Chapter 468

Equivalence Tests for the Ratio of Two Poisson Rates

Introduction

This procedure may be used to calculate power and sample size for equivalence 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.

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

Average exposure time: μ_t

Equivalence ratios: R_{Lower} ($R_{Lower} < 1$); R_{Upper} ($R_{Upper} > 1$)

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

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Hypotheses

The equivalence test hypotheses are

$$H_0: \frac{\lambda_2}{\lambda_1} \leq R_{Lower} \; or \; \frac{\lambda_2}{\lambda_1} \geq R_{Upper} \quad \text{vs.} \quad H_1: R_{Lower} < \frac{\lambda_2}{\lambda_1} < R_{Upper}$$

where $R_{Lower} < 1$ and $R_{Upper} > 1$.

For a given equivalence test with significance level α, a two-sided confidence interval with $100(1 – 2\alpha)\%$ confidence is typically used. H_0 is rejected if the confidence interval falls completely between R_{Lower} and R_{Upper}.

Power Calculation

Power Calculation

Zhu (2016) bases the power calculation on an equivalence test derived from a Poisson regression model. The power calculation is

$$Power = \Phi\left(\frac{\sqrt{N_1}(\log(\lambda_2/\lambda_1) - logR_{Lower}) - z_\alpha\sqrt{V_0^-}}{\sqrt{V_1}}\right) + \Phi\left(\frac{\sqrt{N_1}\left(logR_{Upper} - \log(\lambda_2/\lambda_1)\right) - z_\alpha\sqrt{V_0^+}}{\sqrt{V_1}}\right) - 1$$

where

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

and V_0^- and V_0^+ may be calculated in either of two ways.

V_0 Calculation Method 1 (using assumed true rates)

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

Using Method 1, V_0^-, V_0^+, and V_1 are equal.

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

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

$$V_{02}^+ = \frac{\varphi\left(1 + R_{Upper}\theta\right)^2}{\mu_t R_{Upper}\theta(\lambda_1 + \theta\lambda_2)}$$

Zhu (2016) did not give a recommendation regarding whether Method 1 or Method 2 should be used, except to say that “in summary, based on scenarios simulated, all of the sample size methods derived in this paper calculated reasonably accurate sample sizes for the intended power. Although some methods seemed slightly better than the others for some scenarios, the sample size differences were very small relative to the actual sample sizes.”

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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.

Design Tab

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

Solve For

Solve For

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

Variance Calculation

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.

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*.

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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 $\geq Y$.

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

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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.

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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.

Effect Size

RU (Upper Equivalence Limit)

Enter the upper equivalence limit for the ratio of the two Poisson event rates ($\lambda 2$ / $\lambda 1$). This value is entered as a ratio, not a percentage. When the ratio of the Poisson event rates is between this value and RL, the two rates are said to be 'equivalent'. This value must be greater than one. Common choices are 1.1, 1.2, 1.25, and 1/RL. If you enter '1/RL', RU will be calculated from RL as RU = 1/RL. The choice '1/RL' is popular because RL and RU = 1/RL are limits that are of equal magnitude on the log scale.

RL (Lower Equivalence Limit)

Enter the lower equivalence limit for the ratio of the two Poisson event rates ($\lambda 2$ / $\lambda 1$). This value is entered as a ratio, not a percentage. When the ratio of the Poisson event rates is between this value and RU, the two rates are said to be 'equivalent'. This value must be less than one. Common choices are 0.8, 0.9, and 1/RU. If you enter '1/RU', RL will be calculated from RU as RL = 1/RU. The choice '1/RU' is popular because RU and RL = 1/RU are limits that are of equal magnitude on the log scale.

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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 λ1 = 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 λ1 = 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 λ1 > 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 λ2 = 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 λ2 = 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 λ2 > 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 λ2 / λ1 > 0 and RL < λ2 / λ1 < RU. 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 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.

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Example 1 – Calculating Sample Size

Researchers wish to determine whether the average Poisson rate of those receiving a new treatment is equivalent to a current control. The average exposure time for all subjects is 2.5 years. The two treatments will be considered equivalent if the event rate ratio is between 0.8 and 1.25. The event rate of the control group is 2.2 events per year. The researchers would like to examine the effect on sample size of a range of treatment group event rates from 1.9 to 2.5. 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 **Equivalence 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
Design Tab	
Solve For	**Sample Size**
Variance Calculation Method	**Using Assumed True Rates**
Power	**0.90**
Alpha	**0.025**
μ(t) (Average Exposure Time)	**2.5**
Group Allocation	**Equal (N1 = N2)**
RU (Upper Equivalence Limit)	**1.25**
RL (Lower Equivalence Limit)	**0.8**
λ1 (Event Rate of Group 1)	**2.2**
Enter λ2 or Ratio for Group 2	**λ2 (Event Rate of Group 2)**
λ2 (Event Rate of Group 2)	**1.9 to 2.5 by 0.1**
φ (Dispersion)	**1**

Annotated Output

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

Numeric Results

Numeric Results for Equivalence Tests of the Ratio of Two Poisson Rates
H0: λ2 / λ1 ≤ RL or λ2 / λ1 ≥ RU vs.
H1: RL < λ2 / λ1 < RU
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	Lower Equiv. Limit RL	Upper Equiv. Limit RU	Disper-sion φ	Alpha
0.90012	704	704	1408	2.50	2.20	1.90	0.864	0.800	1.250	1.00	0.025
0.90057	246	246	492	2.50	2.20	2.00	0.909	0.800	1.250	1.00	0.025
0.90001	126	126	252	2.50	2.20	2.10	0.955	0.800	1.250	1.00	0.025
0.90039	95	95	190	2.50	2.20	2.20	1.000	0.800	1.250	1.00	0.025
0.90047	118	118	236	2.50	2.20	2.30	1.045	0.800	1.250	1.00	0.025
0.90059	198	198	396	2.50	2.20	2.40	1.091	0.800	1.250	1.00	0.025
0.90045	396	396	792	2.50	2.20	2.50	1.136	0.800	1.250	1.00	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.
RL and RU are the respective lower and upper equivalence limits for the event rate ratio.
Dispersion (φ) is the dispersion parameter (φ > 1 implies over-dispersion, φ < 1 implies under-dispersion).
Alpha is the probability of rejecting the null hypothesis when it is true.

Summary Statements

For an equivalence test of H0: λ2 / λ1 ≤ 0.800 or λ2 / λ1 ≥ 1.250 vs. H1: 0.800 < λ2 / λ1 < 1.250, and using the variance calculation method with assumed true rates, samples of 704 and 704 subjects with average exposure time 2.50 achieve 90.012% power to detect an event rate ratio λ2 / λ1 of 0.864 when the event rate in group 1 (λ1) is 2.20, the event rate in group 2 (λ2) is 1.90, the dispersion is 1.00, 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%	704	704	1408	880	880	1760	176	176	352
20%	246	246	492	308	308	616	62	62	124
20%	126	126	252	158	158	316	32	32	64
20%	95	95	190	119	119	238	24	24	48
20%	118	118	236	148	148	296	30	30	60
20%	198	198	396	248	248	496	50	50	100
20%	396	396	792	495	495	990	99	99	198

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.

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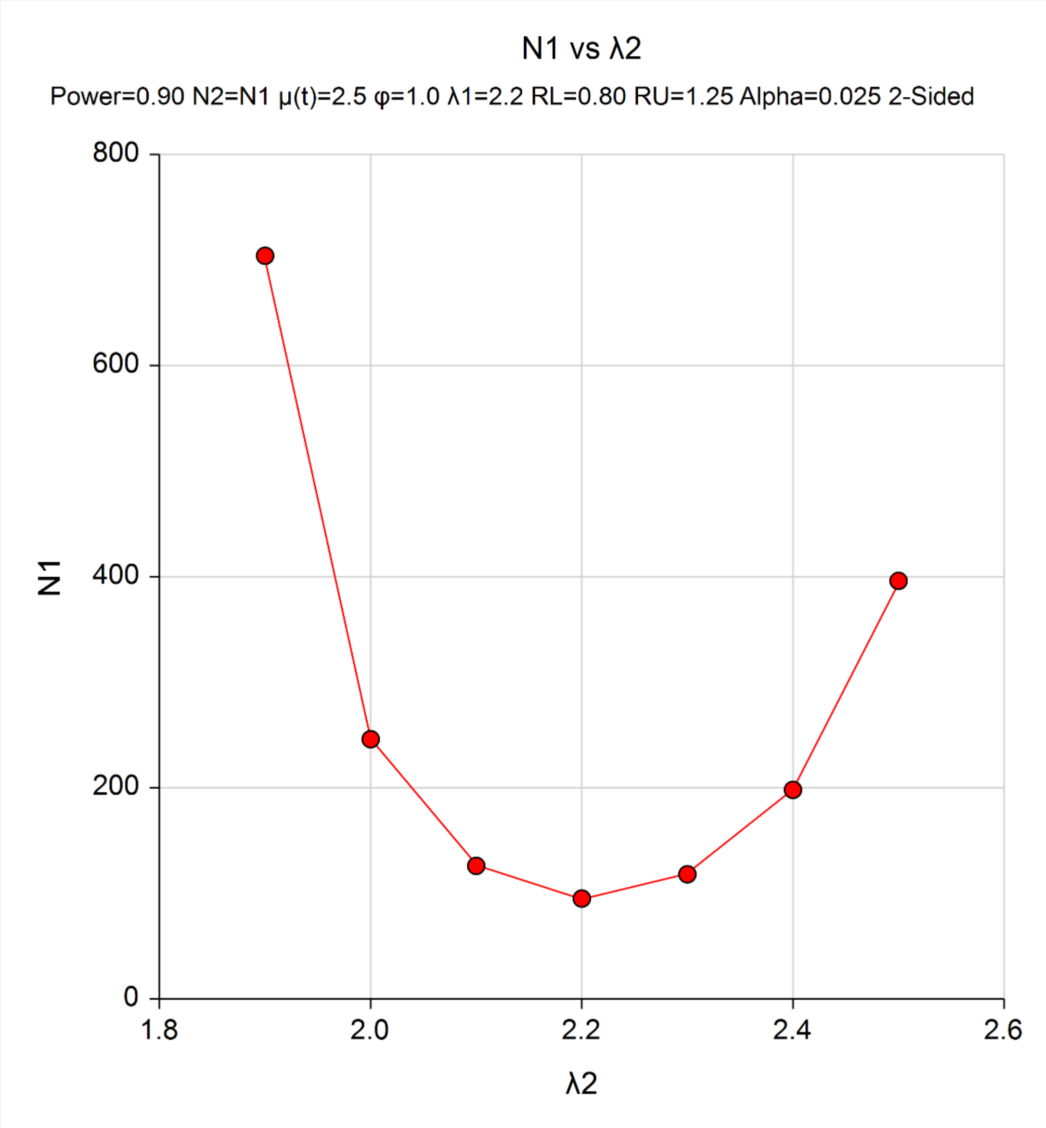
Plots Section



This plot represents the required sample sizes for various values of λ2.

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Example 2 – Validation using Zhu (2016)

Zhu (2016) presents an example (see Supplementary Table 3) of solving for sample size where the event rates are both 1.0, the dispersion parameter is 1.0, the average duration is 0.7, the equivalence limits are 0.9 and 1.1111 (1 / 0.9), the power is 0.8, and the Type I error rate is 0.025.

The calculated total sample sizes are 5410 and 5418 for the Assumed True Rate and Fixed Marginal Total or REML variance calculation methods, respectively.

Setup

This section presents the values of each of the parameters needed to run this example. First load the **Equivalence 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 2 (a or b)** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Variance Calculation Method	**Using Assumed True Rates (2nd run: Fixed Marginal Total or REML)**
Power	**0.80**
Alpha	**0.025**
μ(t) (Average Exposure Time)	**0.7**
Group Allocation	**Equal (N1 = N2)**
RU (Upper Equivalence Limit)	**1/RL**
RL (Lower Equivalence Limit)	**0.9**
λ1 (Event Rate of Group 1)	**1.0**
Enter λ2 or Ratio for Group 2	**λ2 / λ1 (Ratio of Event Rates)**
λ2 / λ1 (Ratio of Event Rates)	**1**
φ (Dispersion)	**1.0**

Annotated Output

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

Numeric Results

Numeric Results for Equivalence Tests of the Ratio of Two Poisson Rates
H0: λ2 / λ1 ≤ RL or λ2 / λ1 ≥ RU vs.
H1: RL < λ2 / λ1 < RU
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	Lower Equiv. Limit RL	Upper Equiv. Limit RU	Disper-sion φ	Alpha
0.80012	2705	2705	5410	0.70	1.00	1.00	1.000	0.900	1.250	1.00	0.025
Variance Calculation Method: Fixed Marginal Total or REML											
0.80001	2709	2709	5418	0.70	1.00	1.00	1.000	0.900	1.250	1.00	0.025

The sample sizes calculated in **PASS** match those of Zhu (2016) exactly.

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