Chapter 524

Equivalence Tests for the Ratio of Two Poisson Rates 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 75-88. Consider a 2×2 cross-over design and let $Y_{ij}^{(g)}$ represent the frequency of event occurrences for the j^{th} subject, j = 1, …, n_g, in the i^{th} period (i = 1, 2), in sequence g (g = 1, 2). Let $X_{ij}^{(g)}$ represent the treatment-received covariate for the j^{th} subject, j = 1, …, n_g, in the i^{th} period (i = 1, 2), in sequence g (g = 1, 2) such that $X_{ij}^{(g)} = 1$ for a subject receiving the experimental treatment and $X_{ij}^{(g)} = 0$ for a subject receiving the control or standard treatment. Let $Z_{ij}^{(g)}$ represent the period covariate for the j^{th} subject, j = 1, …, n_g, in the i^{th} period (i = 1, 2), in sequence g (g = 1, 2) such that $Z_{ij}^{(g)} = 1$ for period 2 and $Z_{ij}^{(g)} = 0$ for period 1. Finally, assume that the $Y_{ij}^{(g)}$ follow a Poisson distribution with mean

$$E\left(Y_{ij}^{(g)}\right) = \mu_j^{(g)} \exp\left(\eta X_{ij}^{(g)} + \gamma Z_{ij}^{(g)}\right)$$

where $\mu_j^{(g)}$ represents the random effect of the j^{th} subject assigned to sequence g and has overall mean μ, η is the relative effect of the treatment to the control, and γ is the relative effect of period 2 to period 1. For a fixed period, the ratio, R, of mean event rates for the treatment versus the control is

$$R = \frac{\lambda_T}{\lambda_C} = e^{\eta}.$$

Similarly, the ratio of mean event rates for period 2 versus period 1 is

$$R_p = \frac{\lambda_2}{\lambda_1} = e^{\gamma}.$$

Equivalence Test Statistics

The null and alternative hypotheses for an equivalence test are

$$H_0: R \le R_{0L} \text{ or } R \ge R_{0U} \quad \text{vs} \quad H_A: R_{0L} < R < R_{0U}$$

where R_{0L} and R_{0U} are the lower and upper equivalence bounds, respectively (i.e. the smallest and largest event rate ratios (λ_T/λ_C) 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

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

which are each asymptotically distributed as standard normal under the null hypothesis. The event rate ratio estimate, $\hat{R}$, and the variance estimate, $\widehat{Var}\left(\log(\hat{R})\right)$, are calculated as described in Lui (2016) on pages 77 through 79.

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 $\hat{R}$ is the estimate of the event rate ratio, then $\hat{\eta} = \log(\hat{R})$ has asymptotic variance

$$Var\left(\log(\hat{R})\right) = \frac{V(\mu, \eta, \gamma)}{n}$$

where

$$V(\mu, \eta, \gamma) = \frac{1}{4}\left(\frac{1}{\mu(1 + e^{\eta+\gamma})p_1(1-p_1)} + \frac{1}{\mu(e^{\eta} + e^{\gamma})p_2(1-p_2)}\right)$$

with

$$p_1 = \frac{e^{\eta+\gamma}}{1 + e^{\eta+\gamma}}$$

$$p_2 = \frac{e^{\gamma}}{e^{\eta} + e^{\gamma}}.$$

On page 88 of Lui (2016), the power for an equivalence test of $H_0: R \le R_{0L}$ or $R \ge R_{0U}$ versus $H_A: R_{0L} < R < R_{0U}$ is given as

$$\Phi\left(\frac{\sqrt{n}\left(\log(R_{0U}) - \log(R_1)\right)}{\sqrt{V(\mu, \eta, \gamma)}} - Z_{1-\alpha}\right) - \Phi\left(\frac{\sqrt{n}\left(\log(R_{0L}) - \log(R_1)\right)}{\sqrt{V(\mu, \eta, \gamma)}} + Z_{1-\alpha}\right)$$

where $\Phi()$ is the standard normal distribution function, R_1 is the actual value of the event rate ratio 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 (R1)* 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 Event Rate Ratios

R0.U (Upper Equivalence Ratio)

Specify the upper equivalence bound for the event rate ratio. This value along with the lower equivalence ratio (R0.L) is used to setup the hypothesis test. This value represents the largest ratio (λt/λc) 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 R0.U > 1 and R0.U > R1.

R0.L (Lower Equivalence Ratio)

Specify the lower equivalence bound for the event rate ratio. This value along with the upper equivalence ratio (R0.U) is used to setup the hypothesis test. This value represents the smallest ratio (λt/λc) for which the treatment and control will be considered equivalent. For log-scale-symmetric bounds, enter *1/R0.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 < R0.L < 1 and R0.L < R1. Note that if you enter values for R0.L other than "1/R0.U", they are used in pairs with the values of R0.U. Thus, the first values of R0.U and R0.L are used, then the second values of each are used, and so on.

Effect Size – Actual Event Rate Ratio

R1 (Actual Ratio)

Specify the actual event rate ratio 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 R1 > 0 and R0.L < R1 < R0.U.

Effect Size – Additional Parameters

Fixed Mean Rate (μ)

Enter a value for the fixed mean rate of underlying random effects for the two treatments. This is usually estimated from a previous study. 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 μ > 0.

Period Rate Ratio (Rp)

Enter a value for the rate ratio for period 2 vs. period 1 on a given subject, given a fixed treatment. This is usually estimated from a previous study. 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 Rp > 0.

Example 1 – Power Analysis

Suppose you want to consider the power of an equivalence test of the hypotheses $H_0: OR \leq 0.833$ or $OR \geq 1.2$ versus $H_A: 0.833 < OR < 1.2$ in a balanced cross-over design with a Poisson count endpoint where the test is based on the ratio for sequence sample sizes between 100 and 300. The equivalence bounds in this example are log-scale symmetric since 0.833 = 1/1.2. Let's assume that the actual ratio is 1.0, the fixed mean rate is estimated to be 1, and the period rate ratio is estimated to be between 0.9 and 1.1. 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 Ratio of Two Poisson Rates in a 2x2 Cross-Over Design** procedure window by expanding **Rates and Counts**, then **Cross-Over (2x2) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Ratio of Two Poisson Rates 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**
R0.U (Upper Equivalence Ratio)	**1.2**
R0.L (Lower Equivalence Ratio)	**1/R0.U**
R1 (Actual Ratio)	**1**
Fixed Mean Rate (μ)	**1**
Period Rate Ratio (Rp)	**0.9 1.0 1.1**

Annotated Output

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

Numeric Results

Numeric Results for an Equivalence Test
H0: R ≤ R0.L or R ≥ R0.U vs. H1: R0.L < R < R0.U

Power	Sequence Sample Size n	Total Sample Size N	Lower Equiv. Ratio R0.L	Upper Equiv. Ratio R0.U	Actual Ratio R1	Fixed Mean Rate μ	Period Rate Ratio Rp	Alpha
0.10322	100	200	0.833	1.200	1.000	1.000	0.900	0.050
0.14156	100	200	0.833	1.200	1.000	1.000	1.000	0.050
0.17512	100	200	0.833	1.200	1.000	1.000	1.100	0.050
0.40289	150	300	0.833	1.200	1.000	1.000	0.900	0.050
0.44355	150	300	0.833	1.200	1.000	1.000	1.000	0.050
0.47826	150	300	0.833	1.200	1.000	1.000	1.100	0.050
0.61285	200	400	0.833	1.200	1.000	1.000	0.900	0.050
0.64947	200	400	0.833	1.200	1.000	1.000	1.000	0.050
0.67989	200	400	0.833	1.200	1.000	1.000	1.100	0.050
0.75436	250	500	0.833	1.200	1.000	1.000	0.900	0.050
0.78425	250	500	0.833	1.200	1.000	1.000	1.000	0.050
0.80836	250	500	0.833	1.200	1.000	1.000	1.100	0.050
0.84694	300	600	0.833	1.200	1.000	1.000	0.900	0.050
0.86973	300	600	0.833	1.200	1.000	1.000	1.000	0.050
0.88757	300	600	0.833	1.200	1.000	1.000	1.100	0.050

Equivalence Tests for the Ratio of Two Poisson Rates in a 2x2 Cross-Over Design

References
Lui, Kung-Jong. 2016. Crossover Designs: Testing, Estimation, and Sample Size. John Wiley & Sons Ltd. Chichester, West Sussex, England.
Lui, Kung-Jong. 2013. Sample size determination for testing equality in Poisson frequency data under an AB/BA crossover trial. Pharmaceutical Statistics. Volume 12, pages 74-81.

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 sample size from both sequences. The sample is divided equally among sequences.
R0.L is the lower equivalence ratio used to specify the hypothesis test.
R0.U is the upper equivalence ratio used to specify the hypothesis test.
R1 is the actual event rate ratio (λt/λc) at which power is calculated.
μ is the fixed mean rate of underlying random effects for the two treatments.
Rp is the rate ratio for period 2 vs. period 1 on a given subject, given a fixed treatment.
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 10.322% power to detect an event rate ratio of 1.000 using an equivalence test with lower and upper equivalence bounds of 0.833 and 1.200, respectively, with a significance level of 0.050 when the fixed mean rate of underlying random effects for the two treatments is 1.000 and the rate ratio for period 2 vs. period 1 on a given patient, given a fixed treatment, is 0.900.

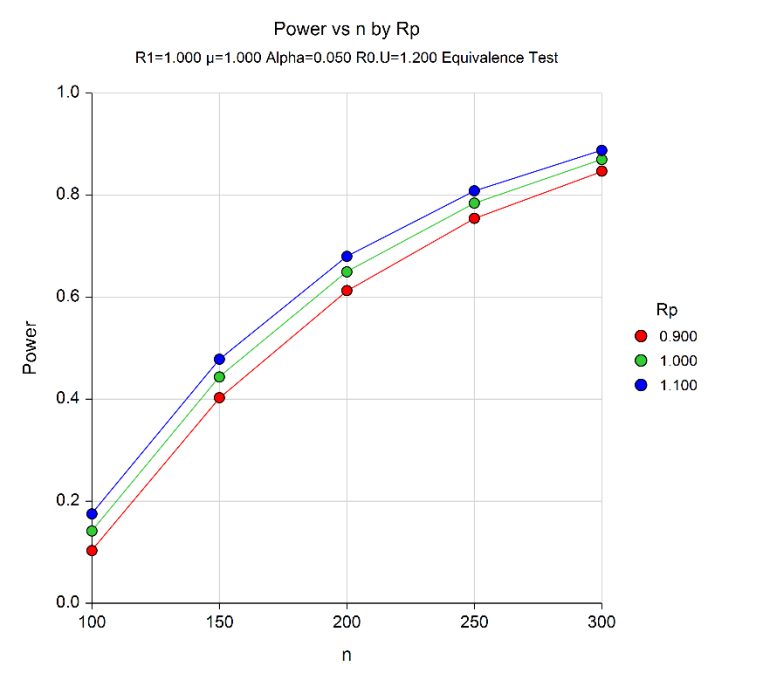
Dropout-Inflated Sample Size

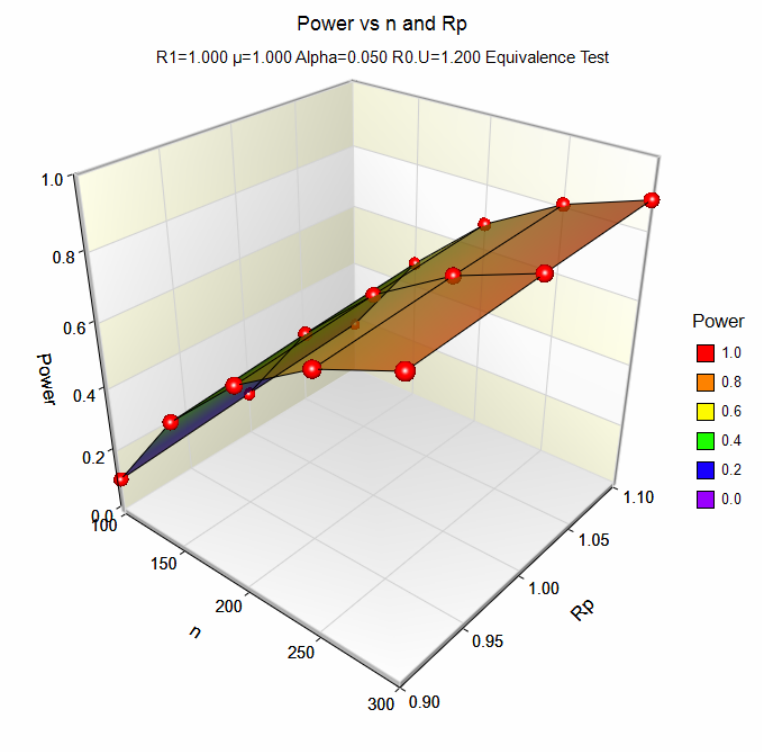
	Sample Size		Dropout-Inflated Enrollment Sample Size		Expected Number of Dropouts	
Dropout Rate	n	N	n'	N'	d	D
20%	100	200	125	250	25	50
20%	150	300	188	376	38	76
20%	200	400	250	500	50	100
20%	250	500	313	626	63	126
20%	300	600	375	750	75	150

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.

This report shows the values of each of the parameters, one scenario per row.

Chart Section





These plots show the relationship between sample size, Rp, and power. We see that sample sizes of between about 240 and 300 per sequence are required to detect an actual event rate ratio of 1 with 80% power.

Example 2 – Calculating Sample Size (Validation using Hand Calculations)

This example demonstrates how to calculate the sample size when estimating the standard deviation of the log odds ratio from data in a previous study using the method in Lui (2016) on page 42. 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 $H_0: OR \leq 0.833$ or $OR \geq 1.2$ versus $H_A: 0.833 < OR < 1.2$. The SD is estimated from discordant proportions in a previous study.

In this example, we'll demonstrate how to compute sample size for an equivalence test of two Poisson rates from a 2x2 cross-over design. This example will also serve as validation for this procedure. We couldn't find any published examples of this test, so we'll validate the procedure by hand. Let's find the sample size required to detect and actual event rate ratio of 1 with 80% power at a significance level of 0.05 in an equivalence test of the hypotheses $H_0: OR \leq 0.833$ or $OR \geq 1.2$ versus $H_A: 0.833 < OR < 1.2$. Assume both the fixed mean rate and period rate ratio are equal to 1. These values are similar to those used in Table II on page 78 of Lui (2013) for a test of inequality.

First, we need to compute the variance component with

$$p_1 = \frac{e^{\eta+\gamma}}{1+e^{\eta+\gamma}} = \frac{e^{\eta}e^{\gamma}}{1+e^{\eta}e^{\gamma}} = \frac{1}{1+1} = 0.5$$

$$p_2 = \frac{e^{\gamma}}{e^{\eta}+e^{\gamma}} = \frac{1}{1+1} = 0.5$$

$$\begin{aligned} V(\mu,\eta,\gamma) &= \frac{1}{4}\left(\frac{1}{\mu(1+e^{\eta+\gamma})p_1(1-p_1)} + \frac{1}{\mu(e^{\eta}+e^{\gamma})p_2(1-p_2)}\right) \\ &= \frac{1}{4}\left(\frac{1}{1(1+1)0.5(1-0.5)} + \frac{1}{1(1+1)0.5(1-0.5)}\right) \\ &= \frac{1}{4}\left(\frac{1}{0.5} + \frac{1}{0.5}\right) = 1.0 \end{aligned}$$

The formula for power given in Lui (2016) on page 88 is

$$\text{Power} = \Phi\left(\frac{\sqrt{n}\left(\log(R_{0U}) - \log(R_1)\right)}{\sqrt{V(\mu,\eta,\gamma)}} - Z_{1-\alpha}\right) - \Phi\left(\frac{\sqrt{n}\left(\log(R_{0L}) - \log(R_1)\right)}{\sqrt{V(\mu,\eta,\gamma)}} + Z_{1-\alpha}\right).$$

The power for a sample size of n = 257 is

$$\begin{aligned} \text{Power}_{(n=257)} &= \Phi\left(\frac{\sqrt{257}\left(\log(1.2) - \log(1)\right)}{\sqrt{1}} - 1.644854\right) - \Phi\left(\frac{\sqrt{257}\left(\log(0.833) - \log(1)\right)}{\sqrt{1}} + 1.644854\right) \\ &= 0.7987 \end{aligned}$$

$$\begin{aligned} \text{Power}_{(n=258)} &= \Phi\left(\frac{\sqrt{258}\left(\log(1.2) - \log(1)\right)}{\sqrt{1}} - 1.644854\right) - \Phi\left(\frac{\sqrt{258}\left(\log(0.833) - \log(1)\right)}{\sqrt{1}} + 1.644854\right) \\ &= 0.8007 \end{aligned}$$

These results indicate that the minimum required sample size per group is 258, since it is the smallest sample size that achieves the desired 80% power.

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 Ratio of Two Poisson Rates in a 2x2 Cross-Over Design** procedure window by expanding **Rates and Counts**, then **Cross-Over (2x2) Design**, then clicking on **Equivalence**, and then clicking on **Equivalence Tests for the Ratio of Two Poisson Rates 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**
R0.U (Upper Equivalence Ratio)	**1.2**
R0.L (Lower Equivalence Ratio)	**1/R0.U**
R1 (Actual Ratio)	**1**
Fixed Mean Rate (μ)	**1**
Period Rate Ratio (Rp)	**1**

Output

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

Numeric Results

Numeric Results for an Equivalence Test

H0: R ≤ R0.L or R ≥ R0.U vs. H1: R0.L < R < R0.U

Power	Sequence Sample Size n	Total Sample Size N	Lower Equiv. Ratio R0.L	Upper Equiv. Ratio R0.U	Actual Ratio R1	Fixed Mean Rate μ	Period Rate Ratio Rp	Alpha
0.80074	258	516	0.833	1.200	1.000	1.000	1.000	0.050

The sample size of 258 per sequence and power of 0.80074 calculated by **PASS** match our hand calculations.