Chapter 723

Assurance for Non-Inferiority Tests for Two Survival Curves using Cox's Proportional Hazards Model

Introduction

This procedure calculates the assurance of non-inferiority of a treatment over a control using a regression coefficient test from Cox proportional hazards regression. The formulation for testing the significance of a Cox regression coefficient is identical to that of the standard logrank test, so the power and sample size formulas for one analysis also works for the other. This procedure is documented in Chow, Shao, and Wang (2008) which summarizes the work of Schoenfeld (1981, 1983). Refer to the *Non-Inferiority Tests for Two Survival Curves using Cox's Proportional Hazards Model* procedure for more details. The assurance calculation used in this procedure is based on O'Hagan, Stevens, and Campbell (2005).

The Cox Regression model has the added benefit over the exponential model that it does not assume that the hazard rates are constant across time, but only that they are proportional. That is, that the hazard ratio remains constant throughout the experiment, even if the hazard rates vary from one time point to another.

The assurance calculation in this procedure 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.

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).

Technical Details

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.

Cox's Proportional Hazards Regression

Cox's proportional hazards regression is widely used for survival data. The regression model is

$$h(t|z) = h(t|0) \exp(bz)$$

where

b is the regression coefficient which is equal to $\log[h(t|1)/h(t|0)] = \log(HR)$

z is a binary indicator variable of the treatment group.

t is elapsed time.

$h(t|z)$ is the hazard rate at time t, given covariate z.

HR is the hazard ratio $h(t|1)/h(t|0)$.

Non-Inferiority Hypothesis

Lower Hazards Better

Assuming that lower hazard rates are better, non-inferiority means that the treatment hazard rate is at most, only slightly higher than the control hazard rate. We find it more convenient to state the hypotheses in terms of the hazard ratio, *HR*, rather than the Cox regression coefficient, *b*. Remembering that *b* = log(*HR*) and assuming that *NIHR* > 1, non-inferiority requires that *HR* < *NIHR*. Here, *NIHR* is the boundary of clinical insignificance or the non-inferiority boundary.

The statistical hypotheses that result in the conclusion of non-inferiority when the null hypothesis is rejected are

$$H_0: \log(HR) \geq \log(NIHR) \quad \text{versus} \quad H_1: \log(HR) < \log(NIHR)$$

Higher Hazards Better

Assuming that higher hazard rates are better, non-inferiority means that the treatment hazard rate is at most, only slightly lower than the control hazard rate. We find it more convenient to state the hypotheses in terms of the hazard ratio, *HR*, rather than the Cox regression coefficient, *b*. Remembering that *b* = log(*HR*) and assuming that *NIHR* < 1, non-inferiority requires that *HR* > *NIHR*. Here, *NIHR* is called the boundary of clinical insignificance or the non-inferiority boundary.

The statistical hypotheses that results in the conclusion of non-inferiority when the null hypothesis is rejected is

$$H_0: \log(HR) \leq \log(NIHR) \quad \text{versus} \quad H_1: \log(HR) > \log(NIHR)$$

Test Statistic

It can be shown that the test of *b* based on the partial likelihood method of Cox (1972) coincides with the common logrank test statistic shown next.

Logrank Test

The logrank test statistic is

$$L = \frac{\sum_{k=1}^{K} \left(I_k - \frac{Y_{1i} NIHR}{Y_{1i} NIHR + Y_{2i}} \right)}{\left[\sum_{k=1}^{K} \left(\frac{Y_{1i} Y_{2i} NIHR}{(Y_{1i} NIHR + Y_{2i})^2} \right) \right]^{-\frac{1}{2}}}$$

where *K* is the number of deaths, Y_{ij} is the number of subjects at risk just prior to the jth observed event in the ith group, and I_k is a binary variable indicating whether the kth even is from group 1 or not.

The distribution of L is approximately normal with mean $\left(\log(HR) - \log(NIHR)\right)\sqrt{P_1 P_2 dN}$ and unit variance, where

P_1 is the proportion of N that is in the control group.

P_2 is the proportion of N that is in the treatment group.

N is the total sample size.

N_1 is the sample size from the control group, $N_1 = N(P_1)$.

N_2 is the sample size from the treatment group, $N_2 = N(P_2)$.

Pev_1 is probability that the event of interest is observed in the control group during the study.

Pev_2 is probability that the event of interest is observed in the treatment group during the study.

d is the overall probability of an event, $d = Pev_1 P_1 + Pev_2 P_2.$

b is the Cox regression coefficient, $b = \log(HR)$.

Power Calculations

The power of the statistical test of b is given by

$$\Phi\left(\left(\log(HR) - \log(NIHR)\right)\sqrt{P_1 P_2 dN} - z_{1-\alpha}\right)$$

where HR is the actual assumed value of the hazard ratio under the alternative hypothesis.

Assurance Calculation

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

Let $P_1(R|Pev_1, Pev_2, HR)$ be the power function described above where R is the event that the null hypothesis is rejected conditional on the parameter values. The specification of $Pev_1, Pev_2,$ and HR 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 $Pev_1, Pev_2,$ and HR. Hence, assurance is

$$Assurance = E_{Pev_1, Pev_2, HR}\left(P_1(R|Pev_1, Pev_2, HR)\right)$$

$$= \iiint P_1(R|Pev_1, Pev_2, HR)f(Pev_1, Pev_2, HR)dPev_1 dPev_2 dHR$$

where $f(Pev_1, Pev_2, HR)$ is the joint prior distribution of $Pev_1, Pev_2,$ and HR.

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 $f(Pev_1, Pev_2, HR)$. 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:

$$f(Pev_1, Pev_2, HR) = f_1(Pev_1)f_2(Pev_2)f_3(HR)$$

where $f_1(Pev_1)$ is the prior distribution of Pev_1, $f_2(Pev_2)$ is the prior distribution of Pev_2, and $f_3(HR)$ is the prior distribution of w. This method is also available in **PASS**. The definition of assurance becomes

$$Assurance = E_{Pev_1,Pev_2,HR}\big(P_1(R|Pev_1, Pev_2, HR)\big)$$

$$= \iiint P_1(R|Pev_1, Pev_2, HR)f_1(Pev_1)f_2(Pev_2)f_3(HR)dPev_1 dPev_2 dHR$$

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 $1 - \text{Prob}(Min \leq X \leq Max)$ 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 $1 - \text{Prob}(Min \leq X \leq Max)$ 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

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

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

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

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 $1 - \text{Prob}(Min \leq X \leq Max)$ 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 non-inferiority of a new treatment compared to the current treatment using a one-sided test with a significance level of 0.025. Previous studies with similar treatments have shown a hazard ratio of 0.9. The non-inferiority hazard ratio boundary is set at 1.25. The researchers conjecture that about 55% of the subjects in either group will have experienced the event by the end of the study.

The researchers want to run an assurance analysis for a range of group sample sizes from 200 to 800. An elicitation exercise determined that the prior distribution of Pev1 is Normal (0.55, 0.05). The elicitation also concluded that prior distribution of Pev2 is Normal (0.55, 0.07). Finally, the prior distribution of *HR* should be Normal (0.9, 0.05).

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)**
Higher Hazards Are ....**Worse (H1: HR < NIHR)**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **200 400 600 800**
Prior Distribution of Pev1 ....**Normal (Mean, SD)**
Mean...**0.55**
SD..**0.05**
Truncation Boundaries.................................**None**
Prior Distribution of Pev2 ....**Normal (Mean, SD)**
Mean...**0.55**
SD..**0.07**
Truncation Boundaries.................................**None**
Prior Distribution of HR ....**Normal (Mean, SD)**
Mean...**0.9**
SD..**0.05**
Truncation Boundaries.................................**None**
NIHR (Non-Inferiority Hazard Ratio) **1.25**

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
Higher Hazards Are: Worse
Hypotheses: H0: HR ≥ NIHR vs. H1: HR < NIHR
Test Statistic: Treatment Regression Coefficient from Cox Regression
Prior Type: Independent Univariate Distributions

Prior Distributions
Pev1: Normal (Mean = 0.55, SD = 0.05).
Pev2: Normal (Mean = 0.55, SD = 0.07).
HR: Normal (Mean = 0.9, SD = 0.05).
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		Required Number of Events			Sample Size			Expected Probability of Observing an Event in Group 1	Expected Probability of Observing an Event in Group 2	Expected Hazard Ratio	Non-Inferiority Hazard Ratio	
Assurance*	Power‡	E1	E2	E	N1	N2	N	E(Pev1)	E(Pev2)	E(HR)	NIHR	Alpha
0.67225	0.68307	110	110	220	200	200	400	0.55	0.55	0.9	1.25	0.025
0.90160	0.93128	220	220	440	400	400	800	0.55	0.55	0.9	1.25	0.025
0.96826	0.98808	330	330	660	600	600	1200	0.55	0.55	0.9	1.25	0.025
0.98872	0.99821	440	440	880	800	800	1600	0.55	0.55	0.9	1.25	0.025

* The number of points used for computation of the prior(s) was 50.
‡ Power was calculated using Pev1 = E(Pev1) = 0.55, Pev2 = E(Pev2) = 0.55, and HR = E(HR) = 0.9.

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(Pev1)	The expected value over its prior distribution of the probability of observing an event during the study for a subject in group 1.
E(Pev2)	The expected value over its prior distribution of the probability of observing an event during the study for a subject in group 2.
E(HR)	The expected value over its prior distribution of the hazard ratio.
NIHR	The non-inferiority hazard ratio boundary.
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 2 (treatment) hazard rate is non-inferior to the
Group 1 (control) hazard rate, with a non-inferiority hazard ratio of 1.25 (H0: HR ≥ 1.25 versus H1: HR < 1.25, HR
= Hazard Rate 2 / Hazard Rate 1). The comparison will be made using a one-sided, two-sample logrank test (or an
appropriate Cox proportional hazards regression coefficient test), with a Type I error rate (α) of 0.025. It is assumed
that the hazard ratio remains constant throughout the study. The prior distribution used for the probability of
observing an event in Group 1 is Normal (Mean = 0.55, SD = 0.05). The prior distribution used for the probability of
observing an event in Group 2 is Normal (Mean = 0.55, SD = 0.07). The prior distribution used for the hazard ratio
(Hazard Rate 2 / Hazard Rate 1) is Normal (Mean = 0.9, SD = 0.05). With sample sizes of 200 for Group 1 (control)
and 200 for Group 2 (treatment), the assurance (average power) is 0.67225.
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References
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O'Hagan, A., Stevens, J.W., and Campbell, M.J. 2005. 'Assurance in clinical trial design'. Pharmaceutical Statistics,
    Volume 4, Pages 187-201.
Ciarleglio, M.M., Arendt, C.D., and Peduzzi, P.N. 2016. 'Selection of the effect size for sample size determination
    for a continuous response in a superiority clinical trial using a hybrid classical and Bayesian procedure'. Clinical
    Trials, Volume 13(3), pages 275-285.
Dias, L.C., Morton, A., and Quigley, J. 2018. Elicitation, The Science and Art of Structuring Judgement. Springer.
Schoenfeld, David A. 1983. 'Sample Size Formula for the Proportional-Hazards Regression Model', Biometrics,
    Volume 39, Pages 499-503.
Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third
    Edition. Taylor & Francis/CRC. Boca Raton, Florida.
Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2018. Sample Size Tables for Clinical Studies, 4th Edition.
    John Wiley & Sons. Hoboken, NJ.
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These reports show the assurance values obtained by each sample size.

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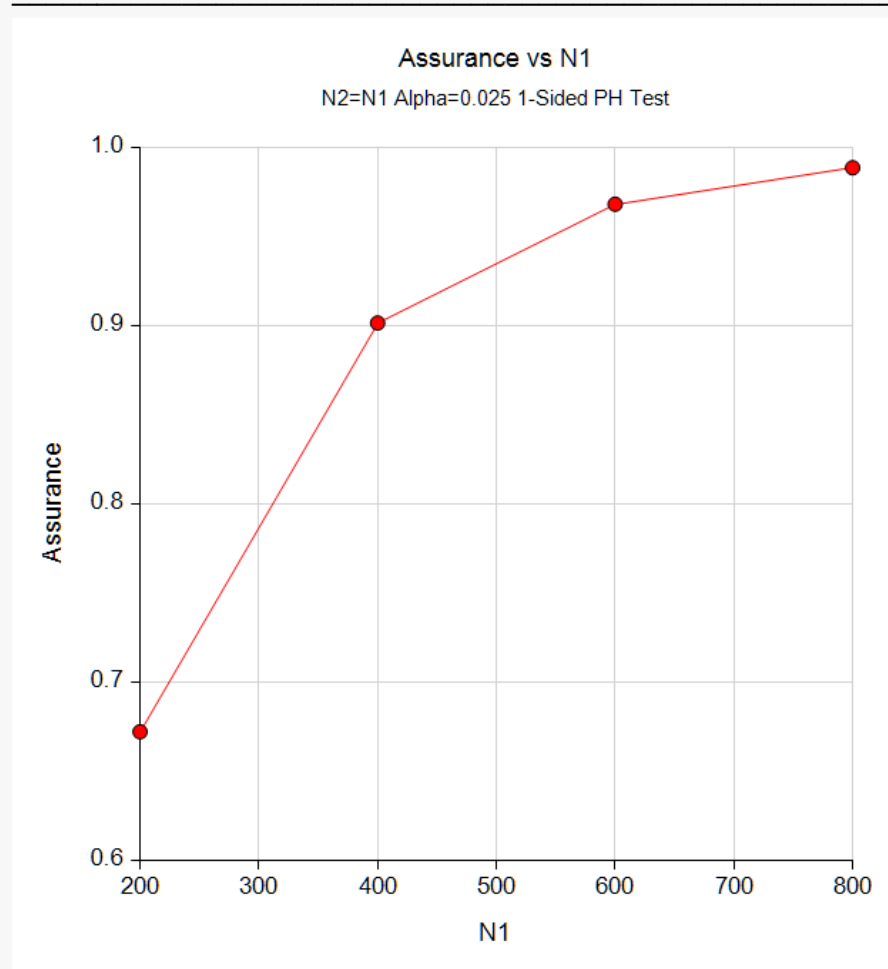
Plots
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This plot shows the relationship between the assurance and sample size. Note the diminishing impact on assurance of each increase in the number of subjects.

Comparison Plots Section

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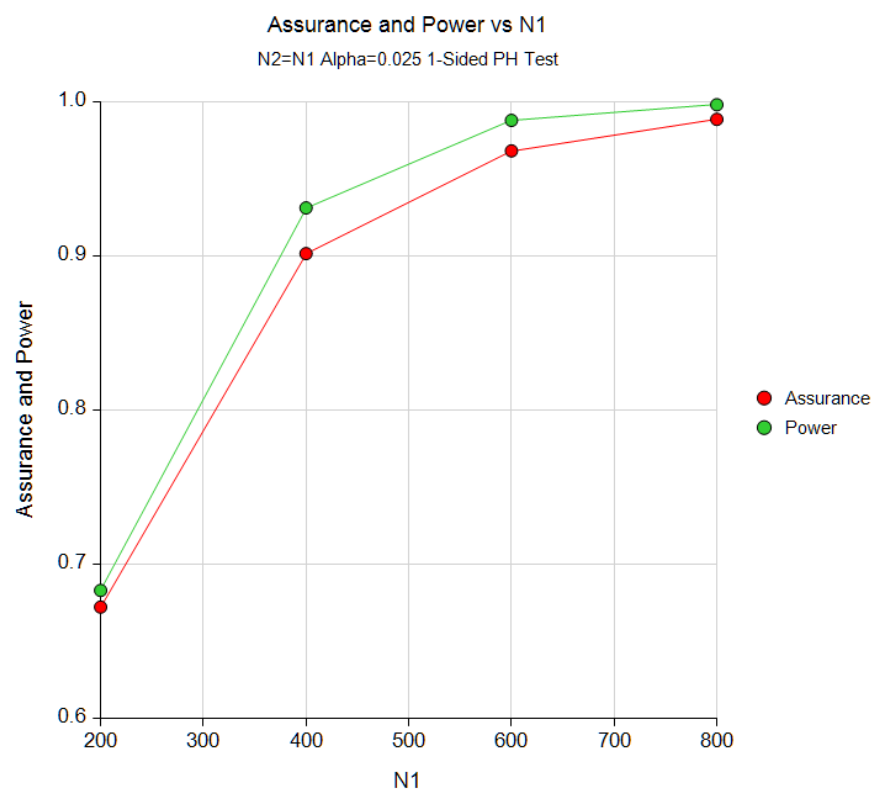
This plot compares the assurance and power across values of sample size. Note that assurance does not increase as fast as power.

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, non-inferiority test based on a Cox regression will be used in which N1 = N2 = 150 and the significance level is 0.025.

The prior distribution of Pev1 will be approximated by the following table.

Pev1 **Prob**
0.46 **0.2**
0.5   **0.6**
0.54 **0.2**

The prior distribution of the Pev2 will be approximated by the following table.

Pev2 **Prob**
0.44 **0.2**
0.5   **0.6**
0.56 **0.2**

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

HR   **Prob**
0.65 **0.3**
0.8   **0.4**
0.95 **0.3**

The *Non-Inferiority Tests for Two Survival Curves using Cox's Proportional Hazards Model* procedure is used to compute the power for each of the 27 combinations of *Pev1*, *Pev2*, and *HR*. The results of these calculations are shown next.

Numeric Results
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Solve For: Power
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: HR ≥ HR0   vs.   Ha: HR < HR0
_____

| | Sample Size | | | Percent Group 1 | Number of Events | | | Hazard Ratio | | Event Probability | | |
| | | | | | | | | Non-Inferiority | Actual | | | |
Power	N	N1	N2	%N1	E	E1	E2	HR0	HR1	Pev1	Pev2	Alpha
0.96704	300	150	150	50	135	69	66	1.25	0.65	0.46	0.44	0.025
0.73654	300	150	150	50	135	69	66	1.25	0.80	0.46	0.44	0.025
0.35732	300	150	150	50	135	69	66	1.25	0.95	0.46	0.44	0.025
0.97521	300	150	150	50	144	69	75	1.25	0.65	0.46	0.50	0.025
0.76355	300	150	150	50	144	69	75	1.25	0.80	0.46	0.50	0.025
0.37701	300	150	150	50	144	69	75	1.25	0.95	0.46	0.50	0.025
0.98144	300	150	150	50	153	69	84	1.25	0.65	0.46	0.56	0.025
0.78819	300	150	150	50	153	69	84	1.25	0.80	0.46	0.56	0.025
0.39640	300	150	150	50	153	69	84	1.25	0.95	0.46	0.56	0.025
0.97273	300	150	150	50	141	75	66	1.25	0.65	0.50	0.44	0.025
0.75481	300	150	150	50	141	75	66	1.25	0.80	0.50	0.44	0.025
0.37048	300	150	150	50	141	75	66	1.25	0.95	0.50	0.44	0.025
0.97955	300	150	150	50	150	75	75	1.25	0.65	0.50	0.50	0.025
0.78023	300	150	150	50	150	75	75	1.25	0.80	0.50	0.50	0.025
0.38997	300	150	150	50	150	75	75	1.25	0.95	0.50	0.50	0.025
0.98473	300	150	150	50	159	75	84	1.25	0.65	0.50	0.56	0.025
0.80338	300	150	150	50	159	75	84	1.25	0.80	0.50	0.56	0.025
0.40916	300	150	150	50	159	75	84	1.25	0.95	0.50	0.56	0.025

0.97748	300	150	150	50	147	81	66	1.25	0.65	0.54	0.44	0.025
0.77202	300	150	150	50	147	81	66	1.25	0.80	0.54	0.44	0.025
0.38351	300	150	150	50	147	81	66	1.25	0.95	0.54	0.44	0.025
0.98316	300	150	150	50	156	81	75	1.25	0.65	0.54	0.50	0.025
0.79591	300	150	150	50	156	81	75	1.25	0.80	0.54	0.50	0.025
0.40280	300	150	150	50	156	81	75	1.25	0.95	0.54	0.50	0.025
0.98745	300	150	150	50	165	81	84	1.25	0.65	0.54	0.56	0.025
0.81763	300	150	150	50	165	81	84	1.25	0.80	0.54	0.56	0.025
0.42177	300	150	150	50	165	81	84	1.25	0.95	0.54	0.56	0.025

The assurance calculation is made by summing the quantities $\left[(power_{i,j,k})(p(Pev1_i))\left(p(Pev2_j)\right)(p(HR_k))\right]$ as follows

$$Assurance = (0.96704 \times 0.2 \times 0.2 \times 0.3) + (0.73654 \times 0.2 \times 0.6 \times 0.3) + \cdots + (0.42177 \times 0.2 \times 0.2 \times 0.3)$$

$$= 0.72252.$$

To run this example, the spreadsheet will need to be loaded with the following six columns in which the first two are for Pev1, the second two are for Pev2, and the third two are for HR.

C1	C2	C3	C4	C5	C6
0.46	0.2	0.44	0.2	0.65	0.3
0.5	0.6	0.5	0.6	0.8	0.4
0.54	0.2	0.56	0.2	0.95	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)**

Higher Hazards Are ....**Worse (H1: HR < NIHR)**

Alpha..**0.025**

Group Allocation ....**Equal (N1 = N2)**

Sample Size Per Group **150**

Prior Distribution of Pev1 ....**Custom (Values and Probabilities in Spreadsheet)**

Column of Values **C1**

Column of Pr(Values)....................................**C2**

Prior Distribution of Pev2 ....**Custom (Values and Probabilities in Spreadsheet)**

Column of Values **C3**

Column of Pr(Values)....................................**C4**

Prior Distribution of HR ....**Custom (Values and Probabilities in Spreadsheet)**

Column of Values **C5**

Column of Pr(Values)....................................**C6**

NIHR (Non-Inferiority Hazard Ratio) **1.25**

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	0.44	0.2	0.65	0.3
2	0.50	0.6	0.50	0.6	0.80	0.4
3	0.54	0.2	0.56	0.2	0.95	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
Higher Hazards Are:	Worse
Hypotheses:	H0: HR ≥ NIHR vs. H1: HR < NIHR
Test Statistic:	Treatment Regression Coefficient from Cox Regression
Prior Type:	Independent Univariate Distributions

Prior Distributions
Pev1: Point List (Values = C1, Probs = C2).
  C1: 0.46 0.5 0.54
  C2: 0.2 0.6 0.2
Pev2: Point List (Values = C3, Probs = C4).
  C3: 0.44 0.5 0.56
  C4: 0.2 0.6 0.2
HR: Point List (Values = C5, Probs = C6).
  C5: 0.65 0.8 0.95
  C6: 0.3 0.4 0.3
_____

		Required Number of Events			Sample Size			Expected Probability of Observing an Event in Group 1	Expected Probability of Observing an Event in Group 2	Expected Hazard Ratio	Non-Inferiority Hazard Ratio	
Assurance	Power‡	E1	E2	E	N1	N2	N	E(Pev1)	E(Pev2)	E(HR)	NIHR	Alpha
0.72252	0.78023	75	75	150	150	150	300	0.5	0.5	0.8	1.25	0.025

_____

‡ Power was calculated using Pev1 = E(Pev1) = 0.5, Pev2 = E(Pev2) = 0.5, and HR = E(HR) = 0.8.

PASS has also calculated the assurance as 0.72252 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.

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)**
Higher Hazards Are ....**Worse (H1: HR < NIHR)**
Assurance...**0.4 0.6 0.8**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Prior Distribution of Pev1 ....**Normal (Mean, SD)**
Mean..**0.55**
SD...**0.05**
Truncation Boundaries..................................**None**
Prior Distribution of Pev2 ....**Normal (Mean, SD)**
Mean..**0.55**
SD...**0.07**
Truncation Boundaries..................................**None**
Prior Distribution of HR ....**Normal (Mean, SD)**
Mean..**0.9**
SD...**0.05**
Truncation Boundaries..................................**None**
NIHR (Non-Inferiority Hazard Ratio) **1.25**

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
_____

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hazard Ratio (HR):   Hazard Rate 2 / Hazard Rate 1
Higher Hazards Are: Worse
Hypotheses: H0: HR ≥ NIHR vs. H1: HR < NIHR
Test Statistic: Treatment Regression Coefficient from Cox Regression
Prior Type: Independent Univariate Distributions

Prior Distributions
Pev1:   Normal (Mean = 0.55, SD = 0.05).
Pev2:   Normal (Mean = 0.55, SD = 0.07).
HR: Normal (Mean = 0.9, SD = 0.05).
_____

| Assurance*			Required Number of Events			Sample Size			Expected Probability of Observing an Event in Group 1	Expected Probability of Observing an Event in Group 2	Expected Hazard Ratio	Non-Inferiority Hazard Ratio	
Actual	Target	Power‡	E1	E2	E	N1	N2	N	E(Pev1)	E(Pev2)	E(HR)	NIHR	Alpha
0.40244	0.4	0.39616	54	53	107	97	97	194	0.55	0.55	0.9	1.25	0.025
0.60069	0.6	0.60497	92	92	184	167	167	334	0.55	0.55	0.9	1.25	0.025
0.80056	0.8	0.82457	156	155	311	282	282	564	0.55	0.55	0.9	1.25	0.025
_____

* The number of points used for computation of the prior(s) was 50.
‡ Power was calculated using Pev1 = E(Pev1) = 0.55, Pev2 = E(Pev2) = 0.55, and HR = E(HR) = 0.9.

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

Plots Section
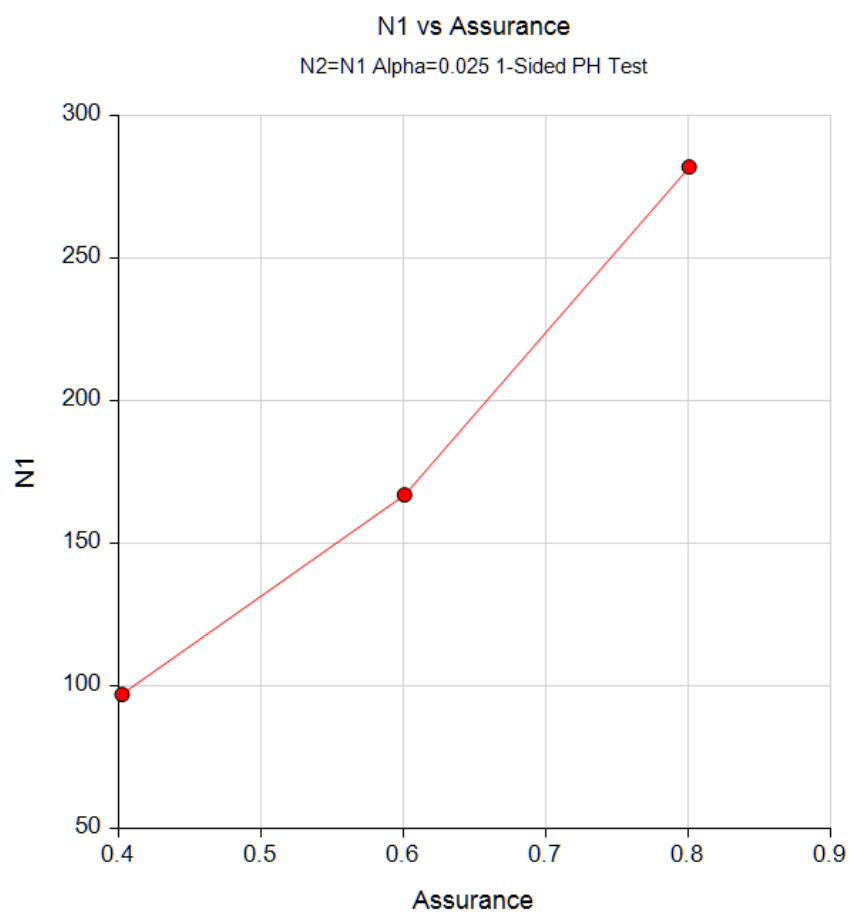
Plots
_____

This plot shows the relationship between the assurance and sample size.

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 non-inferiority test will be used in which N1 = N2 = (50 100 150 200) and the significance level is 0.025. The non-inferiority hazard ratio boundary is set at 1.25. Further suppose that the joint prior distribution of the Pev1, Pev2, and HR 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.

Pev1	Pev2	HR	Prob
0.60	0.60	0.9	0.2
0.65	0.65	0.9	0.4
0.70	0.70	0.9	0.2
0.63	0.63	0.9	0.4
0.68	0.68	0.9	0.6
0.73	0.73	0.9	0.4
0.66	0.66	0.9	0.2
0.71	0.71	0.9	0.4
0.76	0.76	0.9	0.2
0.60	0.60	0.7	0.1
0.65	0.65	0.7	0.2
0.70	0.70	0.7	0.1
0.63	0.63	0.7	0.2
0.68	0.68	0.7	0.3
0.73	0.73	0.7	0.2
0.66	0.66	0.7	0.1
0.71	0.71	0.7	0.3
0.76	0.76	0.7	0.1

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

C1	C2	C3	C4
0.60	0.60	0.9	0.2
0.65	0.65	0.9	0.4
0.70	0.70	0.9	0.2
0.63	0.63	0.9	0.4
0.68	0.68	0.9	0.6
0.73	0.73	0.9	0.4
0.66	0.66	0.9	0.2
0.71	0.71	0.9	0.4
0.76	0.76	0.9	0.2
0.60	0.60	0.7	0.1
0.65	0.65	0.7	0.2
0.70	0.70	0.7	0.1
0.63	0.63	0.7	0.2
0.68	0.68	0.7	0.3

0.73	0.73	0.7	0.2
0.66	0.66	0.7	0.1
0.71	0.71	0.7	0.3
0.76	0.76	0.7	0.1

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)**
Higher Hazards Are ....**Worse (H1: HR < NIHR)**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **50 100 150 200**
Column of Pev1 Values **C1**
Column of Pev2 Values **C2**
Column of HR Values **C3**
Column of Pr(Values)....................................**C4**
NIHR (Non-Inferiority Hazard Ratio) **1.25**

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	0.60	0.9	0.2
2	0.65	0.65	0.9	0.4
3	0.70	0.70	0.9	0.2
4	0.63	0.63	0.9	0.4
5	0.68	0.68	0.9	0.6
6	0.73	0.73	0.9	0.4
7	0.66	0.66	0.9	0.2
8	0.71	0.71	0.9	0.4
9	0.76	0.76	0.9	0.2
10	0.60	0.60	0.7	0.1
11	0.65	0.65	0.7	0.2
12	0.70	0.70	0.7	0.1
13	0.63	0.63	0.7	0.2
14	0.68	0.68	0.7	0.3
15	0.73	0.73	0.7	0.2
16	0.66	0.66	0.7	0.1
17	0.71	0.71	0.7	0.3
18	0.76	0.76	0.7	0.1

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
Higher Hazards Are:	Worse
Hypotheses:	H0: HR ≥ NIHR vs. H1: HR < NIHR
Test Statistic:	Treatment Regression Coefficient from Cox Regression
Prior Type:	Joint Multivariate Distribution

Prior Distribution
Point Lists

Pev1:	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
Pev2:	C2:	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
HR:	C3:	0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.7 0.7 0.7 0.7 0.7 0.7 0.7 0.7 0.7
Prob:	C4:	0.2 0.4 0.2 0.4 0.6 0.4 0.2 0.4 0.2 0.1 0.2 0.1 0.2 0.3 0.2 0.1 0.3 0.1

——

		Required Number of Events			Sample Size			Expected Probability of Observing an Event in Group 1	Expected Probability of Observing an Event in Group 2	Expected Hazard Ratio	Non-Inferiority Hazard Ratio	
Assurance	Power‡	E1	E2	E	N1	N2	N	E(Pev1)	E(Pev2)	E(HR)	NIHR	Alpha
0.40965	0.39242	35	34	69	50	50	100	0.68065	0.68065	0.83043	1.25	0.025
0.63487	0.66485	69	68	137	100	100	200	0.68065	0.68065	0.83043	1.25	0.025
0.76612	0.83195	103	102	205	150	150	300	0.68065	0.68065	0.83043	1.25	0.025
0.85030	0.92131	137	136	273	200	200	400	0.68065	0.68065	0.83043	1.25	0.025

——

‡ Power was calculated using Pev1 = E(Pev1) = 0.68065, Pev2 = E(Pev2) = 0.68065, and HR = E(HR) = 0.83043.

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 parameters are

Pev1	Prob
0.46	0.2
0.5	0.6
0.54	0.2

Pev2	Prob
0.44	0.2
0.5	0.6
0.56	0.2

HR	Prob
0.65	0.3
0.8	0.4
0.95	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.

Pev1	Pev2	HR	Prob
0.46	0.44	0.65	0.012
0.46	0.44	0.8	0.016
0.46	0.44	0.95	0.012
0.46	0.5	0.65	0.036
0.46	0.5	0.8	0.048
0.46	0.5	0.95	0.036
0.46	0.56	0.65	0.012
0.46	0.56	0.8	0.016
0.46	0.56	0.95	0.012
0.5	0.44	0.65	0.036
0.5	0.44	0.8	0.048
0.5	0.44	0.95	0.036
0.5	0.5	0.65	0.108
0.5	0.5	0.8	0.144
0.5	0.5	0.95	0.108
0.5	0.56	0.65	0.036
0.5	0.56	0.8	0.048
0.5	0.56	0.95	0.036
0.54	0.44	0.65	0.012
0.54	0.44	0.8	0.016
0.54	0.44	0.95	0.012
0.54	0.5	0.65	0.036
0.54	0.5	0.8	0.048

0.54   0.5   0.95   0.036
0.54   0.56   0.65   0.012
0.54   0.56   0.8   0.016
0.54   0.56   0.95   0.012

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

C1	C2	C3	C4
0.46	0.44	0.65	0.012
0.46	0.44	0.8	0.016
0.46	0.44	0.95	0.012
0.46	0.5	0.65	0.036
0.46	0.5	0.8	0.048
0.46	0.5	0.95	0.036
0.46	0.56	0.65	0.012
0.46	0.56	0.8	0.016
0.46	0.56	0.95	0.012
0.5	0.44	0.65	0.036
0.5	0.44	0.8	0.048
0.5	0.44	0.95	0.036
0.5	0.5	0.65	0.108
0.5	0.5	0.8	0.144
0.5	0.5	0.95	0.108
0.5	0.56	0.65	0.036
0.5	0.56	0.8	0.048
0.5	0.56	0.95	0.036
0.54	0.44	0.65	0.012
0.54	0.44	0.8	0.016
0.54	0.44	0.95	0.012
0.54	0.5	0.65	0.036
0.54	0.5	0.8	0.048
0.54	0.5	0.95	0.036
0.54	0.56	0.65	0.012
0.54	0.56	0.8	0.016
0.54	0.56	0.95	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)**
Higher Hazards Are ....**Worse (H1: HR < NIHR)**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **150**
Column of Pev1 Values **C1**
Column of Pev2 Values **C2**
Column of HR Values **C3**
Column of Pr(Values).....................................**C4**
NIHR (Non-Inferiority Hazard Ratio) **1.25**

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	0.44	0.65	0.012
2	0.46	0.44	0.80	0.016
3	0.46	0.44	0.95	0.012
4	0.46	0.50	0.65	0.036
5	0.46	0.50	0.80	0.048
6	0.46	0.50	0.95	0.036
7	0.46	0.56	0.65	0.012
8	0.46	0.56	0.80	0.016
9	0.46	0.56	0.95	0.012
10	0.50	0.44	0.65	0.036
11	0.50	0.44	0.80	0.048
12	0.50	0.44	0.95	0.036
13	0.50	0.50	0.65	0.108
14	0.50	0.50	0.80	0.144
15	0.50	0.50	0.95	0.108
16	0.50	0.56	0.65	0.036
17	0.50	0.56	0.80	0.048
18	0.50	0.56	0.95	0.036
19	0.54	0.44	0.65	0.012
20	0.54	0.44	0.80	0.016
21	0.54	0.44	0.95	0.012
22	0.54	0.50	0.65	0.036
23	0.54	0.50	0.80	0.048

24	0.54	0.50	0.95	0.036
25	0.54	0.56	0.65	0.012
26	0.54	0.56	0.80	0.016
27	0.54	0.56	0.95	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
Higher Hazards Are:	Worse
Hypotheses:	H0: HR ≥ NIHR vs. H1: HR < NIHR
Test Statistic:	Treatment Regression Coefficient from Cox Regression
Prior Type:	Joint Multivariate Distribution

Prior Distribution
Point Lists
Pev1: 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
Pev2: C2: 0.44 0.44 0.44 0.5 0.5 0.5 0.56 0.56 0.56 0.44 0.44 0.44 0.5 0.5 0.5 0.56 0.56 0.56 0.44 0.44 0.44 0.5 0.5 0.5 0.56 0.56 0.56
HR: C3: 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95 0.65 0.8 0.95
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 Probability of Observing an Event in Group 1	Expected Probability of Observing an Event in Group 2	Expected Hazard Ratio	Non-Inferiority Hazard Ratio	
Assurance	Power‡	E1	E2	E	N1	N2	N	E(Pev1)	E(Pev2)	E(HR)	NIHR	Alpha
0.72252	0.78023	75	75	150	150	150	300	0.5	0.5	0.8	1.25	0.025

‡ Power was calculated using Pev1 = E(Pev1) = 0.5, Pev2 = E(Pev2) = 0.5, and HR = E(HR) = 0.8.

PASS has also calculated the assurance as 0.72252 which matches Example 2 and thus validates the procedure.