



nQuery

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.

The 'Select Test' dialog box is shown with the following configuration:

- Design:** Fixed, Bayesian, Adaptive
- Goals:** Means, Proportions, Survival, Counts, Agreement, Regression
- No. of Groups:** One Group, Paired, Cross-over, Two, > 2, Hierarchical
- Analysis Methods:** Inequality, Equivalence, Non-inferiority, Intervals

The list of tests below the columns includes:

- MGE0** Non-Inferiority Test for Means in a Three Armed Trial with Common Variance (highlighted)
- MGE1 Non-Inferiority Test for Means in a Three Armed Trial with Uncommon Variance
- MGE2 Non-Inferiority Test for Poisson Rates in a Three Armed Trial
- MGE3 Non-Inferiority Test for Negative Binomial Rates in a Three Armed Trial
- MTE25 Non-Inferiority Test for Pairwise Mean Differences in a Williams Crossover Design
- MTE27 Superiority by a Margin Test for Pairwise Mean Differences in a Williams Crossover Design

At the bottom of the dialog, there is a search bar containing the text 'Type here to search all tests...', a 'Clear Search' button, and 'OK' and 'Cancel' buttons.

Step 2:

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

The screenshot shows the nQuery software interface with a menu bar (File, Edit, View, Assistants, Plot, Help) and a toolbar. The active window is titled "Non-Inferiority Test for" and contains a table for "MGE0-1 / Non-Inferiority Test for Means in a Three Armed Trial with Common Variance". The table has 5 columns (1, 2, 3, 4) and 15 rows of parameters and results. The first column lists parameters, and the subsequent columns show values for four different arms. The first three columns have values, while the fourth column is empty. The last three rows (Experiment, Reference, and Placebo Arm Sample Size) are highlighted in grey.

| | 1 | 2 | 3 | 4 |
|---|-------|---|---|---|
| Test Significance Level, α | 0.025 | | | |
| Experiment Arm Mean, $\mu(E)$ | 1.560 | | | |
| Reference Arm Mean, $\mu(R)$ | 1.560 | | | |
| Placebo Arm Mean, $\mu(P)$ | 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, $\mu(E)$ | 1.560 | | | |
| Reference Arm Mean, $\mu(R)$ | 1.560 | | | |
| Placebo Arm Mean, $\mu(P)$ | 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.

Output

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.

How the output statement appears in nQuery.

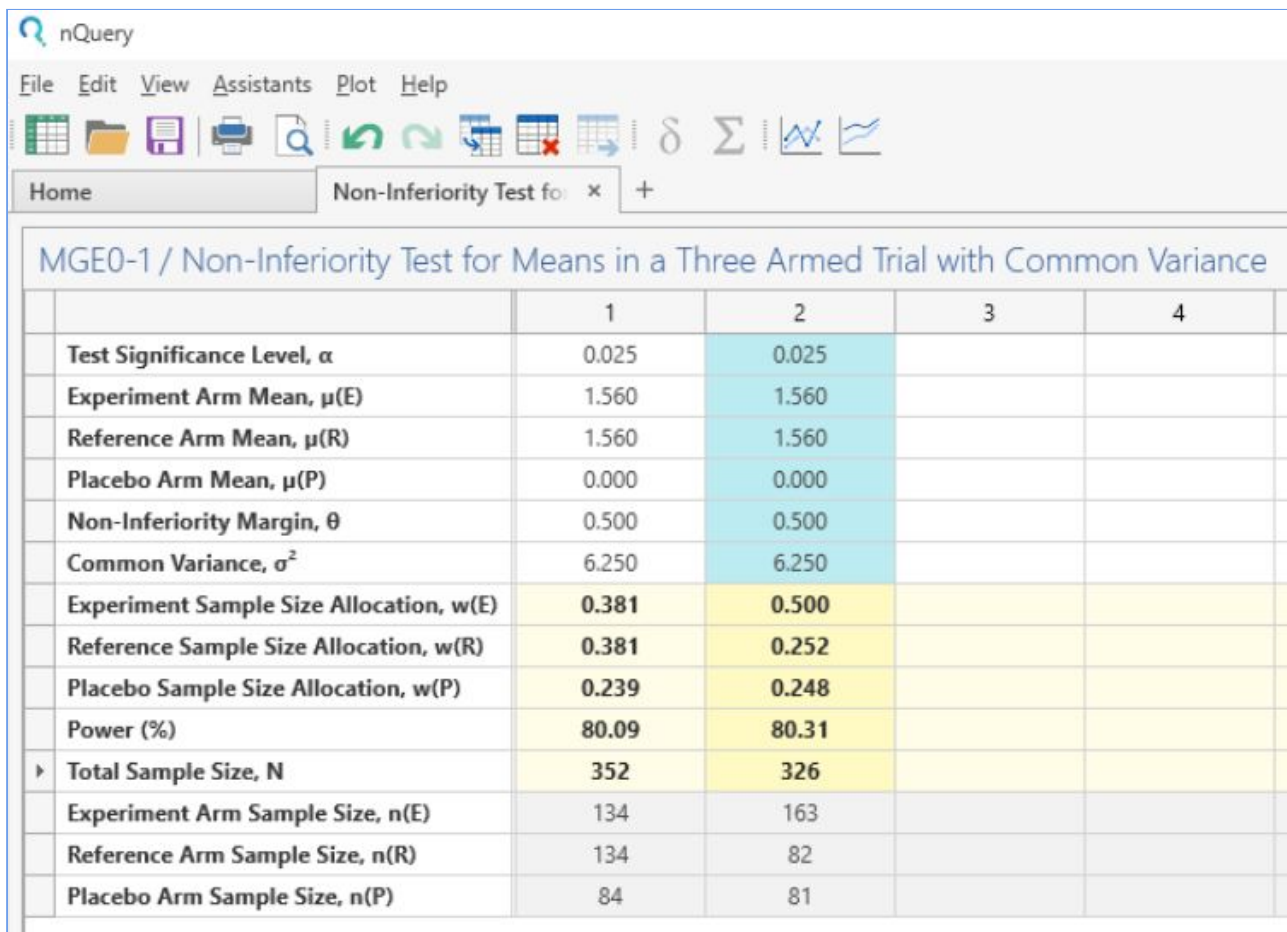
Step 3:

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 $w(E) = 0.5$, $w(R) = \theta/2$ and $w(P) = (1-\theta)/2$ ”

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.



The screenshot shows the nQuery software interface with a menu bar (File, Edit, View, Assistants, Plot, Help) and a toolbar. The active window is titled "Non-Inferiority Test for...". The main content area displays a table titled "MGE0-1 / Non-Inferiority Test for Means in a Three Armed Trial with Common Variance".

| | 1 | 2 | 3 | 4 |
|---|-------|-------|---|---|
| Test Significance Level, α | 0.025 | 0.025 | | |
| Experiment Arm Mean, $\mu(E)$ | 1.560 | 1.560 | | |
| Reference Arm Mean, $\mu(R)$ | 1.560 | 1.560 | | |
| Placebo Arm Mean, $\mu(P)$ | 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.

Select X-axis, Y-axis ✕

X-axis and Y-axis variables

X-axis: ▼

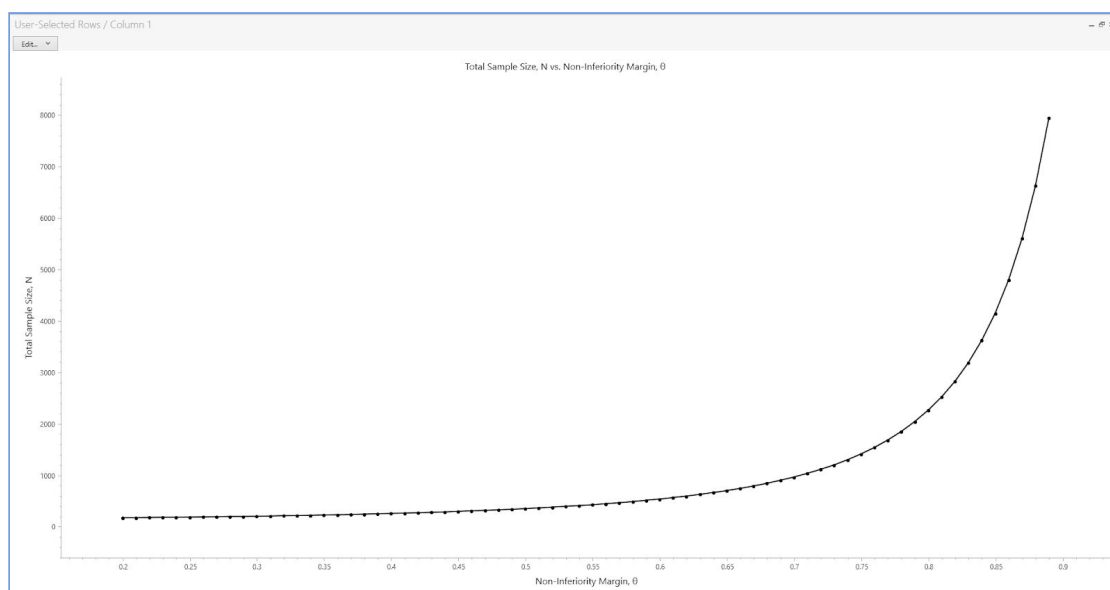
Y-axis: ▼

X-axis range and step size

Min value: ▼

Max value: ▼

Step size: ▼



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