nQuery

WORKED EXAMPLE

Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers

Title: Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers.

Objective: The aim of this study was to assess the bioequivalence between the new sildenafil 100 mg orodispersible film and the conventional marketed 100 mg film-coated tablet after single-dose administration to healthy male volunteers.

Year: 2012

Source: Drug Design, Development and Therapy

Link: https://doi.org/10.2147/DDDT.S124034

Protocol: N/A

Clinical Area: Sexual Health

Sample Size Section in Paper/Protocol:

“Sildenafil and N-desmethyl-sildenafil rate (Cmax) and extent (AUC) of absorption were compared between test and reference using analysis of variance for a crossover design on log-transformed data”

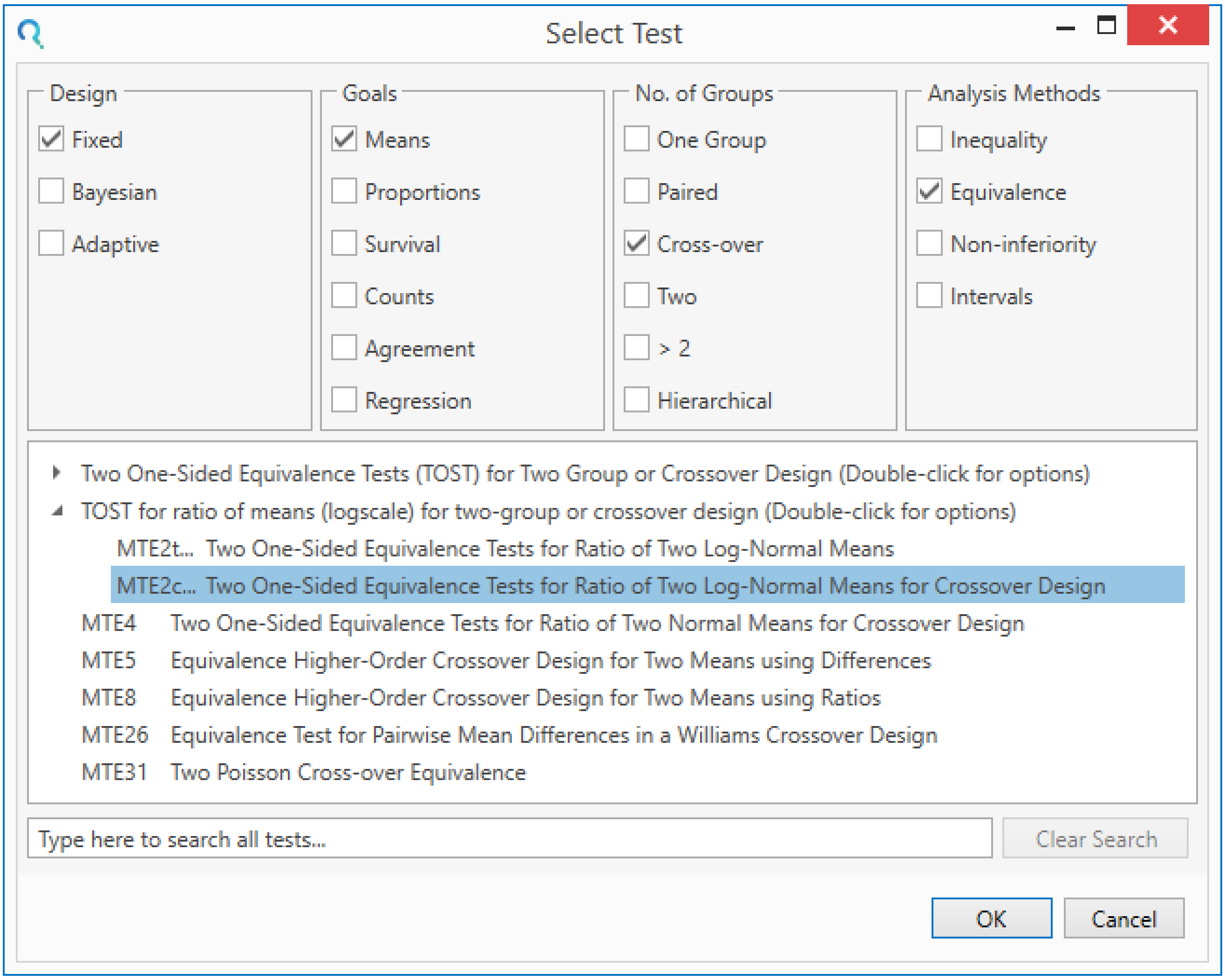
“The highest **coefficient of variance for the pharmacokinetic parameters Cmax and AUC was estimated to be 0.383** … Fixing the **significance level α at 5% and the hypothesized test/reference mean ratio to 1**, 50 subjects were considered sufficient to attain a **power of 80%** to correctly conclude the **bioequivalence between the two formulations within the range 80.00%–125.00%** for all parameters (Cmax and AUC)”

Summary of Necessary Parameter Estimates for Sample Size Calculation

Parameter	Value
Significance Level	0.05
Lower Equivalence Limit	0.8
Upper Equivalence Limit	1.25
Expected Ratio	1
Coefficient of Variation	0.383
Power	80%

Step 1:
Select the **MTE2co Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design** table from the Study Design Pane.

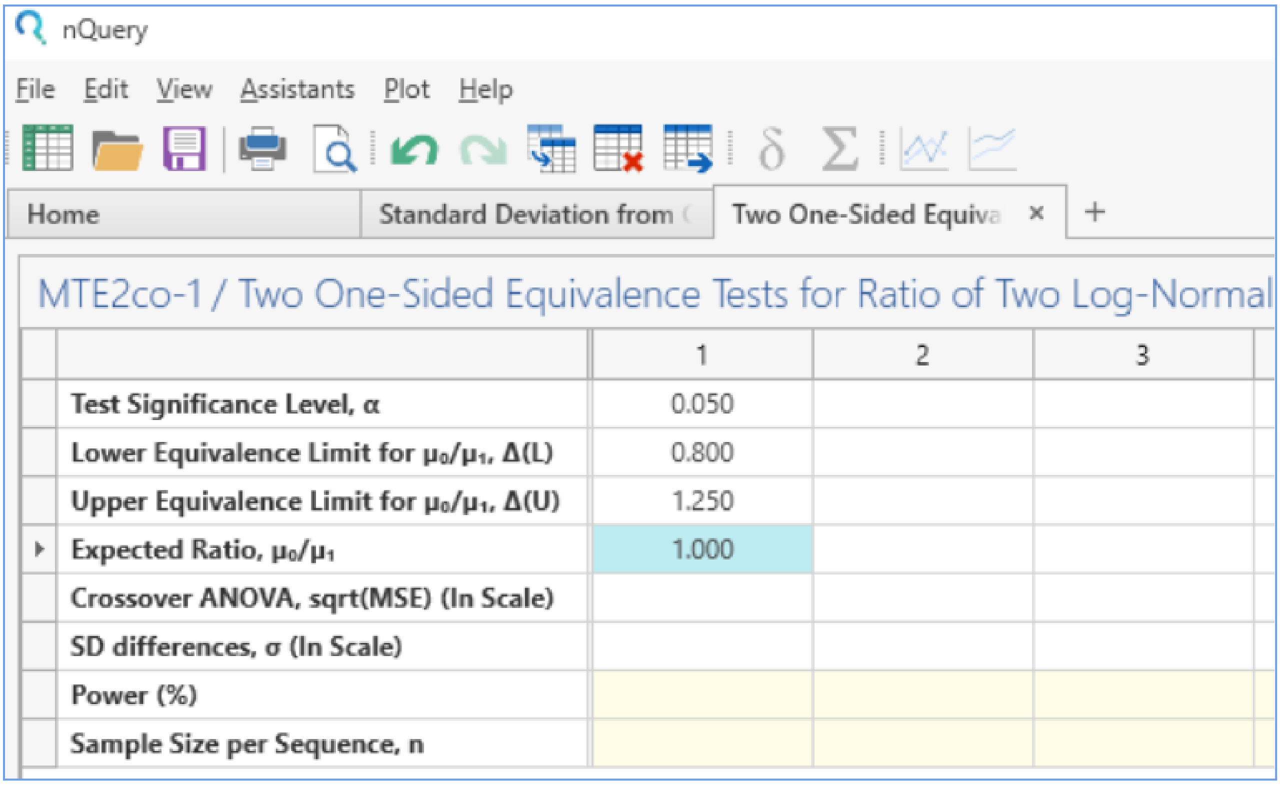
This can be done **using the radio buttons** or alternatively, you can **use the search bar** at the end of the Select Test Design & Goal window.



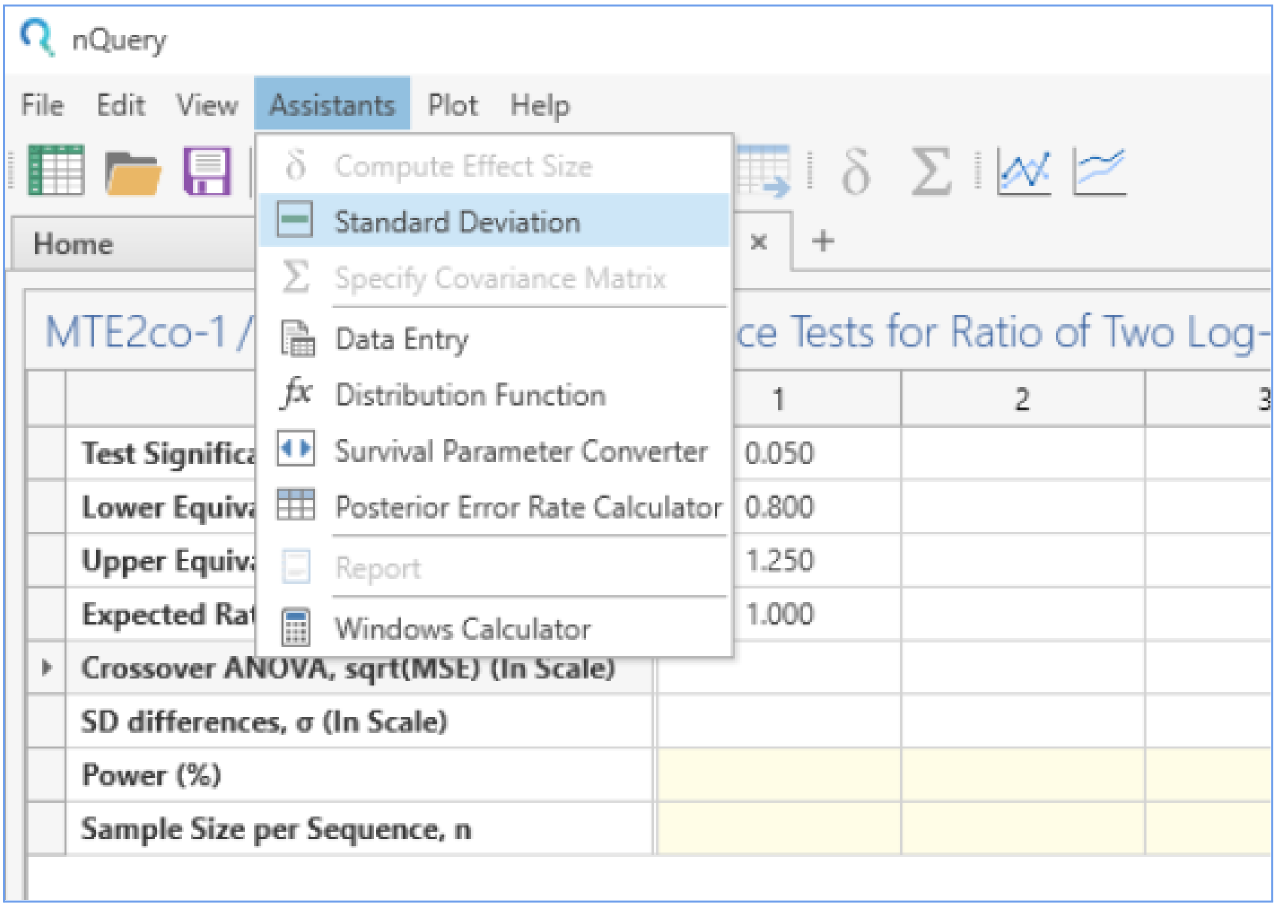
Step 2:

Enter the parameter values for sample size calculation taken from the study description.

The significance level, equivalence limits, expected ratio and power can be entered directly from the study design.



The square root of the mean square error parameter is estimated from the coefficient of variation. A table for this conversion can be accessed from the **Assistants** menu. Go to the menu and select **Assistants > Standard Deviation > From Coefficient of Variation.**


nQuery
File
Edit
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Assistants
Plot
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Compute Effect Size
Standard Deviation
Specify Covariance Matrix
Data Entry
Distribution Function
Survival Parameter Converter
Posterior Error Rate Calculator
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Windows Calculator
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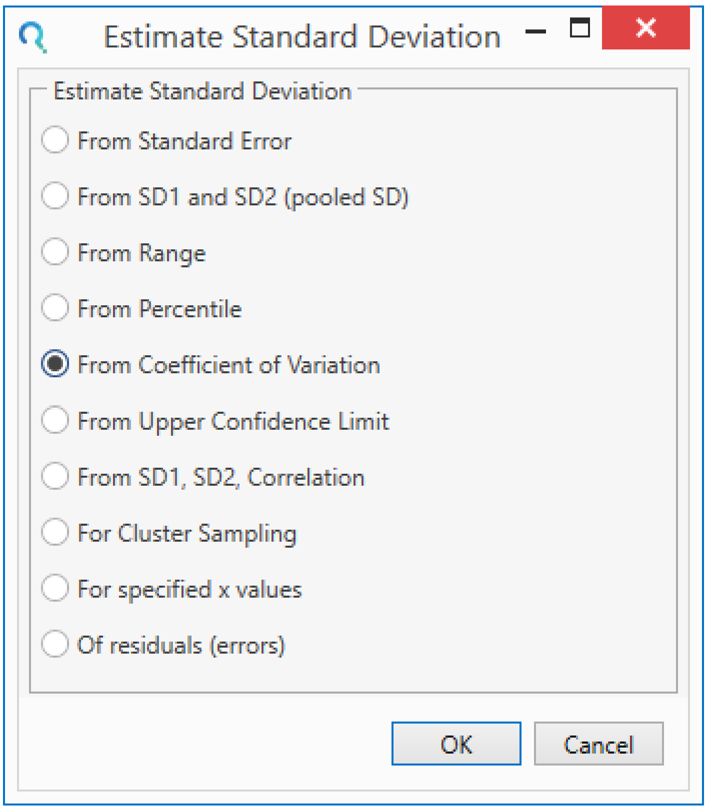
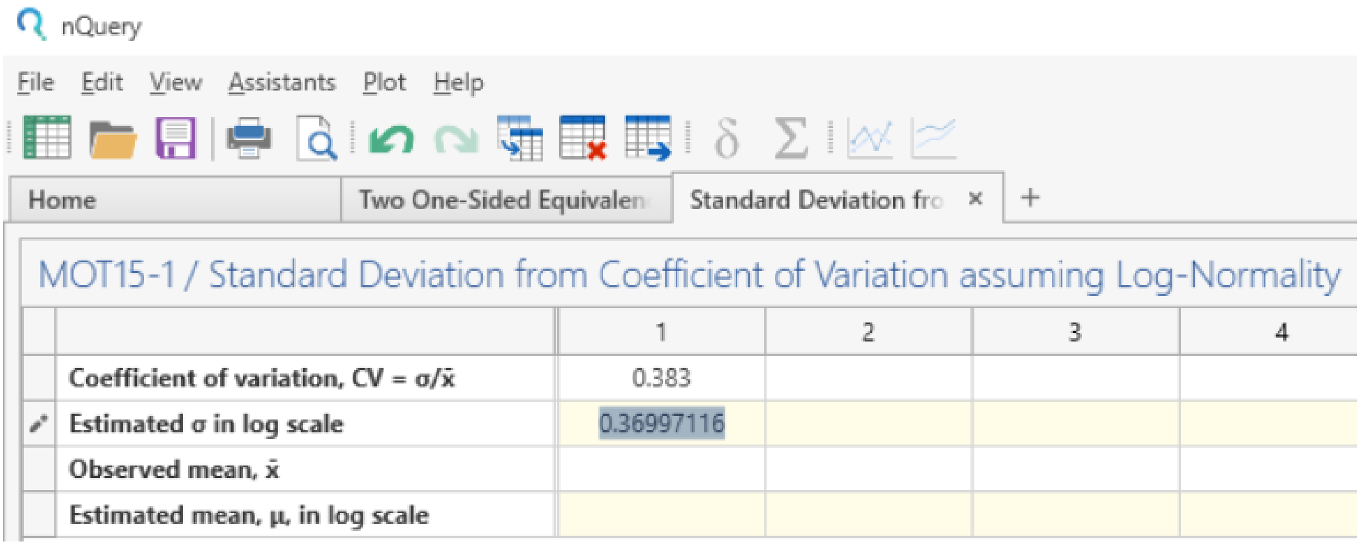
MTE2co-1 /
ce Tests for Ratio of Two Log-
1
2
Test Significa
0.050
Lower Equiva
0.800
Upper Equiva
1.250
Expected Rat
1.000
Crossover ANOVA, sqrt(MSE) (ln Scale)
SD differences, σ (ln Scale)
Power (%)
Sample Size per Sequence, n


Estimate Standard Deviation
Estimate Standard Deviation
From Standard Error
From SD1 and SD2 (pooled SD)
From Range
From Percentile
From Coefficient of Variation
From Upper Confidence Limit
From SD1, SD2, Correlation
For Cluster Sampling
For specified x values
Of residuals (errors)
OK
Cancel

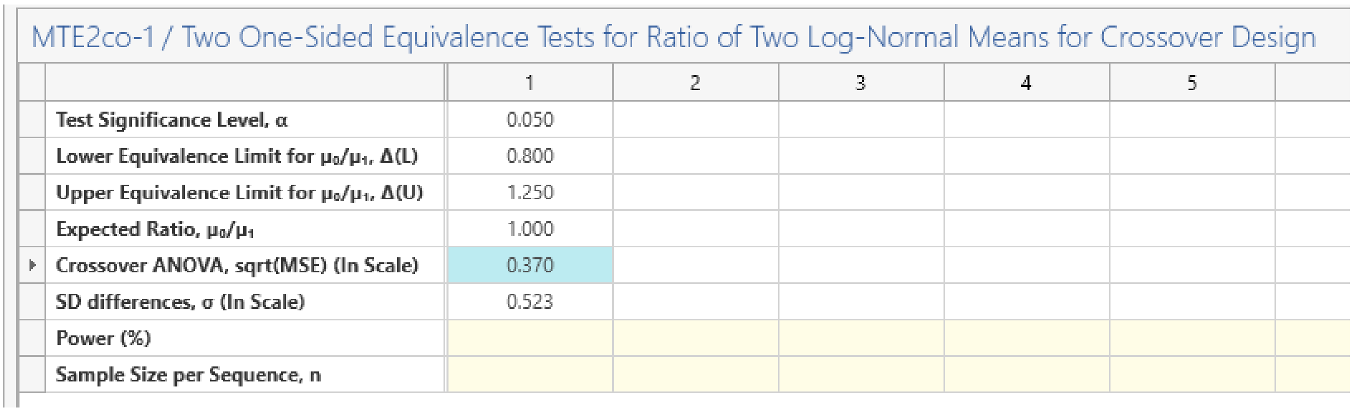
Enter the Coefficient of Variation into the conversion table and the estimate of the standard deviation will automatically be calculated.



MOT15-1 / Standard Deviation from Coefficient of Variation assuming Log-Normality

	1	2	3	4
Coefficient of variation, CV = $\sigma/\bar{x}$	0.383			
Estimated σ in log scale	0.36997116			
Observed mean, $\bar{x}$				
Estimated mean, μ, in log scale				

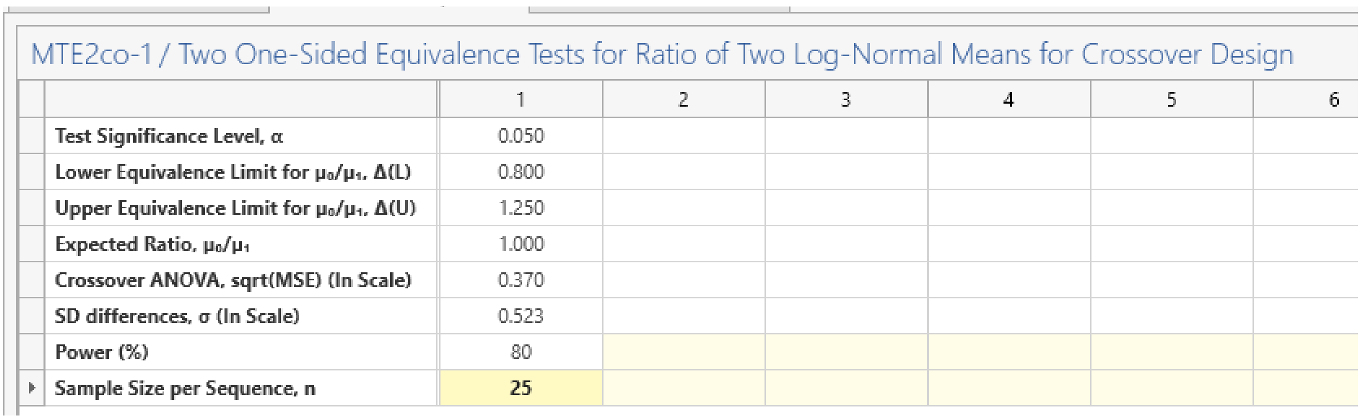
Enter the estimate of standard deviation in the main table and the standard deviation of the differences will automatically be calculated.



MTE2co-1 / Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design

	1	2	3	4	5
Test Significance Level, α	0.050				
Lower Equivalence Limit for μ_0/μ_1, $\Delta(L)$	0.800				
Upper Equivalence Limit for μ_0/μ_1, $\Delta(U)$	1.250				
Expected Ratio, μ_0/μ_1	1.000				
Crossover ANOVA, sqrt(MSE) (ln Scale)	0.370				
SD differences, σ (ln Scale)	0.523				
Power (%)					
Sample Size per Sequence, n					

Finally, enter the required power and the sample size per sequence will automatically be calculated.



MTE2co-1 / Two One-Sided Equivalence Tests for Ratio of Two Log-Normal Means for Crossover Design

	1	2	3	4	5	6
Test Significance Level, α	0.050					
Lower Equivalence Limit for μ_0/μ_1, $\Delta(L)$	0.800					
Upper Equivalence Limit for μ_0/μ_1, $\Delta(U)$	1.250					
Expected Ratio, μ_0/μ_1	1.000					
Crossover ANOVA, sqrt(MSE) (ln Scale)	0.370					
SD differences, σ (ln Scale)	0.523					
Power (%)	80					
Sample Size per Sequence, n	25					

The analysis requires a sample size of 25 subjects per sequence (total sample size of 50) to achieve a power of 80% to reject the null hypothesis that the standard and experimental treatments are not equivalent. This is consistent with the sample size reported in the study design.

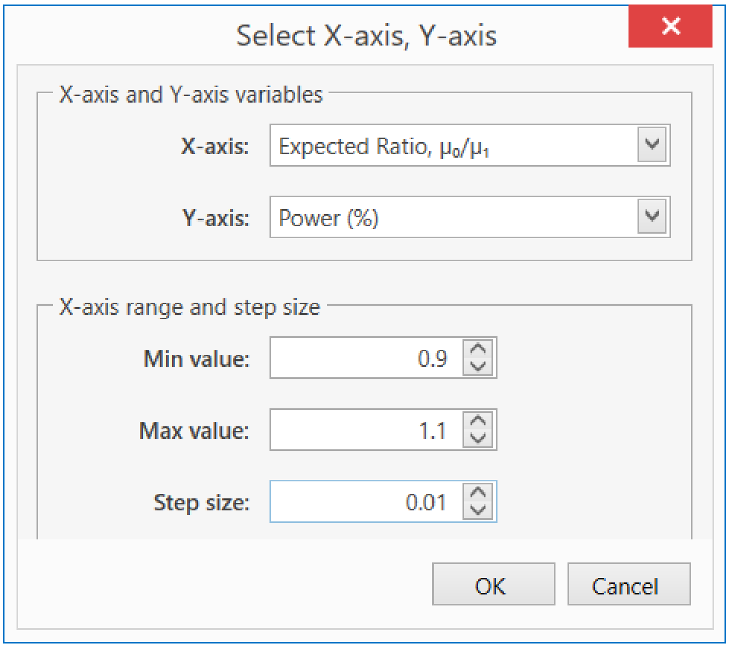
Output Statement:

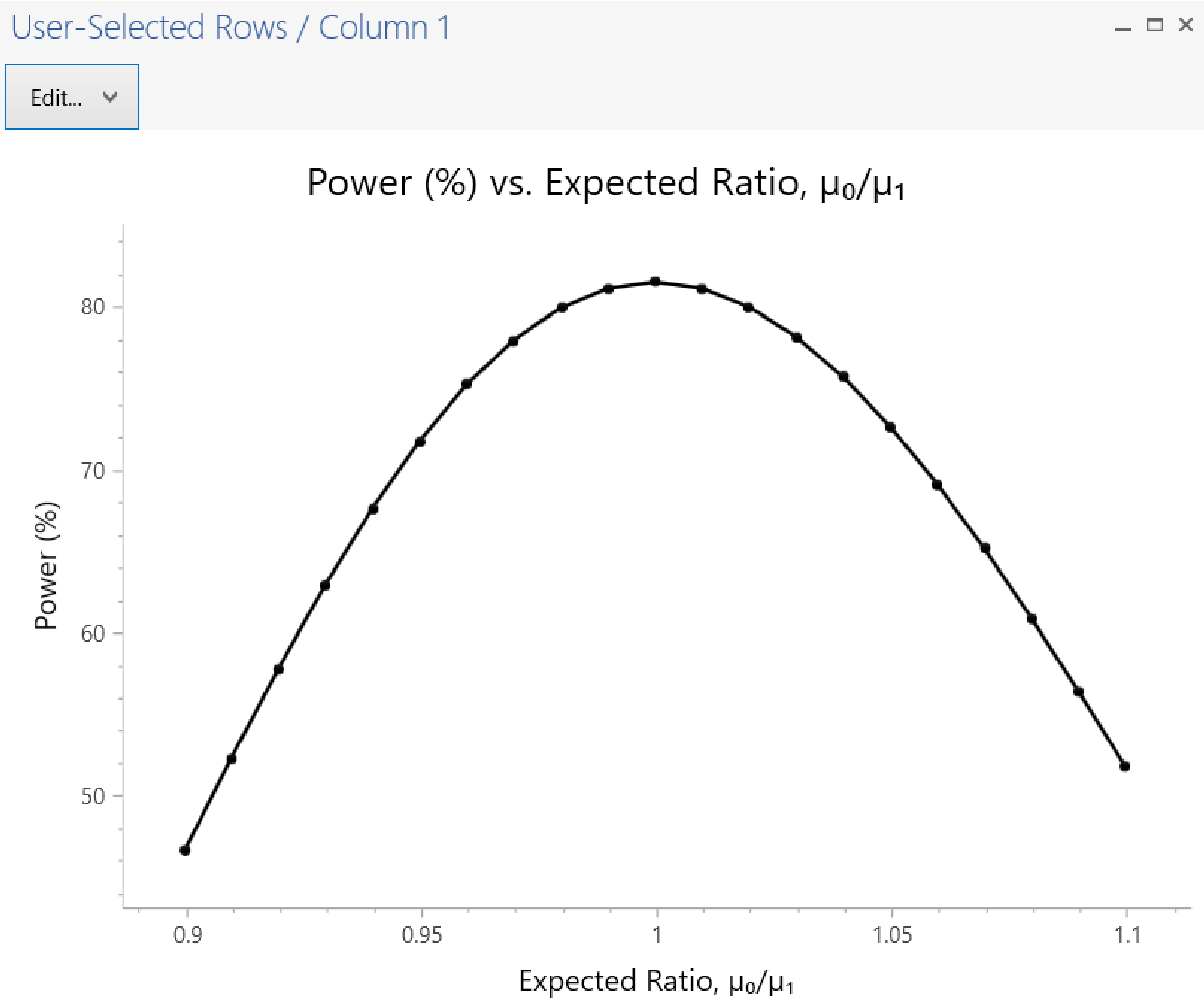
"When the sample size in each sequence group is 25 (and the total sample size is 50), a crossover design will have 80% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 0.8 and the null hypothesis that the ratio of test mean to the standard mean is above 1.25; i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two treatments are equivalent, assuming that the expected ratio of means is 1, the Crossover ANOVA, √MSE (ln scale) is 0.37 (the SD differences, σ (ln scale) is 0.523), that data will be analyzed in the natural log scale using t-tests for differences in means, and that each t-test is made at the 5% level."

Step 3:

nQuery also provides plotting options. To access the plotting tools, highlight the completed columns that you wish to work with, go to the menu and select: **Plot > User-Selected Rows.**

In this case, we will demonstrate how the sample size per sequence is affected when the expected geometric mean ratio varies. We will see the effect on power with a total sample size of 50 (25 per sequence) for true mean ratios between 0.9 to 1.1. We would expect the power to decrease as the mean difference approaches either equivalence margin and be maximised at a value of 1 (i.e. equidistant between the lower and upper equivalence limits).





Note that the true equivalent ratio above and below one in this example is equal to the reciprocal (i.e. 1/ratio) so the power for 0.9 and 1.1 would not be expected to be the same as can be seen above. However, a ratio of 1.11111111 (i.e. 1/0.9) would give the same power as 0.9

The **Edit** button at the top of the output allows users to customise the appearance of the plot.