Chapter 161

Non-Inferiority Tests for the Ratio of Two Correlated Proportions

Introduction

This module computes power and sample size for non-inferiority tests of the ratio in which two dichotomous responses are measured on each subject. When one is interested in showing that the true proportions are different, the data are often analyzed with McNemar's test. However, we are interested in showing non-inferiority rather than difference. For example, suppose a diagnostic procedure is accurate, but is expensive to apply or has serious side effects. A replacement procedure is sought which is no less accurate but is less expensive or has fewer side effects. In this case, we are not interested in showing that the two diagnostic procedures are different, but rather that the second is no worse than the first. *Non-inferiority tests* were designed for this situation.

These tests are often divided into two categories: *equivalence* (two-sided) tests and *non-inferiority* (one-sided) tests. Here, the term *equivalence tests* means that we want to show that two diagnostic procedures are equivalent—that is, their accuracy is about the same. This requires a two-sided hypothesis test. On the other hand, *non-inferiority tests* are used when we want to show that a new (experimental) procedure is no worse than the existing (reference or gold-standard) one. This requires a one-sided hypothesis test. The procedures discussed in this chapter deal with the non-inferiority (one-sided) case.

Technical Details

The results of a study in which two dichotomous responses are measured on each subject can be displayed in a 2-by-2 table in which one response is shown across the columns and the other is shown down the rows. In the discussion to follow, the columns of the table represent the standard (reference or control) response and the rows represent the treatment (experimental) response. The outcome probabilities can be classified into the following table.

Experimental Diagnosis	**Standard Diagnosis**		
	Yes	No	**Total**
Yes	p_{11}	p_{10}	P_T
No	p_{01}	p_{00}	$1 - P_T$
Total	P_S	$1 - P_S$	1

In this table, $p_{ij} = p_{Treatment,Standard}$. That is, the first subscript represents the response of the new, experimental procedure while the second subscript represents the response of the standard procedure. Thus, p_{01} represents the proportion having a negative treatment response and a positive standard response.

Sensitivity, Specificity, and Prevalence

To aid in interpretation, analysts have developed a few proportions that summarize the table. Three of the most popular ratios are *sensitivity*, *specificity,* and *prevalence*.

Sensitivity

Sensitivity is the proportion of subjects with a positive standard response who also have a positive experimental response. In terms of proportions from a 2-by-2 table,

$$\text{Sensitivity} = \frac{p_{11}}{(p_{01} + p_{11})} = \frac{p_{11}}{P_S}$$

Specificity

Specificity is the proportion of subjects with a negative standard response who also have a negative experimental response. In terms of proportions from a 2-by-2 table,

$$\text{Specificity} = \frac{p_{00}}{(p_{10} + p_{00})}$$

Prevalence

Prevalence is the overall proportion of individuals with the disease (or feature of interest). In terms of proportions from a 2-by-2 table,

$$\text{Prevalence} = P_S$$

Table Probabilities

The outcome counts from a sample of *n* subjects can be classified into the following table.

Experimental Diagnosis	**Standard Diagnosis**		**Total**
	Yes	No	
Yes	n_{11}	n_{10}	n_T
No	n_{01}	n_{00}	$n - n_T$
Total	n_S	$n - n_S$	n

Note that $n_{11} + n_{00}$ is the number of matches (*concordant pairs*) and $n_{01} + n_{10}$is the number of *discordant pairs*.

The hypothesis of interest concerns the two marginal probabilities P_T and P_S. P_S represents the accuracy or success of the standard test and P_T represents the accuracy or success of the new, experimental test. Non-inferiority is defined in terms of either the difference of these two proportions, $D = P_T - P_S$, or the relative risk ratio, $R = P_T/P_S$. The choice between D and R will usually lead to different sample sizes to achieve the same power.

Non-Inferiority Hypotheses using Ratios

The following is based on Nam and Blackwelder (2002). We refer you to this paper for the complete details of which we will only provide a brief summary here.

If we define R_0 as the non-inferiority ratio with $0 < R_0 < 1$, then the null and alternative hypotheses of non-inferiority in terms of the ratio are

$$H_0: P_T/P_S \leq R_0 \quad \text{versus} \quad H_1: P_T/P_S > R_0.$$

Test Statistics

The test statistic for an asymptotic test based on constrained maximum likelihood for large *n* is given by

$$Z(R_0) = \sqrt{\frac{n\left(\hat{P}_T - R_0\hat{P}_S\right)}{R_0(\tilde{p}_{10} + \tilde{p}_{01})}}$$

where

$$\tilde{p}_{10} = \frac{-\hat{P}_T + R_0^2\left(\hat{P}_S + 2\hat{p}_{10}\right) + \sqrt{\left(\hat{P}_T - R_0^2\hat{P}_S\right)^2 + 4R_0^2\hat{p}_{10}\hat{p}_{01}}}{2R_0(R_0 + 1)}$$

$$\tilde{p}_{10} = R_0\tilde{p}_{10} - (R_0 - 1)(1 - \hat{p}_{00})$$

$$\hat{p}_{01} = \frac{n_{01}}{n}, \hat{p}_{10} = \frac{n_{10}}{n}, \hat{P}_T = \frac{n_{10} + n_{11}}{n}, \hat{P}_S = \frac{n_{01} + n_{11}}{n}$$

Power Formula

The power when the true value of the relative risk ratio is R_1 can be evaluated exactly using the multinomial distribution. When *n* is large, we use a normal approximation to the multinomial distribution which leads to

$$\text{Power} = 1 - \Phi(c_{NI})$$

where

$$c_{NI} = \frac{z_{1-\alpha}\sqrt{\bar{V}_0(R_0)} - E_1(R_0)}{\sqrt{V_1(R_0)}}$$

$$\bar{V}_0(R_0) = \frac{R_0(\bar{p}_{10} + \bar{p}_{01})}{n}$$

$$E_1(R_0) = P_S(R_1 - R_0)$$

$$V_1(R_0) = \frac{P_S(R_1 + R_0^2) - 2R_0 p_{11} - P_S^2(R_1 - R_0)^2}{n}$$

$$\bar{p}_{10} = \frac{-P_T + R_0^2(P_S + 2p_{10}) + \sqrt{(P_T - R_0^2 P_S)^2 + 4R_0^2 p_{10} p_{01}}}{2R_0(R_0 + 1)}$$

$$\bar{p}_{01} = R_0\bar{p}_{10} - (R_0 - 1)(1 - p_{00})$$

Nuisance Parameter

The 2-by-2 table includes four parameters, p_{11}, p_{10}, p_{01}, and p_{00}, but the power calculations only require two parameters: P_S and R_1. A third parameter is defined implicitly since the sum of the four parameters is one. Thus, one parameter (known as a nuisance parameter) remains unaccounted for. This parameter must be addressed to fully specify the problem. This fourth parameter can be specified using any one of the following: p_{11}, p_{10}, p_{01}, p_{00}, $p_{10} + p_{01}$, $p_{11} + p_{00}$, the sensitivity of the experimental response, p_{11}/P_S, or the within-subject correlation, ρ.

It may be difficult to specify a reasonable value for the nuisance parameter since its value may not be even approximately known until after the study is conducted. Because of this, we suggest that you calculate power or sample size for a range of values of the nuisance parameter. This will allow you to determine how sensitive the results are to its value.

Estimating P11, P01, and P10 using Pt, Ps, and ρ

Sometimes, obtaining estimates of *P*11, *P*01, and/or *P*10 is problematic. This problem is solved by using the marginal probabilities and the within-subject correlation coefficient, which may be easier to estimate. As outlined in Zhang, Cao, and Ahn (2017), the relationship between *P*11, *Pt*, *Ps* and the correlation is

$$\rho = \frac{P11 - P_s P_t}{\sqrt{P_s P_t (1 - P_s)(1 - P_t)}}$$

Using this relationship, values of ρ can be entered and transformed to the corresponding value of *P*11 using the equation

$$P11 = \rho\sqrt{P_s P_t (1 - P_s)(1 - P_t)} + P_s P_t$$

The only concern is that values of ρ be used that limit *P*11, *P*01, *P*10, and *P*00 to be between 0 and 1. The lower and upper limits of the correlation are

$$\rho_L = \max\left\{-\sqrt{\frac{P_s P_t}{(1 - P_s)(1 - P_t)}}, -\sqrt{\frac{(1 - P_s)(1 - P_t)}{P_s P_t}}\right\}$$

$$\rho_U = \min\left\{\sqrt{\frac{P_s(1 - P_t)}{P_t(1 - P_s)}}, \sqrt{\frac{P_t(1 - P_s)}{P_s(1 - P_t)}}\right\}$$

*P*11, along with *Pt* and *Ps*, can then be used to calculate *P*01 and *P*10.

Example 1 – Finding Power

Researchers have developed a new treatment for migraine headaches which is less expensive than a current standard. The researchers need to show that the proportion of individuals who respond to the new treatment is not inferior to the standard treatment. The new treatment will be considered non-inferior if its success rate is no less than 95% of the success rate of the standard, which is about 0.65. They want to study the power for various sample sizes between 500 and 4000 at the 5% significance level. They'll study various values of the nuisance parameter: P11/Ps = sensitivity (0.5 to 0.9).

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	**Power**
Power Calculation Method	**Normal Approximation**
Alpha	**0.05**
N (Sample Size)	**500 to 4000 by 500**
R0 (Non-Inferiority Ratio)	**0.95**
R1 (Actual Ratio)	**1.0**
Ps (Standard Proportion)	**0.65**
Nuisance Parameter Type	**P11/Ps (Sensitivity)**
Nuisance Parameter Value	**0.5 to 0.9 by 0.1**

Output

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

Numeric Reports

Numeric Results

Solve For: Power
Hypotheses: H0: Pt/Ps ≤ R0 vs. H1: Pt/Ps > R0

		Ratios		Proportions			
Power*	Sample Size N	Non-Inferiority R0	Actual R1	Treatment Pt	Standard Ps	Nuisance Parameter P11/Ps	Alpha
0.23552	500	0.95	1	0.65	0.65	0.5	0.05
0.27009	500	0.95	1	0.65	0.65	0.6	0.05
0.32464	500	0.95	1	0.65	0.65	0.7	0.05
0.42349	500	0.95	1	0.65	0.65	0.8	0.05
0.64700	500	0.95	1	0.65	0.65	0.9	0.05
0.36772	1000	0.95	1	0.65	0.65	0.5	0.05
0.42680	1000	0.95	1	0.65	0.65	0.6	0.05
0.51572	1000	0.95	1	0.65	0.65	0.7	0.05
0.65984	1000	0.95	1	0.65	0.65	0.8	0.05
0.89100	1000	0.95	1	0.65	0.65	0.9	0.05
0.48241	1500	0.95	1	0.65	0.65	0.5	0.05
0.55722	1500	0.95	1	0.65	0.65	0.6	0.05
0.66224	1500	0.95	1	0.65	0.65	0.7	0.05
0.80955	1500	0.95	1	0.65	0.65	0.8	0.05
0.97046	1500	0.95	1	0.65	0.65	0.9	0.05
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.

* Power was computed using the normal approximation method.

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The number of subjects, the sample size.
R0	The ratio at which the treatment will be considered non-inferior to the standard.
R1	The actual ratio at which the power is calculated. R1 = Pt/Ps.
Pt	The response proportion in the treatment (experimental) group.
Ps	The response proportion in the standard (baseline, reference, or control) group.
Nuisance Parameter	A value that is needed but is not a direct part of the hypotheses.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A paired design will be used to test whether the treatment proportion (Pt) is non-inferior to the standard proportion (Ps), with a non-inferiority ratio bound of 0.95 (H0: Pt / Ps ≤ 0.95 versus H1: Pt / Ps > 0.95). The comparison will be made using a constrained maximum likelihood asymptotic test, with a Type I error rate (α) of 0.05. The nuisance parameter (P11/Ps) is assumed to be 0.5. To detect a ratio of the proportions of 1 (Pt = 0.65, Ps = 0.65) with a sample size of 500 pairs, the power is 0.23552.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	500	625	125
20%	1000	1250	250
20%	1500	1875	375
20%	2000	2500	500
20%	2500	3125	625
20%	3000	3750	750
20%	3500	4375	875
20%	4000	5000	1000

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.
N	The evaluable sample size at which power is computed (as entered by the user). If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' 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.)
D	The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 625 subjects should be enrolled to obtain a final sample size of 500 subjects.

References

Lewis, J.A. 1999. 'Statistical principles for clinical trials (ICH E9) an introductory note on an international guideline.' Statistics in Medicine, 18, pages 1903-1942.

Liu, J., Hsueh, H., Hsieh, E., and Chen, J.J. 2002. 'Tests for equivalence or non-inferiority for paired binary data', Statistics in Medicine, Volume 21, pages 231-245.

Nam, Jun-mo. 1997. 'Establishing equivalence of two treatments and sample size requirements in matched-pairs design', Biometrics, Volume 53, pages 1422-1430.

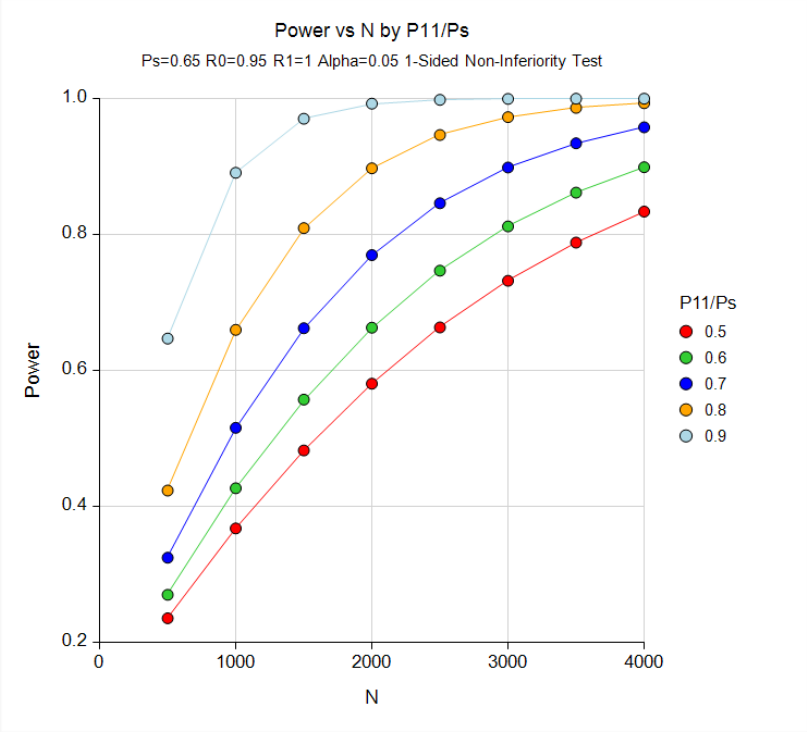
Nam, Jun-mo and Blackwelder, W.C. 2002. 'Analysis of the ratio of marginal probabilities in a matched-pair setting', Statistics in Medicine, Volume 21, pages 689-699.

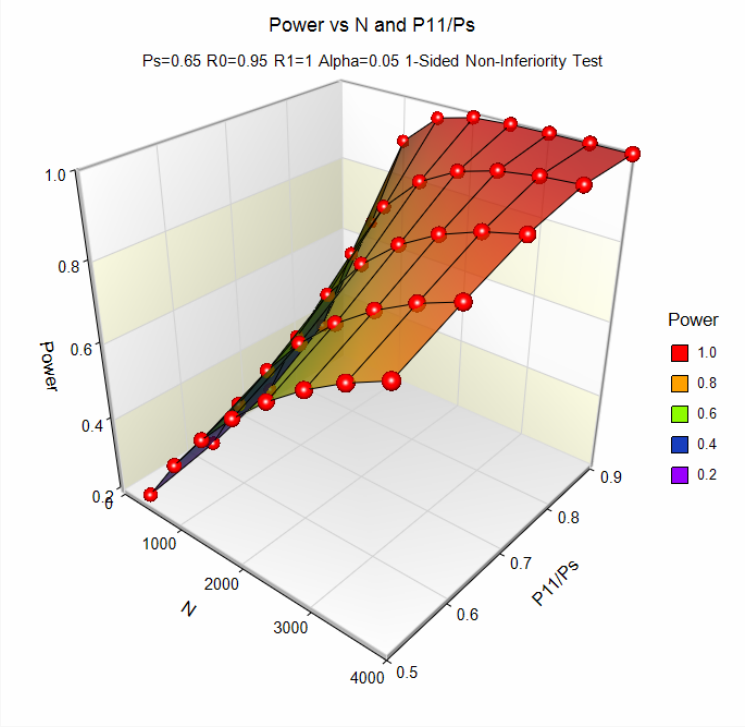
Zhang, S., Cao, J., Ahn, C. 2017. 'Inference and sample size calculation for clinical trials with incomplete observations of paired binary outcomes'. Statistics in Medicine. Volume 36. Pages 581-591.

This report shows the power for the indicated scenarios. All of the columns are defined in the ‘Report Definitions’ section.

Plots Section

Plots





These plots show the power versus the sample size for the various values of sensitivity. In this example, we see that the value of the nuisance parameter has a large effect on the calculated power.

Example 2 – Finding Sample Size

Continuing with Example 1, the analysts want to determine the exact sample size necessary to achieve 90% power for all values of the nuisance parameter.

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**
Power Calculation Method	**Normal Approximation**
Power	**0.90**
Alpha	**0.05**
R0 (Non-Inferiority Ratio)	**0.95**
R1 (Actual Ratio)	**1.0**
Ps (Standard Proportion)	**0.65**
Nuisance Parameter Type	**P11/Ps (Sensitivity)**
Nuisance Parameter Value	**0.5 to 0.9 by 0.1**

Output

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

Numeric Results

Solve For: Sample Size
Hypotheses: H0: Pt/Ps ≤ R0 vs. H1: Pt/Ps > R0

		Ratios		Proportions			
Power*	Sample Size N	Non-Inferiority R0	Actual R1	Treatment Pt	Standard Ps	Nuisance Parameter P11/Ps	Alpha
0.90004	5013	0.95	1	0.65	0.65	0.5	0.05
0.90001	4013	0.95	1	0.65	0.65	0.6	0.05
0.90004	3015	0.95	1	0.65	0.65	0.7	0.05
0.90011	2020	0.95	1	0.65	0.65	0.8	0.05
0.90016	1035	0.95	1	0.65	0.65	0.9	0.05

* Power was computed using the normal approximation method.

These scenarios require large sample sizes.

Example 3 – Validation using Nam and Blackwelder (2002)

Nam and Blackwelder (2002) give an example in which Ps is 0.80, P10 is 0.05, R1 is 1.00, R0 is 0.80, the significance level is 0.05, and the power is 80%. From their Table III, the sample size is 34. Note that their calculations use the approximate formula.

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 3** 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**
Power Calculation Method	**Normal Approximation**
Power	**0.80**
Alpha	**0.05**
R0 (Non-Inferiority Ratio)	**0.80**
R1 (Actual Ratio)	**1.0**
Ps (Standard Proportion)	**0.80**
Nuisance Parameter Type	**P10 (% +Trt -Std)**
Nuisance Parameter Value	**0.05**

Output

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

Numeric Results

Solve For: Sample Size
Hypotheses: H0: Pt/Ps ≤ R0 vs. H1: Pt/Ps > R0

		Ratios		Proportions			
Power*	Sample Size N	Non-Inferiority R0	Actual R1	Treatment Pt	Standard Ps	Nuisance Parameter P10	Alpha
0.8005	34	0.8	1	0.8	0.8	0.05	0.05

* Power was computed using the normal approximation method.

The calculated sample size of 34 matches the results of Nam and Blackwelder (2002).