

## Chapter 457

# Superiority by a Margin Tests for the Ratio of Two Poisson Rates

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## Introduction

This procedure may be used to calculate power and sample size for superiority by a margin tests involving the ratio of two Poisson rates. This procedure includes the option of accounting for over-dispersion.

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

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## Technical Details

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### 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	$\lambda_1$	$\lambda_2$

Dispersion parameter:  $\varphi$  ( $\varphi > 1$  implies over-dispersion;  $\varphi < 1$  implies under-dispersion)

Average exposure time:  $\mu_t$

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

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

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

### 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 Poisson regression model. The calculations for a superiority by a margin test are the same. The sample size calculation is

$$N_1 \geq \frac{(z_\alpha \sqrt{V_0} + z_\beta \sqrt{V_1})^2}{(\log R_0 - \log(\lambda_2/\lambda_1))^2}$$

$$N_2 = \theta N_1$$

where

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

and  $V_0$  may be calculated in either of two ways.

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

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

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

**$V_0$  Calculation Method 2** (fixed marginal total or restricted maximum likelihood estimation)

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

Zhu (2016) did not give a recommendation regarding whether Method 1 or Method 2 should be used, except to say that “sample sizes calculated using Method 2 are slightly larger compared to those calculated by Method 1 for most simulated scenarios...”.

#### Power Calculation

The corresponding power calculation to the sample size calculation above is

$$Power \geq 1 - \Phi \left( \frac{\sqrt{N_1}(\log R_0 - \log(\lambda_2/\lambda_1)) - z_\alpha \sqrt{V_0}}{\sqrt{V_1}} \right)$$

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## 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.

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### Design Tab

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

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#### Solve For

##### Solve For

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

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#### Test

##### Higher Poisson Rates Are

Specify whether higher Poisson 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

$H_0: \lambda_2 / \lambda_1 \leq R_0$  vs.  $H_1: \lambda_2 / \lambda_1 > R_0$ , and  $R_0 > 1$ .

When higher rates are worse (lower are better), the superiority by a margin test hypotheses are

$H_0: \lambda_2 / \lambda_1 \geq R_0$  vs.  $H_1: \lambda_2 / \lambda_1 < R_0$ , and  $R_0 < 1$ .

##### Variance Calculation Method

Select among the two 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 or REML**  
This method assumes a fixed number of events. This method gives the same result as that derived using restricted maximum likelihood estimation.
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### 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.

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

### 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*.

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### $\mu(t)$ (Average Exposure Time)

#### $\mu(t)$ (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*.

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### 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  $\geq 2$ . 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,

$$R = N2 / N1.$$

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

Use this value to fix the ratio of  $N_2$  to  $N_1$  while solving for  $N_1$  and  $N_2$ . Only sample size combinations with this ratio are considered.

$N_2$  is related to  $N_1$  by the formula:

$$N_2 = [R \times N_1],$$

where the value  $[Y]$  is the next integer  $\geq Y$ .

For example, setting  $R = 2.0$  results in a Group 2 sample size that is double the sample size in Group 1 (e.g.,  $N_1 = 10$  and  $N_2 = 20$ , or  $N_1 = 50$  and  $N_2 = 100$ ).

$R$  must be greater than 0. If  $R < 1$ , then  $N_2$  will be less than  $N_1$ ; if  $R > 1$ , then  $N_2$  will be greater than  $N_1$ . 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  $N_1$  and  $N_2$ ."*

Use this value to fix the percentage of the total sample size allocated to Group 1 while solving for  $N_1$  and  $N_2$ . 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.

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## 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 ( $N_1 = N_2$ )**  
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  $N_1$  and  $N_2$  individually**  
This choice permits you to enter different values for  $N_1$  and  $N_2$ .
- **Enter  $N_1$  and  $R$ , where  $N_2 = R * N_1$**   
Choose this option to specify a value (or values) for  $N_1$ , and obtain  $N_2$  as a ratio (multiple) of  $N_1$ .
- **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  $N_1$  as a percentage of  $N$ , and then  $N_2$  as  $N - N_1$ .

### Sample Size Per Group

*This option is displayed only if Group Allocation = "Equal ( $N_1 = N_2$ )."*

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  $N_1$ , and also the value for  $N_2$ .

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

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

### 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  $\geq 2$ . 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  $\geq 2$ . 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  $\geq Y$ .

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.

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

### 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  $H_0: \lambda_2 / \lambda_1 \leq R_0$  vs.  $H_1: \lambda_2 / \lambda_1 > R_0$ , and  $R_0 > 1$ . When higher rates are worse (lower are better), the superiority by a margin test hypotheses are  $H_0: \lambda_2 / \lambda_1 \geq R_0$  vs.  $H_1: \lambda_2 / \lambda_1 < R_0$ , and  $R_0 < 1$ .

#### $\lambda_1$ (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 $\lambda_1$

If 200 patients were exposed for 1 year (i.e.  $t_1 = 1$  year) and 40 experienced the event of interest, then the mean event rate would be  $\lambda_1 = 40/(200*1) = 0.2$  per patient-year. If 200 patients were exposed for 2 years (i.e.  $t_1 = 2$  years) and 40 experienced the event of interest, then the mean event rate would be  $\lambda_1 = 40/(200*2) = 0.1$  per patient-year.  $\lambda_1$  is used with  $\lambda_2$  to calculate the event rate ratio as  $\lambda_2 / \lambda_1$ . The range is  $\lambda_1 > 0$ . 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 $\lambda_2$ or Ratio for Group 2

Indicate whether to enter the Group 2 event rate ( $\lambda_2$ ) directly or the event rate ratio ( $\lambda_2 / \lambda_1$ ) to specify  $\lambda_2$ . The event rate ratio is calculated from  $\lambda_2$  and  $\lambda_1$  as  $\lambda_2 / \lambda_1$ .

#### $\lambda_2$ (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 $\lambda_2$

If 200 patients were exposed for 1 year (i.e.  $t_1 = 1$  year) and 40 experienced the event of interest, then the mean event rate would be  $\lambda_2 = 40/(200*1) = 0.2$  per patient-year. If 200 patients were exposed for 2 years (i.e.  $t_1 = 2$  years) and 40 experienced the event of interest, then the mean event rate would be  $\lambda_2 = 40/(200*2) = 0.1$  per patient-year.  $\lambda_1$  is used with  $\lambda_2$  to calculate the event rate ratio as  $\lambda_2 / \lambda_1$ . The range is  $\lambda_2 > 0$ . 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.

#### $\lambda_2 / \lambda_1$ (Ratio of Event Rates)

This is the (assumed, known, true) value of the ratio of the two event rates,  $\lambda_1$  and  $\lambda_2$ , at which the power is to be calculated. The event rate ratio is calculated from  $\lambda_1$  and  $\lambda_2$  as  $\lambda_2 / \lambda_1$ . The range is  $\lambda_2 / \lambda_1 > 0$  and  $\lambda_2 / \lambda_1 \neq R_0$ . When higher rates are better,  $\lambda_2 / \lambda_1 > R_0$  and  $R_0 > 1$ . When higher rates are worse (lower are better),  $\lambda_2 / \lambda_1 < R_0$ , and  $R_0 < 1$ . 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.

#### $\phi$ (Dispersion)

Enter a value or series of values for the anticipated dispersion. Dispersion values lower than 1 indicate under-dispersion, which implies the variance is less than the mean. Dispersion values greater than 1 indicate over-dispersion, which implies the variance is greater than the mean. If over-dispersion or under-dispersion are not anticipated, enter a value of 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.

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

### Example 1 – Calculating Sample Size

Researchers wish to determine whether the average Poisson rate of those receiving a new treatment is more than 10% lower than the current control. In the scenario, lower Poisson 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.

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 Poisson 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
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Higher Poisson Rates Are .....	<b>Worse</b>
Variance Calculation Method.....	<b>Using Assumed True Rates</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.025</b>
$\mu(t)$ (Average Exposure Time) .....	<b>1.8</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
R0 (Superiority Margin Ratio) .....	<b>0.9</b>
$\lambda_1$ (Event Rate of Group 1).....	<b>2.6</b>
Enter $\lambda_2$ or Ratio for Group 2 .....	<b><math>\lambda_2</math> (Event Rate of Group 2)</b>
$\lambda_2$ (Event Rate of Group 2).....	<b>1.5 to 2.2 by 0.1</b>
$\phi$ (Dispersion) .....	<b>1</b>

### 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 Poisson Rates

Test Direction Assumption: Higher Poisson Rates Are Worse

H0:  $\lambda_2 / \lambda_1 \geq R_0$  vs. H1:  $\lambda_2 / \lambda_1 < R_0$

Variance Calculation Method: Using Assumed True Rates

				Average Exposure Time	Grp 1 Cntrl Event Rate	Grp 2 Trt Event Rate	Event Rate Ratio	Superiority Margin Ratio	Dispersion	Alpha
Power	N1	N2	N	$\mu(t)$	$\lambda_1$	$\lambda_2$	$\lambda_2 / \lambda_1$	R0	$\phi$	
0.90851	32	32	64	1.80	2.60	1.50	0.577	0.900	1.00	0.025
0.90151	41	41	82	1.80	2.60	1.60	0.615	0.900	1.00	0.025
0.90190	56	56	112	1.80	2.60	1.70	0.654	0.900	1.00	0.025
0.90096	80	80	160	1.80	2.60	1.80	0.692	0.900	1.00	0.025
0.90102	123	123	246	1.80	2.60	1.90	0.731	0.900	1.00	0.025
0.90069	210	210	420	1.80	2.60	2.00	0.769	0.900	1.00	0.025
0.90059	430	430	860	1.80	2.60	2.10	0.808	0.900	1.00	0.025
0.90021	1288	1288	2576	1.80	2.60	2.20	0.846	0.900	1.00	0.025

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

### 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.

$N_1$  and  $N_2$  are the number of subjects in groups 1 and 2, respectively.

$N$  is the total sample size.  $N = N_1 + N_2$ .

$\mu(t)$  is the average exposure (observation) time across subjects in both groups.

$\lambda_1$  is the event rate per time unit in Group 1 (control).

$\lambda_2$  is the event rate per time unit in Group 2 (treatment).

$\lambda_2 / \lambda_1$  is the (known, true, assumed) ratio of the two event rates.

Dispersion ( $\phi$ ) is the dispersion parameter ( $\phi > 1$  implies over-dispersion,  $\phi < 1$  implies under-dispersion).

$R_0$  is the superiority margin (null hypothesis) ratio.

Alpha is the probability of rejecting the null hypothesis when it is true.

### Summary Statements

For a test of  $H_0: \lambda_2 / \lambda_1 \geq 0.900$  vs.  $H_1: \lambda_2 / \lambda_1 < 0.900$  (assuming higher Poisson rates are worse), and using the variance calculation method with assumed true rates, samples of 32 and 32 subjects with average exposure time 1.80 achieve 90.851% power to detect an event rate ratio  $\lambda_2 / \lambda_1$  of 0.577 when the event rate in group 1 ( $\lambda_1$ ) is 2.60, the event rate in group 2 ( $\lambda_2$ ) is 1.50, the dispersion is 1.00, and the significance level (alpha) is 0.025.

### Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	$N_1$	$N_2$	$N$	$N_1'$	$N_2'$	$N'$	$D_1$	$D_2$	$D$
20%	32	32	64	40	40	80	8	8	16
20%	41	41	82	52	52	104	11	11	22
20%	56	56	112	70	70	140	14	14	28
20%	80	80	160	100	100	200	20	20	40
20%	123	123	246	154	154	308	31	31	62
20%	210	210	420	263	263	526	53	53	106
20%	430	430	860	538	538	1076	108	108	216
20%	1288	1288	2576	1610	1610	3220	322	322	644

### 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").

$N_1$ ,  $N_2$ , and  $N$  are the evaluable sample sizes at which power is computed. If  $N_1$  and  $N_2$  subjects are evaluated out of the  $N_1'$  and  $N_2'$  subjects that are enrolled in the study, the design will achieve the stated power.

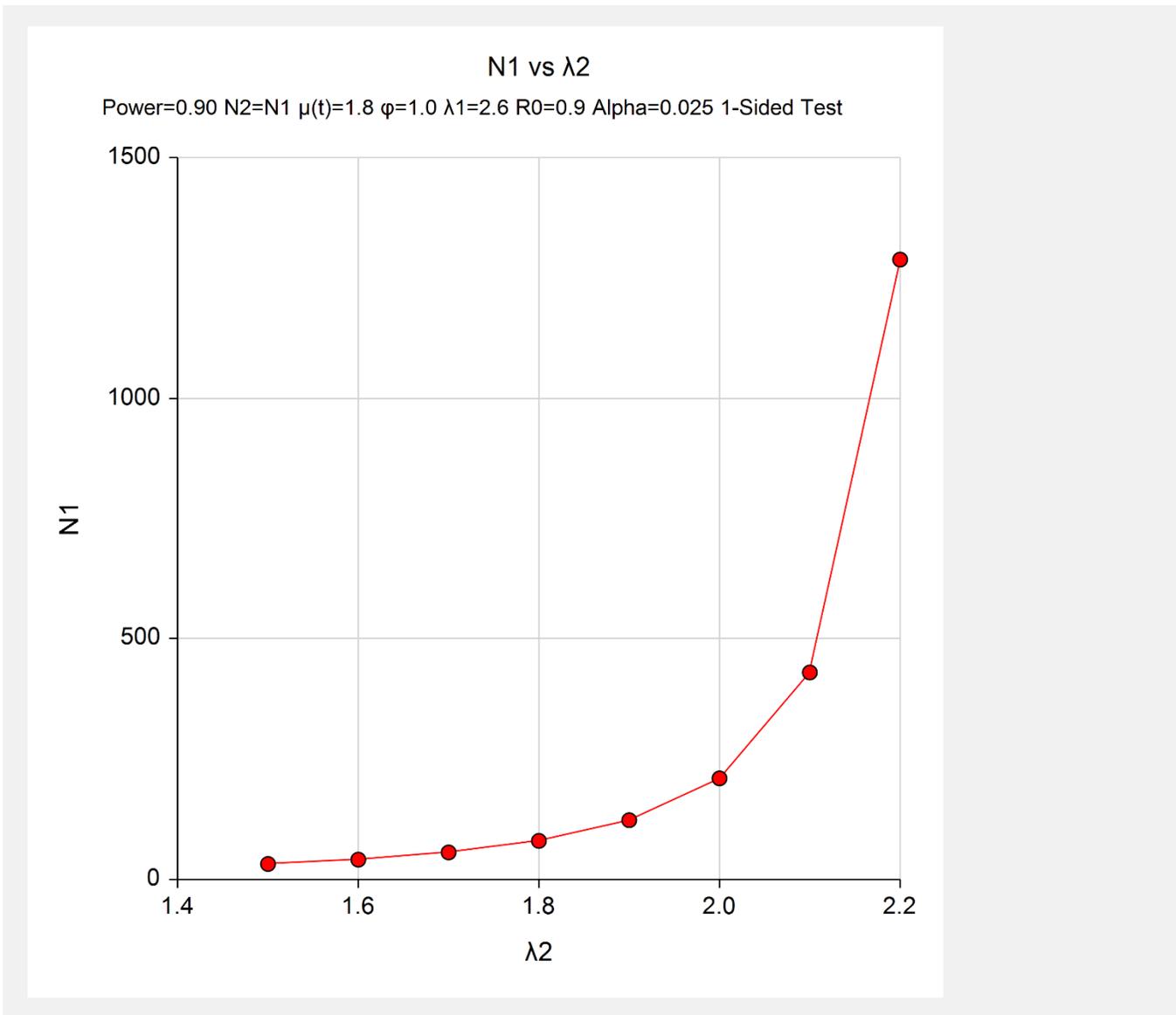
$N_1'$ ,  $N_2'$ , and  $N'$  are the number of subjects that should be enrolled in the study in order to end up with  $N_1$ ,  $N_2$ , and  $N$  evaluable subjects, based on the assumed dropout rate. After solving for  $N_1$  and  $N_2$ ,  $N_1'$  and  $N_2'$  are calculated by inflating  $N_1$  and  $N_2$  using the formulas  $N_1' = N_1 / (1 - DR)$  and  $N_2' = N_2 / (1 - DR)$ , with  $N_1'$  and  $N_2'$  always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., and Wang, H. (2008) pages 39-40.)

$D_1$ ,  $D_2$ , and  $D$  are the expected number of dropouts.  $D_1 = N_1' - N_1$ ,  $D_2 = N_2' - N_2$ , and  $D = D_1 + D_2$ .

This report shows the sample sizes for the indicated scenarios.

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

## Plots Section



This plot represents the required sample sizes for various values of  $\lambda_2$ .

## Example 2 – Validation

We did not find a publication with an example of a superiority by a margin test for the ratio of two Poisson rates. However, Examples 2 and 3 of the Non-Inferiority Tests for the Ratio of Two Poisson Rates chapter use the same formulas and calculations as those used in this procedure. We refer the reader to those examples for validation of this procedure.