Chapter 181

Equivalence Tests for the Generalized Odds Ratio for Ordinal Data in a 2x2 Cross-Over Design

Introduction

Senn (2002) defines a *cross-over* design as one in which each subject receives all treatments and the objective is to study differences among the treatments. The name *cross-over* comes from the most common case in which there are only two treatments. In this case, each subject *crosses over* from one treatment to the other. It is assumed that there is a *washout* period between treatments during which the response returns back to its baseline value. If this does not occur, there is said to be a *carry-over* effect.

A 2×2 cross-over design contains to two *sequences* (treatment orderings) and two time periods (occasions). One sequence receives treatment A followed by treatment B. The other sequence receives B and then A. The design includes a washout period between responses to make certain that the effects of the first drug do not carry over to the second. Thus, the groups in this design are defined by the sequence in which the drugs are administered, not by the treatments they receive. Indeed, higher-order cross-over designs have been used in which the same treatment is used at both occasions.

Cross-over designs are employed because, if the no-carryover assumption is met, treatment differences are measured within a subject rather than between subjects—making a more precise measurement. Examples of the situations that might use a cross-over design are the comparison of anti-inflammatory drugs in arthritis and the comparison of hypotensive agents in essential hypertension. In both cases, symptoms are expected to return to their usual baseline level shortly after the treatment is stopped.

The sample size calculations in the procedure are based on the formulas presented in Lui (2016).

Advantages of Cross-Over Designs

A comparison of treatments on the same subject is expected to be more precise. The increased precision often translates into a smaller sample size. Also, patient enrollment into the study may be easier because each patient will receive both treatments. Finally, it is often more difficult to obtain a subject than to obtain a measurement.

Disadvantages of Cross-Over Designs

The statistical analysis of a cross-over experiment is more complex than a parallel-group experiment and requires additional assumptions. It may be difficult to separate the treatment effect from the period effect, the carry-over effect of the previous treatment, and the interaction between period and treatment.

The design cannot be used when the treatment (or the measurement of the response) alters the subject permanently. Hence, it should not be used to compare treatments that are intended to provide a cure.

Because subjects must be measured at least twice, it is often more difficult to keep patients enrolled in the study. It is arguably simpler to measure a subject once than to obtain their measurement twice. This is particularly true when the measurement process is painful, uncomfortable, embarrassing, or time consuming.

Technical Details

The 2×2 crossover design may be described as follows. Randomly assign the subjects to one of two sequence groups so that there are n_1 subjects in sequence one and n_2 subjects in sequence two. In order to achieve design balance, the sample sizes n_1 and n_2 are assumed to be equal so that $n_1 = n_2 = n = N/2$.

Sequence one is given the control (A) followed by the treatment (B). Sequence two is given the treatment (B) followed by the control (A).

Cross-Over Design

The discussions that follow summarize the results in Lui (2016) on pages 57-70. Consider a 2×2 cross-over design and let $Y_{ij}^{(g)}$ represent the response category for the jth subject, $j = 1, \ldots, n_g$, in the ith period ($i = 1, 2$), in sequence g ($g = 1, 2$) on an ordinal scale with L possible categories, $C_1 < C_2 < C_3 < \cdots < C_L$. Assume that subjects in sequence 1 are given the control or standard in period 1 and then the experimental treatment in period 2. Assume that subjects in sequence 2 are given the experimental treatment in period 1 and then the control or standard in period 2. If we define η as the relative effect of the treatment to the control, then $\eta > 0$ indicates that the response category, C_k, of a subject receiving the treatment tends to be greater than the response category of a subject receiving the control or standard. Similarly, $\eta < 0$ indicates that the response category, C_k, of a subject receiving the treatment tends to be less than the response category of a subject receiving the control or standard.

For a randomly selected subject from sequence g ($g = 1, 2$), the probability that the measured response in period 1, $Y_{1j}^{(g)}$, is less than the measured response in period 2, $Y_{2j}^{(g)}$, is

$$\Pi_C^{(g)} = P\left(Y_{1j}^{(g)} < Y_{2j}^{(g)}\right) = \sum_{r=1}^{L-1} \sum_{s=r+1}^{L} \pi_{rs}^{(g)}$$

where

$$\pi_{rs}^{(g)} = P\left(Y_{1j}^{(g)} = C_r, Y_{2j}^{(g)} = C_s\right) \text{ with } r = 1, 2, \ldots, L \text{ and } s = 1, 2, \ldots, L.$$

Similarly, the probability that the measured response in period 1, $Y_{1j}^{(g)}$, is greater than the measured response in period 2, $Y_{2j}^{(g)}$, is

$$\Pi_D^{(g)} = P\left(Y_{1j}^{(g)} > Y_{2j}^{(g)}\right) = \sum_{r=2}^{L} \sum_{s=1}^{r-1} \pi_{rs}^{(g)}.$$

The generalized odds ratio, $GOR^{(g)}$, of subject responses between periods 1 and 2 for a randomly-selected subject from group g is defined as

$$GOR^{(g)} = \frac{\Pi_C^{(g)}}{\Pi_D^{(g)}}.$$

The generalized odds ratio, GOR, for the treatment versus the control is then

$$GOR = e^{\eta} = \sqrt{\frac{GOR^{(1)}}{GOR^{(2)}}}.$$

Equivalence Test Statistics

The null and alternative hypotheses for an equivalence test are

$$H_0: GOR \leq GOR_{0L} \text{ or } GOR \geq GOR_{0U} \quad \text{vs} \quad H_A: GOR_{0L} < GOR < GOR_{0U}$$

where GOR_{0L} and GOR_{0U} are the lower and upper equivalence bounds, respectively (i.e. the smallest and largest generalized odds ratios for which the treatment and control will be considered equivalent).

The power and sample size calculations are based on the two one-sided test (TOST) statistics

$$Z_L = \frac{\log(\widehat{GOR}) - \log(GOR_{0L})}{\sqrt{\widehat{Var}\left(\log(\widehat{GOR})\right)}} \quad \text{and} \quad Z_U = \frac{\log(\widehat{GOR}) - \log(GOR_{0U})}{\sqrt{\widehat{Var}\left(\log(\widehat{GOR})\right)}}$$

which are each asymptotically distributed as standard normal under the null hypothesis, with

$$\widehat{Var}\left(\log(\widehat{GOR})\right) = \frac{1}{4}\sum_{g=1}^{2}\frac{\widehat{\Pi}_C^{(g)} + \widehat{\Pi}_D^{(g)}}{n_g\widehat{\Pi}_C^{(g)}\widehat{\Pi}_D^{(g)}}.$$

The null hypothesis is rejected in favor of the alternative at level α using the TOST procedure if

$$Z_L > Z_{1-\alpha} \quad \text{and} \quad Z_U < Z_{\alpha}$$

where $Z_{1-\alpha}$ is the upper $1 - \alpha$ percentile and Z_{α} is the lower α percentile of the standard normal distribution.

Equivalence Power Calculation

If $\widehat{GOR}$ is the estimate of the generalized odds ratio, then $\hat{\eta} = \log(\widehat{GOR})$ has asymptotic variance

$$Var\left(\log(\widehat{GOR})\right) = \frac{V\left(\log(\widehat{GOR})\right)}{n},$$

where

$$V\left(\log(\widehat{GOR})\right) = \frac{1}{4}\sum_{g=1}^{2}\frac{\Pi_C^{(g)} + \Pi_D^{(g)}}{\Pi_C^{(g)}\Pi_D^{(g)}}.$$

Also define the standard deviation of log(generalized odds ratio) as

$$SD = \sqrt{V\left(\log(\widehat{GOR})\right)}$$

On page 68 of Lui (2016), the power for an equivalence test of $H_0: GOR \leq GOR_{0L}$ or $GOR \geq GOR_{0U}$ versus $H_A: GOR_{0L} < GOR < GOR_{0U}$ is given as

$$\Phi\left(\frac{\log(GOR_{0U}) - \log(GOR_1)}{\frac{SD}{\sqrt{n}}} - Z_{1-\alpha}\right) - \Phi\left(\frac{\log(GOR_{0L}) - \log(GOR_1)}{\frac{SD}{\sqrt{n}}} + Z_{1-\alpha}\right)$$

where $\Phi()$ is the standard normal distribution function, GOR_1 is the actual value of the generalized odds ratio under the alternative hypothesis, and $Z_{1-\alpha}$ is the upper $1 - \alpha$ percentile of the standard normal distribution. The sample size is determined using a binary search of possible values for n.

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

Solve For

Solve For

This option specifies the parameter to be calculated from the values of the other parameters. Under most conditions, you would select either *Power* or *Sample Size*.

Select *Sample Size* when you want to determine the sample size needed to achieve a given power and alpha level.

Select *Power* when you want to calculate the power of an experiment that has already been run.

Select *Effect Size (GOR1)* when you want to calculate the minimum effect size that can be detected for a particular design.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal means when in fact the means are different.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected. In this procedure, a type-I error occurs when you reject the null hypothesis of equal means when in fact the means are equal.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

n (Sample Size per Sequence)

This is the sample size of each sequence or group (AB and BA) in the cross-over design. The individual sequence sample sizes are assumed to be equal such that the total sample size is equal to $N = 2n$.

You can enter a single value such as *50* or a list of values using the syntax *50 100 150 200 250* or *50 to 250 by 50*.

Effect Size – Equivalence Generalized Odds Ratios for Treatment/Control

GOR0.U (Upper Equivalence Generalized Odds Ratio)

Specify the upper equivalence bound for the generalized odds ratio. This value along with the lower equivalence generalized odds ratio (GOR0.L) is used to setup the hypothesis test. This value represents the largest generalized odds ratio for which the treatment and control will be considered equivalent.

You can enter a single value such as *2* or a series of values such as *1.5 1.75 2* or *1.5 to 2 by 0.25* in the range GOR0.U > 1 and GOR0.U > GOR1.

GOR0.L (Lower Equivalence Generalized Odds Ratio)

Specify the lower equivalence bound for the generalized odds ratio. This value along with the upper equivalence generalized odds ratio (GOR0.U) is used to setup the hypothesis test. This value represents the smallest generalized odds ratio for which the treatment and control will be considered equivalent.

For log-scale-symmetric bounds, enter *1/GOR0.U*. This is the default. You can also enter a single value such as *0.5* or a series of values such as *0.5 0.6 0.7* or *0.5 to 0.7 by 0.1* in the range 0 < GOR0.L < 1 and GOR0.L < GOR1. Note that if you enter values for GOR0.L other than "1/GOR0.U", they are used in pairs with the values of GOR0.U. Thus, the first values of GOR0.U and GOR0.L are used, then the second values of each are used, and so on.

Effect Size – Actual Generalized Odds Ratio for Treatment/Control

GOR1 (Actual Generalized Odds Ratio)

Specify the actual generalized odds ratio for treatment versus control at which power is calculated.

You can enter a single value such as *1* or a series of values such as *1 1.1 1.2* or *1 to 1.2 by 0.1* in the range GOR1 > 0 and GOR0.L < GOR1 < GOR0.U.

Effect Size – Standard Deviation of Log(Generalized Odds Ratio)

Standard Deviation Estimation Method

Choose how the standard deviation of the log generalized odds ratio (SD) will be estimated.

The options are

- **Enter SD Directly**

  Input log generalized odds ratio SD values directly. This option allows you to input any value for SD, regardless of how it was estimated.

- **Use Estimated Cumulative Proportions**

  Input cumulative proportions from a previous 2x2 cross-over study. These estimates are used only to calculate the standard deviation and are not necessarily related to the value used for GOR1.

Standard Deviation (SD)

Enter a value for the standard deviation of the log generalized odds ratio, SD.

Estimating SD using Previously-Estimated Discordant Cell Proportions

The standard deviation may be estimated using cumulative proportions from a previous study using the method of Lui (2016) on page 67, where

$$SD = \sqrt{(1/4) * \Sigma g[(\prod C(g) + \prod D(g)) / (\prod C(g) * \prod D(g))]}.$$

PASS will calculate the SD for you using this method if you set Estimation Method to "Use Estimated Cumulative Proportions" and enter cumulative proportions from a previous 2x2 cross-over study.

Cumulative Proportions

Enter the corresponding cumulative proportion from a previous 2x2 cross-over study.

The estimated proportions are defined as follows:

Sequence 1 = C → T

Sequence 2 = T → C

$\prod C(g)$ = Proportion of (Response from Period 1 < Response from Period 2) in Sequence g

$\prod D(g)$ = Proportion of (Response from Period 1 > Response from Period 2) in Sequence g

The standard deviation of the log generalized odds ratio is calculated by PASS as described in Lui (2016) on page 67 as

$$SD = \sqrt{(1/4) * \Sigma g[(\prod C(g) + \prod D(g)) / (\prod C(g) * \prod D(g))]}.$$

These estimates are used only to calculate the standard deviation of the log generalized odds ratio and are not necessarily related to the value used for GOR1.

Range: $0 < \prod C(g) < 1$, $0 < \prod D(g) < 1$, $\prod C(g) + \prod D(g) \leq 1$

Example 1 – Power Analysis

Suppose you want to consider the power of an equivalence test of the hypotheses $H_0: OR \leq 0.667$ or $OR \geq 1.5$ versus $H_A: 0.667 < OR < 1.5$ in a balanced cross-over design with ordinal data where the test is computed based on the generalized odds ratio for sequence sample sizes between 100 and 300. The equivalence bounds in this example are log-scale symmetric since $0.667 = 1/1.5$. Let's assume that the actual odds ratio is 1 and the estimated standard deviation of the log odds ratio is 2.5. The significance level is 0.05.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Generalized Odds Ratio for Ordinal Data in a 2x2 Cross-Over Design** procedure window by expanding **Proportions**, then **Cross-Over (2x2) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Generalized Odds Ratio for Ordinal Data in a 2x2 Cross-Over Design**. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Power**
Alpha..	**0.05**
n (Sample Size per Sequence).........................	**100 to 300 by 50**
GOR0.U (Upper Equiv. Gen. Odds Ratio)........	**1.5**
GOR0.L (Lower Equiv. Gen. Odds Ratio)	**1/GOR0.U**
GOR1 (Actual Gen. Odds Ratio)	**1**
Estimation Method...	**Enter SD Directly**
Standard Deviation (SD)..................................	**2.5**

Annotated Output

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

Numeric Results

Numeric Results for an Equivalence Test ———————————————————————————————————
H0: GOR ≤ GOR0.L or GOR ≥ GOR0.U vs. H1: GOR0.L < GOR < GOR0.U

Power	Sequence Sample Size n	Total Sample Size N	Lower Equiv. Gen. Odds Ratio GOR0.L	Upper Equiv. Gen. Odds Ratio GOR0.U	Actual Gen. Odds Ratio GOR1	Standard Deviation SD	Alpha
0.00000	100	200	0.667	1.500	1.000	2.500	0.050
0.26728	150	300	0.667	1.500	1.000	2.500	0.050
0.48353	200	400	0.667	1.500	1.000	2.500	0.050
0.64218	250	500	0.667	1.500	1.000	2.500	0.050
0.75569	300	600	0.667	1.500	1.000	2.500	0.050

References
Lui, Kung-Jong. 2016. Crossover Designs: Testing, Estimation, and Sample Size. John Wiley & Sons Ltd.
    Chichester, West Sussex, England.

Equivalence Tests for the Generalized Odds Ratio for Ordinal Data in a 2x2 Cross-Over Design

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.

n is the sample size in each sequence (or group).

N is the total combined sample size from both sequences.

GOR0.L is the lower equivalence generalized odds ratio used to specify the hypothesis test.

GOR0.U is the upper equivalence generalized odds ratio used to specify the hypothesis test.

GOR1 is the actual generalized odds ratio at which power is calculated.

SD is the user-entered standard deviation of log generalized odds ratio. This is estimated from a previous study.

Alpha is the probability of rejecting a true null hypothesis. It should be small.

Summary Statements ───

For a 2x2 cross-over design, a sample size of 100 in each sequence for a total of 200 achieves 0.000% power to detect a generalized odds ratio of 1.000 using an equivalence test with lower and upper equivalence bounds of 0.667 and 1.500, respectively, with a significance level of 0.050 when the standard deviation is 2.500.

Dropout-Inflated Sample Size ──

	— Sample Size —		Dropout-Inflated Enrollment — Sample Size —		Expected Number of — Dropouts —	
Dropout Rate	n	N	n'	N'	d	D
20%	100	200	125	250	25	50
20%	150	300	188	376	38	76
20%	200	400	250	500	50	100
20%	250	500	313	626	63	126
20%	300	600	375	750	75	150

Definitions

Dropout Rate (DR) is 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").

n and N are the evaluable group and total sample sizes, respectively, at which power is computed (as entered by the user). If n subjects from each group are evaluated out of the n' subjects that are enrolled in the study, the design will achieve the stated power. N = 2n.

n' and N' are the number of subjects that should be enrolled in the study in order to end up with n and 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., and Wang, H. (2008) pages 39-40.). N' = 2n'.

d and D are the expected number of group and total dropouts, respectively. d = n' - n and D = 2d.

Charts Section
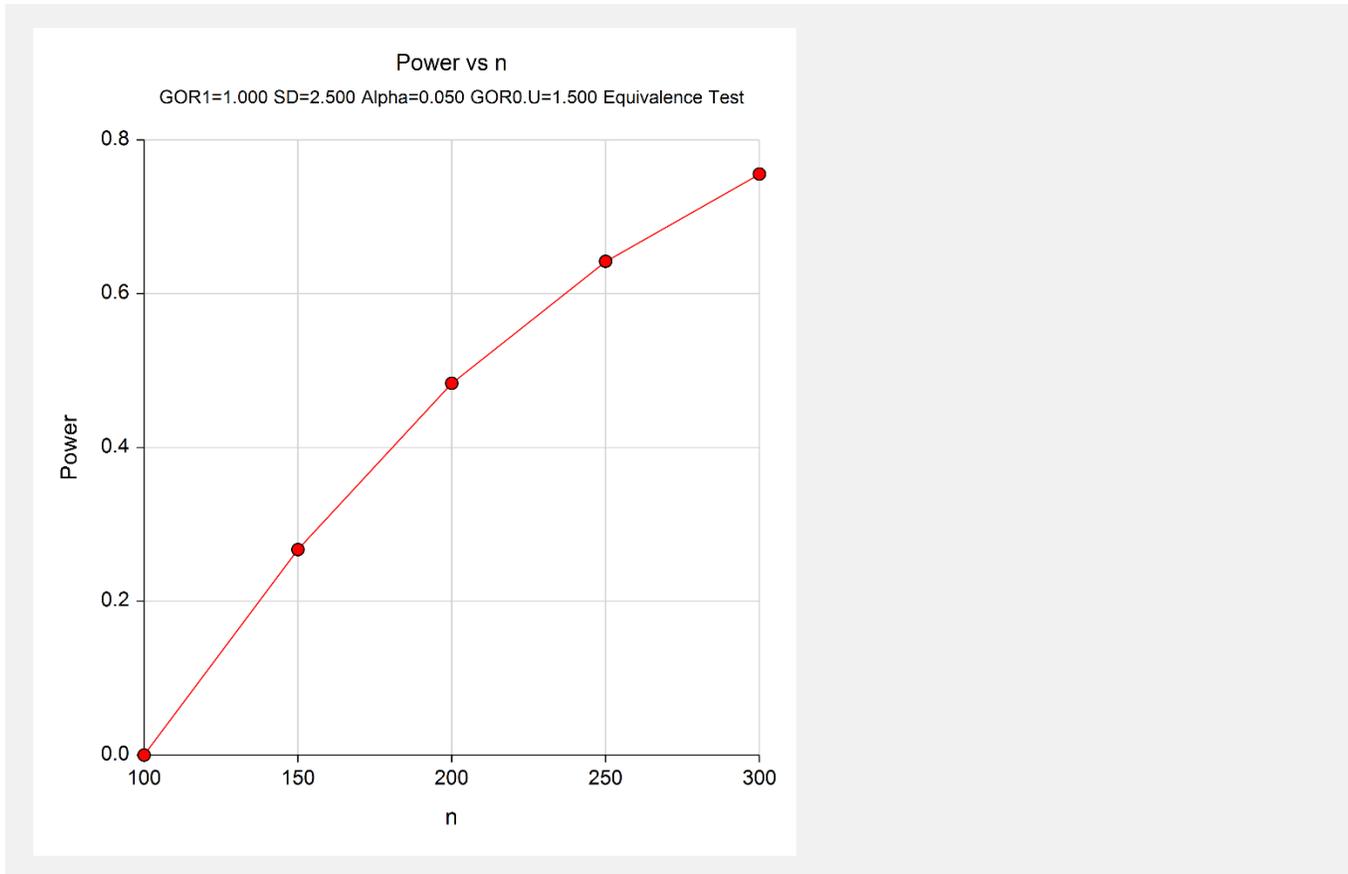
This report shows the values of each of the parameters, one scenario per row. This plot shows the relationship between sample size and power. We see that a sample size of greater than 300 per sequence is required for 80% power if the actual generalized odds ratio is 1.

Example 2 – Calculating Sample Size when Estimating the Standard Deviation from a Previous Study (Validation using Hand Calculations)

This example demonstrates how to calculate the sample size when estimating the standard deviation of the log generalized odds ratio from data in a previous study using the method in Lui (2016) on page 67. In this example we'll find the sample size required to detect an odds ratio of 1 with 80% power at a significance level of 0.05 in an equivalence test of the hypotheses $H_0: OR \leq 0.667$ or $OR \geq 1.5$ versus $H_A: 0.667 < OR < 1.5$. The SD is estimated from cumulative proportions from a previous study.

Suppose the cumulative proportions are

$$\Pi_C^{(1)} = 0.11$$

$$\Pi_D^{(1)} = 0.29$$

$$\Pi_C^{(2)} = 0.23$$

$$\Pi_D^{(2)} = 0.11$$

Using the method of Lui (2016) on page 67, SD is calculated as

$$SD = \sqrt{\frac{1}{4} \sum_{g=1}^{2} \frac{\Pi_C^{(g)} + \Pi_D^{(g)}}{\Pi_C^{(g)} \Pi_D^{(g)}}}$$

$$= \sqrt{\frac{1}{4} \left(\frac{0.11 + 0.29}{0.11(0.29)} + \frac{0.23 + 0.11}{0.23(0.11)} \right)}$$

$$= \mathbf{2.5484}$$

PASS will calculate this SD value for you automatically when you input the cumulative proportions.

Since there is no example given for this calculation in the book, we'll validate this procedure using hand calculations. The power for per-sequence sample sizes of 338 and 339 calculated by hand using the equation on Lui (2016) page 68 is

$$\text{Power} = \Phi \left(\frac{\log(GOR_{0U}) - \log(GOR_1)}{\frac{SD}{\sqrt{n}}} - Z_{1-\alpha} \right) - \Phi \left(\frac{\log(GOR_{0L}) - \log(GOR_1)}{\frac{SD}{\sqrt{n}}} + Z_{1-\alpha} \right)$$

$$\text{Power}_{(n=338)} = \Phi \left(\frac{\log(1.5) - \log(1)}{\frac{2.5484}{\sqrt{338}}} - 1.644854 \right) - \Phi \left(\frac{\log\left(\frac{1}{1.5}\right) - \log(1)}{\frac{2.5484}{\sqrt{338}}} + 1.644854 \right)$$

$$= 0.7995$$

$$\text{Power}_{(n=339)} = \Phi \left(\frac{\log(1.5) - \log(1)}{\frac{2.5484}{\sqrt{339}}} - 1.644854 \right) - \Phi \left(\frac{\log\left(\frac{1}{1.5}\right) - \log(1)}{\frac{2.5484}{\sqrt{339}}} + 1.644854 \right)$$

$$= 0.8011$$

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Equivalence Tests for the Generalized Odds Ratio for Ordinal Data in a 2x2 Cross-Over Design** procedure window by expanding **Proportions**, then **Cross-Over (2x2) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Generalized Odds Ratio for Ordinal Data in a 2x2 Cross-Over Design**. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option   **Value**

Design Tab

Solve For ....**Sample Size**

Power...**0.80**

Alpha..**0.05**

GOR0.U (Upper Equiv. Gen. Odds Ratio)........**1.5**

GOR0.L (Lower Equiv. Gen. Odds Ratio) **1/GOR0.U**

GOR1 (Actual Gen. Odds Ratio) **1**

Estimation Method...**Use Estimated Cumulative Proportions**

∏C(1)..**0.11**

∏D(1)..**0.29**

∏C(2)..**0.23**

∏D(2)..**0.11**

Output

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

Numeric Results

Numeric Results for an Equivalence Test —————————————————————————————————
H0: GOR ≤ GOR0.L or GOR ≥ GOR0.U vs. H1: GOR0.L < GOR < GOR0.U

Power	Sequence Sample Size n	Total Sample Size N	Lower Equiv. Gen. Odds Ratio GOR0.L	Upper Equiv. Gen. Odds Ratio GOR0.U	Actual Gen. Odds Ratio GOR1	Standard Deviation SD*	Alpha
0.80105	339	678	0.667	1.500	1.000	2.548	0.050

* SD Estimated using Previously-Estimated Cumulative Proportions:
  ∏C(1) = 0.11, ∏D(1) = 0.29, ∏C(2) = 0.23, ∏D(2) = 0.11

This report indicates that the estimated standard deviation using the method of Lui (2016) is 2.548 and the required sample size is 339 per sequence with 80.105% power. The cumulative proportions are also listed. These values for power, SD, and *n* computed by **PASS** match our hand calculations above.