

## Chapter 457

# Superiority by a Margin Tests for the Ratio of Two Poisson Rates

## Introduction

This procedure may be used to calculate power and sample size for superiority by a margin 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	$\lambda_1$	$\lambda_2$
Dispersion parameter:	$\varphi$ ( $\varphi > 1$ implies over-dispersion; $\varphi < 1$ implies under-dispersion)	
Average exposure time:	$\mu_t$	
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  $R_0 > 1$ .

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

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  $R_0 < 1$ .

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## 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 calculations for a superiority by a margin test are the same. The sample size calculation is

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

$$N_2 = \theta N_1$$

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...”.

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**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 more than 10% lower than the current control. In the scenario, lower Poisson 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.

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 .....	<b>Sample Size</b>
Higher Poisson Rates Are.....	<b>Worse</b>
Variance Calculation Method .....	<b>Using Assumed True Rates</b>
Power.....	<b>0.90</b>
Alpha.....	<b>0.025</b>
$\mu(t)$ (Average Exposure Time).....	<b>1.8</b>
Group Allocation .....	<b>Equal (N1 = N2)</b>
R0 (Superiority Margin Ratio) .....	<b>0.9</b>
$\lambda_1$ (Event Rate of Group 1) .....	<b>2.6</b>
Enter $\lambda_2$ or Ratio for Group 2.....	<b><math>\lambda_2</math> (Event Rate of Group 2)</b>
$\lambda_2$ (Event Rate of Group 2) .....	<b>1.5 to 2.2 by 0.1</b>
$\phi$ (Dispersion) .....	<b>1</b>

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

## 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:  $\lambda_2 / \lambda_1 \geq R_0$  vs. H1:  $\lambda_2 / \lambda_1 < R_0$   
 Variance Calculation Method: Using Assumed True Rates

Power	Sample Size			Average Exposure Time $\mu(t)$	Average Event Rate		Event Rate Ratio		Dispersion $\phi$	Alpha
	N1	N2	N		$\lambda_1$	$\lambda_2$	Actual $\lambda_2 / \lambda_1$	Superiority $R_0$		
0.90851	32	32	64	1.8	2.6	1.5	0.577	0.9	1	0.025
0.90151	41	41	82	1.8	2.6	1.6	0.615	0.9	1	0.025
0.90190	56	56	112	1.8	2.6	1.7	0.654	0.9	1	0.025
0.90096	80	80	160	1.8	2.6	1.8	0.692	0.9	1	0.025
0.90102	123	123	246	1.8	2.6	1.9	0.731	0.9	1	0.025
0.90069	210	210	420	1.8	2.6	2.0	0.769	0.9	1	0.025
0.90059	430	430	860	1.8	2.6	2.1	0.808	0.9	1	0.025
0.90021	1288	1288	2576	1.8	2.6	2.2	0.846	0.9	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.  $N = N1 + N2$ .  
 $\mu(t)$  The average exposure (observation) time across subjects in both groups.  
 $\lambda_1$  The event rate per time unit in Group 1 (control).  
 $\lambda_2$  The event rate per time unit in Group 2 (treatment).  
 $\lambda_2 / \lambda_1$  The known, true, or assumed ratio of the two event rates.  
 $R_0$  The superiority margin (null hypothesis) ratio.  
 $\phi$  The dispersion parameter ( $\phi > 1$  implies over-dispersion,  $\phi < 1$  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 superior to (less than) the Group 1 (control) Poisson rate by a margin, with a superiority margin ratio of 0.9 (H0:  $\lambda_2 / \lambda_1 \geq 0.9$  versus H1:  $\lambda_2 / \lambda_1 < 0.9$ ). 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 ( $\alpha$ ) of 0.025. The dispersion is assumed to be 1. To detect a ratio of Poisson event rates ( $\lambda_2 / \lambda_1$ ) of 0.577 ( $\lambda_2 = 1.5$ ,  $\lambda_1 = 2.6$ ) with 90% power, with average exposure time 1.8, the number of needed subjects will be 32 in Group 1 and 32 in Group 2.

## Superiority by a Margin Tests for the Ratio of Two Poisson Rates

## Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	32	32	64	40	40	80	8	8	16
20%	41	41	82	52	52	104	11	11	22
20%	56	56	112	70	70	140	14	14	28
20%	80	80	160	100	100	200	20	20	40
20%	123	123	246	154	154	308	31	31	62
20%	210	210	420	263	263	526	53	53	106
20%	430	430	860	538	538	1076	108	108	216
20%	1288	1288	2576	1610	1610	3220	322	322	644

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 Lohknygina, 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, 40 subjects should be enrolled in Group 1, and 40 in Group 2, to obtain final group sample sizes of 32 and 32, respectively.

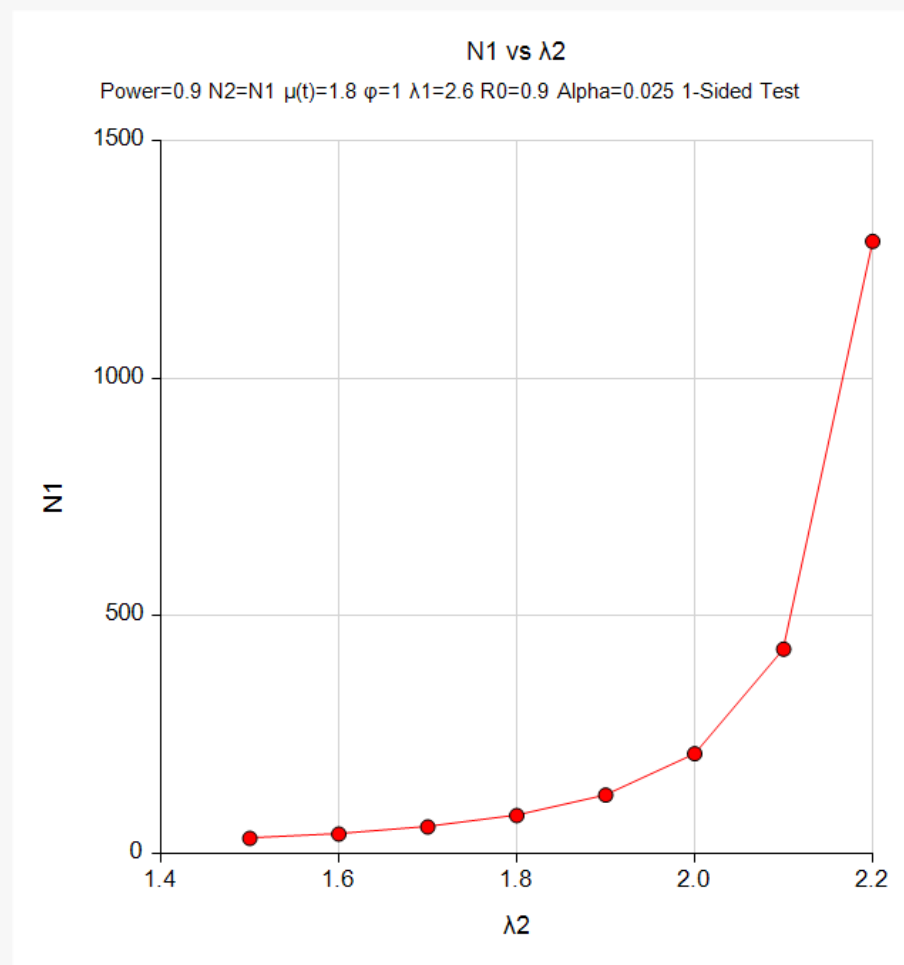
## References

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  $\lambda_2$ .

## Example 2 – Validation

We did not find a publication with an example of a superiority by a margin test for the ratio of two Poisson rates. However, Examples 2 and 3 of the *Non-Inferiority Tests for the Ratio of Two Poisson Rates* chapter use the same formulas and calculations as those used in this procedure. We refer the reader to those examples for validation of this procedure.