WORKED EXAMPLE

A phase 3 trial of the efficacy and safety of oral recombinant calcitonin: The oral calcitonin in postmenopausal osteoporosis (ORACAL) trial

Title: A phase 3 trial of the efficacy and safety of oral recombinant calcitonin: The oral calcitonin in postmenopausal osteoporosis (ORACAL) trial

Objective: To assess the efficacy and safety of oral recombinant calcitonin for treatment of postmenopausal osteoporosis.

Year: 2012

Source: Journal of Bone and Mineral Research

Link: https://doi.org/10.1002/jbmr.1602

Protocol: https://clinicaltrials.gov/ct2/show/NCT00959764

Clinical Area: Rheumatology

Sample Size Section in Paper/Protocol:

"It was assumed that the **placebo-adjusted effect for both treatment groups was 1.56%** and that the **placebo-adjusted effect for the oral rsCT tablets must be at least 0.5 times the placebo-adjusted effect** for the ssCT nasal spray for the study to demonstrate the non-inferiority of the oral rsCT tablets to the ssCT nasal spray. Thus we wished to have 95% confidence that the oral tablets were not less than one-half as effective as nasal spray. **Assuming an SD of 2.5%, power of 80%, and a two-sided 5% level of significance,** it was determined that approximately 133 patients were required for each of the active treatment groups and 84 patients were needed for the placebo treatment group."

Summary of Necessary Parameter Estimates for Sample Size Calculation

Parameter	Value
Significance Level (1-Sided)	0.025
Experiment Arm Mean	1.56
Reference Arm Mean	1.56
Placebo Arm Mean	0
Non-Inferiority Margin	0.5
Common Variance	6.25
Experiment Sample Size Allocation	0.38
Reference Sample Size Allocation	0.38
Placebo Sample Size Allocation	0.24
Power	80%

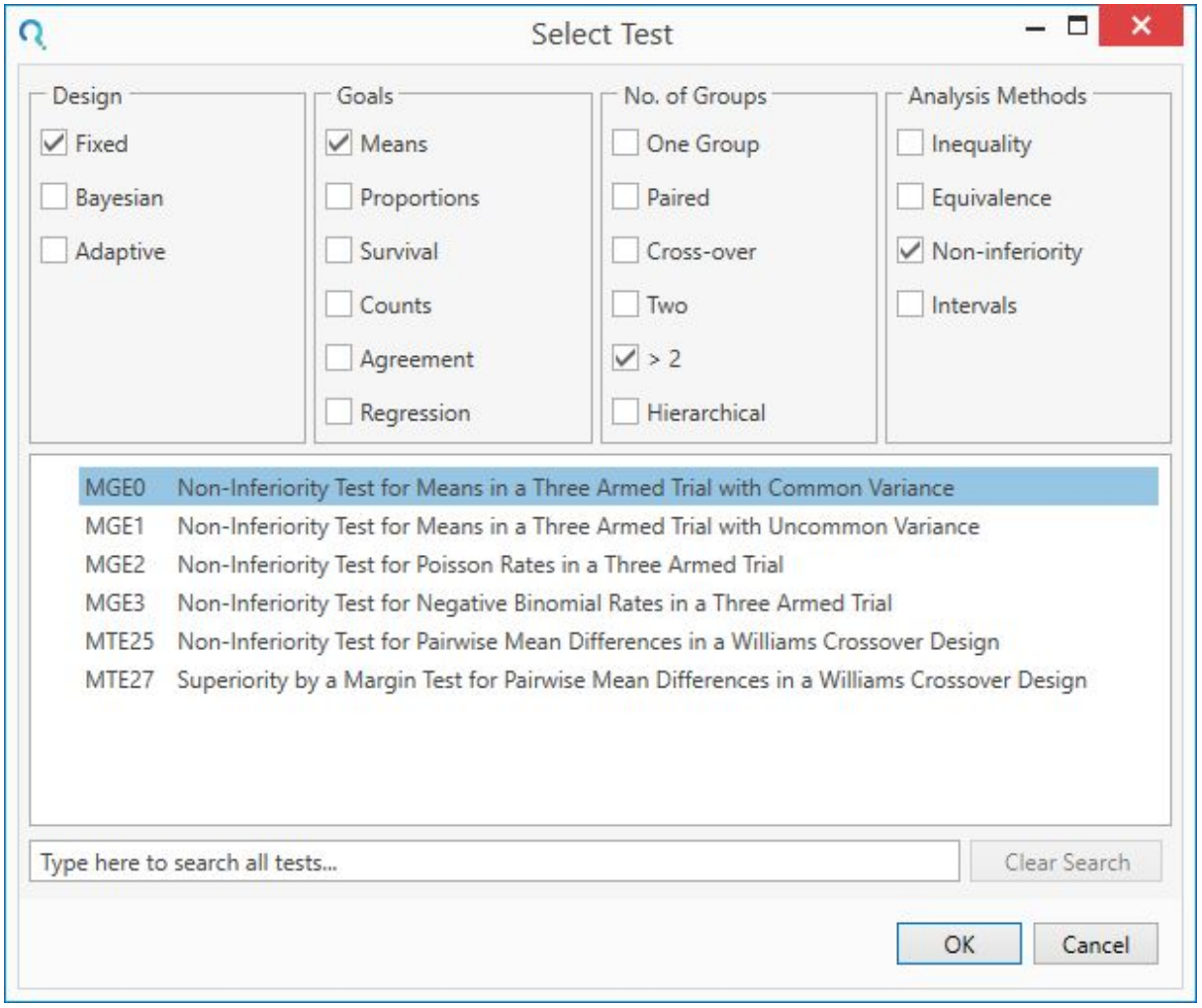
Notes:
The significance level in the nQuery table is assumed to be one-sided so we have adjusted the two-sided 5% level stated in the paper.

The variance value of 6.25 was calculated as the square of the stated standard deviation.

The allocations in each arm were calculated from the sample sizes in each group stated in the paper.

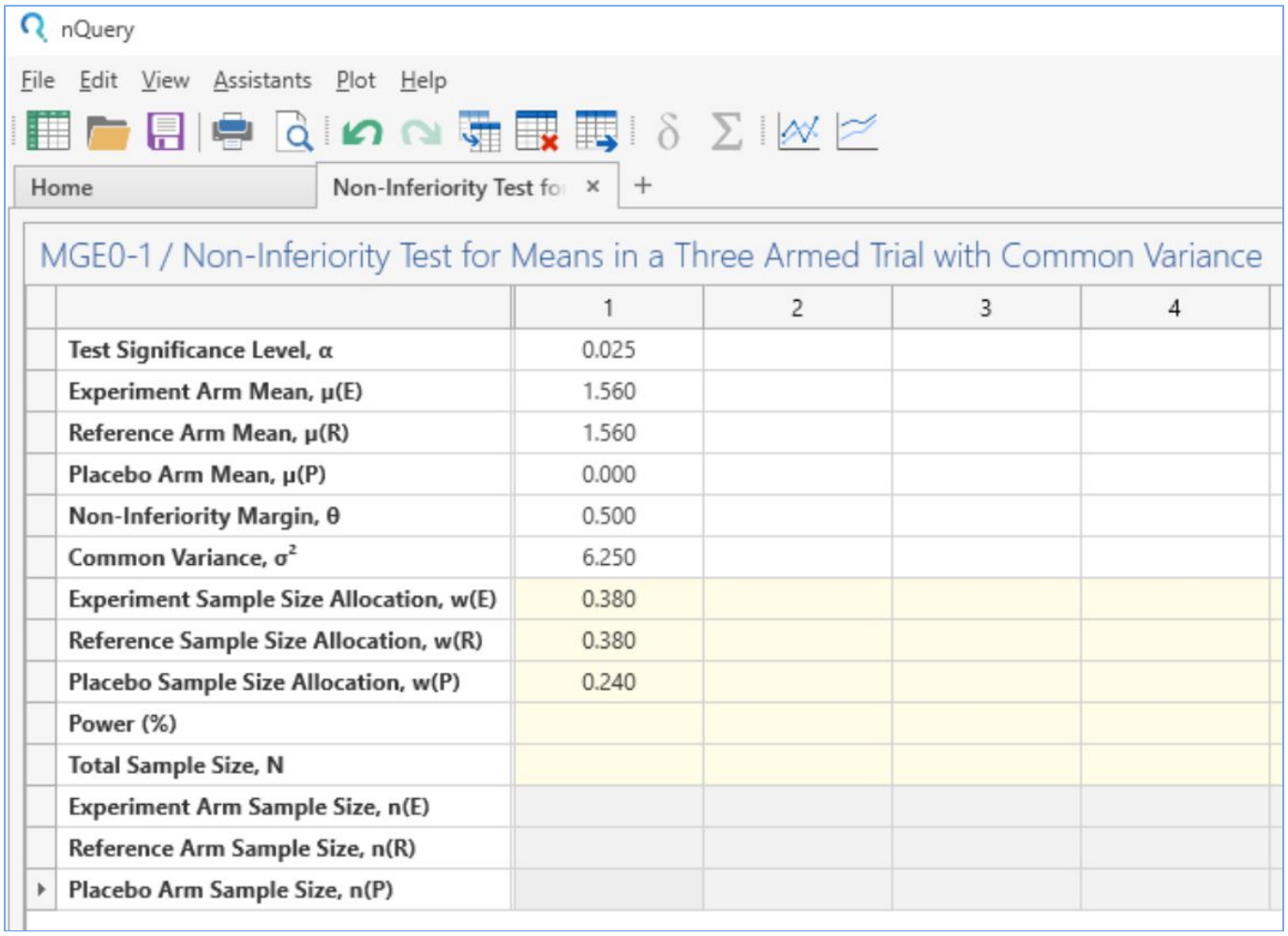
Step 1:
Select the **MGE0 Non-inferiority Test for Means in a Three-Armed Trial with Common Variance** table from the Study Design Pane.

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.



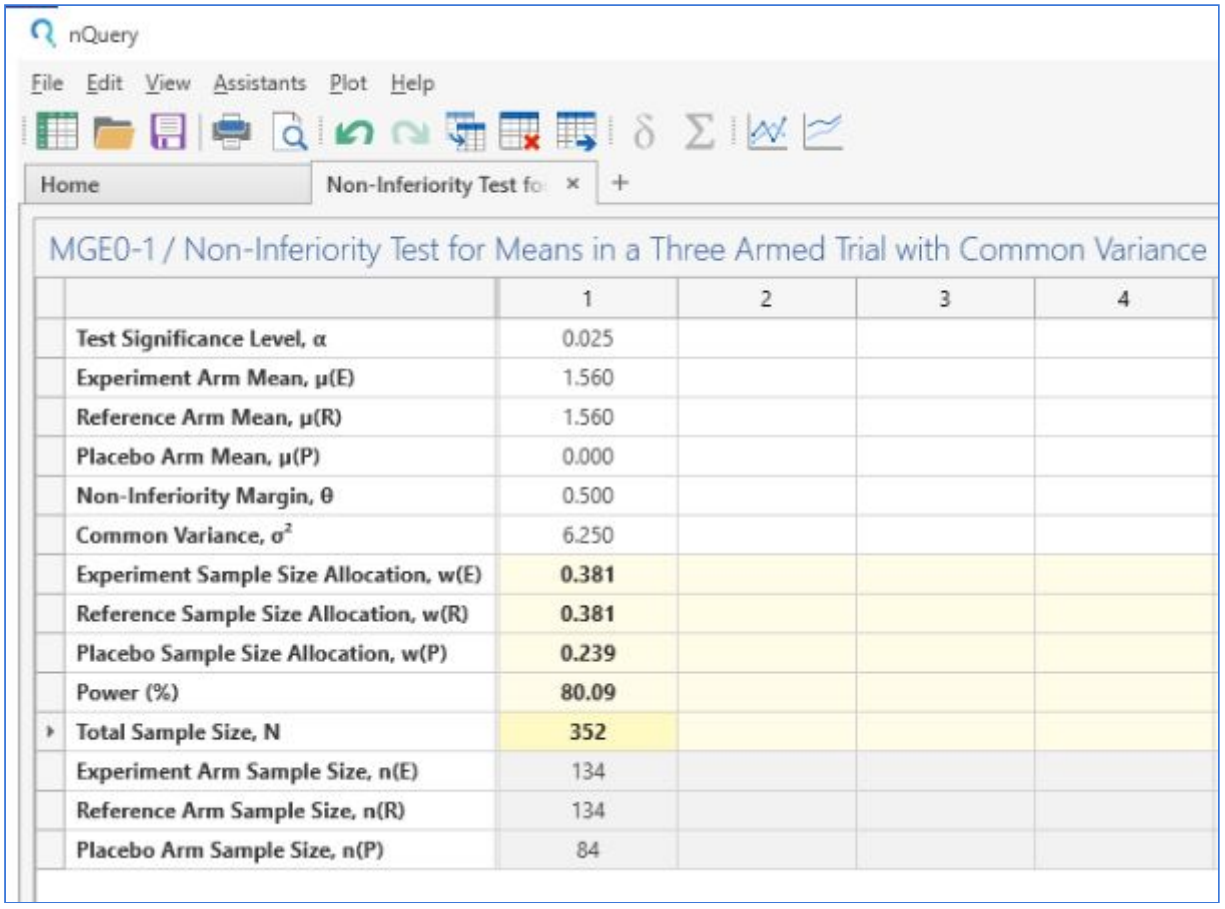
Step 2:

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



	1	2	3	4
Test Significance Level, α	0.025			
Experiment Arm Mean, μ(E)	1.560			
Reference Arm Mean, μ(R)	1.560			
Placebo Arm Mean, μ(P)	0.000			
Non-Inferiority Margin, θ	0.500			
Common Variance, σ^2	6.250			
Experiment Sample Size Allocation, w(E)	0.380			
Reference Sample Size Allocation, w(R)	0.380			
Placebo Sample Size Allocation, w(P)	0.240			
Power (%)				
Total Sample Size, N				
Experiment Arm Sample Size, n(E)				
Reference Arm Sample Size, n(R)				
Placebo Arm Sample Size, n(P)				

Enter the desired power and the required sample size will automatically calculate.



	1	2	3	4
Test Significance Level, α	0.025			
Experiment Arm Mean, μ(E)	1.560			
Reference Arm Mean, μ(R)	1.560			
Placebo Arm Mean, μ(P)	0.000			
Non-Inferiority Margin, θ	0.500			
Common Variance, σ^2	6.250			
Experiment Sample Size Allocation, w(E)	**0.381**			
Reference Sample Size Allocation, w(R)	**0.381**			
Placebo Sample Size Allocation, w(P)	**0.239**			
Power (%)	**80.09**			
Total Sample Size, N	**352**			
Experiment Arm Sample Size, n(E)	134			
Reference Arm Sample Size, n(R)	134			
Placebo Arm Sample Size, n(P)	84			

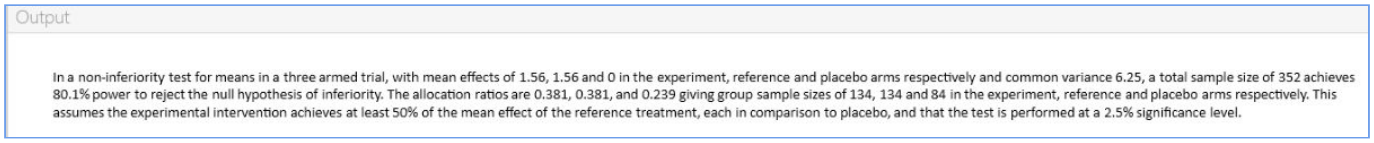
The analysis requires a sample size of 352 subjects to achieve a power of 80.09% to reject the null hypothesis of inferiority. The sample size in the experiment, reference and placebo arms was 134, 134 and 84.

The study design required a sample size of 133 in each active group and 84 in the placebo group. This slight difference is likely due to rounding.

Output Statement:

"In a non-inferiority test for means in a three-armed trial, with mean effects of 1.56, 1.56 and 0 in the experiment, reference and placebo arms respectively and common variance 6.25, a total sample size of 352 achieves 80.1% power to reject the null hypothesis of inferiority. The allocation ratios are 0.381, 0.381, and 0.239 giving group sample sizes of 134, 134 and 84 in the experiment, reference and placebo arms respectively. This assumes the experimental intervention achieves at least 50% of the mean effect of the reference treatment, each in comparison to placebo, and that the test is performed at a 2.5% significance level."

The output statement appears at the bottom of nQuery. This can be printed or copy and pasted into any document.



How the output statement appears in nQuery.

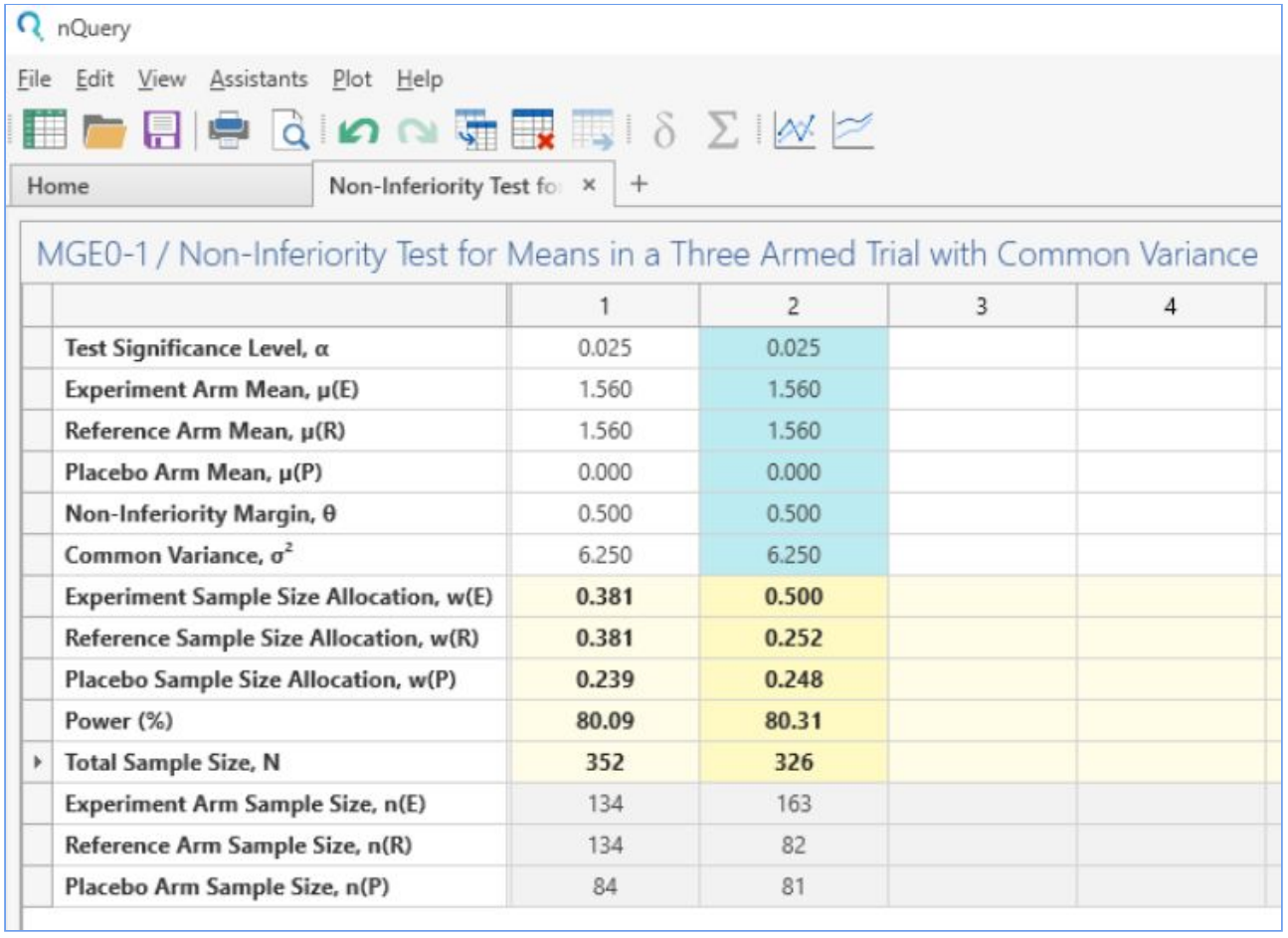
Step 3:

The sample size allocations can be adjusted to optimise power with the smallest total sample size. The nQuery help cards for the sample size allocations state:

"To optimize power with the smallest total sample size, set w(E) = 0.5, w(R) = θ/2 and w(P) = (1-θ)/2 "

In this case, we will have w(E)=0.5 and w(R)=W(P)=0.25.

By re-running the calculation, we see that a sample size of 326 achieves a power of 80.31% when using the optimal allocation. This is a reduction of 26 subjects compared to the original allocation.

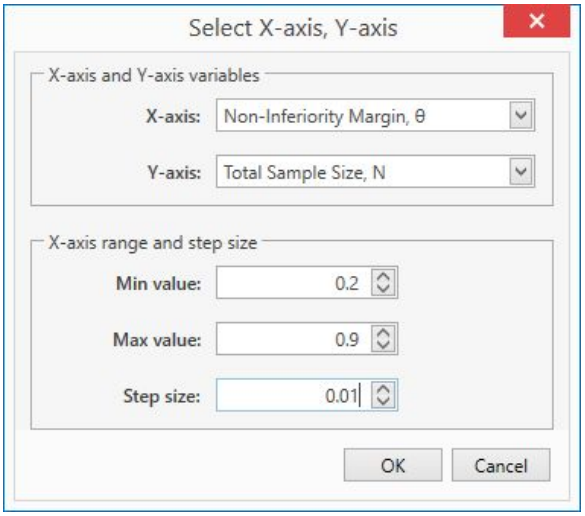


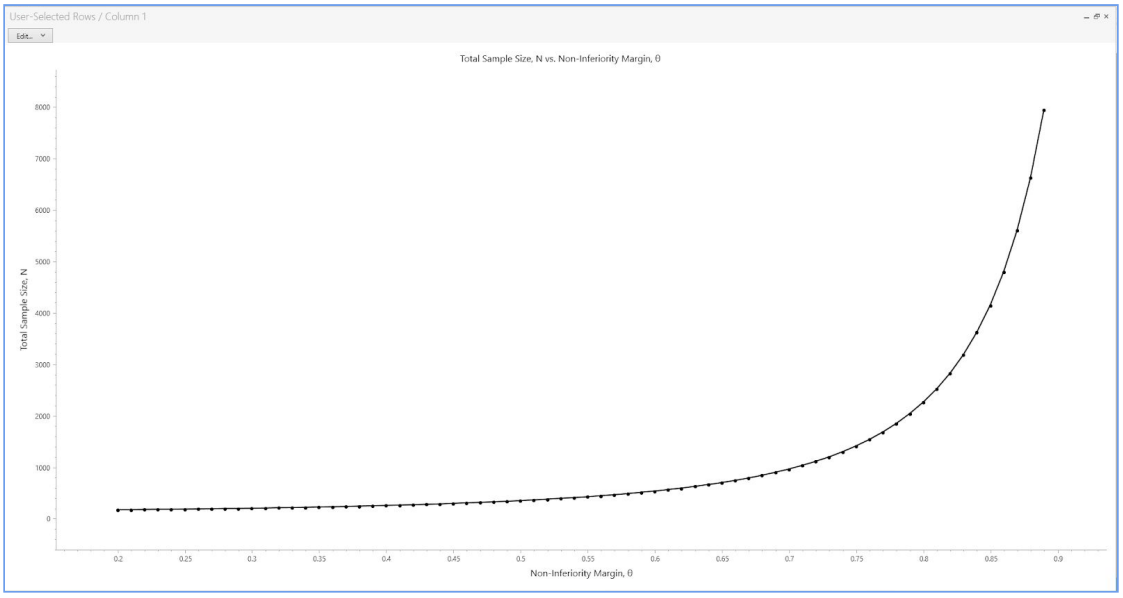
	1	2	3	4
Test Significance Level, α	0.025	0.025		
Experiment Arm Mean, μ(E)	1.560	1.560		
Reference Arm Mean, μ(R)	1.560	1.560		
Placebo Arm Mean, μ(P)	0.000	0.000		
Non-Inferiority Margin, θ	0.500	0.500		
Common Variance, σ^2	6.250	6.250		
Experiment Sample Size Allocation, w(E)	**0.381**	**0.500**		
Reference Sample Size Allocation, w(R)	**0.381**	**0.252**		
Placebo Sample Size Allocation, w(P)	**0.239**	**0.248**		
Power (%)	**80.09**	**80.31**		
Total Sample Size, N	**352**	**326**		
Experiment Arm Sample Size, n(E)	134	163		
Reference Arm Sample Size, n(R)	134	82		
Placebo Arm Sample Size, n(P)	84	81		

Step 4:

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 total sample size is affected when the non-inferiority margin varies between 0.2 and 0.9, keeping all other parameters constant. A non-inferiority margin of 0.2 would require that the experimental treatment achieves at least 20% of the reference treatment, each in comparison to placebo. A non-inferiority margin of 0.9 would require that the experimental treatment achieves at least 90% of the reference treatment, each in comparison to placebo. With this in mind, we expect the sample size to increase as the non-inferiority margin increases.





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