazard Ratio	
Assurance	Power‡	E1	E2	E	N1	N2	N	E(w)	E(S1)	E(S2)	HR	Alpha
0.32274	0.29796	35	35	70	100	100	200	0.05652	0.68	0.58	1.41245	0.025
0.52020	0.52469	70	70	140	200	200	400	0.05652	0.68	0.58	1.41245	0.025
0.64227	0.69719	105	105	210	300	300	600	0.05652	0.68	0.58	1.41245	0.025
0.72028	0.81528	140	140	280	400	400	800	0.05652	0.68	0.58	1.41245	0.025
0.77291	0.89163	175	175	350	500	500	1000	0.05652	0.68	0.58	1.41245	0.025

‡ Power was calculated using S1 = E(S1) = 0.68, S2 = E(S2) = 0.58, and w = E(w) = 0.05652.

This report shows the assurance values obtained by each sample size.

Example 5 – Joint Prior Validation

The problem given in Example 2 will be used to validate the joint prior distribution method. This will be done by running the independent-prior scenario used in that example through the joint-prior method and checking that the assurance values match.

In Example 2, the prior distributions of the S1, S2, and w are

S1	Prob
0.46	0.2
0.5	0.6
0.54	0.2

S2	Prob
0.55	0.2
0.7	0.6
0.85	0.2

w	Prob
0.0	0.3
0.05	0.4
0.1	0.3

The joint prior distribution can be found by multiplying the three independent probabilities in each row. This results in the following discrete probability distribution.

S1	S2	w	Prob
0.46	0.55	0.0	0.012
0.46	0.55	0.05	0.016
0.46	0.55	0.1	0.012
0.46	0.7	0.0	0.036
0.46	0.7	0.05	0.048
0.46	0.7	0.1	0.036
0.46	0.85	0.0	0.012
0.46	0.85	0.05	0.016
0.46	0.85	0.1	0.012
0.5	0.55	0.0	0.036
0.5	0.55	0.05	0.048
0.5	0.55	0.1	0.036
0.5	0.7	0.0	0.108
0.5	0.7	0.05	0.144
0.5	0.7	0.1	0.108
0.5	0.85	0.0	0.036
0.5	0.85	0.05	0.048
0.5	0.85	0.1	0.036
0.54	0.55	0.0	0.012
0.54	0.55	0.05	0.016
0.54	0.55	0.1	0.012
0.54	0.7	0.0	0.036
0.54	0.7	0.05	0.048

0.54	0.7	0.1	0.036
0.54	0.85	0.0	0.012
0.54	0.85	0.05	0.016
0.54	0.85	0.1	0.012

To run this example, the spreadsheet is loaded with the following four columns.

C1	C2	C3	C4
0.46	0.55	0.0	0.012
0.46	0.55	0.05	0.016
0.46	0.55	0.1	0.012
0.46	0.7	0.0	0.036
0.46	0.7	0.05	0.048
0.46	0.7	0.1	0.036
0.46	0.85	0.0	0.012
0.46	0.85	0.05	0.016
0.46	0.85	0.1	0.012
0.5	0.55	0.0	0.036
0.5	0.55	0.05	0.048
0.5	0.55	0.1	0.036
0.5	0.7	0.0	0.108
0.5	0.7	0.05	0.144
0.5	0.7	0.1	0.108
0.5	0.85	0.0	0.036
0.5	0.85	0.05	0.048
0.5	0.85	0.1	0.036
0.54	0.55	0.0	0.012
0.54	0.55	0.05	0.016
0.54	0.55	0.1	0.012
0.54	0.7	0.0	0.036
0.54	0.7	0.05	0.048
0.54	0.7	0.1	0.036
0.54	0.85	0.0	0.012
0.54	0.85	0.05	0.016
0.54	0.85	0.1	0.012

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 5** 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 ....**Assurance**
Prior Entry Method..**Combined (Enter parameter values and**
                                                                           probabilities on spreadsheet)
Alternative Hypothesis ....**One-Sided (H1: S1 < S2)**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **70**
Column of w Values.......................................**C3**
Column of S1 Values **C1**
Column of S2 Values **C2**
Column of Pr(Values).....................................**C4**

Options Tab

Number of Computation Points for each........**50**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data
_____

Row	C1	C2	C3	C4
1	0.46	0.55	0.00	0.012
2	0.46	0.55	0.05	0.016
3	0.46	0.55	0.10	0.012
4	0.46	0.70	0.00	0.036
5	0.46	0.70	0.05	0.048
6	0.46	0.70	0.10	0.036
7	0.46	0.85	0.00	0.012
8	0.46	0.85	0.05	0.016
9	0.46	0.85	0.10	0.012
10	0.50	0.55	0.00	0.036
11	0.50	0.55	0.05	0.048
12	0.50	0.55	0.10	0.036
13	0.50	0.70	0.00	0.108
14	0.50	0.70	0.05	0.144
15	0.50	0.70	0.10	0.108
16	0.50	0.85	0.00	0.036
17	0.50	0.85	0.05	0.048
18	0.50	0.85	0.10	0.036
19	0.54	0.55	0.00	0.012
20	0.54	0.55	0.05	0.016
21	0.54	0.55	0.10	0.012
22	0.54	0.70	0.00	0.036
23	0.54	0.70	0.05	0.048

24	0.54	0.70	0.10	0.036
25	0.54	0.85	0.00	0.012
26	0.54	0.85	0.05	0.016
27	0.54	0.85	0.10	0.012

Output

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

Numeric Results
───
Solve For: Assurance
Groups: 1 = Control, 2 = Treatment
Hazard Ratio (HR): Hazard Rate 2 / Hazard Rate 1
Hypotheses: H0: S1 ≥ S2 vs. H1: S1 < S2
Test Statistic: Logrank or Cox Regression
Prior Type: Joint Multivariate Distribution

Prior Distribution
Point Lists
S1:   C1: 0.46 0.46 0.46 0.46 0.46 0.46 0.46 0.46 0.46 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.54 0.54 0.54 0.54 0.54 0.54 0.54 0.54 0.54
S2:   C2: 0.55 0.55 0.55 0.7 0.7 0.7 0.85 0.85 0.85 0.55 0.55 0.55 0.7 0.7 0.7 0.85 0.85 0.85 0.55 0.55 0.55 0.7 0.7 0.7 0.85 0.85 0.85
w: C3: 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1 0 0.05 0.1
Prob: C4: 0.012 0.016 0.012 0.036 0.048 0.036 0.012 0.016 0.012 0.036 0.048 0.036 0.108 0.144 0.108 0.036 0.048 0.036 0.012 0.016 0.012 0.036 0.048 0.036 0.012 0.016 0.012
───

| | | Required Number of Events | | | Sample Size | | | Expected Proportion Lost During Follow Up | Expected Proportion Surviving in Group 1 | Expected Proportion Surviving in Group 2 | Hazard Ratio | |
Assurance	Power‡	E1	E2	E	N1	N2	N	E(w)	E(S1)	E(S2)	HR	Alpha
0.59944	0.64719	27	27	54	70	70	140	0.05	0.5	0.7	0.51457	0.025

‡ Power was calculated using S1 = E(S1) = 0.5, S2 = E(S2) = 0.7, and w = E(w) = 0.05.

PASS has also calculated the assurance as 0.59944 which matches Example 2 and thus validates the procedure.