Chapter 776

Assurance for Non-Inferiority Tests for Vaccine Efficacy using the Ratio of Two Proportions

Introduction

This procedure calculates the assurance of non-inferiority tests for vaccine efficacy (VE) using the ratio of two proportions.

VE is a traditional index of the protective efficacy of a vaccine. It is calculated as

$$VE = \frac{p_2 - p_1}{p_2} = 1 - \frac{p_1}{p_2}$$

where p_1 and p_2 are *attack rates* of the disease being studied among those vaccinated and a control group. An attack rate is the probability that a subject without the disease at the beginning of the study is infected by it during the duration of the study. Hence, an analysis of vaccine effectiveness reduces to an analysis of the ratio of two proportions.

Note that because $p_1 < p_2$, the value of $VE < 1$.

The calculation is based on a user-specified prior distribution of the effect size parameters. This procedure may also be used to determine the needed sample size to obtain a specified assurance.

The methods for assurance calculation in this procedure are based on O'Hagan, Stevens, and Campbell (2005).

This routine is partially based on Blackwelder (1993).

Relative Vaccine Efficacy

Often, the goal of the study is to show that the attack rate of a new vaccine is no worse than that of the current standard vaccine. For example, the standard vaccine might have serious side effects, be expensive to produce, etc. In this case, the trial is conducted to show that the new vaccine is an attractive replace for the standard vaccine. In this case, the control group does not receive a placebo. Rather, it receives the standard vaccine. In this case, the quantity of interest is called the *relative vaccine efficacy (rVE).* It is calculated as

$$rVE = \frac{p_2 - p_1}{p_2} = 1 - \frac{p_1}{p_2}$$

where now p_2 is the attack rate for those receiving the standard vaccine.

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 the effect size 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 effect size 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 effect size 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).

Test Procedure

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability (or risk) of obtaining the event of interest in population 1 (the treatment group) is P_1 and in population 2 (the control group) is P_2. The corresponding failure proportions are given by $Q_1 = 1 - P_1$ and $Q_2 = 1 - P_2$.

The assumption is made that the responses from each group follow a binomial distribution. This means that the event probability, P_i, is the same for all subjects within the group and that the response from one subject is independent of that of any other subject.

Random samples of $N_1$and N_2 individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows

Group	Success	Failure	Total
Treatment	x_{11}	x_{12}	N_1
Control	x_{21}	x_{22}	N_2
Total	M_1	M_2	N

The binomial proportions P_1 and P_2 are estimated from these data using the formulae

$$\hat{P}_1 = \frac{x_{11}}{N_1}$$

$$\hat{P}_2 = \frac{x_{21}}{N_2}$$

Let $P_{1.0} = P1|H0$ and $P_{1.1} = P1|H1$. The value of P_2 remains the same for both hypotheses, so $P_2 = P_2|H0 = P_2|H1$. In this procedure, our attention will focus on the using the ratio (often called the risk ratio) to compare the two binomial proportions. The (risk) ratio $\phi = p_1/p_2$ gives the relative change in the disease risk due to the application of the treatment.

Non-Inferiority Z-Test

A *non-inferiority test* tests that the treatment proportion is not worse than the reference proportion by more than a small, non-inferiority margin. The actual direction of the hypothesis depends on the response variable being studied. We let

$$VE_0 = \frac{P_2 - P_{1.0}}{P_2} = \frac{P_2 - P_{1.0}}{P_2} = 1 - R_0$$

refer to the non-inferiority ratio (or margin).

When dealing with vaccine efficacy, it is usually assumed that lower proportions (attack rates) are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment proportion is only slightly greater than the control proportion. The statistical hypotheses are

$$H_0: VE \leq VE_0 \text{ versus } H_1: VE > VE_0.$$

This is equivalent to

$$H_0: P_1/P_2 \geq R_0 \text{ versus } H_1: P_1/P_2 < R_0.$$

Test Statistics

Several test statistics have been proposed for testing whether the difference, ratio, or odds ratio are different from a specified value. The main difference among the several test statistics is in the formula used to compute the standard error used in the denominator.

Following is a list of the test statistics available in **PASS** for testing proportion ratios. The availability of several test statistics begs the question of which test statistic you should use. The answer is simple: you should use the test statistic that you will use to analyze your data. You may choose a method because it is a standard in your industry, because it seems to have better statistical properties, or because your statistical package calculates it. Whatever your reasons for selecting a certain test statistic, you should use the same test statistic during power or sample calculations.

Miettinen and Nurminen's Likelihood Score Test

Miettinen and Nurminen (1985) proposed a test statistic for testing whether the ratio is equal to a specified value, R_0. The regular MLE's, $\hat{p}_1$ and $\hat{p}_2$, are used in the numerator of the score statistic while MLE's $\tilde{p}_1$ and $\tilde{p}_2$, constrained so that $\tilde{p}_1/\tilde{p}_2 = \mathrm{R}_0$, are used in the denominator. A correction factor of *N*/(*N*-1) is applied to make the variance estimate less biased. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing this test statistic is

$$z_{MNR} = \frac{\hat{p}_1 \,/\, \hat{p}_2 - \mathrm{R}_0}{\hat{\sigma}_{MNR}}$$

where

$$\hat{\sigma}_{MNR} = \sqrt{\left(\frac{\tilde{p}_1\tilde{q}_1}{N_1} + \mathrm{R}_0^2\frac{\tilde{p}_2\tilde{q}_2}{N_2}\right)\left(\frac{N}{N-1}\right)}$$

$$\tilde{p}_1 = \tilde{p}_2\mathrm{R}_0$$

$$\tilde{p}_2 = \frac{-B - \sqrt{B^2 - 4AC}}{2A}$$

$$A = N\mathrm{R}_0$$

$$B = -[N_1R_0 + x_{11} + N_2 + x_{21}R_0]$$

$$C = M_1$$

Farrington and Manning's Likelihood Score Test

Farrington and Manning (1990) proposed a test statistic for testing whether the ratio is equal to a specified value, R_0. The regular MLE's, $\hat{p}_1$ and $\hat{p}_2$, are used in the numerator of the score statistic while MLE's $\tilde{p}_1$ and $\tilde{p}_2$, constrained so that $\tilde{p}_1/\tilde{p}_2 = \mathrm{R}_0$, are used in the denominator. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{FMR} = \frac{\hat{p}_1 \,/\, \hat{p}_2 - \mathrm{R}_0}{\sqrt{\left(\frac{\tilde{p}_1\tilde{q}_1}{N_1} + \mathrm{R}_0^2\frac{\tilde{p}_2\tilde{q}_2}{N_2}\right)}}$$

where the estimates, $\tilde{p}_1$ and $\tilde{p}_2$, are computed as in the corresponding test of Miettinen and Nurminen (1985) given above.

Gart and Nam's Likelihood Score Test

Gart and Nam (1988), page 329, proposed a modification to the Farrington and Manning (1988) ratio test that corrected for skewness. Let $z_{FMR}(R_0)$ stand for the Farrington and Manning ratio test statistic described above. The skewness corrected test statistic, z_{GNR}, is the appropriate solution to the quadratic equation

$$\left(-\tilde{\psi}\right)z_{GNR}^2 + (-1)z_{GNR} + \left(z_{FMR}(R_0) + \tilde{\psi}\right) = 0$$

where

$$\tilde{\psi} = \frac{1}{6\tilde{u}^{3/2}}\left(\frac{\tilde{q}_1(\tilde{q}_1 - \tilde{p}_1)}{N_1^2\tilde{p}_1^2} - \frac{\tilde{q}_2(\tilde{q}_2 - \tilde{p}_2)}{N_2^2\tilde{p}_2^2}\right)$$

$$\tilde{u} = \frac{\tilde{q}_1}{N_1\tilde{p}_1} + \frac{\tilde{q}_2}{N_2\tilde{p}_2}$$

Adapting the Ratio of Two Proportions to Vaccine Efficacy Studies

A traditional index of the protective efficacy of a vaccine is called the vaccine efficacy (VE). It is calculated as

$$VE = \frac{p_2 - p_1}{p_2} = 1 - \frac{p_1}{p_2}$$

Note that VE is a simple transformation of the ratio made by subtracting it from one. Thus, the above methods for the ratio of two proportions can be easily adapted for vaccine efficacy studies. Blackwelder (1993) gives the details. He recommends using the score test of Gart and Nam.

Non-Inferiority Bound

The idea of a non-inferiority test is that a new treatment is no worse than the current treatment it is being compared to. To allow the comparison to be made, you must determine a non-inferiority boundary. In this procedure, that means that p_1 can only be slightly larger than p_2. When $p_1 > p_2$, the risk ratio will be greater than one so that the value of VE will be negative. See Nauta (2020) page 94 for a discussion and example of this.

Hence, one task that will have to be completed is to determine how much worse the new vaccine can be without causing it to be rejected.

Power Calculations

The power is calculated using the standard formulas for the z-test. The differences in the results of the above tests occur because of the different formulas that are used for the standard error. To compute the power, the values of $\hat{p}_1$ and $\hat{p}_2$ in the test statistic are replaced by the corresponding values of P_1 and P_2. The power is then computed using the normal approximation to the binomial as presented in Chow et al. (2008).

Assurance Calculation

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

Let $P'(H|VE_1, P_2)$ be the power function described above where H is the event that null hypothesis is rejected conditional on the parameter values. The specification of VE_1 and P_2 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 the parameters VE_1 and P_2. Hence, the definition of assurance is

$$Assurance = E_{VE_1,P_2}\left(P'(H|VE_1, P_2)\right) = \iint P'(H|VE_1, P_2) f(VE_1, P_2) dVE_1\, dP_2$$

where $f(VE_1, P_2)$ is the joint prior distribution of VE_1 and P_2.

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 $f(VE_1, P_2)$. This provides flexibility in specifying the joint prior distribution. In the two-parameter case, three columns are entered on the spreadsheet: two for the parameters and a third 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 two independent univariate distributions as follows

$$f(VE_1, P_2) = f_1(VE_1) f_2(P_2)$$

where $f_1(VE_1)$ is the prior distribution of VE_1 and $f_2(P_2)$ is the prior distribution of P_2. This method is also available in **PASS**. In this case, the definition of assurance becomes

$$Assurance = E_{VE_1,P_2}\left(P'(H|VE_1, P_2)\right) = \iint P'(H|VE_1, P_2) f_1(VE_1) f_2(P_2) dVE_1\, dP_2$$

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* ~ gamma, then *X* = 1 / *Y* ~ 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

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

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 $X = e^{\mu+\sigma Z}$ ~ 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 $1 - \text{Prob}(Min \le X \le Max)$ 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

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

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

Suppose a study is being designed to establish the non-inferiority of vaccine 1 (new treatment) compared to vaccine 2 (control). The researchers plan to use the Gart and Nam likelihood score test to analyze the data. The event probability of the vaccine 2 is 0.05. The non-inferiority vaccine efficacy bound is set to -0.1. Since this is a one-sided test, the significance level will be 0.025.

To complete their sample size study, the researchers want to run an assurance analysis for a range of group sample sizes from 1000 to 3000. An elicitation exercise determined that the prior distribution of the VE1 should be normal with mean 0.0 and standard deviation 0.04. The elicitation also concluded that the prior distribution of P2 should be normal with mean 0.44 and standard deviation 0.01.

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)**
Test Type	**Likelihood Score w/Skewness (Gart & Nam)**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**1000 1500 2000 2500 3000**
VE0 (Non-Inferiority VE Bound)	**-0.1**
Prior Distribution of VE1	**Normal (Mean, SD)**
Mean	**0**
SD	**0.04**
Truncation Boundaries	**None**
Prior Distribution of P2	**Normal (Mean, SD)**
Mean	**0.44**
SD	**0.01**
Truncation Boundaries	**None**

Options Tab	
Number of Computation Points for each Prior Distribution	**20**
Maximum N1 in Sample Size Search	**50000**

Output

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

Numeric Reports

Numeric Results

Solve For: Assurance
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0
Test Statistic: Gart & Nam Likelihood Score Test
Prior Type: Independent Univariate Distributions

Prior Distributions
VE1: Normal (Mean = 0, SD = 0.04).
P2: Normal (Mean = 0.44, SD = 0.01).

					Event Probability			Vaccine Efficacy		
						Vaccinated				
Assurance*	Power‡	N1	N2	N	Control E(P2)	N.I. P1.0	Actual P1.1	N.I. VE0	Actual E(VE1)	Alpha
0.47769	0.47156	1000	1000	2000	0.44	0.484	0.44	-0.1	0	0.025
0.60225	0.63774	1500	1500	3000	0.44	0.484	0.44	-0.1	0	0.025
0.68621	0.76105	2000	2000	4000	0.44	0.484	0.44	-0.1	0	0.025
0.74460	0.84718	2500	2500	5000	0.44	0.484	0.44	-0.1	0	0.025
0.78664	0.90473	3000	3000	6000	0.44	0.484	0.44	-0.1	0	0.025

* The number of points used for computation of the prior(s) was 20.
‡ Power was calculated using VE1 = E(VE1) = 0 and P2 = E(P2) = 0.44.

Assurance	The expected power where the expectation is with respect to the prior distribution(s).
Power	The power calculated using the parameter values shown in the footnote. Note that these parameter values may be different from those shown in the report.
N1	The number of subjects in vaccinated group.
N2	The number of subjects in control group.
N	The total sample size. N = N1 + N2.
E(P2)	The expected value over its prior distribution of the event probability (attack rate) of the control group.
P1.0	The largest value of the event probability for vaccinated group that still yields a non-inferiority conclusion.
P1.1	The value of the event probability for the vaccinated group that is assumed by the alternative hypothesis, H1.
VE0	This is the non-inferiority boundary of the vaccine efficacy assumed by the null hypothesis, H0. VE0 = 1 - P1.0 / P2.
E(VE1)	The expected value over the joint prior distribution of the vaccine efficacy assumed by the alternative hypothesis, H1. This is the VE value at which the power is calculated. VE1 = 1 - P1.1 / P2.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

Sample sizes of 1000 in the vaccine group and 1000 in the control group achieve 0.47769 assurance using the non-inferiority Gart & Nam Likelihood Score Test. The non-inferiority vaccine efficacy boundary was set to -0.1. The significance level (alpha) of the test was set to 0.025. The prior distribution used for the anticipated vaccine efficacy is Normal (Mean = 0, SD = 0.04). The prior distribution used for the control group event probability is Normal (Mean = 0.44, SD = 0.01).

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	1000	1000	2000	1250	1250	2500	250	250	500
20%	1500	1500	3000	1875	1875	3750	375	375	750
20%	2000	2000	4000	2500	2500	5000	500	500	1000
20%	2500	2500	5000	3125	3125	6250	625	625	1250
20%	3000	3000	6000	3750	3750	7500	750	750	1500

Dropout Rate — The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.

N1, N2, and N — The evaluable sample sizes at which power is computed (as entered by the user). If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.

N1', N2', and N' — The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)

D1, D2, and D — The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements

Anticipating a 20% dropout rate, 1250 subjects should be enrolled in Group 1, and 1250 in Group 2, to obtain final group sample sizes of 1000 and 1000, respectively.

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Julious, S. A. and Campbell, M. J. 2012. 'Tutorial in biostatistics: sample sizes for parallel group clinical trials with binary data.' Statistics in Medicine, 31:2904-2936.

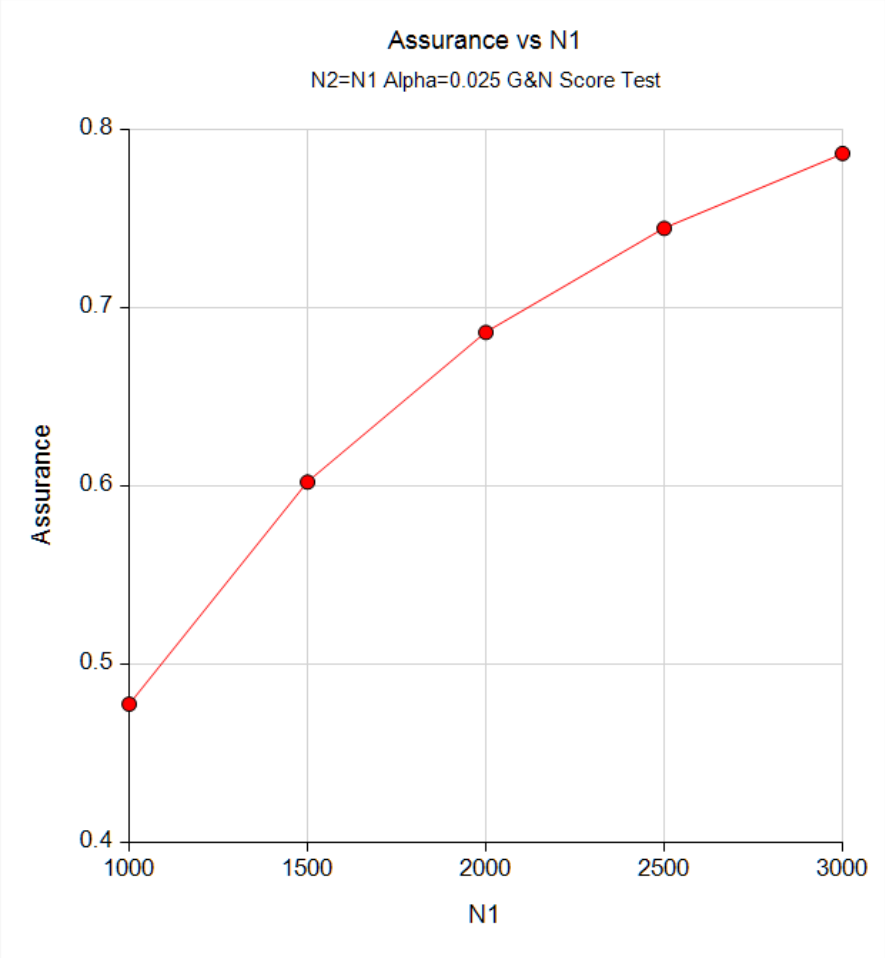
Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, Mass.

Miettinen, O.S. and Nurminen, M. 1985. 'Comparative analysis of two rates.' Statistics in Medicine 4: 213-226.

This report shows the assurance values obtained by the various sample sizes.

Plots Section

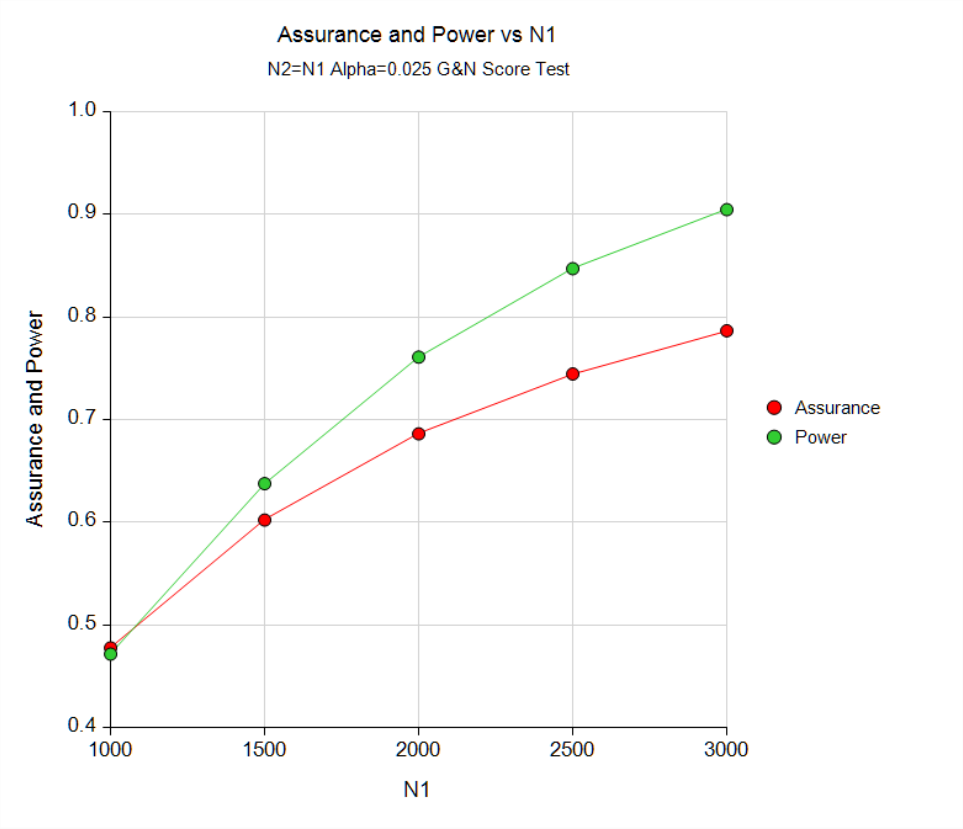
Plots



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

Comparison Plots Section

Comparison Plots



This plot compares the assurance and power across values of sample size.

Example 2 – Validation using Hand Computation

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

Suppose a non-inferiority Gart and Nam Likelihood Score Test is used where N1 = N2 = 1000 and the significance level is 0.025. Further suppose that VE0 ratio is -0.1.

The prior distribution of VE1 is approximated by the following table.

VE1	Prob
0.00	0.3
0.05	0.4
0.10	0.3

The prior distribution of P2 is approximated by the following table.

P2	Prob
0.42	0.2
0.44	0.6
0.46	0.2

Note that in both of these tables, the parameter values are equi-spaced. This is important when using a discrete approximation such as we have here.

The *Non-Inferiority Tests for Vaccine Efficacy using the Ratio of Two Proportions* procedure is used to compute the power for each of the nine combinations of VE1 and P2. The results of these calculations are shown next.

Numeric Results

Solve For: Power
Test Statistic: Gart & Nam Likelihood Score Test
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0

				Event Probability			Vaccine Efficacy		
Power*	N1	N2	N	Cntl P2	N.I. Vax P1.0	Act Vax P1.1	N.I. VE0	Act VE1	Alpha
0.44175	1000	1000	2000	0.42	0.462	0.420	-0.1	0.00	0.025
0.47156	1000	1000	2000	0.44	0.484	0.440	-0.1	0.00	0.025
0.50246	1000	1000	2000	0.46	0.506	0.460	-0.1	0.00	0.025
0.77900	1000	1000	2000	0.42	0.462	0.399	-0.1	0.05	0.025
0.81058	1000	1000	2000	0.44	0.484	0.418	-0.1	0.05	0.025
0.84000	1000	1000	2000	0.46	0.506	0.437	-0.1	0.05	0.025
0.95478	1000	1000	2000	0.42	0.462	0.378	-0.1	0.10	0.025
0.96709	1000	1000	2000	0.44	0.484	0.396	-0.1	0.10	0.025
0.97671	1000	1000	2000	0.46	0.506	0.414	-0.1	0.10	0.025

* Power was computed using the normal approximation method.

The assurance calculation is made by summing the quantities $\left[\left(power_{i,j}\right)\left(p(VE1_i)\right)\left(p\left(P2_j\right)\right)\right]$ as follows

$$Assurance = (0.44175 \times 0.3 \times 0.2) + (0.47156 \times 0.3 \times 0.6) + \cdots + (0.97671 \times 0.3 \times 0.2) = 0.75556.$$

To run this example, the spreadsheet will need to be loaded with the following four columns in which the first two are for VE1 and the second two are for P2.

C1	C2	C3	C4
0.00	**0.3**	**0.42**	**0.2**
0.05	**0.4**	**0.44**	**0.6**
0.10	**0.3**	**0.46**	**0.2**

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)**
Test Type	**Likelihood Score w/Skewness (Gart & Nam)**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**1000**
VE0 (Non-Inferiority VE Bound)	**-0.1**
Prior Distribution of VE1	**Custom (Values and Probabilities in Spreadsheet)**
Column of Values	**C1**
Column of Pr(Values)	**C2**
Prior Distribution of P2	**Custom (Values and Probabilities in Spreadsheet)**
Column of Values	**C3**
Column of Pr(Values)	**C4**

Options Tab

Number of Computation Points for each Prior Distribution	**20**
Maximum N1 in Sample Size Search	**50000**

Input Spreadsheet Data

Row	C1	C2	C3	C4
1	0.00	0.3	0.42	0.2
2	0.05	0.4	0.44	0.6
3	0.10	0.3	0.46	0.2

Output

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

Numeric Results

Solve For: Assurance
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0
Test Statistic: Gart & Nam Likelihood Score Test
Prior Type: Independent Univariate Distributions

Prior Distributions
VE1: Point List (Values = C1, Probs = C2).
C1: 0 0.05 0.1
C2: 0.3 0.4 0.3
P2: Point List (Values = C3, Probs = C4).
C3: 0.42 0.44 0.46
C4: 0.2 0.6 0.2

					Event Probability			Vaccine Efficacy		
						Vaccinated				
Assurance	Power‡	N1	N2	N	Control E(P2)	N.I. P1.0	Actual P1.1	N.I. VE0	Actual E(VE1)	Alpha
0.75556	0.81058	1000	1000	2000	0.44	0.484	0.418	-0.1	0.05	0.025

‡ Power was calculated using VE1 = E(VE1) = 0.05 and P2 = E(P2) = 0.44.

PASS has also calculated the assurance as 0.75556 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, 0.5, 0.6, 0.7, 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)**
Test Type	**Likelihood Score w/Skewness (Gart & Nam)**
Assurance	**0.4 0.5 0.6 0.7 0.8**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
VE0 (Non-Inferiority VE Bound)	**-0.1**
Prior Distribution of VE1	**Normal (Mean, SD)**
Mean	**0**
SD	**0.04**
Truncation Boundaries	**None**
Prior Distribution of P2	**Normal (Mean, SD)**
Mean	**0.44**
SD	**0.01**
Truncation Boundaries	**None**

Options Tab	
Number of Computation Points for each Prior Distribution	**20**
Maximum N1 in Sample Size Search	**50000**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0
Test Statistic: Gart & Nam Likelihood Score Test
Prior Type: Independent Univariate Distributions

Prior Distributions
VE1: Normal (Mean = 0, SD = 0.04).
P2: Normal (Mean = 0.44, SD = 0.01).

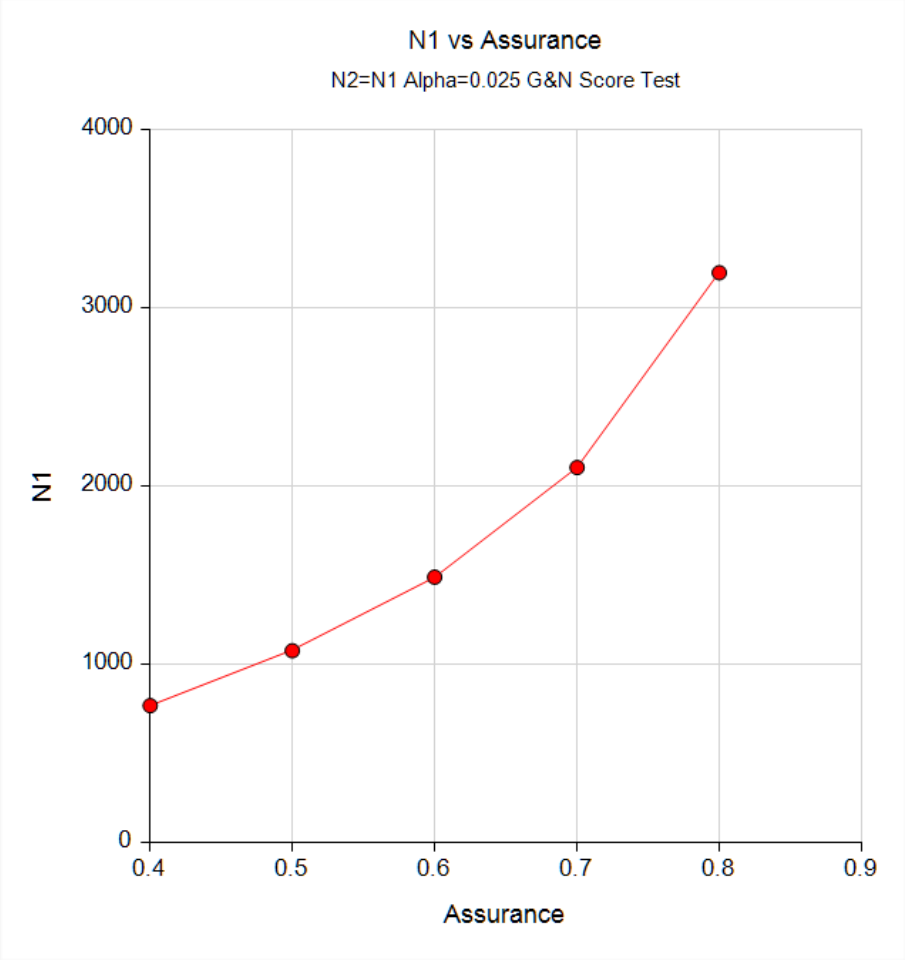
Assurance*						Event Probability			Vaccine Efficacy		
							Vaccinated				
Actual	Target	Power‡	N1	N2	N	Control E(P2)	N.I. P1.0	Actual P1.1	N.I. VE0	Actual E(VE1)	Alpha
0.40025	0.4	0.38038	768	768	1536	0.44	0.484	0.44	-0.1	0	0.025
0.50005	0.5	0.49960	1076	1076	2152	0.44	0.484	0.44	-0.1	0	0.025
0.60002	0.6	0.63455	1489	1489	2978	0.44	0.484	0.44	-0.1	0	0.025
0.70008	0.7	0.78175	2104	2104	4208	0.44	0.484	0.44	-0.1	0	0.025
0.80000	0.8	0.92139	3197	3197	6394	0.44	0.484	0.44	-0.1	0	0.025

* The number of points used for computation of the prior(s) was 20.
‡ Power was calculated using VE1 = E(VE1) = 0 and P2 = E(P2) = 0.44.

This report shows the required sample size for each assurance target.

Plots Section

Plots



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

Example 4 – Joint Prior Distribution

The following example shows the complexity required to specify a joint distribution for two parameters.

Suppose a non-inferiority Gart and Name Likelihood Score Test will be used for a study in which higher values of the response proportion are better. In this study, N1 = N2 = 1000, the significance level is 0.025, and the non-inferiority ratio (VE0) is -0.1.

Further suppose that the joint prior distribution of the VE1 and P2 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.

VE1	P2	Prob
0	0.42	0.1
0	0.44	0.2
0	0.46	0.3
0.05	0.42	0.4
0.05	0.44	0.5
0.05	0.46	0.2
0.1	0.42	0.1
0.1	0.44	0.2
0.1	0.46	0.2

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

C1	C2	C3
0	0.42	0.1
0	0.44	0.2
0	0.46	0.3
0.05	0.42	0.4
0.05	0.44	0.5
0.05	0.46	0.2
0.1	0.42	0.1
0.1	0.44	0.2
0.1	0.46	0.2

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)**
Test Type	**Likelihood Score w/Skewness (Gart & Nam)**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**1000**
VE0 (Non-Inferiority VE Bound)	**-0.1**
Column of VE1 Values	**C1**
Column of P2 Values	**C2**
Column of Pr(Values)	**C3**

Options Tab

Number of Computation Points for each Prior Distribution	**20**
Maximum N1 in Sample Size Search	**50000**

Input Spreadsheet Data

Row	C1	C2	C3
1	0.00	0.42	0.1
2	0.00	0.44	0.2
3	0.00	0.46	0.3
4	0.05	0.42	0.4
5	0.05	0.44	0.5
6	0.05	0.46	0.2
7	0.10	0.42	0.1
8	0.10	0.44	0.2
9	0.10	0.46	0.2

Output

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

Numeric Results

Solve For: Assurance
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0
Test Statistic: Gart & Nam Likelihood Score Test
Prior Type: Joint Multivariate Distribution

Prior Distribution
Point Lists
VE1: C1: 0 0 0 0.05 0.05 0.05 0.1 0.1 0.1
P2: C2: 0.42 0.44 0.46 0.42 0.44 0.46 0.42 0.44 0.46
Prob: C3: 0.1 0.2 0.3 0.4 0.5 0.2 0.1 0.2 0.2

					Event Probability			Vaccine Efficacy		
						Vaccinated				
Assurance	Power‡	N1	N2	N	Control E(P2)	N.I. P1.0	Actual P1.1	N.I. VE0	Actual E(VE1)	Alpha
0.7538	0.80002	1000	1000	2000	0.44091	0.485	0.41987	-0.1	0.04773	0.025

‡ Power was calculated using VE1 = E(VE1) = 0.04773 and P2 = E(P2) = 0.44091.

PASS has calculated the assurance as 0.7538.

Example 5 – Joint Prior Validation

The settings 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 VE1 and P2 are

VE1	Prob
0.00	0.3
0.05	0.4
0.10	0.3

P2	Prob
0.42	0.2
0.44	0.6
0.46	0.2

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

VE1	P2	Prob
0	0.42	0.06
0	0.44	0.18
0	0.46	0.06
0.05	0.42	0.08
0.05	0.44	0.24
0.05	0.46	0.08
0.1	0.42	0.06
0.1	0.44	0.18
0.1	0.46	0.06

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

C1	C2	C3
0	0.42	0.06
0	0.44	0.18
0	0.46	0.06
0.05	0.42	0.08
0.05	0.44	0.24
0.05	0.46	0.08
0.1	0.42	0.06
0.1	0.44	0.18
0.1	0.46	0.06

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)**
Test Type	**Likelihood Score w/Skewness (Gart & Nam)**
Alpha	**0.025**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**1000**
VE0 (Non-Inferiority VE Bound)	**-0.1**
Column of VE1 Values	**C1**
Column of P2 Values	**C2**
Column of Pr(Values)	**C3**

Options Tab

Number of Computation Points for each Prior Distribution	**20**
Maximum N1 in Sample Size Search	**50000**

Input Spreadsheet Data

Row	C1	C2	C3
1	0.00	0.42	0.06
2	0.00	0.44	0.18
3	0.00	0.46	0.06
4	0.05	0.42	0.08
5	0.05	0.44	0.24
6	0.05	0.46	0.08
7	0.10	0.42	0.06
8	0.10	0.44	0.18
9	0.10	0.46	0.06

Output

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

Numeric Results

Solve For: Assurance
Hypotheses: H0: VE ≤ VE0 vs. H1: VE > VE0
Test Statistic: Gart & Nam Likelihood Score Test
Prior Type: Joint Multivariate Distribution

Prior Distribution
Point Lists
VE1: C1: 0 0 0 0.05 0.05 0.05 0.1 0.1 0.1
P2: C2: 0.42 0.44 0.46 0.42 0.44 0.46 0.42 0.44 0.46
Prob: C3: 0.06 0.18 0.06 0.08 0.24 0.08 0.06 0.18 0.06

					Event Probability			Vaccine Efficacy		
						Vaccinated				
Assurance	Power‡	N1	N2	N	Control E(P2)	N.I. P1.0	Actual P1.1	N.I. VE0	Actual E(VE1)	Alpha
0.75556	0.81058	1000	1000	2000	0.44	0.484	0.418	-0.1	0.05	0.025

‡ Power was calculated using VE1 = E(VE1) = 0.05 and P2 = E(P2) = 0.44.

PASS has also calculated the assurance as 0.75556 which matches Example 2 and thus validates the procedure.