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 (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

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 (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 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

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)....................... **1.8**
Group Allocation .... **Equal (N1 = N2)**
R0 (Superiority 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**

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	Superiority R0	Dispersion φ	Alpha
0.90380	53	53	106	1.8	2.6	1.5	0.577	0.9	0.20	0.025
0.90054	70	70	140	1.8	2.6	1.6	0.615	0.9	0.20	0.025
0.90061	97	97	194	1.8	2.6	1.7	0.654	0.9	0.20	0.025
0.90043	141	141	282	1.8	2.6	1.8	0.692	0.9	0.20	0.025
0.90074	220	220	440	1.8	2.6	1.9	0.731	0.9	0.20	0.025
0.90001	380	380	760	1.8	2.6	2.0	0.769	0.9	0.20	0.025
0.90035	789	789	1578	1.8	2.6	2.1	0.808	0.9	0.20	0.025
0.90008	2392	2392	4784	1.8	2.6	2.2	0.846	0.9	0.20	0.025
0.90195	58	58	116	1.8	2.6	1.5	0.577	0.9	0.25	0.025
0.90313	78	78	156	1.8	2.6	1.6	0.615	0.9	0.25	0.025
0.90241	108	108	216	1.8	2.6	1.7	0.654	0.9	0.25	0.025
0.90171	157	157	314	1.8	2.6	1.8	0.692	0.9	0.25	0.025
0.90041	244	244	488	1.8	2.6	1.9	0.731	0.9	0.25	0.025
0.90026	423	423	846	1.8	2.6	2.0	0.769	0.9	0.25	0.025
0.90008	878	878	1756	1.8	2.6	2.1	0.808	0.9	0.25	0.025
0.90007	2668	2668	5336	1.8	2.6	2.2	0.846	0.9	0.25	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 superiority margin (null hypothesis) 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 superior to (less than) the Group 1 (control) Negative Binomial rate by a margin, with a superiority margin ratio of 0.9 (H0: λ2 / λ1 ≥ 0.9 versus H1: λ2 / λ1 < 0.9). 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 0.577 (λ2 = 1.5, λ1 = 2.6) with 90% power, with average exposure time 1.8, the number of needed subjects will be 53 in Group 1 and 53 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%	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
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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, 67 subjects should be enrolled in Group 1, and 67 in Group 2, to obtain final group sample sizes of 53 and 53, respectively.

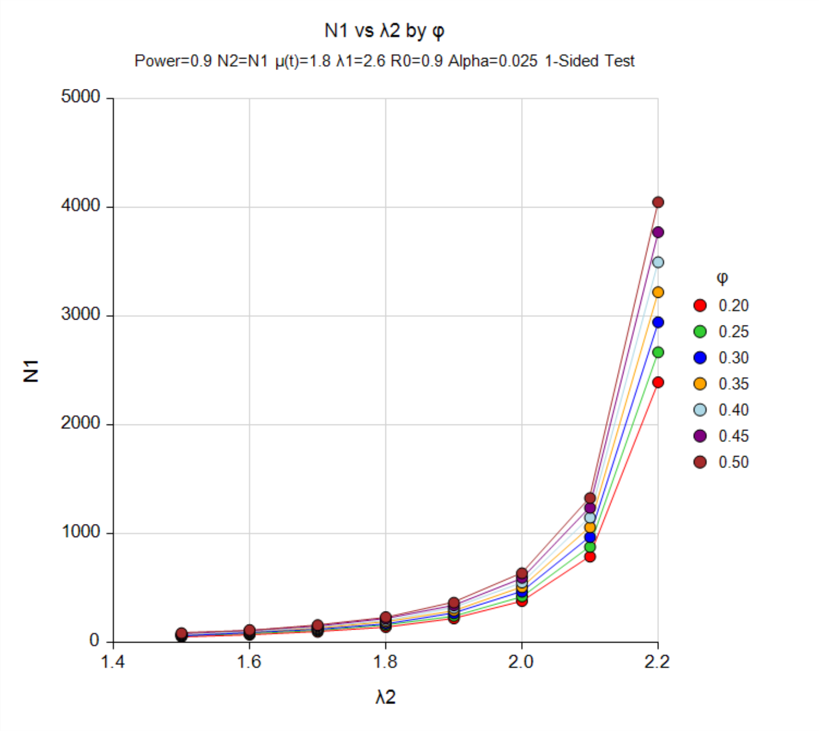
References

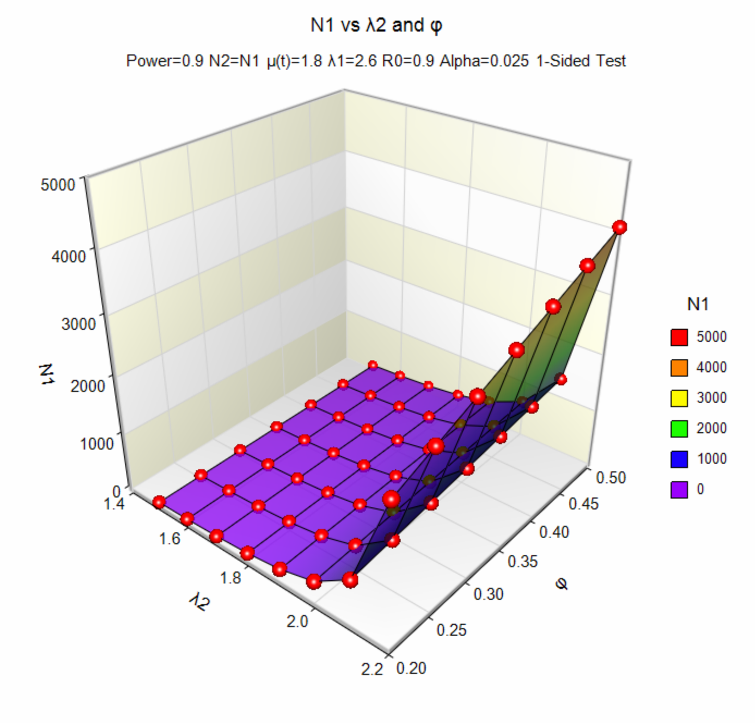
Zhu, H. 2017. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' Statistics in Biopharmaceutical Research, 9(1), 107-115, doi:10.1080/19466315.2016.1225594.

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

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 superiority ratio is 1.1, the power is 0.9, and the Type I error rate is 0.025.

The calculated sample size is 2372 for the REML variance calculation method.

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 .... **Sample Size**
Higher Negative Binomial Rates Are .... **Worse**
Variance Calculation Method .... **Restricted Maximum Likelihood Estimation**
Power... **0.90**
Alpha.. **0.025**
μ(t) (Average Exposure Time)........................ **0.85**
Group Allocation .... **Equal (N1 = N2)**
R0 (Superiority Margin 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.

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 Time	Average Event Rate		Event Rate Ratio			
Power	N1	N2	N	μ(t)	λ1	λ2	Actual λ2 / λ1	Superiority 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.