Chapter 459

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

Introduction

This procedure may be used to calculate power and sample size for superiority by a margin tests involving the ratio of two Negative Binomial rates.

The calculation details upon which this procedure is based are found in Zhu (2016). Some of the details are summarized below.

Technical Details

Definition of Terms

The following table presents the various terms that are used.

Group	1 (Control)	2 (Treatment)
Sample size	N_1	N_2
Individual event rates	λ_1	λ_2

Dispersion parameter: φ (Negative Binomial dispersion)

Average exposure time: μ_t

Superiority margin ratio: R_0 ($R_0 > 1$ when higher rates are better; $R_0 < 1$ when higher rates are worse)

Sample size ratio: $\theta = N_2/N_1$

Hypotheses

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

$$H_0: \frac{\lambda_2}{\lambda_1} \leq R_0 \quad \text{vs.} \quad H_1: \frac{\lambda_2}{\lambda_1} > R_0$$

where $R_0 > 1$.

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

$$H_0: \frac{\lambda_2}{\lambda_1} \geq R_0 \quad \text{vs.} \quad H_1: \frac{\lambda_2}{\lambda_1} < R_0$$

where $R_0 < 1$.

Sample Size and Power Calculations

Sample Size Calculation

Zhu (2016) bases the sample size calculations on a non-inferiority test derived from a Negative Binomial regression model. The sample size calculation is

$$N_1 \geq \frac{\left(z_\alpha \sqrt{V_0} + z_\beta \sqrt{V_1}\right)^2}{(logR_0 - \log(\lambda_2/\lambda_1))^2}$$

$$N_2 = \theta N_1$$

where

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

and V_0 may be calculated in any of 3 ways.

V_0 Calculation Method 1 (using assumed true rates)

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

Using Method 1, V_0 and V_1 are equal.

V_0 Calculation Method 2 (fixed marginal total)

$$V_{02} = \frac{(1+R_0\theta)^2}{\mu_t R_0 \theta(\lambda_1 + \theta\lambda_2)} + \frac{(1+\theta)\varphi}{\theta}$$

V_0 Calculation Method 3 (restricted maximum likelihood estimation)

$$V_{03} = \frac{2a}{\mu_t\left(-b - \sqrt{b^2 - 4ac}\right)}\left(1 + \frac{1}{\theta R_0}\right) + \frac{(1+\theta)\varphi}{\theta}$$

where

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

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

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

Zhu (2016) 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

$$Power \geq 1 - \Phi\left(\frac{\sqrt{N_1}(logR_0 - \log(\lambda_2/\lambda_1)) - z_\alpha\sqrt{V_0}}{\sqrt{V_1}}\right)$$

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains the parameters associated with this test such as the Negative Binomial rates, sample sizes, alpha, and power.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters.

Test

Higher Negative Binomial Rates Are

Specify whether higher Negative Binomial rates are better or worse. This selection determines the direction of the null and alternative hypotheses. When higher rates are better, the superiority by a margin test hypotheses are

H0: $\lambda 2 / \lambda 1 \leq$ R0 vs. H1: $\lambda 2 / \lambda 1 >$ R0, and R0 > 1.

When higher rates are worse (lower are better), the non-inferiority test hypotheses are

H0: $\lambda 2 / \lambda 1 \geq$ R0 vs. H1: $\lambda 2 / \lambda 1 <$ R0, and R0 < 1.

Variance Calculation Method

Select among the three methods for calculating the V0 variance component (see the documentation above for details).

- **Using Assumed True Rates**
  For this choice, the variance component V0 is based the values entered for $\lambda 1$ and $\lambda 2$.
- **Fixed Marginal Total**
  This method assumes a fixed number of events.
- **Restricted Maximum Likelihood Estimation**
  This method uses the variance calculation based on restricted maximum likelihood estimation.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of inferiority when in fact the treatment mean is non-inferior.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected. In this procedure, a type-I error occurs when rejecting the null hypothesis of inferiority when in fact the treatment group is not inferior to the reference group.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

μ(t) (Average Exposure Time)

μ(t) (Average Exposure Time)

Enter a value (or range of values) for the average exposure (observation) time for each subject in each group. A value of one is commonly entered when exposure times are all equal. The range is $\mu(t) > 0$. You can enter a single value such as 1 or a series of values such as 0.8 0.9 1 or 0.8 to 1.2 by 0.1.

Sample Size (When Solving for Sample Size)

Group Allocation

Select the option that describes the constraints on *N1* or *N2* or both.

The options are

- **Equal (N1 = N2)**

  This selection is used when you wish to have equal sample sizes in each group. Since you are solving for both sample sizes at once, no additional sample size parameters need to be entered.

- **Enter N2, solve for N1**

  Select this option when you wish to fix *N2* at some value (or values), and then solve only for *N1*. Please note that for some values of *N2*, there may not be a value of *N1* that is large enough to obtain the desired power.

- **Enter R = N2/N1, solve for N1 and N2**

  For this choice, you set a value for the ratio of *N2* to *N1*, and then PASS determines the needed *N1* and *N2*, with this ratio, to obtain the desired power. An equivalent representation of the ratio, *R*, is

  $$N2 = R * N1.$$

- **Enter percentage in Group 1, solve for N1 and N2**

  For this choice, you set a value for the percentage of the total sample size that is in Group 1, and then PASS determines the needed *N1* and *N2* with this percentage to obtain the desired power.

N2 (Sample Size, Group 2)

This option is displayed if Group Allocation = "Enter N2, solve for N1"

N2 is the number of items or individuals sampled from the Group 2 population.

N2 must be ≥ 2. You can enter a single value or a series of values.

R (Group Sample Size Ratio)

This option is displayed only if Group Allocation = "Enter R = N2/N1, solve for N1 and N2."

R is the ratio of *N2* to *N1*. That is,

$$R = N2 / N1.$$

Use this value to fix the ratio of *N2* to *N1* while solving for *N1* and *N2*. Only sample size combinations with this ratio are considered.

N2 is related to *N1* by the formula:

$$N2 = [R \times N1],$$

where the value *[Y]* is the next integer ≥ *Y*.

For example, setting *R* = 2.0 results in a Group 2 sample size that is double the sample size in Group 1 (e.g., *N1* = 10 and *N2* = 20, or *N1* = 50 and *N2* = 100).

R must be greater than 0. If *R* < 1, then *N2* will be less than *N1*; if *R* > 1, then *N2* will be greater than *N1*. You can enter a single or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter percentage in Group 1, solve for N1 and N2."

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for *N1* and *N2*. Only sample size combinations with this Group 1 percentage are considered. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single or a series of values.

Sample Size (When Not Solving for Sample Size)

Group Allocation

Select the option that describes how individuals in the study will be allocated to Group 1 and to Group 2.

The options are

- **Equal (N1 = N2)**
  This selection is used when you wish to have equal sample sizes in each group. A single per group sample size will be entered.

- **Enter N1 and N2 individually**
  This choice permits you to enter different values for *N1* and *N2*.

- **Enter N1 and R, where N2 = R * N1**
  Choose this option to specify a value (or values) for *N1*, and obtain *N2* as a ratio (multiple) of *N1*.

- **Enter total sample size and percentage in Group 1**
  Choose this option to specify a value (or values) for the total sample size (*N*), obtain *N1* as a percentage of *N*, and then *N2* as *N* - *N1*.

Sample Size Per Group

This option is displayed only if Group Allocation = "Equal (N1 = N2)."

The Sample Size Per Group is the number of items or individuals sampled from each of the Group 1 and Group 2 populations. Since the sample sizes are the same in each group, this value is the value for *N1*, and also the value for *N2*.

The Sample Size Per Group must be ≥ 2. You can enter a single value or a series of values.

N1 (Sample Size, Group 1)

*This option is displayed if Group Allocation = "Enter N1 and N2 individually" or "Enter N1 and R, where N2 = R * N1."*

N1 is the number of items or individuals sampled from the Group 1 population.

N1 must be ≥ 2. You can enter a single value or a series of values.

N2 (Sample Size, Group 2)

This option is displayed only if Group Allocation = "Enter N1 and N2 individually."

N2 is the number of items or individuals sampled from the Group 2 population.

N2 must be ≥ 2. You can enter a single value or a series of values.

R (Group Sample Size Ratio)

*This option is displayed only if Group Allocation = "Enter N1 and R, where N2 = R * N1."*

R is the ratio of *N2* to *N1*. That is,

$$R = N2/N1$$

Use this value to obtain *N2* as a multiple (or proportion) of *N1*.

N2 is calculated from *N1* using the formula:

$$N2=[R \times N1],$$

where the value *[Y]* is the next integer ≥ *Y*.

For example, setting *R* = 2.0 results in a Group 2 sample size that is double the sample size in Group 1.

R must be greater than 0. If *R* < 1, then *N2* will be less than N1; if *R* > 1, then *N2* will be greater than *N1*. You can enter a single value or a series of values.

Total Sample Size (N)

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This is the total sample size, or the sum of the two group sample sizes. This value, along with the percentage of the total sample size in Group 1, implicitly defines *N1* and *N2*.

The total sample size must be greater than one, but practically, must be greater than 3, since each group sample size needs to be at least 2.

You can enter a single value or a series of values.

Percent in Group 1

This option is displayed only if Group Allocation = "Enter total sample size and percentage in Group 1."

This value fixes the percentage of the total sample size allocated to Group 1. Small variations from the specified percentage may occur due to the discrete nature of sample sizes.

The Percent in Group 1 must be greater than 0 and less than 100. You can enter a single value or a series of values.

Effect Size

R0 (Superiority Margin Ratio)

Enter a value (or range of values) for the ratio of the two mean event rates assumed by the superiority by a margin null hypothesis. The range of possible values depends on the test direction. When higher rates are better, the superiority by a margin test hypotheses are H0: $\lambda2 / \lambda1 \leq R0$ vs. H1: $\lambda2 / \lambda1 > R0$, and $R0 > 1$. When higher rates are worse (lower are better), the superiority by a margin test hypotheses are H0: $\lambda2 / \lambda1 \geq R0$ vs. H1: $\lambda2 / \lambda1 < R0$, and $R0 < 1$.

λ1 (Event Rate of Group 1)

Enter a value (or range of values) for the mean event rate per time unit in group 1 (control).

Example of Estimating λ1

If 200 patients were exposed for 1 year (i.e. t1 = 1 year) and 40 experienced the event of interest, then the mean event rate would be $\lambda1 = 40/(200*1) = 0.2$ per patient-year. If 200 patients were exposed for 2 years (i.e. t1 = 2 years) and 40 experienced the event of interest, then the mean event rate would be $\lambda1 = 40/(200*2) = 0.1$ per patient-year.

λ1 is used with λ2 to calculate the event rate ratio as λ2 / λ1. The range is $\lambda1 > 0$. You can enter a single value such as 1 or a series of values such as 1 1.2 1.4 or 1 to 2 by 0.5.

Enter λ2 or Ratio for Group 2

Indicate whether to enter the Group 2 event rate (λ2) directly or the event rate ratio (λ2 / λ1) to specify λ2. The event rate ratio is calculated from λ2 and λ1 as λ2 / λ1.

λ2 (Event Rate of Group 2)

Enter a value (or range of values) for the mean event rate per time unit in group 2 (treatment).

Example of Estimating λ2

If 200 patients were exposed for 1 year (i.e. t1 = 1 year) and 40 experienced the event of interest, then the mean event rate would be $\lambda2 = 40/(200*1) = 0.2$ per patient-year. If 200 patients were exposed for 2 years (i.e. t1 = 2 years) and 40 experienced the event of interest, then the mean event rate would be $\lambda2 = 40/(200*2) = 0.1$ per patient-year.

λ1 is used with λ2 to calculate the event rate ratio as λ2 / λ1. The range is $\lambda2 > 0$. You can enter a single value such as 1 or a series of values such as 1 1.2 1.4 or 1 to 2 by 0.5.

λ2 / λ1 (Ratio of Event Rates)

This is the (assumed, known, true) value of the ratio of the two event rates, λ1 and λ2, at which the power is to be calculated. The event rate ratio is calculated from λ1 and λ2 as λ2 / λ1. The range is $\lambda2 / \lambda1 > 0$ and $\lambda2 / \lambda1 \neq R0$. When higher rates are better, $\lambda2 / \lambda1 > R0$ and $R0 < 1$. When higher rates are worse (lower are better), $\lambda2 / \lambda1 < R0$, and $R0 > 1$. You can enter a single value such as 1 or a series of values such as 0.9 0.95 1 1.05 1.1 or 0.9 to 1.1 by 0.05.

φ (Dispersion)

Enter a value or series of values for the anticipated Negative Binomial dispersion. You can enter a single value such as 0.4 or a series of values such as 0.2 0.3 0.4 0.5 or 0.2 to 0.5 by 0.1.

Example 1 – Calculating Sample Size

Researchers wish to determine whether the average Negative Binomial rate of those receiving a new treatment is more than 10% lower than the current control. In the scenario, lower rates are better than higher rates. The average exposure time for all subjects is 1.8 years. The event rate of the control group is 2.6 events per year. The researchers would like to examine the effect on sample size of a range of treatment group event rates from 2.2 down to 1.5. Over-dispersion is not anticipated. Dispersion values ranging from 0.2 to 0.5 will be considered.

The desired power is 0.9 and the significance level will be 0.025. The variance calculation method used will be the method where the assumed rates are used.

Setup

This section presents the values of each of the parameters needed to run this example. First load the **Superiority by a Margin Tests for the Ratio of Two Negative Binomial Rates** procedure window from the menus. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Higher Negative Binomial Rates Are	**Worse**
Variance Calculation Method	**Using Assumed True Rates**
Power	**0.90**
Alpha	**0.025**
μ(t) (Average Exposure Time)	**1.8**
Group Allocation	**Equal (N1 = N2)**
R0 (Non-Inferiority Ratio)	**0.9**
λ1 (Event Rate of Group 1)	**2.6**
Enter λ2 or Ratio for Group 2	**λ2 (Event Rate of Group 2)**
λ2 (Event Rate of Group 2)	**1.5 to 2.2 by 0.1**
φ (Dispersion)	**0.2 to 0.5 by 0.05**

Annotated Output

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

Numeric Results

Numeric Results for Superiority by a Margin Tests of the Ratio of Two Negative Binomial Rates
Test Direction Assumption: Higher Negative Binomial Rates Are Worse
H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method: Using Assumed True Rates

Power	N1	N2	N	Average Exposure Time μ(t)	Grp 1 Cntrl Event Rate λ1	Grp 2 Trt Event Rate λ2	Event Rate Ratio λ2 / λ1	Superiority Margin Ratio R0	Disper-sion φ	Alpha
0.90380	53	53	106	1.80	2.60	1.50	0.577	0.900	0.20	0.025
0.90054	70	70	140	1.80	2.60	1.60	0.615	0.900	0.20	0.025
0.90061	97	97	194	1.80	2.60	1.70	0.654	0.900	0.20	0.025
0.90043	141	141	282	1.80	2.60	1.80	0.692	0.900	0.20	0.025
0.90074	220	220	440	1.80	2.60	1.90	0.731	0.900	0.20	0.025
0.90001	380	380	760	1.80	2.60	2.00	0.769	0.900	0.20	0.025
0.90035	789	789	1578	1.80	2.60	2.10	0.808	0.900	0.20	0.025
0.90008	2392	2392	4784	1.80	2.60	2.20	0.846	0.900	0.20	0.025
0.90195	58	58	116	1.80	2.60	1.50	0.577	0.900	0.25	0.025
0.90313	78	78	156	1.80	2.60	1.60	0.615	0.900	0.25	0.025
0.90241	108	108	216	1.80	2.60	1.70	0.654	0.900	0.25	0.025
0.90171	157	157	314	1.80	2.60	1.80	0.692	0.900	0.25	0.025
0.90041	244	244	488	1.80	2.60	1.90	0.731	0.900	0.25	0.025
0.90026	423	423	846	1.80	2.60	2.00	0.769	0.900	0.25	0.025
0.90008	878	878	1756	1.80	2.60	2.10	0.808	0.900	0.25	0.025
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References
Zhu, H. 2016. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' Statistics in Biopharmaceutical Research, Accepted Manuscript.

Report Definitions
Power is the probability of rejecting the null hypothesis when it is false.
N1 and N2 are the number of subjects in groups 1 and 2, respectively.
N is the total sample size. N = N1 + N2.
μ(t) is the average exposure (observation) time across subjects in both groups.
λ1 is the event rate per time unit in Group 1 (control).
λ2 is the event rate per time unit in Group 2 (treatment).
λ2 / λ1 is the (known, true, assumed) ratio of the two event rates.
R0 is the superiority margin (null hypothesis) ratio.
Dispersion (φ) is the Negative Binomial dispersion parameter.
Alpha is the probability of rejecting the null hypothesis when it is true.

Summary Statements
For a test of H0: λ2 / λ1 ≥ 0.900 vs. H1: λ2 / λ1 < 0.900 (assuming higher Negative Binomial rates are worse), and using the variance calculation method with assumed true rates, samples of 53 and 53 subjects with average exposure time 1.80 achieve 90.380% power to detect an event rate ratio λ2 / λ1 of 0.577 when the event rate in group 1 (λ1) is 2.60, the event rate in group 2 (λ2) is 1.50, the Negative Binomial dispersion is 0.20, and the significance level (alpha) is 0.025.

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%	53	53	106	67	67	134	14	14	28
20%	70	70	140	88	88	176	18	18	36
20%	97	97	194	122	122	244	25	25	50
20%	141	141	282	177	177	354	36	36	72
20%	220	220	440	275	275	550	55	55	110
20%	380	380	760	475	475	950	95	95	190
20%	789	789	1578	987	987	1974	198	198	396
20%	2392	2392	4784	2990	2990	5980	598	598	1196
20%	58	58	116	73	73	146	15	15	30
20%	78	78	156	98	98	196	20	20	40
20%	108	108	216	135	135	270	27	27	54
20%	157	157	314	197	197	394	40	40	80
20%	244	244	488	305	305	610	61	61	122
20%	423	423	846	529	529	1058	106	106	212
20%	878	878	1756	1098	1098	2196	220	220	440
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Definitions

Dropout Rate (DR) is 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").

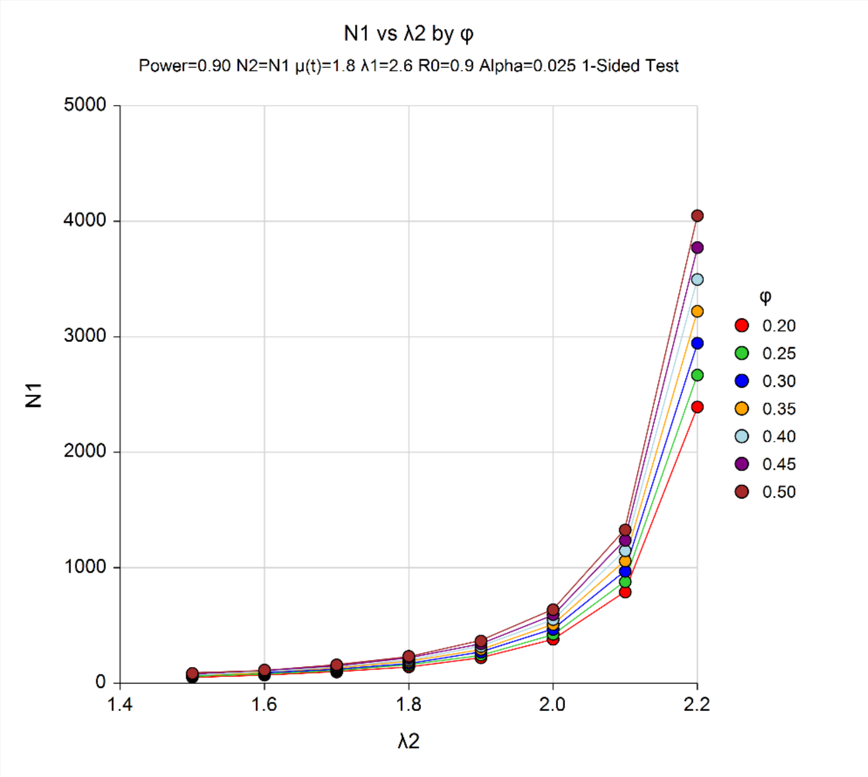
N1, N2, and N are the evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.

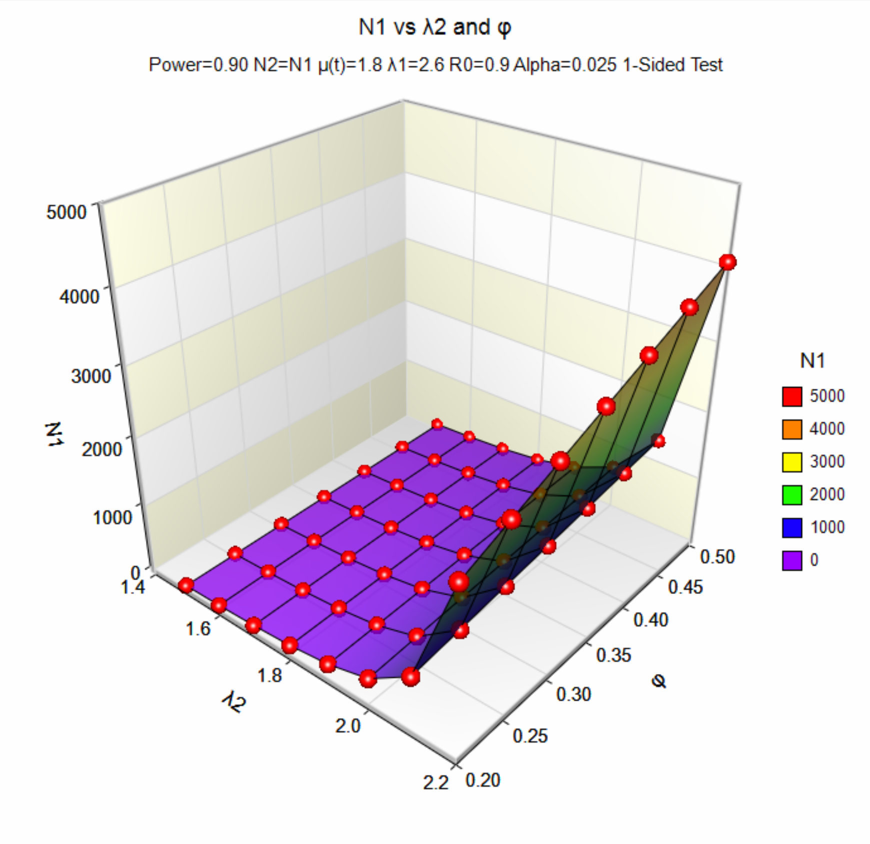
N1', N2', and N' are the number of subjects that should be enrolled in the study in order to end up with N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., and Wang, H. (2008) pages 39-40.)

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

This report shows the sample sizes for the indicated scenarios.

Plots Section





These plots represent the required sample sizes for various values of λ2 and the dispersion parameter.

Example 2 – Validation

We did not find a publication with an example of a superiority by a margin test for the ratio of two Negative Binomial rates. However, Example 2 of the Non-Inferiority Tests for the Ratio of Two Negative Binomial Rates chapter uses the same formulas and calculations as those used in this procedure. We refer the reader to those examples for validation of this procedure.