Chapter 458

Non-Inferiority Tests for the Ratio of Two Negative Binomial Rates

Introduction

This procedure may be used to calculate power and sample size for non-inferiority tests involving the ratio of two Negative Binomial rates.

The calculation details upon which this procedure is based are found in Zhu (2017). 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

Non-inferiority 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 non-inferiority 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 non-inferiority 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 (2017) bases the sample size calculations on a non-inferiority test derived from a Negative Binomial regression model. The sample size calculation is

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

$$N_2 = \theta N_1$$

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 (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

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

Example 1 – Calculating Sample Size

Researchers wish to determine whether the average Negative Binomial rate of those receiving a new treatment is non-inferior to a current control. In the scenario, higher rates are worse than lower rates. The average exposure time for all subjects is 2.5 years. The event rate ratio at which the new treatment will be considered non-inferior is 1.2. 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 1.8 to 2.4. 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

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 .... **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)....................... **2.5**
Group Allocation .... **Equal (N1 = N2)**
R0 (Non-Inferiority Ratio)............................... **1.2**
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)............................ **1.8 to 2.4 by 0.1**
φ (Dispersion).. **0.2 to 0.5 by 0.05**

Output

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

Numeric Reports

Numeric Results

Solve For:	Sample Size
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			
Power	N1	N2	N	μ(t)	λ1	λ2	Actual λ2 / λ1	Non-Inferiority R0	Dispersion φ	Alpha
0.90198	58	58	116	2.5	2.2	1.8	0.818	1.2	0.20	0.025
0.90018	77	77	154	2.5	2.2	1.9	0.864	1.2	0.20	0.025
0.90112	107	107	214	2.5	2.2	2.0	0.909	1.2	0.20	0.025
0.90008	155	155	310	2.5	2.2	2.1	0.955	1.2	0.20	0.025
0.90072	242	242	484	2.5	2.2	2.2	1.000	1.2	0.20	0.025
0.90016	418	418	836	2.5	2.2	2.3	1.045	1.2	0.20	0.025
0.90008	866	866	1732	2.5	2.2	2.4	1.091	1.2	0.20	0.025
0.90105	65	65	130	2.5	2.2	1.8	0.818	1.2	0.25	0.025
0.90110	87	87	174	2.5	2.2	1.9	0.864	1.2	0.25	0.025
0.90186	121	121	242	2.5	2.2	2.0	0.909	1.2	0.25	0.025
0.90158	176	176	352	2.5	2.2	2.1	0.955	1.2	0.25	0.025
0.90001	273	273	546	2.5	2.2	2.2	1.000	1.2	0.25	0.025
0.90058	474	474	948	2.5	2.2	2.3	1.045	1.2	0.25	0.025
0.90016	982	982	1964	2.5	2.2	2.4	1.091	1.2	0.25	0.025
0.90030	72	72	144	2.5	2.2	1.8	0.818	1.2	0.30	0.025
0.90183	97	97	194	2.5	2.2	1.9	0.864	1.2	0.30	0.025
0.90034	134	134	268	2.5	2.2	2.0	0.909	1.2	0.30	0.025
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Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1 and N2	The number of subjects in groups 1 and 2, respectively.
N	The total sample size. N = N1 + N2.
μ(t)	The average exposure (observation) time across subjects in both groups.
λ1	The event rate per time unit in Group 1 (control).
λ2	The event rate per time unit in Group 2 (treatment).
λ2 / λ1	The known, true, or assumed ratio of the two event rates.
R0	The non-inferiority (boundary) ratio.
φ	The Negative Binomial dispersion parameter.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group design (where higher Negative Binomial rates are considered worse) will be used to test whether the Group 2 (treatment) Negative Binomial rate is non-inferior to the Group 1 (control) Negative Binomial rate, with a non-inferiority ratio of 1.2 (H0: λ2 / λ1 ≥ 1.2 versus H1: λ2 / λ1 < 1.2). The comparison will be made using a one-sided, two-sample, Negative Binomial regression term Z-test using the variance calculation method with assumed true rates, with a Type I error rate (α) of 0.025. The Negative Binomial dispersion is assumed to be 0.2. To detect a ratio of Negative Binomial event rates (λ2 / λ1) of 0.818 (λ2 = 1.8, λ1 = 2.2) with 90% power, with average exposure time 2.5, the number of needed subjects will be 58 in Group 1 and 58 in Group 2.

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%	58	58	116	73	73	146	15	15	30
20%	77	77	154	97	97	194	20	20	40
20%	107	107	214	134	134	268	27	27	54
20%	155	155	310	194	194	388	39	39	78
20%	242	242	484	303	303	606	61	61	122
20%	418	418	836	523	523	1046	105	105	210
20%	866	866	1732	1083	1083	2166	217	217	434
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.	.	.	.	.	.	.	.	.	.
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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. 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. 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., 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, 73 subjects should be enrolled in Group 1, and 73 in Group 2, to obtain final group sample sizes of 58 and 58, respectively.

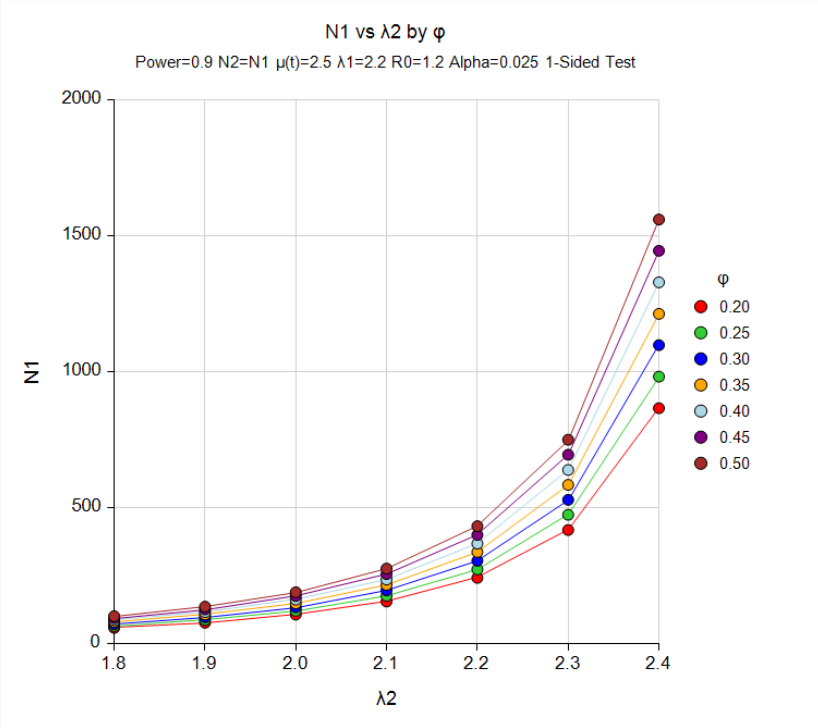
References

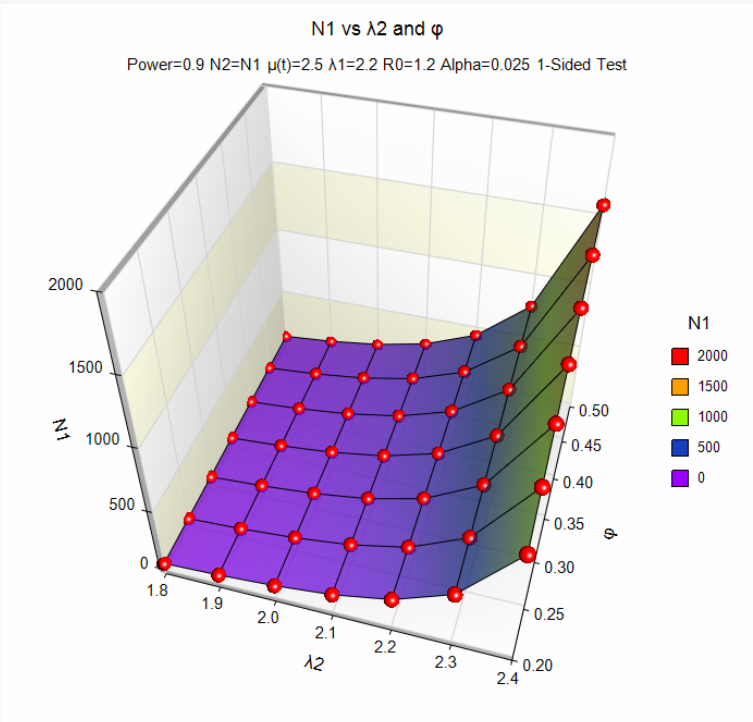
Zhu, H. 2017. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' Statistics in Biopharmaceutical Research, 9(1), 107-115, doi:10.1080/19466315.2016.1225594.

This report shows the sample sizes for the indicated scenarios.

Plots Section

Plots





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

Example 2 – Validation using Zhu (2017)

Zhu (2017) presents an example of solving for sample size where lower negative binomial rates are better, the event rates are both 1.5, the dispersion is 0.24, the average duration is 0.85, the non-inferiority ratio is 1.1, the power is 0.9, and the Type I error rate is 0.025.

The calculated sample sizes are 2370, 2373, and 2372 for the Assumed True Rate, Fixed Marginal Total, and REML variance calculation methods, respectively.

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 (a, b, or c)** settings files. 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**
Higher Negative Binomial Rates Are .... **Worse**
Variance Calculation Method .... **Using Assumed True Rates**
(2nd run: Fixed Marginal Total
3rd run: Restricted Maximum Likelihood Estimation)
Power.. **0.90**
Alpha... **0.025**
μ(t) (Average Exposure Time)........................ **0.85**
Group Allocation .... **Equal (N1 = N2)**
R0 (Non-Inferiority Ratio)............................... **1.1**
λ1 (Event Rate of Group 1)............................ **1.5**
Enter λ2 or Ratio for Group 2......................... **λ2 (Event Rate of Group 2)**
λ2 (Event Rate of Group 2)............................ **1.5**
φ (Dispersion).. **0.24**

Output

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

1st Run (Example 2a)

Numeric Results

Solve For:	Sample Size
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	Average Event Rate		Event Rate Ratio			
Power	N1	N2	N	Time μ(t)	λ1	λ2	Actual λ2 / λ1	Non-Inferiority R0	Dispersion φ	Alpha
0.90004	2370	2370	4740	0.85	1.5	1.5	1	1.1	0.24	0.025

2nd Run (Example 2b)

Numeric Results

Solve For:	Sample Size
Groups:	1 = Control, 2 = Treatment
Higher Negative Binomial Rates Are:	Worse
Hypotheses:	H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method:	Fixed Marginal Total

	Sample Size			Average Exposure	Average Event Rate		Event Rate Ratio			
Power	N1	N2	N	Time μ(t)	λ1	λ2	Actual λ2 / λ1	Non-Inferiority R0	Dispersion φ	Alpha
0.90011	2373	2373	4746	0.85	1.5	1.5	1	1.1	0.24	0.025

3rd Run (Example 2c)

Numeric Results

Solve For:	Sample Size
Groups:	1 = Control, 2 = Treatment
Higher Negative Binomial Rates Are:	Worse
Hypotheses:	H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method:	Restricted Maximum Likelihood

	Sample Size			Average Exposure	Average Event Rate		Event Rate Ratio			
Power	N1	N2	N	Time μ(t)	λ1	λ2	Actual λ2 / λ1	Non-Inferiority R0	Dispersion φ	Alpha
0.90006	2372	2372	4744	0.85	1.5	1.5	1	1.1	0.24	0.025

The sample sizes calculated in **PASS** match those of Zhu (2017) exactly.