WORKED EXAMPLE

Effect of Neladenoson Bialanate on Exercise Capacity Among Patients with Heart Failure with Preserved Ejection Fraction: A Randomized Clinical Trial.

Title: Effect of Neladenoson Bialanate on Exercise Capacity Among Patients with Heart Failure with Preserved Ejection Fraction: A Randomized Clinical Trial.

Objective: To determine whether neladenoson improves exercise capacity, physical activity, cardiac biomarkers, and quality of life in patients with HFpEF and to find the optimal dose.

Year: 2019

Source: Journal of the American Medical Association

Link: https://doi.org/10.1001/jama.2019.6717

Protocol: https://clinicaltrials.gov/ct2/show/NCT03098979

Clinical Area: Cardiology

Sample Size Section in Paper/Protocol:

"Based on the assumption of a maximum effect for an absolute increase in 6-minute walk test distance of **40 m for a particular dose** of neladenoson bialanate, an absolute increase of **0 m with placebo**, and an **SD of 80 m**, an **overall sample size of 216** randomized patients (using a **1:2:2:2:2:3 randomization ratio** corresponding to the 5 neladenoson doses and placebo) was required to ensure a **minimum power of 80%** to detect the presence of a dose response."

"Patients (were) randomized to receive neladenoson **(5 mg, 10 mg, 20 mg, 30 mg, or 40 mg**) or placebo"

"A multiple comparison procedure with 5 modelling techniques (**linear**, **Emax**, **2 variations of sigmoidal Emax**, and **quadratic**) was used to evaluate diverse dose-response profiles."

"All statistical tests were performed at a **significance level of .05**. Significance testing was **1-sided**."

Summary of Necessary Parameter Estimates for Sample Size Calculation

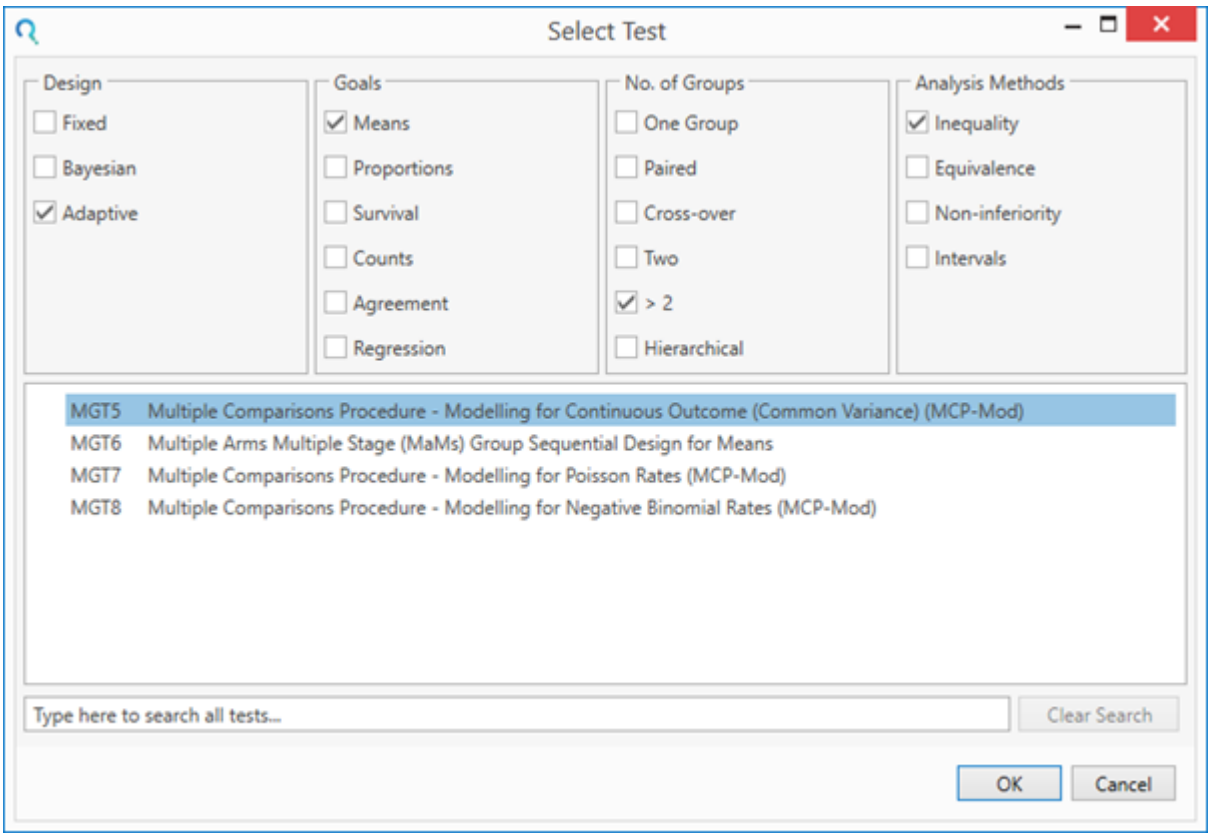
Parameter	Value
Significance Level (1-sided)	0.05
Number of Doses	6 (0mg, 5mg, 10mg, 20mg, 30mg, 40mg)
Sample Size Ratio per Dose	3:1:2:2:2:2
Number of Models	5 (Linear, Emax, Sigmoid Emax (x2), Quadratic)
Power Criterion	Minimum
Placebo Effect, δ_0	0
Max Treatment Effect, δ_1	40
Standard Deviation, σ	80
Power	80%

Parameter Values for Dose-Response Models

Model (Table 10-1 in Clinical Study Protocol)	Parameter Values
Linear: $f(d) = d$	No input required
Emax: $f(d) = \frac{41.25d}{1.25+d}$	θ_1= 1.25
Sigmoid Emax 1: $f(d) = \frac{40.1d^4}{9^4+d^4}$	θ_1= 9, θ_2= 4
Sigmoid Emax 2: $f(d) = \frac{45d^3}{20^3+d^3}$	θ_1= 20, θ_2= 3
Quadratic: $f(d) = 2.667d - 0.044d^2$	θ_1= -0.044/2.667

Step 1:
Select the **MGT5 Multiple Comparisons Procedure - Modelling for Continuous Outcome (Common Variance) (MCP-Mod)** table from the Study Design Pane.

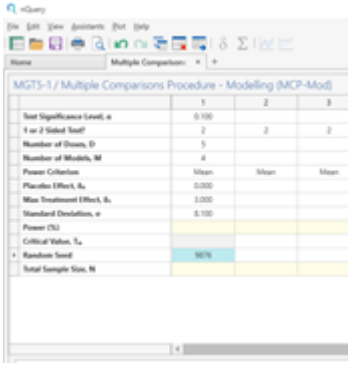
This can be done **using the radio buttons** or alternatively, you can **use the search bar** at the end of the Select Test Design & Goal window.



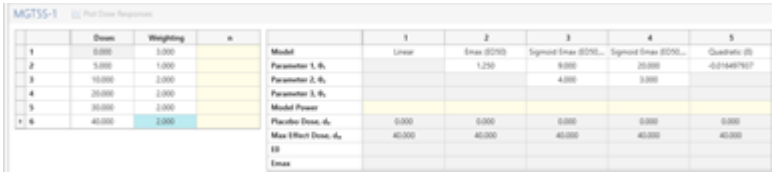
Step 2:
Enter the parameter values in the main table for the sample size calculation taken from the study description.

First, complete the **main table**. Note: Minimum power criterion implies that the total power of the test will be equal to the minimum power of the candidate models.

An optional random seed is also specified here to allow replicable results.



Next, complete the Dose Levels and Candidate Models **side table.** The weighting is used to distribute the sample size across the dose groups as specified.



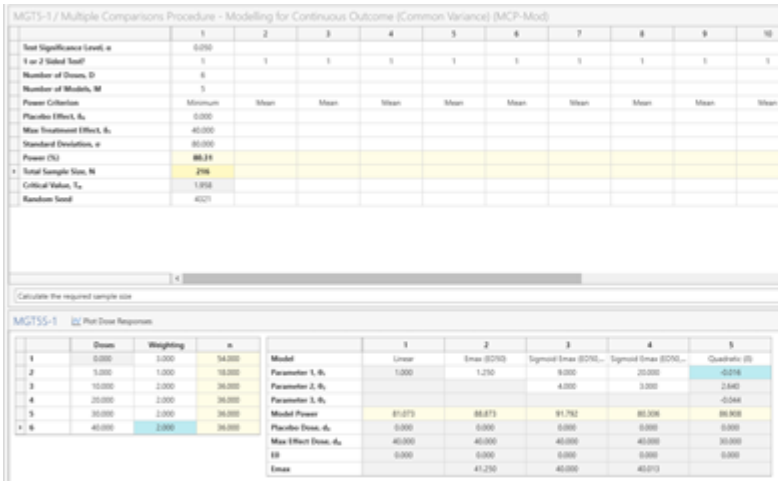
Step 3:
Enter the required **power** in the main table and the **sample size** and **candidate model powers** will be calculated.

The analysis calculates a total sample size of 216 with 54 subjects in the placebo group, 18 subjects in the 5mg dose group and 36 subjects in each of the remaining dose groups.

A minimum power of 80.31% was achieved with this sample size. The per-model powers ranged from 80.31% (Sigmoid Emax model with parameters 20 & 3) to 91.79% (Sigmoid Emax model with parameters 9 & 4).

The maximum effect dose was the 40mg dose for the Linear, Emax and Sigmoid Emax models while the Quadratic model achieved the maximum effect at the 30mg dose.

This sample size is consistent with the source paper.



Output Statement:

"A total sample size of 216 is required to ensure a minimum power of 80.31% for an MCP-Mod analysis rejecting the null hypothesis of no difference between doses using the multiple comparisons procedure (MCP) assuming a placebo dose-response effect of 0, a maximum dose-response effect (in the dose range) of 40 and a common (residual) standard deviation of 80 per dose and one-sided family-wise error rate of 0.05, corresponding to critical multivariate t-statistic of 1.958.

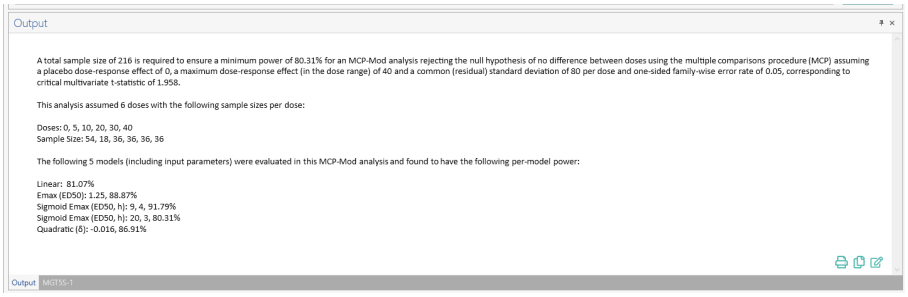
This analysis assumed 6 doses with the following sample sizes per dose:

Doses: 0, 5, 10, 20, 30, 40
Sample Size: 54, 18, 36, 36, 36, 36

The following 5 models (including input parameters) were evaluated in this MCP-Mod analysis and found to have the following per-model power:

Linear: 81.07%
Emax (ED50): 1.25, 88.87%
Sigmoid Emax (ED50, h): 9, 4, 91.79%
Sigmoid Emax (ED50, h): 20, 3, 80.31%
Quadratic (δ): -0.016, 86.91%"

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 4:

nQuery can also be used to plot the dose responses for each model. To generate these plots, click on the “Plot Dose Responses” button on top of the side table.