Chapter 738

# Assurance for Superiority by a Margin Tests for the Ratio of Two Negative Binomial Rates

## Introduction

This procedure calculates the assurance of superiority by a margin tests of the ratio of two independent negative binomial event rates. A negative binomial regression model gives the probability distribution of the number of events occurring in a specified interval of time or space. The negative binomial distribution is characterized by a single parameter which is the mean number of occurrences during the specified interval. The negative binomial distribution is often used to fit count data, such as the number of legions on a subject's legs or the number of episodes during a year.

Count data arise from counting the number of events of a particular type that occur during a specified time interval. Traditionally, the Poisson distribution (e.g., Poisson regression) has been used to model count data. The Poisson model assumes that the mean and variance are equal, but in many clinical trials the variance is observed to be greater than the mean in a condition called *overdispersion*. When overdispersion occurs, the Poisson model provides a poor fit to the data. As an alternative, the negative binomial model is increasingly used to model overdispersed count data. While the Poisson distribution is characterized by a single parameter which represents both the mean and the variance, the negative binomial distribution includes two parameters, allowing for greater flexibility in modeling the mean-variance relationship that is observed in overdispersed, heterogeneous count data.

This procedure is based on the formulas and results outlined in Zhu (2017).

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).

## 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).

# Technical Details

## The Negative Binomial Model

As in Zhu and Lakkis (2014), define $y_{ij}$ as the number of events during time $t_{ij}$ for subject *i* (*i* = 1 to $n_j$) in group *j* (*j* = 1, 2). Usually, group 1 is considered the control or reference group and group 2 is considered the treatment group. If $y_{ij}$ follows a negative binomial distribution with mean $\mu_{ij}$ and dispersion parameter $\kappa$, the probability function for $y_{ij}$ is

$$P(y_{ij}) = \frac{\Gamma(\kappa^{-1} + y_{ij})}{\Gamma(\kappa^{-1})y_{ij}!}\left(\frac{\kappa\mu_{ij}}{1+\kappa\mu_{ij}}\right)^{y_{ij}}\left(\frac{1}{1+\kappa\mu_{ij}}\right)^{1/\kappa}$$

where $\Gamma(.)$ is the gamma function. Using negative binomial regression, $\mu_{ij}$ can be modeled as

$$\log(\mu_{ij}) = \log(t_{ij}) + \beta_0 + \beta_1 x_{ij}$$

such that

$$\log\left(\frac{\mu_{ij}}{t_{ij}}\right) = \beta_0 + \beta_1 x_{ij}$$

where $x_{ij} = 0$ if the $i^{th}$ subject is in group 1 and $x_{ij} = 1$ if the $i^{th}$ subject is in group 2.

Further define $\lambda_1$ and $\lambda_2$ as the mean event rates per time unit for groups 1 and 2, respectively, and $RR = \lambda_2/\lambda_1$ as the ratio of event rates. Using the negative binomial model, it follows then that

$$\lambda_1 = e^{\beta_0}$$

$$\lambda_2 = e^{\beta_0+\beta_1}$$

$$RR = \frac{\lambda_2}{\lambda_1} = e^{\beta_1}$$

If we define $\hat{\beta}_1$ as the asymptotic maximum likelihood estimate of $\beta_1$, then the variance of $\hat{\beta}_1$ can be written as

$$\mathrm{Var}(\hat{\beta}_1) = \frac{1}{N_1}\left[\frac{1}{\mu_t}\left(\frac{1}{\lambda_1} + \frac{1}{R\lambda_2}\right) + \frac{(1+R)\kappa}{R}\right]$$

where $N_1$ and $N_2$ are the sample sizes and $\lambda_1$ and $\lambda_2$ are the event rates from groups 1 and 2, respectively, $R = N_2/N_1$ is the sample allocation ratio, $\kappa$ is the negative binomial dispersion parameter, and $\mu_t$ is the average exposure time across all subjects (i.e., $t_{ij}$ = $\mu_t$ for all *i*, *j*).

## Hypotheses

When higher rates are better, the superiority by a margin test hypotheses are

$$H_0{:}\frac{\lambda_2}{\lambda_1} \le RR_0 \quad \text{vs.} \quad H_1{:}\frac{\lambda_2}{\lambda_1} > RR_0$$

where $RR_0 > 1$.

When higher rates are worse, the superiority by a margin test hypotheses are

$$H_0{:}\frac{\lambda_2}{\lambda_1} \ge RR_0 \quad \text{vs.} \quad H_1{:}\frac{\lambda_2}{\lambda_1} < RR_0$$

where $RR_0 < 1$.

# Sample Size and Power Calculations

## Sample Size Calculation

Zhu (2017) bases the sample size calculations on a superiority by a margin test derived from a Negative Binomial regression model. The sample size calculation is

$$N_1 \geq \frac{\left(z_\alpha\sqrt{V_0} + z_\beta\sqrt{V_1}\right)^2}{(\log RR_0 - \log\left(\lambda_2/\lambda_1\right))^2}$$

$$N_2 = \theta N_1$$

where

$$V_1 = \frac{1}{\mu_t}\left(\frac{1}{\lambda_1} + \frac{1}{\theta\lambda_2}\right) + \frac{(1+\theta)\kappa}{\theta}$$

and $V_0$ may be calculated in any of 3 ways.

**$V_0$ Calculation Method 1** (using assumed true rates)

$$V_{01} = \frac{1}{\mu_t}\left(\frac{1}{\lambda_1} + \frac{1}{\theta\lambda_2}\right) + \frac{(1+\theta)\kappa}{\theta}$$

Using Method 1, $V_0$ and $V_1$ are equal.

**$V_0$ Calculation Method 2** (fixed marginal total)

$$V_{02} = \frac{(1 + RR_0\theta)^2}{\mu_t RR_0\theta(\lambda_1 + \theta\lambda_2)} + \frac{(1+\theta)\kappa}{\theta}$$

**$V_0$ Calculation Method 3** (restricted maximum likelihood estimation)

$$V_{03} = \frac{2a}{\mu_t\left(-b - \sqrt{b^2 - 4ac}\right)}\left(1 + \frac{1}{\theta RR_0}\right) + \frac{(1+\theta)\kappa}{\theta}$$

where

$$a = -\kappa\mu_t R_0(1+\theta),$$

$$b = \kappa\mu_t(\lambda_1 R_0 + \theta\lambda_2) - (1 + \theta R_0),$$

$$c = \lambda_1 + \theta\lambda_2$$

Zhu (2017) did not give a recommendation regarding whether Method 1, 2, or 3 should be used, except to say that "for many scenarios, Methods 1 and 2 gave the smallest and largest sample sizes, respectively, while the sample sizes given by Method 3 were between the other two methods and had the closest simulated power values to the targeted power."

## Power Calculation

The corresponding power calculation to the sample size calculation above is

$$Power \geq 1 - \Phi\left(\frac{\sqrt{N_1}(\log RR_0 - \log(\lambda_2/\lambda_1)) - z_\alpha\sqrt{V_0}}{\sqrt{V_1}}\right)$$

# Assurance Calculation

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

Let $P'(H|\lambda_1, \lambda_2, \mu_t, \kappa)$ be the power function described above where *H* is the event that null hypothesis is rejected conditional on the parameter values. The specification of $\lambda_1, \lambda_2, \mu_t,$ and $\kappa$ 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 $\lambda_1, \lambda_2, \mu_t,$ and $\kappa$. Hence, the definition of assurance is

$$Assurance = E_{\lambda_1,\lambda_2,\mu_t,\kappa}\left(P'(H|\lambda_1, \lambda_2, \mu_t, \kappa)\right) = \int\int\int\int P'(H|\lambda_1, \lambda_2, \mu_t, \kappa) f(\lambda_1, \lambda_2, \mu_t, \kappa) d\lambda_1\, d\lambda_2\, d\mu_t\, d\kappa$$

where $f(\lambda_1, \lambda_2, \mu_t, \kappa)$ is the joint prior distribution using the four parameters.

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 $f(\lambda_1, \lambda_2, \mu_t, \kappa)$. This provides flexibility in specifying the joint prior distribution. In the four-parameter case, five columns are entered on the spreadsheet: four for the parameters and a fifth 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

$$f(\lambda_1, \lambda_2, \mu_t, \kappa) = f_1(\lambda_1) f_2(\lambda_2) f_3(\mu_t) f_4(\kappa)$$

where $f_1(\lambda_1)$ is the prior distribution of $\lambda_1$, $f_2(\lambda_2)$ is the prior distribution of $\lambda_2$, and so on. This method is also available in **PASS**. In this case, the definition of assurance becomes

$$Assurance = E_{\lambda_1, \lambda_2, \mu_t, \kappa}\left(P'(H|\lambda_1, \lambda_2, \mu_t, \kappa)\right)$$

$$= \int \int \int \int P'(H|\lambda_1, \lambda_2, \mu_t, \kappa) f_1(\lambda_1) f_2(\lambda_2) f_3(\mu_t) f_4(\kappa) d\lambda_1\, d\lambda_2\, d\mu_t\, d\kappa$$

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 ($\alpha$ and $\beta$) 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 $\alpha$ and $\beta$. 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, $\kappa$, and a scale parameter, $\theta$, 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, $\alpha$, and a scale parameter, $\beta$, 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, $\mu$, 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, $\nu$, control the distribution. Note that $\nu$ 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, $\mu$, and a scale parameter, $\sigma$, 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, $\mu$, a scale parameter, $\sigma$, and a shape parameter, $\nu$, control the distribution. Note that $\nu$ 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 $\mu$ 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

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

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, $\kappa$, and a scale parameter, $\lambda$, 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

Researchers wish to compare two drugs to determine whether there is a meaningful decrease in the treatment event rate from the control event rate. In this case, higher rates are worse. They will analyze the data using a negative binomial regression model and will use restricted maximum likelihood. A one-sided test of the regression coefficient identifying the treatment group will have a significance level of 0.025.

The average exposure time for all subjects is one year. The event rate ratio at which the new treatment will be considered superior (RR0) is 0.9. The event rate of the control group is 1.0 events per year. The researchers would like to examine a treatment group event rate of 0.7. The dispersion is about 1.8.

To complete their sample size 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 $\lambda_1 \sim N(1.0, 0.05^2)$, $\lambda_2 \sim N(0.7, 0.15^2)$, $\mu_t \sim N(1.0, 0.03^2)$, and $\kappa \sim N(1.8, 0.04^2)$.

## 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 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 Poisson Rates Are | **Worse** |
| Variance Calculation Method | **Restricted Maximum Likelihood Estimation** |
| Alpha | **0.025** |
| Prior Distribution of μ(t) | **Normal (Mean, SD)** |
| Mean | **1** |
| SD | **0.03** |
| Truncation Boundaries | **None** |
| Group Allocation | **Equal (N1 = N2)** |
| Sample Size Per Group | **200 400 600 800** |
| RR0 (Superiority Margin Ratio) | **0.9** |
| Prior Distribution of λ1 | **Normal (Mean, SD)** |
| Mean | **1** |
| SD | **0.05** |
| Truncation Boundaries | **None** |
| Prior Distribution of λ2 | **Normal (Mean, SD)** |
| Mean | **0.7** |
| SD | **0.15** |
| Truncation Boundaries | **None** |
| Prior Distribution of κ | **Normal (Mean, SD)** |
| Mean | **1.8** |
| SD | **0.04** |
| Truncation Boundaries | **None** |

Options Tab

Number of Computation Points for each Prior Distribution........**20**
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: Assurance
Test Direction Assumption: Higher Negative Binomial Rates Are Worse
Hypotheses: H0: λ2 / λ1 ≥ RR0 vs. H1: λ2 / λ1 < RR0
Variance Calculation Method: Restricted Maximum Likelihood
Prior Type: Independent Univariate Distributions

**Prior Distributions**
μ(t): Normal (Mean = 1, SD = 0.03).
λ1: Normal (Mean = 1, SD = 0.05).
λ2: Normal (Mean = 0.7, SD = 0.15).
κ: Normal (Mean = 1.8, SD = 0.04).

| | | Sample Size | | | Expected Average Exposure Time | Expected Event Rate Group 1 | Expected Event Rate Group 2 | Rate Ratio | | Expected Dispersion | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Assurance* | Power‡ | N1 | N2 | N | E(μ(t)) | E(λ1) | E(λ2) | Actual RR | Superiority Margin RR0 | E(κ) | Alpha |
| 0.38680 | 0.30759 | 200 | 200 | 400 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.52547 | 0.53859 | 400 | 400 | 800 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.59879 | 0.71122 | 600 | 600 | 1200 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.64461 | 0.82762 | 800 | 800 | 1600 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |

* The number of points used for computation of the prior(s) was 20.
‡ Power was calculated using λ1 = E(λ1) = 1, λ2 = E(λ2) = 0.7, μ(t) = E(μ(t)) = 1, and κ = E(κ) = 1.8.

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 group 1.
N2 The number of subjects in group 2.
N The total sample size. N = N1 + N2.
E(μ(t)) The expected value over its prior distribution of the average exposure time across subjects in both groups.
E(λ1) The expected value over its prior distribution of the group 1 mean event rate.
E(λ2) The expected value over its prior distribution of the group 2 mean event rate.
RR The ratio of the average event rates (λ2 / λ1).
RR0 The superiority margin ratio is the smallest (or largest) the ratio can be and still be called superior.
E(κ) The expected value over its prior distribution of the dispersion parameter.
Alpha The probability of rejecting a true null hypothesis.

**Summary Statements**

A parallel two-group design will be used to test whether the Group 2 (treatment) event rate is superior to the Group 1 (control) event rate by a margin, with a superiority event rate ratio of 0.9 (H0: λ2 / λ1 ≥ 0.9 versus H1: λ2 / λ1 < 0.9). The hypotheses are based on the general assumption that lower event rates are better. The comparison will be made using a one-sided, two-sample negative binomial regression coefficient test of the rate ratio, with a Type I error rate (α) of 0.025. The variance of the regression coefficient to be tested will be calculated using the restricted maximum likelihood estimation method. The prior distribution used for the Group 1 event rate is Normal (Mean = 1, SD = 0.05). The prior distribution used for the Group 2 event rate is Normal (Mean = 0.7, SD = 0.15). The prior distribution used for the average exposure time is Normal (Mean = 1, SD = 0.03). The prior distribution used for the dispersion factor is Normal (Mean = 1.8, SD = 0.04). With sample sizes of 200 for Group 1 (control) and 200 for Group 2 (treatment), the assurance (average power) is 0.3868.

**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% | 200 | 200 | 400 | 250 | 250 | 500 | 50 | 50 | 100 |
| 20% | 400 | 400 | 800 | 500 | 500 | 1000 | 100 | 100 | 200 |
| 20% | 600 | 600 | 1200 | 750 | 750 | 1500 | 150 | 150 | 300 |
| 20% | 800 | 800 | 1600 | 1000 | 1000 | 2000 | 200 | 200 | 400 |

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, 250 subjects should be enrolled in Group 1, and 250 in Group 2, to obtain final group sample sizes of 200 and 200, respectively.

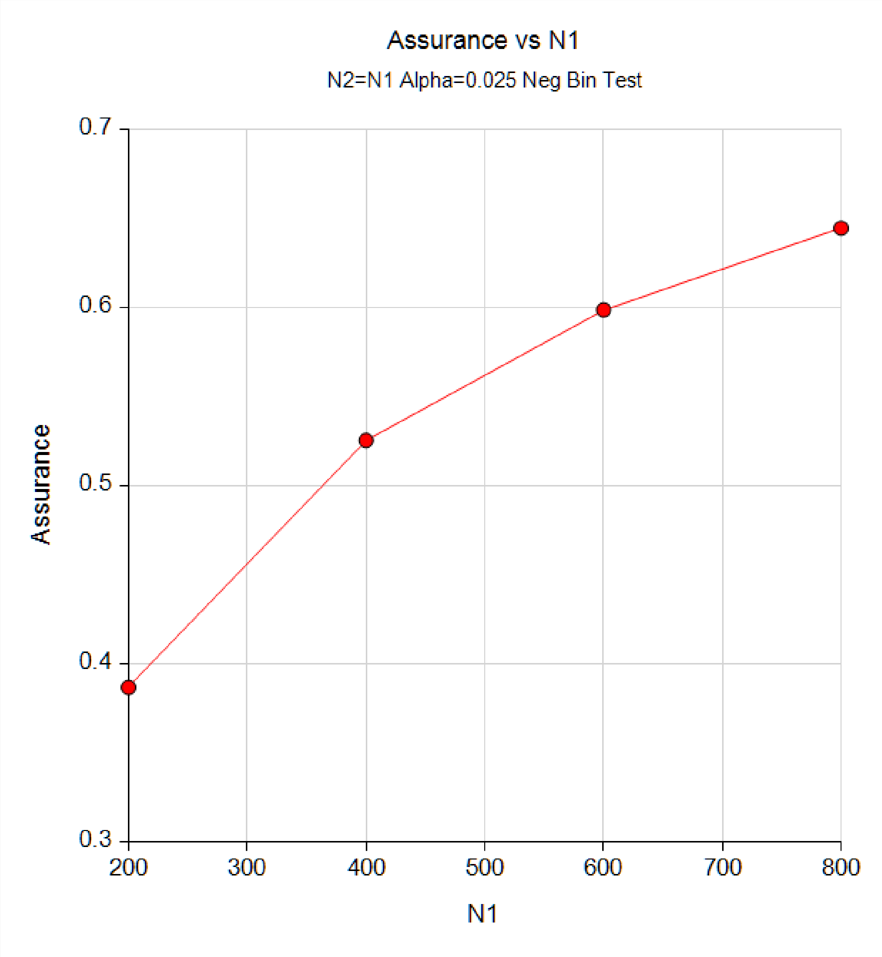
**References**

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.
Zhu, H. 2017. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' Statistics in Biopharmaceutical Research, 9(1), 107-115, doi:10.1080/19466315.2016.1225594.
Zhu, H. and Lakkis, H. 2014. 'Sample Size Calculation for Comparing Two Negative Binomial Rates.' Statistics in Medicine, Volume 33, Pages 376-387.

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

## Plots Section

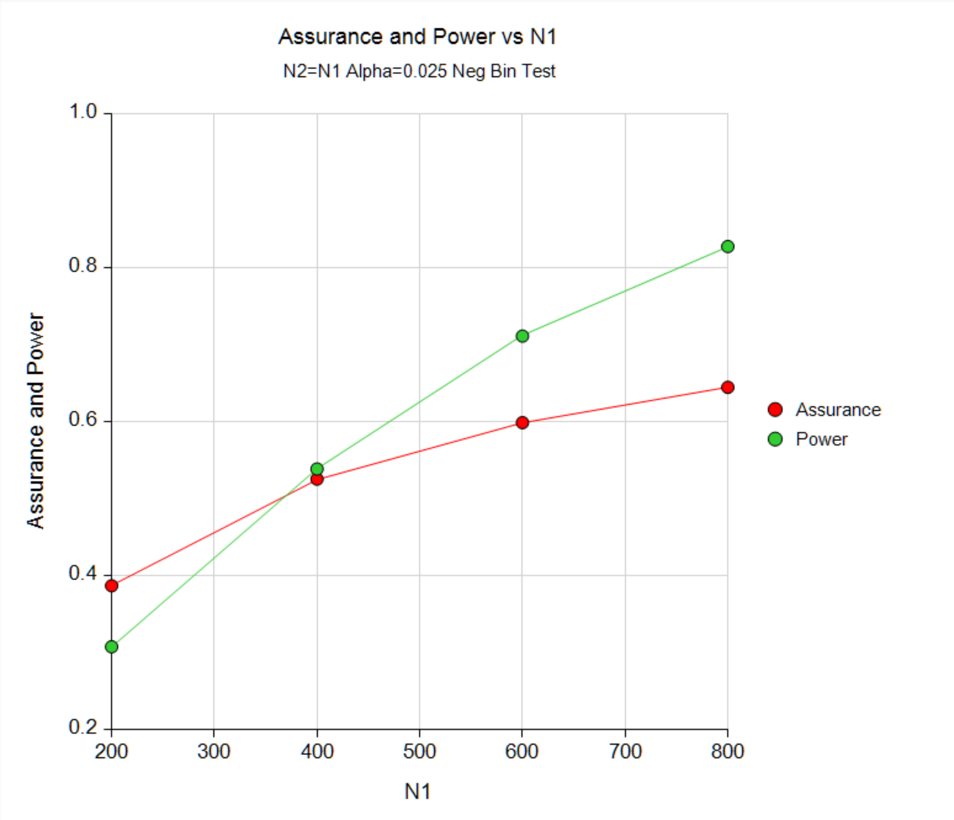
**Plots**




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

## Comparison Plots Section

### Comparison Plots




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

# 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 superiority by a margin test is used in which N1 = N2 = 500, RR0 = 0.9, and the significance level is 0.025. The variance calculation method will be using assumed true rates.

The prior distribution of λ1 is approximated by the following table.

| λ1 | Prob |
|---|---|
| 0.95 | 0.4 |
| 1.05 | 0.6 |

The prior distribution of λ2 is approximated by the following table.

| λ2 | Prob |
|---|---|
| 0.6 | 0.4 |
| 0.8 | 0.6 |

The prior distribution of μ(t) is approximated by the following table.

| μ(t) | Prob |
|---|---|
| 0.96 | 0.5 |
| 1.04 | 0.5 |

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

| κ | Prob |
|---|---|
| 1.7 | 0.5 |
| 1.9 | 0.5 |

The *Superiority by a Margin Tests for the Ratio of Two Negative Binomial Rates* procedure is used to compute the power for each of the 16 combinations of the four parameters. The results of these calculations are shown next.

**Numeric Results**

Solve For: Power
Groups: 1 = Control, 2 = Treatment
Higher Negative Binomial Rates Are: Worse
Hypotheses: H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method: Using Assumed True Rates

| | Sample Size | | | Average Exposure Time | Average Event Rate | | Event Rate Ratio | | Dispersion | |
|---|---|---|---|---|---|---|---|---|---|---|
| Power | N1 | N2 | N | μ(t) | λ1 | λ2 | Actual λ2 / λ1 | Superiority R0 | φ | Alpha |
| 0.88729 | 500 | 500 | 1000 | 0.96 | 0.95 | 0.6 | 0.63158 | 0.9 | 1.7 | 0.025 |
| 0.08971 | 500 | 500 | 1000 | 0.96 | 0.95 | 0.8 | 0.84211 | 0.9 | 1.7 | 0.025 |
| 0.98395 | 500 | 500 | 1000 | 0.96 | 1.05 | 0.6 | 0.57143 | 0.9 | 1.7 | 0.025 |
| 0.34492 | 500 | 500 | 1000 | 0.96 | 1.05 | 0.8 | 0.76190 | 0.9 | 1.7 | 0.025 |
| 0.86760 | 500 | 500 | 1000 | 0.96 | 0.95 | 0.6 | 0.63158 | 0.9 | 1.9 | 0.025 |
| 0.08647 | 500 | 500 | 1000 | 0.96 | 0.95 | 0.8 | 0.84211 | 0.9 | 1.9 | 0.025 |
| 0.97807 | 500 | 500 | 1000 | 0.96 | 1.05 | 0.6 | 0.57143 | 0.9 | 1.9 | 0.025 |
| 0.32594 | 500 | 500 | 1000 | 0.96 | 1.05 | 0.8 | 0.76190 | 0.9 | 1.9 | 0.025 |
| 0.89782 | 500 | 500 | 1000 | 1.04 | 0.95 | 0.6 | 0.63158 | 0.9 | 1.7 | 0.025 |
| 0.09135 | 500 | 500 | 1000 | 1.04 | 0.95 | 0.8 | 0.84211 | 0.9 | 1.7 | 0.025 |
| 0.98663 | 500 | 500 | 1000 | 1.04 | 1.05 | 0.6 | 0.57143 | 0.9 | 1.7 | 0.025 |
| 0.35409 | 500 | 500 | 1000 | 1.04 | 1.05 | 0.8 | 0.76190 | 0.9 | 1.7 | 0.025 |
| 0.87838 | 500 | 500 | 1000 | 1.04 | 0.95 | 0.6 | 0.63158 | 0.9 | 1.9 | 0.025 |
| 0.08791 | 500 | 500 | 1000 | 1.04 | 0.95 | 0.8 | 0.84211 | 0.9 | 1.9 | 0.025 |
| 0.98128 | 500 | 500 | 1000 | 1.04 | 1.05 | 0.6 | 0.57143 | 0.9 | 1.9 | 0.025 |
| 0.33403 | 500 | 500 | 1000 | 1.04 | 1.05 | 0.8 | 0.76190 | 0.9 | 1.9 | 0.025 |

The assurance calculation is made by summing the quantities

$$\left[\left(power_{i,j,k,l}\right)\left(p(\lambda 1_i)\right)\left(p\left(\lambda 2_j\right)\right)\left(p(\mu_k)\right)\left(p(\kappa_l)\right)\right]$$

as follows

$$\begin{aligned} Assurance &= (0.88729 \times 0.4 \times 0.4 \times 0.5 \times 0.5) + (0.08971 \times 0.4 \times 0.6 \times 0.5 \times 0.5) + \cdots \\ &\quad + (0.33403 \times 0.6 \times 0.6 \times 0.5 \times 0.5) \\ &= 0.52067. \end{aligned}$$

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

| C1 | C2 | C3 | C4 | C5 |
|---|---|---|---|---|
| **0.95** | **0.6** | **0.96** | **1.7** | **0.04** |
| **0.95** | **0.8** | **0.96** | **1.7** | **0.06** |
| **1.05** | **0.6** | **0.96** | **1.7** | **0.06** |
| **1.05** | **0.8** | **0.96** | **1.7** | **0.09** |
| **0.95** | **0.6** | **0.96** | **1.9** | **0.04** |
| **0.95** | **0.8** | **0.96** | **1.9** | **0.06** |
| **1.05** | **0.6** | **0.96** | **1.9** | **0.06** |
| **1.05** | **0.8** | **0.96** | **1.9** | **0.09** |
| **0.95** | **0.6** | **1.04** | **1.7** | **0.04** |
| **0.95** | **0.8** | **1.04** | **1.7** | **0.06** |
| **1.05** | **0.6** | **1.04** | **1.7** | **0.06** |
| **1.05** | **0.8** | **1.04** | **1.7** | **0.09** |
| **0.95** | **0.6** | **1.04** | **1.9** | **0.04** |
| **0.95** | **0.8** | **1.04** | **1.9** | **0.06** |
| **1.05** | **0.6** | **1.04** | **1.9** | **0.06** |
| **1.05** | **0.8** | **1.04** | **1.9** | **0.09** |

## 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 ........................................ **Combined (Enter parameter values and probabilities on spreadsheet)**
Higher Poisson Rates Are............................. **Worse**
Variance Calculation Method ......................... **Using Assumed True Rates**
Alpha............................................................. **0.025**
Column of μ(t) Values ................................... **C3**
Group Allocation ........................................... **Equal (N1 = N2)**
Sample Size Per Group ................................. **500**
RR0 (Superiority Margin Ratio)...................... **0.9**
Column of λ1 Values..................................... **C1**
Column of λ2 Values..................................... **C2**
Column of κ Values....................................... **C4**
Column of Pr(Values).................................... **C5**

Options Tab

Number of Computation Points for each Prior Distribution ........ **20**
Maximum N1 in Sample Size Search ............ **5000**

**Input Spreadsheet Data**

| Row | C1 | C2 | C3 | C4 | C5 |
|---|---|---|---|---|---|
| 1 | 0.95 | 0.6 | 0.96 | 1.7 | 0.04 |
| 2 | 0.95 | 0.8 | 0.96 | 1.7 | 0.06 |
| 3 | 1.05 | 0.6 | 0.96 | 1.7 | 0.06 |
| 4 | 1.05 | 0.8 | 0.96 | 1.7 | 0.09 |
| 5 | 0.95 | 0.6 | 0.96 | 1.9 | 0.04 |
| 6 | 0.95 | 0.8 | 0.96 | 1.9 | 0.06 |
| 7 | 1.05 | 0.6 | 0.96 | 1.9 | 0.06 |
| 8 | 1.05 | 0.8 | 0.96 | 1.9 | 0.09 |
| 9 | 0.95 | 0.6 | 1.04 | 1.7 | 0.04 |
| 10 | 0.95 | 0.8 | 1.04 | 1.7 | 0.06 |
| 11 | 1.05 | 0.6 | 1.04 | 1.7 | 0.06 |
| 12 | 1.05 | 0.8 | 1.04 | 1.7 | 0.09 |
| 13 | 0.95 | 0.6 | 1.04 | 1.9 | 0.04 |
| 14 | 0.95 | 0.8 | 1.04 | 1.9 | 0.06 |
| 15 | 1.05 | 0.6 | 1.04 | 1.9 | 0.06 |
| 16 | 1.05 | 0.8 | 1.04 | 1.9 | 0.09 |

## Output

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

**Numeric Results**

| | |
|---|---|
| Solve For: | Assurance |
| Test Direction Assumption: | Higher Negative Binomial Rates Are Worse |
| Hypotheses: | H0: λ2 / λ1 ≥ RR0 vs. H1: λ2 / λ1 < RR0 |
| Variance Calculation Method: | Using Assumed True Rates |
| Prior Type: | Joint Multivariate Distribution |

**Prior Distribution**

Point Lists

| | | |
|---|---|---|
| λ1: | C1: | 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 |
| λ2: | C2: | 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 |
| μ(t): | C3: | 0.96 0.96 0.96 0.96 0.96 0.96 0.96 0.96 1.04 1.04 1.04 1.04 1.04 1.04 1.04 1.04 |
| κ: | C4: | 1.7 1.7 1.7 1.7 1.9 1.9 1.9 1.9 1.7 1.7 1.7 1.7 1.9 1.9 1.9 1.9 |
| Prob: | C5: | 0.04 0.06 0.06 0.09 0.04 0.06 0.06 0.09 0.04 0.06 0.06 0.09 0.04 0.06 0.06 0.09 |

| | | Sample Size | | | Expected Average Exposure | Expected Event Rate | | Rate Ratio | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Assurance | Power‡ | N1 | N2 | N | Time E(μ(t)) | Group 1 E(λ1) | Group 2 E(λ2) | Actual RR | Superiority Margin RR0 | Expected Dispersion E(κ) | Alpha |
| 0.52067 | 0.56813 | 500 | 500 | 1000 | 1 | 1.01 | 0.72 | 0.71287 | 0.9 | 1.8 | 0.025 |

‡ Power was calculated using λ1 = E(λ1) = 1.01, λ2 = E(λ2) = 0.72, μ(t) = E(μ(t)) = 1, and κ = E(κ) = 1.8.

**PASS** has also calculated the assurance as 0.52067 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)** |
| Higher Poisson Rates Are | **Worse** |
| Variance Calculation Method | **Restricted Maximum Likelihood Estimation** |
| Assurance | **0.4 0.5 0.6 0.7 0.8** |
| Alpha | **0.025** |
| Prior Distribution of μ(t) | **Normal (Mean, SD)** |
| Mean | **1** |
| SD | **0.03** |
| Truncation Boundaries | **None** |
| Group Allocation | **Equal (N1 = N2)** |
| RR0 (Superiority Margin Ratio) | **0.9** |
| Prior Distribution of λ1 | **Normal (Mean, SD)** |
| Mean | **1** |
| SD | **0.05** |
| Truncation Boundaries | **None** |
| Prior Distribution of λ2 | **Normal (Mean, SD)** |
| Mean | **0.7** |
| SD | **0.15** |
| Truncation Boundaries | **None** |
| Prior Distribution of κ | **Normal (Mean, SD)** |
| Mean | **1.8** |
| SD | **0.04** |
| Truncation Boundaries | **None** |

Options Tab

| | |
|---|---|
| Number of Computation Points for each Prior Distribution | **20** |
| 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 |
| Test Direction Assumption: | Higher Negative Binomial Rates Are Worse |
| Hypotheses: | H0: λ2 / λ1 ≥ RR0 vs. H1: λ2 / λ1 < RR0 |
| Variance Calculation Method: | Restricted Maximum Likelihood |
| Prior Type: | Independent Univariate Distributions |

**Prior Distributions**
μ(t): Normal (Mean = 1, SD = 0.03).
λ1: Normal (Mean = 1, SD = 0.05).
λ2: Normal (Mean = 0.7, SD = 0.15).
κ: Normal (Mean = 1.8, SD = 0.04).

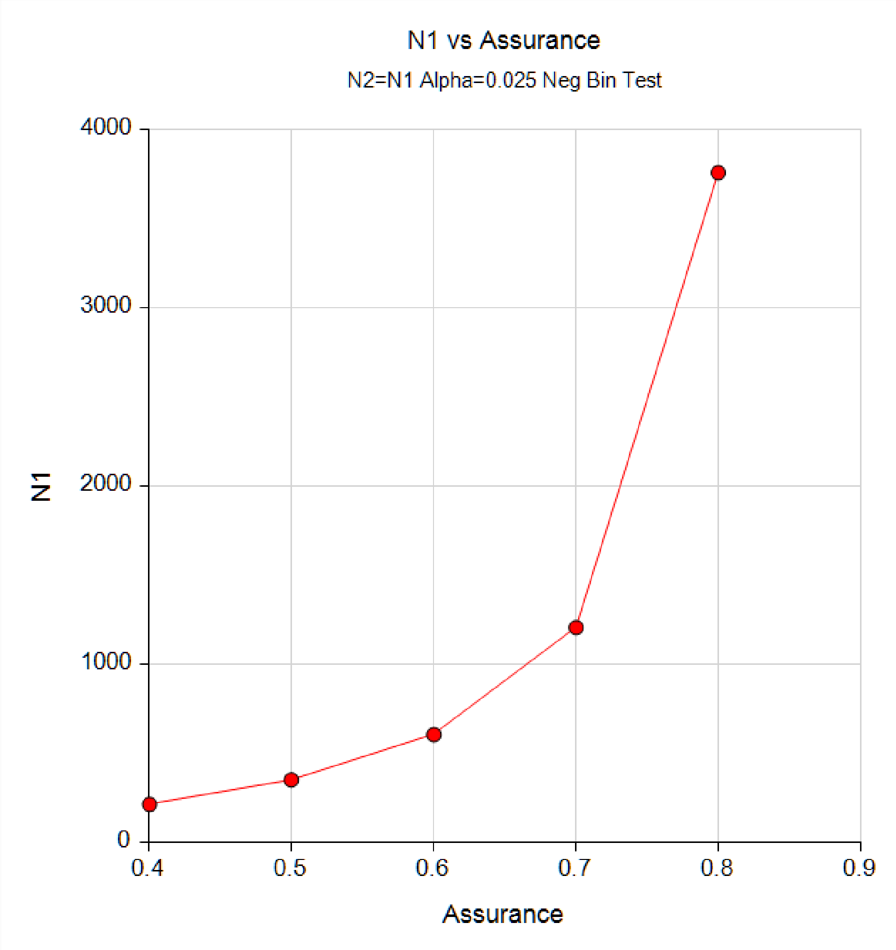
| | | Sample Size | | | Expected Average Exposure Time | Expected Event Rate Group 1 | Expected Event Rate Group 2 | Rate Ratio | | Expected Dispersion | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Assurance | Power‡ | N1 | N2 | N | E(μ(t)) | E(λ1) | E(λ2) | Actual RR | Superiority Margin RR0 | E(κ) | Alpha |
| 0.40045 | 0.32531 | 214 | 214 | 428 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.50010 | 0.48700 | 351 | 351 | 702 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.60019 | 0.71477 | 605 | 605 | 1210 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.70007 | 0.94568 | 1206 | 1206 | 2412 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |
| 0.80000 | 0.99999 | 3758 | 3758 | 7516 | 1 | 1 | 0.7 | 0.7 | 0.9 | 1.8 | 0.025 |

* The number of points used for computation of the prior(s) was 20.
‡ Power was calculated using λ1 = E(λ1) = 1, λ2 = E(λ2) = 0.7, μ(t) = E(μ(t)) = 1, and κ = E(κ) = 1.8.

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 four parameters.

Suppose a superiority by a margin test will be used in which N1 = N2 = 800, RR0 = 0.9, and the significance level is 0.025. The data will be analyzed using restricted maximum likelihood estimation.

Further suppose that the joint prior distribution of the λ1 (control), λ2 (treatment), μ(t), and κ 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.

| λ1 | λ2 | μ(t) | κ | Prob |
|---|---|---|---|---|
| 0.95 | 0.6 | 0.96 | 1.7 | 0.03 |
| 0.95 | 0.8 | 0.96 | 1.7 | 0.06 |
| 1.05 | 0.6 | 0.96 | 1.7 | 0.08 |
| 1.05 | 0.8 | 0.96 | 1.7 | 0.09 |
| 0.95 | 0.6 | 0.96 | 1.9 | 0.13 |
| 0.95 | 0.8 | 0.96 | 1.9 | 0.06 |
| 1.05 | 0.6 | 0.96 | 1.9 | 0.08 |
| 1.05 | 0.8 | 0.96 | 1.9 | 0.09 |
| 0.95 | 0.6 | 1.04 | 1.7 | 0.12 |
| 0.95 | 0.8 | 1.04 | 1.7 | 0.06 |
| 1.05 | 0.6 | 1.04 | 1.7 | 0.08 |
| 1.05 | 0.8 | 1.04 | 1.7 | 0.09 |
| 0.95 | 0.6 | 1.04 | 1.9 | 0.14 |
| 0.95 | 0.8 | 1.04 | 1.9 | 0.06 |
| 1.05 | 0.6 | 1.04 | 1.9 | 0.08 |
| 1.05 | 0.8 | 1.04 | 1.9 | 0.09 |

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

| C1 | C2 | C3 | C4 | C5 |
|---|---|---|---|---|
| 0.95 | 0.6 | 0.96 | 1.7 | 0.03 |
| 0.95 | 0.8 | 0.96 | 1.7 | 0.06 |
| 1.05 | 0.6 | 0.96 | 1.7 | 0.08 |
| 1.05 | 0.8 | 0.96 | 1.7 | 0.09 |
| 0.95 | 0.6 | 0.96 | 1.9 | 0.13 |
| 0.95 | 0.8 | 0.96 | 1.9 | 0.06 |
| 1.05 | 0.6 | 0.96 | 1.9 | 0.08 |
| 1.05 | 0.8 | 0.96 | 1.9 | 0.09 |
| 0.95 | 0.6 | 1.04 | 1.7 | 0.12 |
| 0.95 | 0.8 | 1.04 | 1.7 | 0.06 |
| 1.05 | 0.6 | 1.04 | 1.7 | 0.08 |
| 1.05 | 0.8 | 1.04 | 1.7 | 0.09 |
| 0.95 | 0.6 | 1.04 | 1.9 | 0.14 |
| 0.95 | 0.8 | 1.04 | 1.9 | 0.06 |
| 1.05 | 0.6 | 1.04 | 1.9 | 0.08 |
| 1.05 | 0.8 | 1.04 | 1.9 | 0.09 |

## 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 Poisson Rates Are.............................**Worse**
Variance Calculation Method .........................**Restricted Maximum Likelihood Estimation**
Alpha..........................................................**0.025**
Column of μ(t) Values ...................................**C3**
Group Allocation ...........................................**Equal (N1 = N2)**
Sample Size Per Group ................................**500**
RR0 (Superiority Margin Ratio).....................**0.9**
Column of λ1 Values.....................................**C1**
Column of λ2 Values.....................................**C2**
Column of κ Values.......................................**C4**
Column of Pr(Values)....................................**C5**

Options Tab

Number of Computation Points for each Prior Distribution ........**20**
Maximum N1 in Sample Size Search ............**5000**

**Input Spreadsheet Data**

| Row | C1 | C2 | C3 | C4 | C5 |
|---|---|---|---|---|---|
| 1 | 0.95 | 0.6 | 0.96 | 1.7 | 0.03 |
| 2 | 0.95 | 0.8 | 0.96 | 1.7 | 0.06 |
| 3 | 1.05 | 0.6 | 0.96 | 1.7 | 0.08 |
| 4 | 1.05 | 0.8 | 0.96 | 1.7 | 0.09 |
| 5 | 0.95 | 0.6 | 0.96 | 1.9 | 0.13 |
| 6 | 0.95 | 0.8 | 0.96 | 1.9 | 0.06 |
| 7 | 1.05 | 0.6 | 0.96 | 1.9 | 0.08 |
| 8 | 1.05 | 0.8 | 0.96 | 1.9 | 0.09 |
| 9 | 0.95 | 0.6 | 1.04 | 1.7 | 0.12 |
| 10 | 0.95 | 0.8 | 1.04 | 1.7 | 0.06 |
| 11 | 1.05 | 0.6 | 1.04 | 1.7 | 0.08 |
| 12 | 1.05 | 0.8 | 1.04 | 1.7 | 0.09 |
| 13 | 0.95 | 0.6 | 1.04 | 1.9 | 0.14 |
| 14 | 0.95 | 0.8 | 1.04 | 1.9 | 0.06 |
| 15 | 1.05 | 0.6 | 1.04 | 1.9 | 0.08 |
| 16 | 1.05 | 0.8 | 1.04 | 1.9 | 0.09 |

## Output

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

**Numeric Results**

| | |
|---|---|
| Solve For: | Assurance |
| Test Direction Assumption: | Higher Negative Binomial Rates Are Worse |
| Hypotheses: | H0: λ2 / λ1 ≥ RR0 vs. H1: λ2 / λ1 < RR0 |
| Variance Calculation Method: | Restricted Maximum Likelihood |
| Prior Type: | Joint Multivariate Distribution |

**Prior Distribution**

Point Lists

| | | |
|---|---|---|
| λ1: | C1: | 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 |
| λ2: | C2: | 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 |
| μ(t): | C3: | 0.96 0.96 0.96 0.96 0.96 0.96 0.96 0.96 1.04 1.04 1.04 1.04 1.04 1.04 1.04 1.04 |
| κ: | C4: | 1.7 1.7 1.7 1.7 1.9 1.9 1.9 1.9 1.7 1.7 1.7 1.7 1.9 1.9 1.9 1.9 |
| Prob: | C5: | 0.03 0.06 0.08 0.09 0.13 0.06 0.08 0.09 0.12 0.06 0.08 0.09 0.14 0.06 0.08 0.09 |

| | | Sample Size | | | Expected Average Exposure Time | Expected Event Rate | | Rate Ratio | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Assurance | Power‡ | N1 | N2 | N | E(μ(t)) | Group 1 E(λ1) | Group 2 E(λ2) | Actual RR | Superiority Margin RR0 | Expected Dispersion E(κ) | Alpha |
| 0.61991 | 0.68329 | 500 | 500 | 1000 | 1.00299 | 1.00075 | 0.68955 | 0.68904 | 0.9 | 1.80896 | 0.025 |

‡ Power was calculated using λ1 = E(λ1) = 1.00075, λ2 = E(λ2) = 0.68955, μ(t) = E(μ(t)) = 1.00299, and κ = E(κ) = 1.80896.

**PASS** has calculated the assurance as 0.70103.

# 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.

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

| λ1 | λ2 | μ(t) | κ | Prob |
|---|---|---|---|---|
| 1.3 | 0.6 | 0.94 | 1.72 | 0.04 |
| 1.3 | 0.6 | 0.94 | 1.88 | 0.04 |
| 1.3 | 1.2 | 0.94 | 1.72 | 0.06 |
| 1.3 | 1.2 | 0.94 | 1.88 | 0.06 |
| 1.5 | 0.6 | 0.94 | 1.72 | 0.06 |
| 1.5 | 0.6 | 0.94 | 1.88 | 0.06 |
| 1.5 | 1.2 | 0.94 | 1.72 | 0.09 |
| 1.5 | 1.2 | 0.94 | 1.88 | 0.09 |
| 1.3 | 0.6 | 1.06 | 1.72 | 0.04 |
| 1.3 | 0.6 | 1.06 | 1.88 | 0.04 |
| 1.3 | 1.2 | 1.06 | 1.72 | 0.06 |
| 1.3 | 1.2 | 1.06 | 1.88 | 0.06 |
| 1.5 | 0.6 | 1.06 | 1.72 | 0.06 |
| 1.5 | 0.6 | 1.06 | 1.88 | 0.06 |
| 1.5 | 1.2 | 1.06 | 1.72 | 0.09 |
| 1.5 | 1.2 | 1.06 | 1.88 | 0.09 |

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

| C1 | C2 | C3 | C4 | C5 |
|---|---|---|---|---|
| 1.3 | 0.6 | 0.94 | 1.72 | 0.04 |
| 1.3 | 0.6 | 0.94 | 1.88 | 0.04 |
| 1.3 | 1.2 | 0.94 | 1.72 | 0.06 |
| 1.3 | 1.2 | 0.94 | 1.88 | 0.06 |
| 1.5 | 0.6 | 0.94 | 1.72 | 0.06 |
| 1.5 | 0.6 | 0.94 | 1.88 | 0.06 |
| 1.5 | 1.2 | 0.94 | 1.72 | 0.09 |
| 1.5 | 1.2 | 0.94 | 1.88 | 0.09 |
| 1.3 | 0.6 | 1.06 | 1.72 | 0.04 |
| 1.3 | 0.6 | 1.06 | 1.88 | 0.04 |
| 1.3 | 1.2 | 1.06 | 1.72 | 0.06 |
| 1.3 | 1.2 | 1.06 | 1.88 | 0.06 |
| 1.5 | 0.6 | 1.06 | 1.72 | 0.06 |
| 1.5 | 0.6 | 1.06 | 1.88 | 0.06 |
| 1.5 | 1.2 | 1.06 | 1.72 | 0.09 |
| 1.5 | 1.2 | 1.06 | 1.88 | 0.09 |

## 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 Poisson Rates Are............................. **Worse**
Variance Calculation Method ......................... **Using Assumed True Rates**
Alpha............................................................. **0.025**
Column of μ(t) Values ................................... **C3**
Group Allocation ........................................... **Equal (N1 = N2)**
Sample Size Per Group ................................. **500**
RR0 (Superiority Margin Ratio) ...................... **0.9**
Column of λ1 Values..................................... **C1**
Column of λ2 Values..................................... **C2**
Column of κ Values....................................... **C4**
Column of Pr(Values).................................... **C5**

Options Tab

Number of Computation Points for each Prior Distribution ........ **20**
Maximum N1 in Sample Size Search ............ **5000**

**Input Spreadsheet Data**

| Row | C1 | C2 | C3 | C4 | C5 |
|---|---|---|---|---|---|
| 1 | 0.95 | 0.6 | 0.96 | 1.7 | 0.04 |
| 2 | 0.95 | 0.8 | 0.96 | 1.7 | 0.06 |
| 3 | 1.05 | 0.6 | 0.96 | 1.7 | 0.06 |
| 4 | 1.05 | 0.8 | 0.96 | 1.7 | 0.09 |
| 5 | 0.95 | 0.6 | 0.96 | 1.9 | 0.04 |
| 6 | 0.95 | 0.8 | 0.96 | 1.9 | 0.06 |
| 7 | 1.05 | 0.6 | 0.96 | 1.9 | 0.06 |
| 8 | 1.05 | 0.8 | 0.96 | 1.9 | 0.09 |
| 9 | 0.95 | 0.6 | 1.04 | 1.7 | 0.04 |
| 10 | 0.95 | 0.8 | 1.04 | 1.7 | 0.06 |
| 11 | 1.05 | 0.6 | 1.04 | 1.7 | 0.06 |
| 12 | 1.05 | 0.8 | 1.04 | 1.7 | 0.09 |
| 13 | 0.95 | 0.6 | 1.04 | 1.9 | 0.04 |
| 14 | 0.95 | 0.8 | 1.04 | 1.9 | 0.06 |
| 15 | 1.05 | 0.6 | 1.04 | 1.9 | 0.06 |
| 16 | 1.05 | 0.8 | 1.04 | 1.9 | 0.09 |

## Output

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

**Numeric Results**

Solve For: Assurance
Test Direction Assumption: Higher Negative Binomial Rates Are Worse
Hypotheses: H0: λ2 / λ1 ≥ RR0 vs. H1: λ2 / λ1 < RR0
Variance Calculation Method: Using Assumed True Rates
Prior Type: Joint Multivariate Distribution

**Prior Distribution**
Point Lists
λ1: C1: 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05 0.95 0.95 1.05 1.05
λ2: C2: 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8 0.6 0.8
μ(t): C3: 0.96 0.96 0.96 0.96 0.96 0.96 0.96 0.96 1.04 1.04 1.04 1.04 1.04 1.04 1.04 1.04
κ: C4: 1.7 1.7 1.7 1.7 1.9 1.9 1.9 1.9 1.7 1.7 1.7 1.7 1.9 1.9 1.9 1.9
Prob: C5: 0.04 0.06 0.06 0.09 0.04 0.06 0.06 0.09 0.04 0.06 0.06 0.09 0.04 0.06 0.06 0.09

| | | Sample Size | | | Expected Average Exposure | Expected Event Rate | | Rate Ratio | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Assurance | Power‡ | N1 | N2 | N | Time E(μ(t)) | Group 1 E(λ1) | Group 2 E(λ2) | Actual RR | Superiority Margin RR0 | Expected Dispersion E(κ) | Alpha |
| 0.52067 | 0.56813 | 500 | 500 | 1000 | 1 | 1.01 | 0.72 | 0.71287 | 0.9 | 1.8 | 0.025 |

‡ Power was calculated using λ1 = E(λ1) = 1.01, λ2 = E(λ2) = 0.72, μ(t) = E(μ(t)) = 1, and κ = E(κ) = 1.8.

**PASS** has also calculated the assurance as 0.52067 which matches Example 2 and thus validates the procedure.