Chapter 218

Confidence Intervals for the Odds Ratio of Two Proportions

Introduction

This routine calculates the group sample sizes necessary to achieve a specified interval width of the odds ratio of two independent proportions.

Caution: These procedures assume that the proportions obtained from future samples will be the same as the proportions that are specified. If the sample proportions are different from those specified when running these procedures, the interval width may be narrower or wider than specified.

Technical Details

A background of the comparison of two proportions is given, followed by details of the confidence interval methods available in this procedure.

Comparing Two Proportions

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability (or risk) of obtaining the event of interest in population 1 (the treatment group) is p_1 and in population 2 (the control group) is p_2. The corresponding failure proportions are given by $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$.

The assumption is made that the responses from each group follow a binomial distribution. This means that the event probability p_i is the same for all subjects within a population and that the responses from one subject to the next are independent of one another.

Random samples of *m* and *n* individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows

	Success	**Failure**	**Total**
Population 1	*a*	*c*	*m*
Population 2	*b*	*d*	*n*
Totals	*s*	*f*	*N*

The following alternative notation is sometimes used:

	Success	Failure	Total
Population 1	x_{11}	x_{12}	n_1
Population 2	x_{21}	x_{22}	n_2
Totals	m_1	m_2	N

The binomial proportions p_1 and p_2 are estimated from these data using the formulae

$$\hat{p}_1 = \frac{a}{m} = \frac{x_{11}}{n_1} \text{ and } \hat{p}_2 = \frac{b}{n} = \frac{x_{21}}{n_2}$$

When analyzing studies such as these, you usually want to compare the two binomial probabilities p_1 and p_2. The most direct methods of comparing these quantities are to calculate their difference or their ratio. If the binomial probability is expressed in terms of odds rather than probability, another measure is the odds ratio. Mathematically, these comparison parameters are

<u>**Parameter**</u>	<u>**Computation**</u>
Difference	$\delta = p_1 - p_2$
Risk Ratio	$\phi = p_1/p_2$
Odds Ratio	$\psi = \frac{p_1/q_1}{p_2/q_2} = \frac{p_1 q_2}{p_2 q_1}$

The choice of which of these measures is used might at first seem arbitrary, but it is important. Not only is their interpretation different, but, for small sample sizes, the coverage probabilities may be different. This procedure focuses on the odds ratio. Other procedures are available in **PASS** for computing confidence intervals for the difference and ratio.

Odds Ratio

Chances are usually communicated as long-term proportions or probabilities. In betting, chances are often given as odds. For example, the odds of a horse winning a race might be set at 10-to-1 or 3-to-2. How do you translate from odds to probability? An odds of 3-to-2 means that the event will occur three out of five times. That is, an odds of 3-to-2 (1.5) translates to a probability of winning of 0.60.

The odds of an event are calculated by dividing the event risk by the non-event risk. Thus, in our case of two populations, the odds are

$$o_1 = \frac{p_1}{1 - p_1} \text{ and } o_2 = \frac{p_2}{1 - p_2}$$

For example, if p_1 is 0.60, the odds are 0.60/0.4 = 1.5. Rather than represent the odds as a decimal amount, it is re-scaled into whole numbers. Thus, instead of saying the odds are 1.5-to-1, we say they are 3-to-2.

Another way to compare proportions is to compute the ratio of their odds. The odds ratio of two events is

$$\psi = \frac{o_1}{o_2}$$

$$= \frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}}$$

Although the odds ratio is more complicated to interpret than the risk ratio, it is often the parameter of choice. Reasons for this include the fact that the odds ratio can be accurately estimated from case-control studies, while the risk ratio cannot. Also, the odds ratio is the basis of logistic regression (used to study the influence of risk factors). Furthermore, the odds ratio is the natural parameter in the conditional likelihood of the two-group, binomial-response design. Finally, when the baseline event-rates are rare, the odds ratio provides a close approximation to the risk ratio since, in this case, $1 - p_1 \approx 1 - p_2$, so that

$$\psi = \frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}} \approx \frac{p_1}{p_2} = \phi$$

Confidence Intervals for the Odds Ratio

Many methods have been devised for computing confidence intervals for the odds ratio of two proportions

$$\psi = \frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}}$$

Eight of these methods are available in the Confidence Intervals for Two Proportions [Odds Ratios] procedure. The eight confidence interval methods are

1. Exact (Conditional)
2. Score (Farrington and Manning)
3. Score (Miettinen and Nurminen)
4. Fleiss
5. Logarithm
6. Mantel-Haenszel
7. Simple
8. Simple + 1/2

Conditional Exact

The conditional exact confidence interval of the odds ratio is calculated using the noncentral hypergeometric distribution as given in Sahai and Khurshid (1995). That is, a $100(1-\alpha)\%$ confidence interval is found by searching for ψ_L and ψ_U such that

$$\frac{\sum_{k=x}^{k_2}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_L)^k}{\sum_{k=k_1}^{k_2}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_L)^k}=\frac{\alpha}{2}$$

and

$$\frac{\sum_{k=k_1}^{x}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_U)^k}{\sum_{k=k_1}^{k_2}\binom{n_1}{k}\binom{n_2}{m_1-k}(\psi_U)^k}=\frac{\alpha}{2}$$

where

$k_1=\max(0,m_1-n_1)$ and $k_2=\min(n_1,m_1)$

Farrington and Manning's Score

Farrington and Manning (1990) developed a test statistic similar to that of Miettinen and Nurminen but with the factor *N*/(*N*-1) removed.

The formula for computing this test statistic is

$$z_{FMO}=\frac{\frac{(\hat{p}_1-\tilde{p}_1)}{\tilde{p}_1\tilde{q}_1}-\frac{(\hat{p}_2-\tilde{p}_2)}{\tilde{p}_2\tilde{q}_2}}{\sqrt{\left(\frac{1}{n_1\tilde{p}_1\tilde{q}_1}+\frac{1}{n_2\tilde{p}_2\tilde{q}_2}\right)}}$$

where the estimates $\tilde{p}_1$ and $\tilde{p}_2$ are computed as in the corresponding test of Miettinen and Nurminen (1985) as

$$\tilde{p}_1=\frac{\tilde{p}_2\psi_0}{1+\tilde{p}_2(\psi_0-1)}$$

$$\tilde{p}_2=\frac{-B+\sqrt{B^2-4AC}}{2A}$$

$$A=n_2(\psi_0-1)$$

$$B=n_1\psi_0+n_2-m_1(\psi_0-1)$$

$$C=-m_1$$

Farrington and Manning (1990) proposed inverting their score test to find the confidence interval. The lower limit is found by solving

$$z_{FMO} = |z_{\alpha/2}|$$

and the upper limit is the solution of

$$z_{FMO} = -|z_{\alpha/2}|$$

Miettinen and Nurminen's Score

Miettinen and Nurminen (1985) proposed a test statistic for testing whether the odds ratio is equal to a specified value ψ_0. Because the approach they used with the difference and ratio does not easily extend to the odds ratio, they used a score statistic approach for the odds ratio. The regular MLE's are $\hat{p}_1$ and $\hat{p}_2$. The constrained MLE's are $\tilde{p}_1$ and $\tilde{p}_2$, These estimates are constrained so that $\tilde{\psi} = \psi_0$. A correction factor of N/(N-1) is applied to make the variance estimate less biased. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{MNO} = \frac{\frac{(\hat{p}_1 - \tilde{p}_1)}{\tilde{p}_1\tilde{q}_1} - \frac{(\hat{p}_2 - \tilde{p}_2)}{\tilde{p}_2\tilde{q}_2}}{\sqrt{\left(\frac{1}{n_1\tilde{p}_1\tilde{q}_1} + \frac{1}{n_2\tilde{p}_2\tilde{q}_2}\right)\left(\frac{N}{N-1}\right)}}$$

where

$$\tilde{p}_1 = \frac{\tilde{p}_2\psi_0}{1 + \tilde{p}_2(\psi_0 - 1)}$$

$$\tilde{p}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

$$A = n_2(\psi_0 - 1)$$

$$B = n_1\psi_0 + n_2 - m_1(\psi_0 - 1)$$

$$C = -m_1$$

Miettinen and Nurminen (1985) proposed inverting their score test to find the confidence interval. The lower limit is found by solving

$$z_{MNO} = |z_{\alpha/2}|$$

and the upper limit is the solution of

$$z_{MNO} = -|z_{\alpha/2}|$$

Iterated Method of Fleiss

Fleiss (1981) presents an improve confidence interval for the odds ratio. This method forms the confidence interval as all those values of the odds ratio which would not be rejected by a chi-square hypothesis test. Fleiss gives the following details about how to construct this confidence interval. To compute the lower limit, do the following.

1. For a trial value of ψ, compute the quantities *X, Y, W, F, U,* and *V* using the formulas

$$X = \psi(m+s) + (n-s)$$

$$Y = \sqrt{X^2 - 4ms\psi(\psi - 1)}$$

$$A = \frac{X - Y}{2(\psi - 1)}$$

$$B = s - A$$

$$C = m - A$$

$$D = f - m + A$$

$$W = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}$$

$$F = \left(a - A - \frac{1}{2}\right)^2 W - z_{\alpha/2}^2$$

$$T = \frac{1}{2(\psi - 1)^2}\left(Y - n_{..} - \frac{\psi - 1}{Y}[X(m+s) - 2ms(2\psi - 1)]\right)$$

$$U = \frac{1}{B^2} + \frac{1}{C^2} - \frac{1}{A^2} - \frac{1}{D^2}$$

$$V = T\left[\left(a - A - \frac{1}{2}\right)^2 U - 2W\left(a - A - \frac{1}{2}\right)\right]$$

Finally, use the updating equation below to calculate a new value for the odds ratio using the updating equation

$$\psi^{(k+1)} = \psi^{(k)} - \frac{F}{V}$$

2. Continue iterating until the value of *F* is arbitrarily close to zero.

The upper limit is found by substituting $+\frac{1}{2}$ for $-\frac{1}{2}$ in the formulas for *F* and *V*.

Confidence limits for the *relative risk* can be calculated using the expected counts *A, B, C,* and *D* from the last iteration of the above procedure. The lower limit of the relative risk

$$\phi_{lower} = \frac{A_{lower} n}{B_{lower} m}$$

$$\phi_{upper} = \frac{A_{upper} n}{B_{upper} m}$$

Mantel-Haenszel

The common estimate of the logarithm of the odds ratio is used to create this estimator. That is

$$\ln(\hat{\psi}) = \ln\left(\frac{ad}{bc}\right)$$

The standard error of this estimator is estimated using the Robins, Breslow, Greenland (1986) estimator which performs well in most situations. The standard error is given by

$$se\left(\ln(\hat{\psi})\right) = \sqrt{\frac{A}{2C} + \frac{AD + BC}{2CD} + \frac{B}{2D}}$$

where

$$A = \frac{a + d}{N}$$

$$B = \frac{b + c}{N}$$

$$C = \frac{ad}{N}$$

$$D = \frac{bc}{N}$$

The confidence limits are calculated as

$$\hat{\psi}_{lower} = \exp\left(\ln(\hat{\psi}) - z_{1-\alpha/2} se\left(\ln(\hat{\psi})\right)\right)$$

$$\hat{\psi}_{upper} = \exp\left(\ln(\hat{\psi}) + z_{1-\alpha/2} se\left(\ln(\hat{\psi})\right)\right)$$

Simple, Simple + ½, and Logarithm

The simple estimate of the odds ratio uses the formula

$$\hat{\psi} = \frac{\hat{p}_1\hat{q}_2}{\hat{p}_2\hat{q}_1}$$

$$= \frac{ad}{bc}$$

The standard error of this estimator is estimated by

$$se(\hat{\psi}) = \hat{\psi}\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

Problems occur if any one of the quantities *a*, *b*, *c*, or *d* are zero. To correct this problem, many authors recommend adding one-half to each cell count so that a zero cannot occur. Now, the formulas become

$$\hat{\psi}' = \frac{(a+0.5)(d+0.5)}{(b+0.5)(c+0.5)}$$

and

$$se(\hat{\psi}') = \hat{\psi}'\sqrt{\frac{1}{a+0.5}+\frac{1}{b+0.5}+\frac{1}{c+0.5}+\frac{1}{d+0.5}}$$

The distribution of these direct estimates of the odds ratio do not converge to normality as fast as does their logarithm, so the logarithm of the odds ratio is used to form confidence intervals. The formula for the standard error of the log odds ratio is

$$L' = \ln(\hat{\psi}')$$

and

$$se(L') = \sqrt{\frac{1}{a+0.5}+\frac{1}{b+0.5}+\frac{1}{c+0.5}+\frac{1}{d+0.5}}$$

A $100(1-\alpha)\%$ confidence interval for the log odds ratio is formed using the standard normal distribution as follows

$$\hat{\psi}_{lower} = \exp\left(L' - z_{1-\alpha/2}se(L')\right)$$

$$\hat{\psi}_{upper} = \exp\left(L' + z_{1-\alpha/2}se(L')\right)$$

See Fleiss et al (2003) for more details.

Confidence Level

The confidence level, $1 - \alpha$, has the following interpretation. If thousands of random samples of size n_1 and n_2 are drawn from populations 1 and 2, respectively, and a confidence interval for the true difference/ratio/odds ratio of proportions is calculated for each pair of samples, the proportion of those intervals that will include the true difference/ratio/odds ratio of proportions is $1 - \alpha$.

Example 1 – Calculating Sample Size

Suppose a study is planned in which the researcher wishes to construct a two-sided 95% confidence interval for the odds ratio such that the width of the interval is no wider than 0.5. The confidence interval method to be used is the Logarithm method. The confidence level is set at 0.95, but 0.99 is included for comparative purposes. The odds ratio estimate to be used is 1.5, and the estimate for proportion 2 is 0.4. Instead of examining only the interval width of 0.5, a series of widths from 0.1 to 1.0 will also be considered.

The goal is to determine the necessary sample size.

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**
Confidence Interval Formula.......................... **Logarithm**
Interval Type .... **Two-Sided**
Confidence Level (1 - Alpha) **0.95 0.99**
Group Allocation .... **Equal (N1 = N2)**
Confidence Interval Width (Two-Sided) .... **0.1 to 1.0 by 0.1**
Input Type... **Odds Ratios**
O1/O2 (Odds Ratio)...................................... **1.5**
P2 (Proportion Group 2)................................ **0.4**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Confidence Interval Method: Logarithm
Interval Type: Two-Sided

Confidence Level	Sample Size N1	N2	N	Confidence Interval Width Target	Actual	Sample Proportions P1	P2	Odds Ratio O1/O2	Confidence Interval Limits Lower	Upper
0.95	28244	28244	56488	0.1	0.100	0.5	0.4	1.5	1.45	1.55
0.95	7068	7068	14136	0.2	0.200	0.5	0.4	1.5	1.40	1.60
0.95	3146	3146	6292	0.3	0.300	0.5	0.4	1.5	1.36	1.66
0.95	1774	1774	3548	0.4	0.400	0.5	0.4	1.5	1.31	1.71
0.95	1138	1138	2276	0.5	0.500	0.5	0.4	1.5	1.27	1.77
0.95	793	793	1586	0.6	0.600	0.5	0.4	1.5	1.23	1.83
0.95	585	585	1170	0.7	0.700	0.5	0.4	1.5	1.19	1.89
0.95	450	450	900	0.8	0.800	0.5	0.4	1.5	1.15	1.95
0.95	358	358	716	0.9	0.899	0.5	0.4	1.5	1.11	2.01
0.95	291	291	582	1.0	1.000	0.5	0.4	1.5	1.08	2.08

0.99	48783	48783	97566	0.1	0.100	0.5	0.4	1.5	1.45	1.55
0.99	12208	12208	24416	0.2	0.200	0.5	0.4	1.5	1.40	1.60
0.99	5435	5435	10870	0.3	0.300	0.5	0.4	1.5	1.36	1.66
0.99	3065	3065	6130	0.4	0.400	0.5	0.4	1.5	1.31	1.71
0.99	1967	1967	3934	0.5	0.500	0.5	0.4	1.5	1.27	1.77
0.99	1371	1371	2742	0.6	0.600	0.5	0.4	1.5	1.23	1.83
0.99	1012	1012	2024	0.7	0.700	0.5	0.4	1.5	1.19	1.89
0.99	778	778	1556	0.8	0.800	0.5	0.4	1.5	1.15	1.95
0.99	618	618	1236	0.9	0.900	0.5	0.4	1.5	1.12	2.02
0.99	504	504	1008	1.0	0.999	0.5	0.4	1.5	1.08	2.08

Confidence Level	The proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the true odds ratio of population proportions.
N1 and N2	The number of items sampled from each population.
N	The total sample size. N = N1 + N2.
Confidence Interval Width	The distance from the lower limit to the upper limit.
Target Width	The value of the width that is entered into the procedure.
Actual Width	The value of the width that is obtained from the procedure.
P1 and P2	The assumed sample proportions for sample size calculations.
O1/O2	The sample odds ratio at which sample size calculations are made.
Confidence Interval Limits	The lower and upper limits of the confidence interval for the true odds ratio of proportions (Population Odds 1 / Population Odds 2).

Summary Statements

A parallel two-group design will be used to obtain a two-sided 95% confidence interval for the odds ratio of two proportions (O1 / O2). The Group 1 sample proportion is assumed to be 0.5 and the Group 2 sample proportion is assumed to be 0.4, giving an odds ratio of 1.5. The Logarithm method will be used to compute the confidence interval limits. To produce a confidence interval width of 0.1, the number of subjects needed will be 28244 in Group 1 and 28244 in Group 2. Group sample sizes of 28244 and 28244 produce a two-sided 95% confidence interval for the population odds ratio with a width that is equal to 0.1 when the estimated sample proportion 1 is 0.5, the estimated sample proportion 2 is 0.4, and the sample odds ratio is 1.5.

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%	28244	28244	56488	35305	35305	70610	7061	7061	14122
20%	7068	7068	14136	8835	8835	17670	1767	1767	3534
20%	3146	3146	6292	3933	3933	7866	787	787	1574
20%	1774	1774	3548	2218	2218	4436	444	444	888
20%	1138	1138	2276	1423	1423	2846	285	285	570
20%	793	793	1586	992	992	1984	199	199	398
20%	585	585	1170	732	732	1464	147	147	294
20%	450	450	900	563	563	1126	113	113	226
20%	358	358	716	448	448	896	90	90	180
20%	291	291	582	364	364	728	73	73	146
20%	48783	48783	97566	60979	60979	121958	12196	12196	24392
20%	12208	12208	24416	15260	15260	30520	3052	3052	6104
20%	5435	5435	10870	6794	6794	13588	1359	1359	2718
20%	3065	3065	6130	3832	3832	7664	767	767	1534
20%	1967	1967	3934	2459	2459	4918	492	492	984
20%	1371	1371	2742	1714	1714	3428	343	343	686
20%	1012	1012	2024	1265	1265	2530	253	253	506
20%	778	778	1556	973	973	1946	195	195	390
20%	618	618	1236	773	773	1546	155	155	310
20%	504	504	1008	630	630	1260	126	126	252

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 the confidence interval 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 confidence interval.
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, 35305 subjects should be enrolled in Group 1, and 35305 in Group 2, to obtain final group sample sizes of 28244 and 28244, respectively.

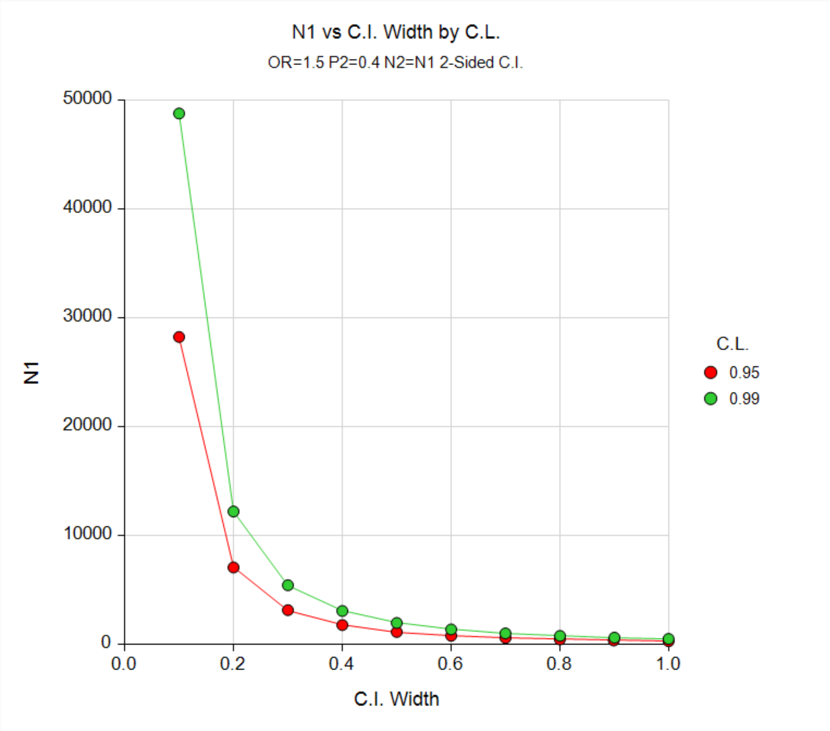
References

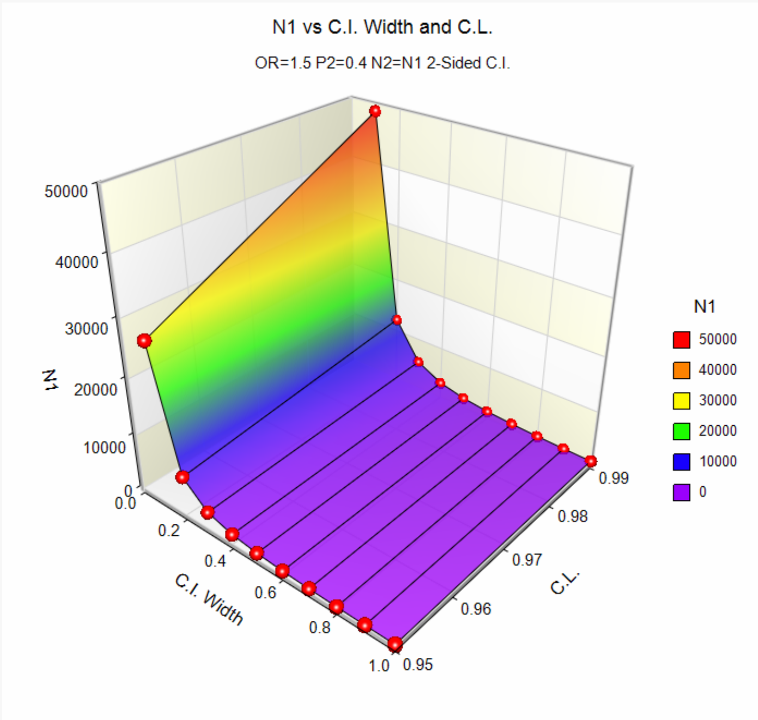
Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.

This report shows the calculated sample sizes for each of the scenarios.

Plots Section

Plots





These plots show the group sample size versus the confidence interval width for the two confidence levels.

Example 2 – Validation using Fleiss et al (2003)

Fleiss et al (2003) pages 117, 119 give an example of a calculation for a confidence interval for the odds ratio when the confidence level is 95%, the sample odds ratio is 2.25 and the sample proportion 2 is 0.1, the sample size for group 2 is 150, and the interval width is 4.387 for the Logarithm method, and 4.980 for the Fleiss method. The necessary sample size for group 1 in each case is 50.

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)** 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**
Confidence Interval Formula.......................... **Varies [Logarithm, Fleiss]**
Interval Type .... **Two-Sided**
Confidence Level (1 - Alpha) **0.95**
Group Allocation .... **Enter N2, solve for N1**
N2 .... **150**
Confidence Interval Width (Two-Sided) .... **Varies [4.387, 4.980]**
Input Type... **Odds Ratios**
O1/O2 (Odds Ratio)...................................... **2.25**
P2 (Proportion Group 2)................................ **0.1**

Output

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

Logarithm

Numeric Results

Solve For: Sample Size
Confidence Interval Method: Logarithm
Interval Type: Two-Sided

Confidence Level	Sample Size N1	Sample Size N2	Sample Size N	Confidence Interval Width Target	Confidence Interval Width Actual	Sample Proportions P1	Sample Proportions P2	Odds Ratio O1/O2	Confidence Interval Limits Lower	Confidence Interval Limits Upper
0.95	50	150	200	4.387	4.387	0.2	0.1	2.25	0.96	5.35

PASS also calculates the necessary sample size for Group 1 to be 50.

Fleiss

Numeric Results

Solve For: Sample Size
Confidence Interval Method: Fleiss
Interval Type: Two-Sided

Confidence Level	Sample Size N1	Sample Size N2	Sample Size N	Confidence Interval Width Target	Confidence Interval Width Actual	Sample Proportions P1	Sample Proportions P2	Odds Ratio O1/O2	Confidence Interval Limits Lower	Confidence Interval Limits Upper
0.95	50	150	200	4.98	4.98	0.2	0.1	2.25	0.86	5.84

PASS also calculates the necessary sample size for Group 1 to be 50.