Chapter 469

Equivalence Tests for the Ratio of Two Negative Binomial Rates

Introduction

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

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

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

Hypotheses

The equivalence test hypotheses are

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

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 – 2α)% confidence is typically used. H_0 is rejected if the confidence interval falls completely between R_{Lower} and R_{Upper}.

Power Calculation

Zhu (2017) bases the power calculation on an equivalence test derived from a Negative Binomial regression model. The power calculation is

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

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^- and V_0^+ may be calculated in any of 3 ways.

V_0 Calculation Method 1 (using assumed true rates)

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

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

V_0 Calculation Method 2 (fixed marginal total)

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

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

V_0 Calculation Method 3 (restricted maximum likelihood estimation)

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

where

$$a = -\varphi\mu_t R_{Lower}(1+\theta),$$

$$b = \varphi\mu_t(\lambda_1 R_{Lower} + \theta\lambda_2) - (1 + \theta R_{Lower}),$$

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

V_{03}^+ is calculated in the same way, replacing R_{Lower} with R_{Upper}.

Zhu (2017) did not give a recommendation regarding whether Method 1, 2, or 3 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.”

Example 1 – Calculating Sample Size

Researchers wish to determine whether the average Negative Binomial rate of those receiving a new treatment is equivalent to a current control. The average exposure time for all subjects is 1.6 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. 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**
Variance Calculation Method	**Using Assumed True Rates**
Power	**0.90**
Alpha	**0.025**
μ(t) (Average Exposure Time)	**1.6**
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)	**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
Hypotheses: H0: λ2 / λ1 ≤ RL or λ2 / λ1 ≥ RU vs. H1: RL < λ2 / λ1 < RU
Variance Calculation Method: Using Assumed True Rates

	Sample Size			Average Exposure Time	Average Event Rate		Event Rate Ratio	Equivalence Limits		Dispersion	
Power	N1	N2	N	μ(t)	λ1	λ2	λ2 / λ1	Lower RL	Upper RU	φ	Alpha
0.90001	1817	1817	3634	1.6	2.2	1.9	0.864	0.8	1.25	0.20	0.025
0.90009	641	641	1282	1.6	2.2	2.0	0.909	0.8	1.25	0.20	0.025
0.90067	333	333	666	1.6	2.2	2.1	0.955	0.8	1.25	0.20	0.025
0.90048	253	253	506	1.6	2.2	2.2	1.000	0.8	1.25	0.20	0.025
0.90042	317	317	634	1.6	2.2	2.3	1.045	0.8	1.25	0.20	0.025
0.90025	536	536	1072	1.6	2.2	2.4	1.091	0.8	1.25	0.20	0.025
0.90014	1081	1081	2162	1.6	2.2	2.5	1.136	0.8	1.25	0.20	0.025
0.90010	1997	1997	3994	1.6	2.2	1.9	0.864	0.8	1.25	0.25	0.025
0.90036	706	706	1412	1.6	2.2	2.0	0.909	0.8	1.25	0.25	0.025
0.90074	367	367	734	1.6	2.2	2.1	0.955	0.8	1.25	0.25	0.025
0.90031	279	279	558	1.6	2.2	2.2	1.000	0.8	1.25	0.25	0.025
0.90028	350	350	700	1.6	2.2	2.3	1.045	0.8	1.25	0.25	0.025
0.90037	593	593	1186	1.6	2.2	2.4	1.091	0.8	1.25	0.25	0.025
0.90021	1197	1197	2394	1.6	2.2	2.5	1.136	0.8	1.25	0.25	0.025
0.90004	2176	2176	4352	1.6	2.2	1.9	0.864	0.8	1.25	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.
RL and RU The respective lower and upper equivalence limits for the event rate ratio.
φ The Negative Binomial dispersion parameter.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A parallel, two-group design will be used to test whether the Group 2 (treatment) Negative Binomial event rate (λ2) is equivalent to the Group 1 (control) Negative Binomial event rate (λ1), by testing whether the event rate ratio (λ2 / λ1) is between 0.8 and 1.25 (H0: λ2 / λ1 ≤ 0.8 or λ2 / λ1 ≥ 1.25 versus H1: 0.8 < λ2 / λ1 < 1.25). The comparison will be made using two one-sided, Negative Binomial regression term Z-tests using the variance calculation method with assumed true rates, with an overall 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 0.864 (λ2 = 1.9, λ1 = 2.2) with 90% power, with average exposure time 1.6, the number of needed subjects will be 1817 in Group 1 and 1817 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%	1817	1817	3634	2272	2272	4544	455	455	910
20%	641	641	1282	802	802	1604	161	161	322
20%	333	333	666	417	417	834	84	84	168
20%	253	253	506	317	317	634	64	64	128
20%	317	317	634	397	397	794	80	80	160
20%	536	536	1072	670	670	1340	134	134	268
20%	1081	1081	2162	1352	1352	2704	271	271	542
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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, 2272 subjects should be enrolled in Group 1, and 2272 in Group 2, to obtain final group sample sizes of 1817 and 1817, respectively.

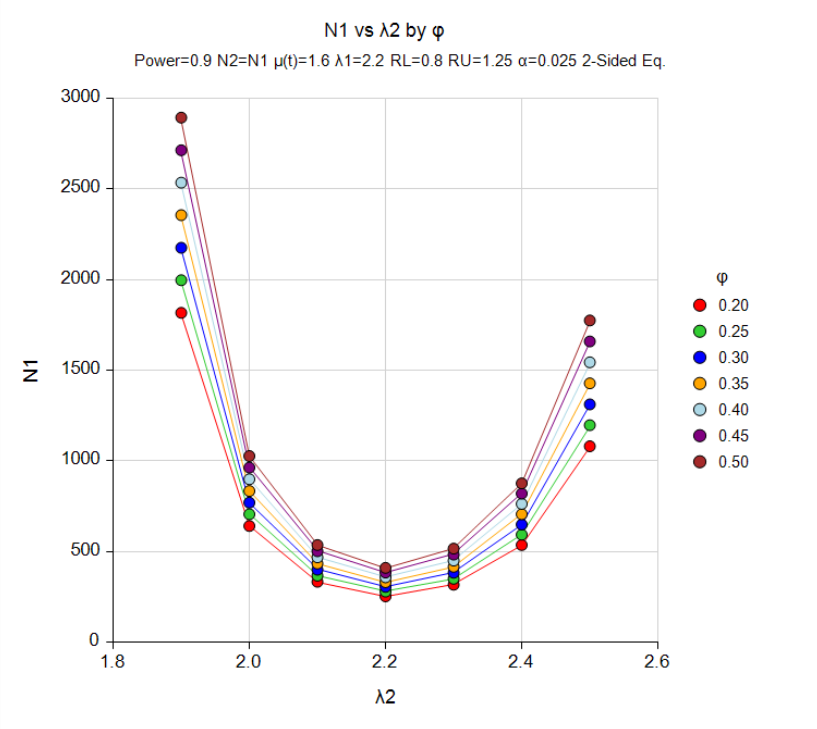
References

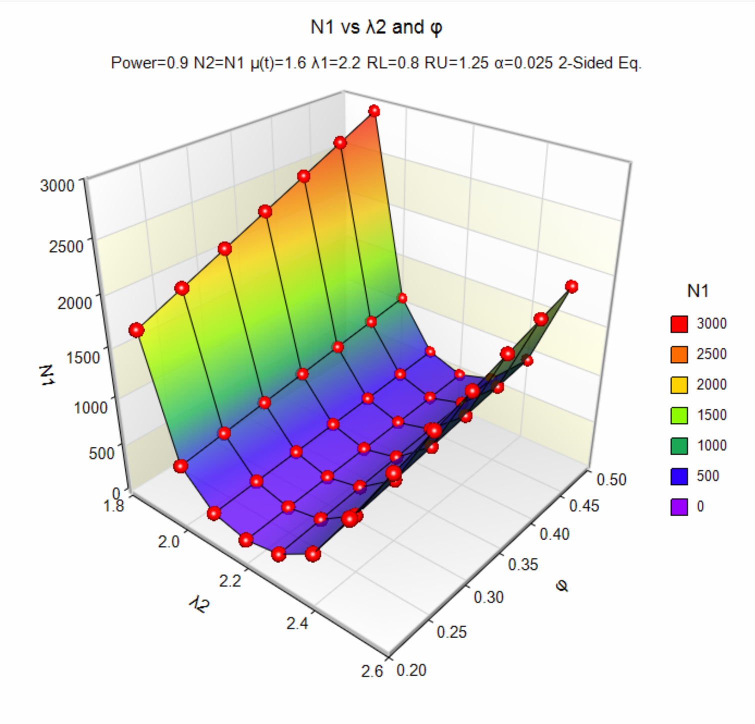
Zhu, H. 2017. 'Sample Size Calculation for Comparing Two Poisson or Negative Binomial Rates in Non-Inferiority or Equivalence Trials.' Statistics in Biopharmaceutical Research, 9(1), 107-115, doi:10.1080/19466315.2016.1225594.

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 the event rates are both 2.5, the dispersion parameter is 0.35, the average duration is 0.9, the equivalence limits are 0.875 and 1.14 (1 / 0.875), the power is 0.9, and the Type I error rate is 0.05.

The calculated total sample sizes are 965, 966, and 966 for the Assumed True Rate, and 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 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**
Variance Calculation Method	**Using Assumed True Rates**
	(2nd run: Fixed Marginal Total
	3rd run: Restricted Maximum Likelihood Estimation)
Power	**0.90**
Alpha	**0.05**
μ(t) (Average Exposure Time)	**0.9**
Group Allocation	**Equal (N1 = N2)**
RU (Upper Equivalence Limit)	**1/RL**
RL (Lower Equivalence Limit)	**0.875**
λ1 (Event Rate of Group 1)	**2.5**
Enter λ2 or Ratio for Group 2	**λ2 / λ1 (Ratio of Event Rates)**
λ2 / λ1 (Ratio of Event Rates)	**1**
φ (Dispersion)	**0.35**

Output

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

Numeric Results (1st Run, Example 2a)

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: λ2 / λ1 ≤ RL or λ2 / λ1 ≥ RU vs. H1: RL < λ2 / λ1 < RU
Variance Calculation Method: Using Assumed True Rates

	Sample Size			Average Exposure Time	Average Event Rate		Event Rate Ratio	Equivalence Limits			
Power	N1	N2	N	μ(t)	λ1	λ2	λ2 / λ1	Lower RL	Upper RU	Dispersion φ	Alpha
0.90022	965	965	1930	0.9	2.5	2.5	1	0.875	1.143	0.35	0.05

Numeric Results (2nd Run, Example 2b)

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: λ2 / λ1 ≤ RL or λ2 / λ1 ≥ RU vs. H1: RL < λ2 / λ1 < RU
Variance Calculation Method: Fixed Marginal Total

	Sample Size			Average Exposure Time	Average Event Rate		Event Rate Ratio	Equivalence Limits			
Power	N1	N2	N	μ(t)	λ1	λ2	λ2 / λ1	Lower RL	Upper RU	Dispersion φ	Alpha
0.90015	966	966	1932	0.9	2.5	2.5	1	0.875	1.143	0.35	0.05

Numeric Results (3rd Run, Example 2c)

Numeric Results

Solve For: Sample Size
Groups: 1 = Control, 2 = Treatment
Hypotheses: H0: λ2 / λ1 ≤ RL or λ2 / λ1 ≥ RU vs. H1: RL < λ2 / λ1 < RU
Variance Calculation Method: Restricted Maximum Likelihood

	Sample Size			Average Exposure Time	Average Event Rate		Event Rate Ratio	Equivalence Limits			
Power	N1	N2	N	μ(t)	λ1	λ2	λ2 / λ1	Lower RL	Upper RU	Dispersion φ	Alpha
0.90034	966	966	1932	0.9	2.5	2.5	1	0.875	1.143	0.35	0.05

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