Chapter 456

Non-Inferiority Tests for the Ratio of Two Poisson Rates

Introduction

This procedure may be used to calculate power and sample size for non-inferiority 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

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 Poisson 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

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

and V_0 may be calculated in either of two ways.

V_0 Calculation Method 1 (using assumed true rates)

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

Using Method 1, V_0 and V_1 are equal.

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

$$V_{02} = \frac{\varphi(1 + R_0\theta)^2}{\mu_t R_0 \theta(\lambda_1 + \theta\lambda_2)}$$

Zhu (2017) did not give a recommendation regarding whether Method 1 or Method 2 should be used, except to say that "sample sizes calculated using Method 2 are slightly larger compared to those calculated by Method 1 for most simulated scenarios…".

Power Calculation

The corresponding power calculation to the sample size calculation above is

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

Example 1 – Calculating Sample Size

Researchers wish to determine whether the average Poisson rate of those receiving a new treatment is non-inferior to a current control. In the scenario, higher Poisson 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. 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**
Higher Poisson 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)	**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
Higher Poisson 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
0.90056	29	29	58	2.5	2.2	1.8	0.818	1.2	1	0.025
0.90649	39	39	78	2.5	2.2	1.9	0.864	1.2	1	0.025
0.90507	53	53	106	2.5	2.2	2.0	0.909	1.2	1	0.025
0.90114	75	75	150	2.5	2.2	2.1	0.955	1.2	1	0.025
0.90014	115	115	230	2.5	2.2	2.2	1.000	1.2	1	0.025
0.90051	197	197	394	2.5	2.2	2.3	1.045	1.2	1	0.025
0.90064	404	404	808	2.5	2.2	2.4	1.091	1.2	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.
R0	The non-inferiority (boundary) 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 (where higher Poisson rates are considered worse) will be used to test whether the Group 2 (treatment) Poisson rate is non-inferior to the Group 1 (control) Poisson 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, Poisson regression term Z-test using the variance calculation method with assumed true rates, with a 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 0.818 (λ2 = 1.8, λ1 = 2.2) with 90% power, with average exposure time 2.5, the number of needed subjects will be 29 in Group 1 and 29 in Group 2.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N1	Sample Size N2	Sample Size N	Dropout-Inflated Enrollment Sample Size N1'	N2'	N'	Expected Number of Dropouts D1	D2	D
20%	29	29	58	37	37	74	8	8	16
20%	39	39	78	49	49	98	10	10	20
20%	53	53	106	67	67	134	14	14	28
20%	75	75	150	94	94	188	19	19	38
20%	115	115	230	144	144	288	29	29	58
20%	197	197	394	247	247	494	50	50	100
20%	404	404	808	505	505	1010	101	101	202

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, 37 subjects should be enrolled in Group 1, and 37 in Group 2, to obtain final group sample sizes of 29 and 29, respectively.

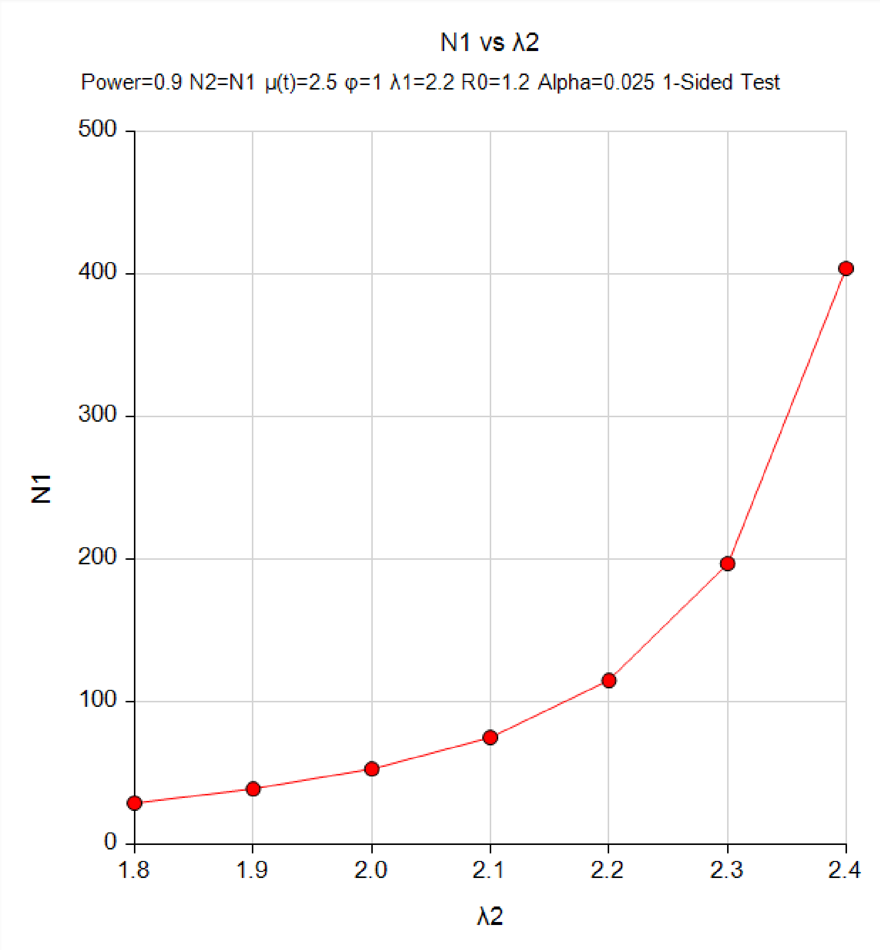
References

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 of solving for sample size where lower Poisson rates are better, the event rates are both 1.5, the (over-)dispersion is 1.35, 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 2450 and 2453 per group 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 2a** and **Example 2b** 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 Poisson Rates Are............................. **Worse**
Variance Calculation Method .... **Using Assumed True Rates**
(2nd run: Fixed Marginal Total or REML)
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)... **1.35**

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 Poisson 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
0.90006	2450	2450	4900	0.85	1.5	1.5	1	1.1	1.35	0.025

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

REML (Example 2b) 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 Poisson Rates Are:	Worse
Hypotheses:	H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method:	Fixed Marginal Total or REML

	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
0.90002	2453	2453	4906	0.85	1.5	1.5	1	1.1	1.35	0.025

The sample sizes calculated in **PASS** match those of Zhu (2017) in this case as well.

Example 3 – Validation using Stucke and Kieser (2013)

Stucke and Kieser (2013) present a table of sample size calculations on page 211. The table assumes a power of 0.8, a Type I error rate of 0.025, an exposure time of 1, and no over- or under-dispersion.

The event rates, the sample size ratios, and the non-inferiority ratios are varied, giving the following sample sizes:

Event Rate	N1/N2	R0	N1	N2	N
0.1	1	2	327	327	654
0.1	2/3	2	409	273	682
0.1	3/2	2	273	409	682
0.2	1	2	164	164	328
0.2	2/3	2	205	137	342
0.2	3/2	2	137	205	342
0.6	1	3/2	160	160	320
0.6	2/3	3/2	199	133	332
0.6	3/2	3/2	133	199	332
1	1	3/2	96	96	192
1	2/3	3/2	80	120	200
1	3/2	3/2	120	80	200
3	1	3/2	32	32	64
3	2/3	3/2	40	27	67
3	3/2	3/2	27	40	682

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 3a** and **Example 3b** 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 Poisson Rates Are............................**Worse**
Variance Calculation Method........................**Using Assumed True Rates**
Power..**0.80**
Alpha..**0.025**
μ(t) (Average Exposure Time).......................**1.0**
Group Allocation ....**Enter R = N2/N1, solve for N1 and N2**
R **0.6666666667 1 1.5**
R0 (Non-Inferiority Ratio)..............................**2** (for first 6 table entries)
1.5 (for last 9 table entries)
λ1 (Event Rate of Group 1)...........................**0.1 0.2** (for first 6 table entries)
0.6 1 3 (for last 9 table entries)
Enter λ2 or Ratio for Group 2........................**λ2 / λ1 (Ratio of Event Rates)**
λ2 (Event Rate of Group 2)...........................**1**
φ (Dispersion)...**1.0**

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 Poisson Rates Are: Worse
Hypotheses: H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method: Using Assumed True Rates

	Sample Size			Allocation Ratio	Average Exposure	Average Event Rate		Event Rate Ratio			
Power	N1	N2	N	N2 / N1 R	Time μ(t)	λ1	λ2	Actual λ2 / λ1	Non-Inferiority R0	Dispersion φ	Alpha
0.80057	409	273	682	0.67	1	0.1	0.1	1	2	1	0.025
0.80152	205	137	342	0.67	1	0.2	0.2	1	2	1	0.025
0.80033	327	327	654	1.00	1	0.1	0.1	1	2	1	0.025
0.80152	164	164	328	1.00	1	0.2	0.2	1	2	1	0.025
0.80104	273	410	683	1.50	1	0.1	0.1	1	2	1	0.025
0.80247	137	206	343	1.50	1	0.2	0.2	1	2	1	0.025

The sample sizes calculated in **PASS** match the table of Stucke and Kieser (2013).

2nd Run (Example 3b) 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 Poisson Rates Are: Worse
Hypotheses: H0: λ2 / λ1 ≥ R0 vs. H1: λ2 / λ1 < R0
Variance Calculation Method: Using Assumed True Rates

	Sample Size			Allocation Ratio	Average Exposure	Average Event Rate		Event Rate Ratio			
Power	N1	N2	N	N2 / N1 R	Time μ(t)	λ1	λ2	Actual λ2 / λ1	Non-Inferiority R0	Dispersion φ	Alpha
0.80015	199	133	332	0.67	1	0.6	0.6	1	1.5	1	0.025
0.80211	120	80	200	0.67	1	1.0	1.0	1	1.5	1	0.025
0.80211	40	27	67	0.67	1	3.0	3.0	1	1.5	1	0.025
0.80211	160	160	320	1.00	1	0.6	0.6	1	1.5	1	0.025
0.80211	96	96	192	1.00	1	1.0	1.0	1	1.5	1	0.025
0.80211	32	32	64	1.00	1	3.0	3.0	1	1.5	1	0.025
0.80113	133	200	333	1.50	1	0.6	0.6	1	1.5	1	0.025
0.80211	80	120	200	1.50	1	1.0	1.0	1	1.5	1	0.025
0.80694	27	41	68	1.50	1	3.0	3.0	1	1.5	1	0.025

The sample sizes calculated in **PASS** match the table of Stucke and Kieser (2013) in this case as well.