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 (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 ($\varphi > 1$ 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:	$\theta = N_2/N_1$

Hypotheses

The equivalence test hypotheses are

$$H_0: \frac{\lambda_2}{\lambda_1} \le R_{Lower} \quad \text{or} \quad \frac{\lambda_2}{\lambda_1} \ge R_{Upper} \quad \text{vs.} \quad H_1: R_{Lower} < \frac{\lambda_2}{\lambda_1} < R_{Upper}$$

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 Poisson 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

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

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 (2017) 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.”

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

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)	**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**

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			
Power	N1	N2	N	μ(t)	λ1	λ2	λ2 / λ1	Lower RL	Upper RU	Dispersion φ	Alpha
0.90012	704	704	1408	2.5	2.2	1.9	0.864	0.8	1.25	1	0.025
0.90057	246	246	492	2.5	2.2	2.0	0.909	0.8	1.25	1	0.025
0.90001	126	126	252	2.5	2.2	2.1	0.955	0.8	1.25	1	0.025
0.90039	95	95	190	2.5	2.2	2.2	1.000	0.8	1.25	1	0.025
0.90047	118	118	236	2.5	2.2	2.3	1.045	0.8	1.25	1	0.025
0.90059	198	198	396	2.5	2.2	2.4	1.091	0.8	1.25	1	0.025
0.90045	396	396	792	2.5	2.2	2.5	1.136	0.8	1.25	1	0.025

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 dispersion parameter (φ > 1 implies over-dispersion, φ < 1 implies under-dispersion).
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) Poisson event rate (λ2) is equivalent to the Group 1 (control) Poisson 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, Poisson 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 dispersion is assumed to be 1. To detect a ratio of Poisson event rates (λ2 / λ1) of 0.864 (λ2 = 1.9, λ1 = 2.2) with 90% power, with average exposure time 2.5, the number of needed subjects will be 704 in Group 1 and 704 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%	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

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, 880 subjects should be enrolled in Group 1, and 880 in Group 2, to obtain final group sample sizes of 704 and 704, respectively.

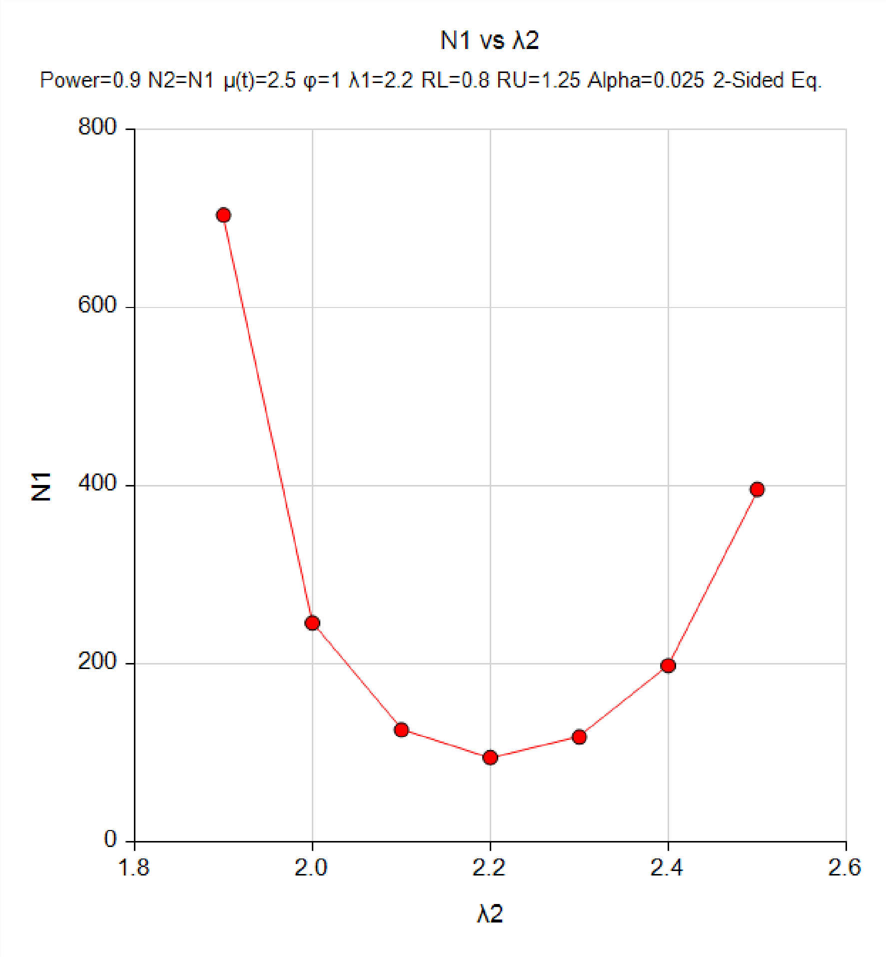
References

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



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

Example 2 – Validation using Zhu (2017)

Zhu (2017) 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

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 or b)** 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 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**

Output (1st Run, Example 2a)

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

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
0.80012	2705	2705	5410	0.7	1	1	1	0.9	1.111	1	0.025

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

Output (2^{nd} Run, Example 2b)

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

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 or REML

	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
0.80001	2709	2709	5418	0.7	1	1	1	0.9	1.111	1	0.025

The sample sizes calculated in **PASS** match those of Zhu (2017) for the second scenario as well.